Joint Meeting of JSTP and AUTP 2022

The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology

The 1st Meeting of Asian Union of Toxicologic Pathology

Program & Abstracts

Create the Future of Toxicologic Pathology: Technology & Creativity

Hybrid Meeting onsite and online

Date January 26-28, 2022

Venue Kobe International Conference Center

President Hideki Wanibuchi, M.D., Ph.D.
Professor, Department of Molecular Pathology
Osaka City University Graduate School of Medicine

デジタル病理をトータル支援

低価格かつ迅速にご活用いただけます

☑ 機材導入等の初期費用不要　☑ スキャナー設置不要

快適な病理診断の環境を構築します

視認性・快適性に優れた独自の高速ビューワーを標準装備しており、
クラウド上でなめらかで快適な病理診断を支援します。

インストール不要、すぐに使い始められて、簡単に症例の共有ができます。


遠隔病理診断・コンサルテーション支援

カンファレンス


症例共有、講義

PidPort　病理診断の現場をテクノロジーでサポート

保管・管理	クラウド上で病理画像データ、症例情報を安全に保管・管理・利活用できます
閲覧・共有	独自の高速ビューワーで画像の閲覧ができ、簡単に症例の共有ができます
AI解析	深層学習によって開発されたAIで組織・細胞を高精度で瞬時にスクリーニングやWチェックできます

※日本国内における AI の解析機能に関しては、将来的な提供を計画しています

Medmain
Imaging Center　デジタル病理の環境構築をサポート

お手元の病理標本を送るだけで、安価で高品質・迅速にデジタル画像化します

POINT 1 診断依頼や症例共有が“**いつでも・どこでも**”できるようになる環境の構築

POINT 2 デジタル化により、病理標本を管理・運搬する**時間やコストの削減**

POINT 3 大規模なデータベースの構築に伴う**医療デジタル化の推進**

デジタル病理を強力に支援するクラウドシステム

PidPort

【問い合わせ先】

メドメイン株式会社
〒107-0062 東京都港区南青山 2-10-11 A青山ビル２F
〒810-0042 福岡市中央区赤坂 2-4-5 104
https://medmain.com/

施設毎のお悩みに合わせ、機能や期間を限定した提供も柔軟に可能です。
予算や導入に向けたお悩みの相談など、お気軽に営業担当までご連絡ください。

sales@medmain.com

Joint Meeting of JSTP and AUTP 2022

第 38 回日本毒性病理学会総会及び学術集会
第 1 回アジア毒性病理学連盟学術集会

目　　次

第 38 回日本毒性病理学会総会及び学術集会
The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology

第 1 回アジア毒性病理学連盟学術集会
The 1st Meeting of Asian Union of Toxicologic Pathology

1. 会　期　　**2022 年 1 月 26 日（水）～ 1 月 28 日（金）**

2. 会　場　　**神戸国際会議場**
〒 650-0046　兵庫県神戸市中央区港島中町 6-9-1

3. テーマ　　**毒性病理学の未来を切り拓く技術と創造性**

4. 年会長　　**鰐渕　英機**
（大阪市立大学大学院医学研究科　分子病理学　教授）

5. プログラム委員会

委員長　高橋　　智　（名古屋市立大学）
委　員　小川　久美子（国立医薬品食品衛生研究所）
太田　恵津子（エーザイ株式会社）
加藤　淳彦　（中外製薬株式会社）
桑村　　充　（大阪府立大学）
小林　欣滋　（株式会社新日本科学）
下井　昭仁　（株式会社イナリサーチ）
中江　　大　（東京農業大学）
林　　新茂　（国立医薬品食品衛生研究所）
松本　泉美　（大日本住友製薬株式会社）
山口　裕子　（株式会社ボゾリサーチセンター）
義澤　克彦　（武庫川女子大学）　　（五十音順）

6. 事務局　　大阪市立大学大学院医学研究科 分子病理学
〒 545-8585　大阪市阿倍野区旭町 1 丁目 4 番 3 号
Email：jstp38@med.osaka-cu.ac.jp

7. 運営事務局　　株式会社プロアクティブ
〒 650-0034　神戸市中央区京町 83 番地　三宮センチュリービル 3 階
TEL：078-332-2505　FAX：078-332-2506
Email：jstp38@pac.ne.jp

8. ホームページ　　https://www.pac-mice.jp/jstp38/

年会長挨拶

第 38 回日本毒性病理学会総会及び学術集会
第 1 回アジア毒性病理学連盟学術集会
年会長　鰐渕　英機
大阪市立大学大学院医学研究科　分子病理学　教授

この度、第 38 回日本毒性病理学会総会及び学術集会の年会長を拝命いたしました。

本学会総会及び学術集会は 2022 年 1 月 27 日（木）および 28 日（金）の 2 日間で、神戸国際会議場（兵庫県神戸市）及びオンラインでの両方で参加できるハイブリッド形式にて実施いたします。また、今回の学術集会は、第 1 回アジア毒性病理学連盟（Asian Union of Toxicologic Pathology）学術集会と合同で、国際学会として開催いたします。さらに、1 月 26 日（水）には、スライドカンファランスならびに日本毒性病理学専門家認定試験における問題解説に加え、日中毒性病理共同教育セミナーを開催します。

本学術集会では、「毒性病理学の未来を切り拓く技術と創造性」をテーマとして掲げました。日本毒性病理学会は、毒性病理学の進化や発展を目的として設立され、これまでに多くの研究成果を生み出し、学術的にも社会的にも貢献して参りました。近年では、低分子医薬品開発で重要な役割を担っていた毒性試験だけでなく、イメージングによる毒性作用機序の解明や新たな薬品に対する安全性評価方法など、新たな領域での発展が必要となってきております。本学会におきましては、上記テーマを掲げて、長年培われてきた毒性病理学の基盤に加え、画像デジタル化や AI による診断、新たな可視化技術などを取り込むことによる病理診断の発展性を紹介するとともに、先端技術として、動物ゲノム編集やがん微小環境への取り組みなどを紹介し、創造性のある学術分野の発展への貢献を目指しております。

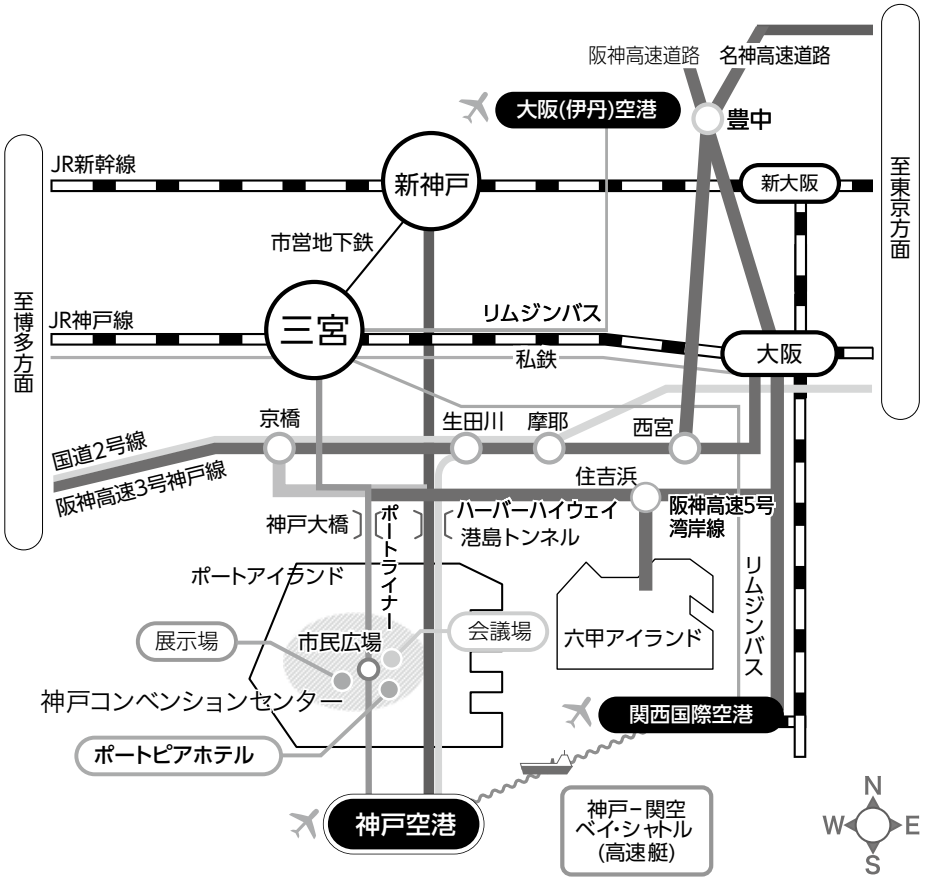
本国際学会により日本毒性病理学会の国際化を進めるとともに、アジア諸国への研究や教育、発展への貢献を目指しております。日本国内からの参加に加え、欧米や中国、韓国、インド、タイ、エジプトからも多く参加される国際的な学会を提供いたします。より開かれた日本毒性病理学会への発展に、今回の学術集会を介して貢献できればと存じます。

学術集会におきましては、会員皆様の日ごろの研究成果を積極的に発表していただき、意見交換の場になることを願っております。多くの皆様の積極的なご参加を心よりお待ちしております。

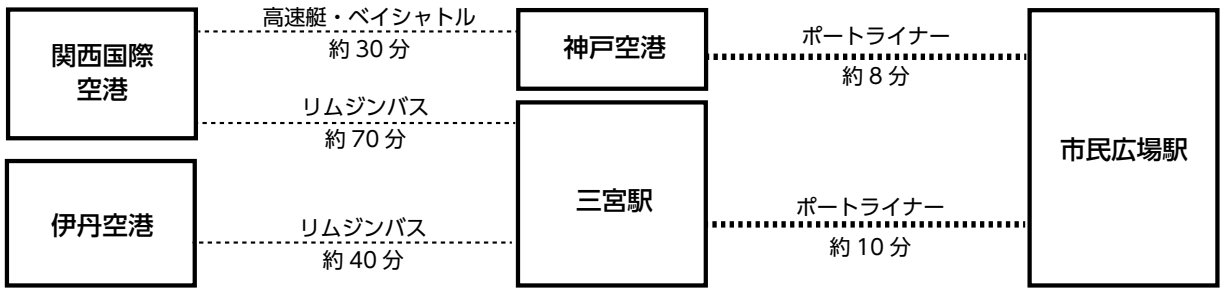
会場へのアクセス

神戸国際会議場

ポートライナー「市民広場（コンベンションセンター）」駅下車すぐ。連絡通路を通り、お越しください。

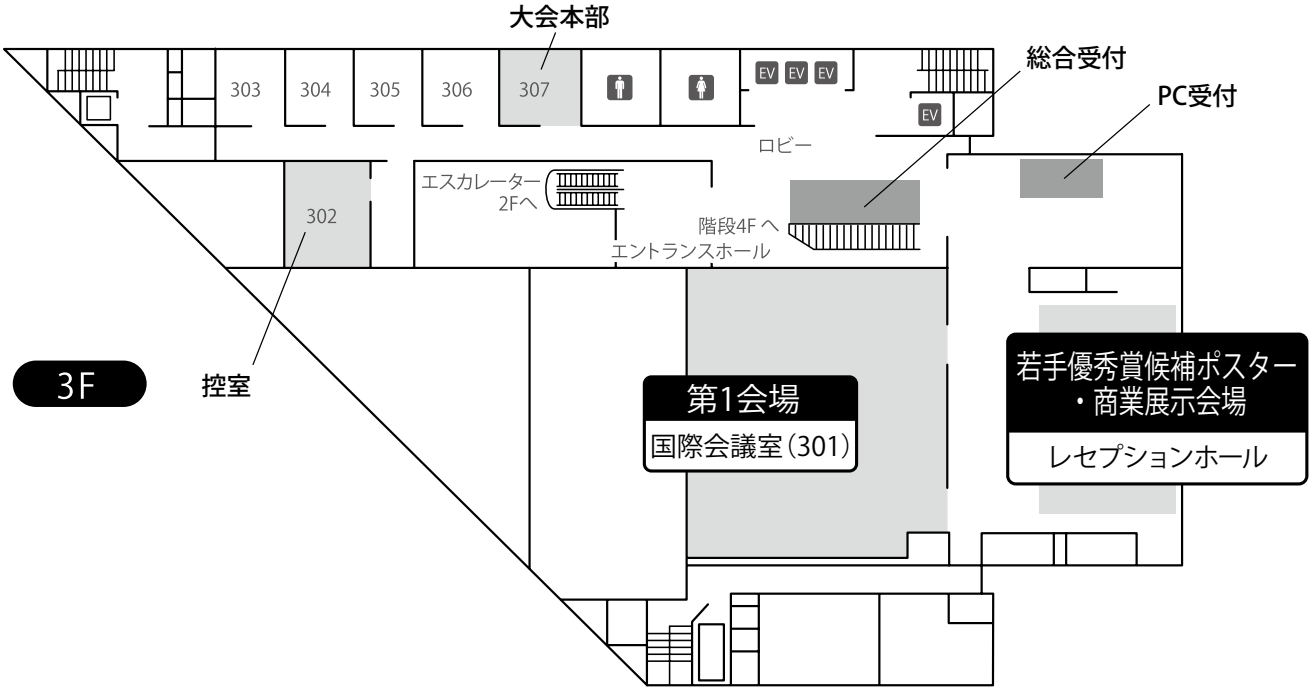


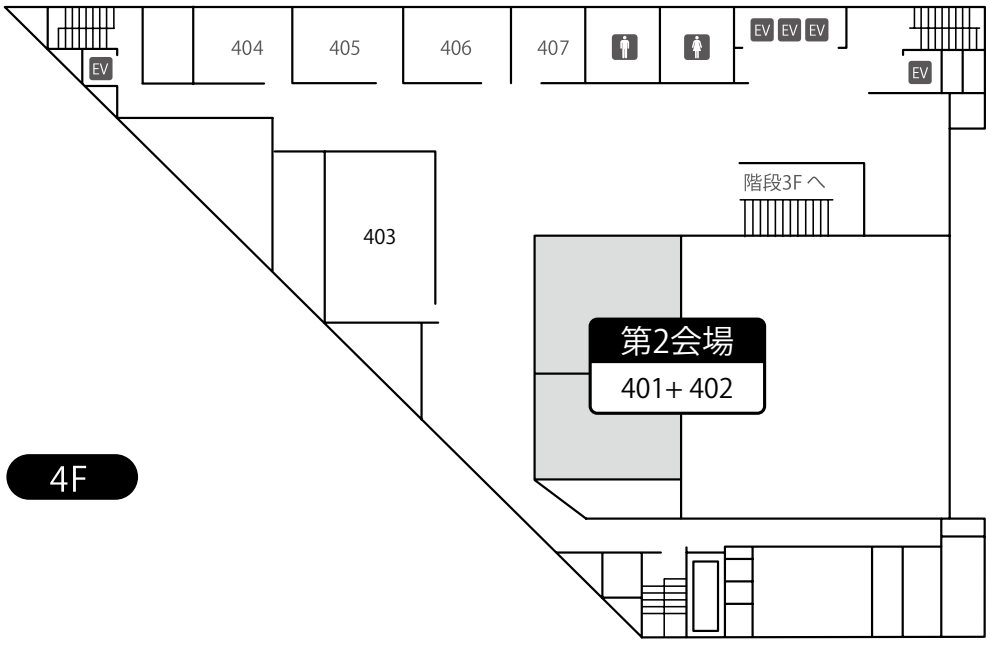
■飛行機でお越しの場合



■新幹線でお越しの場合

会場案内

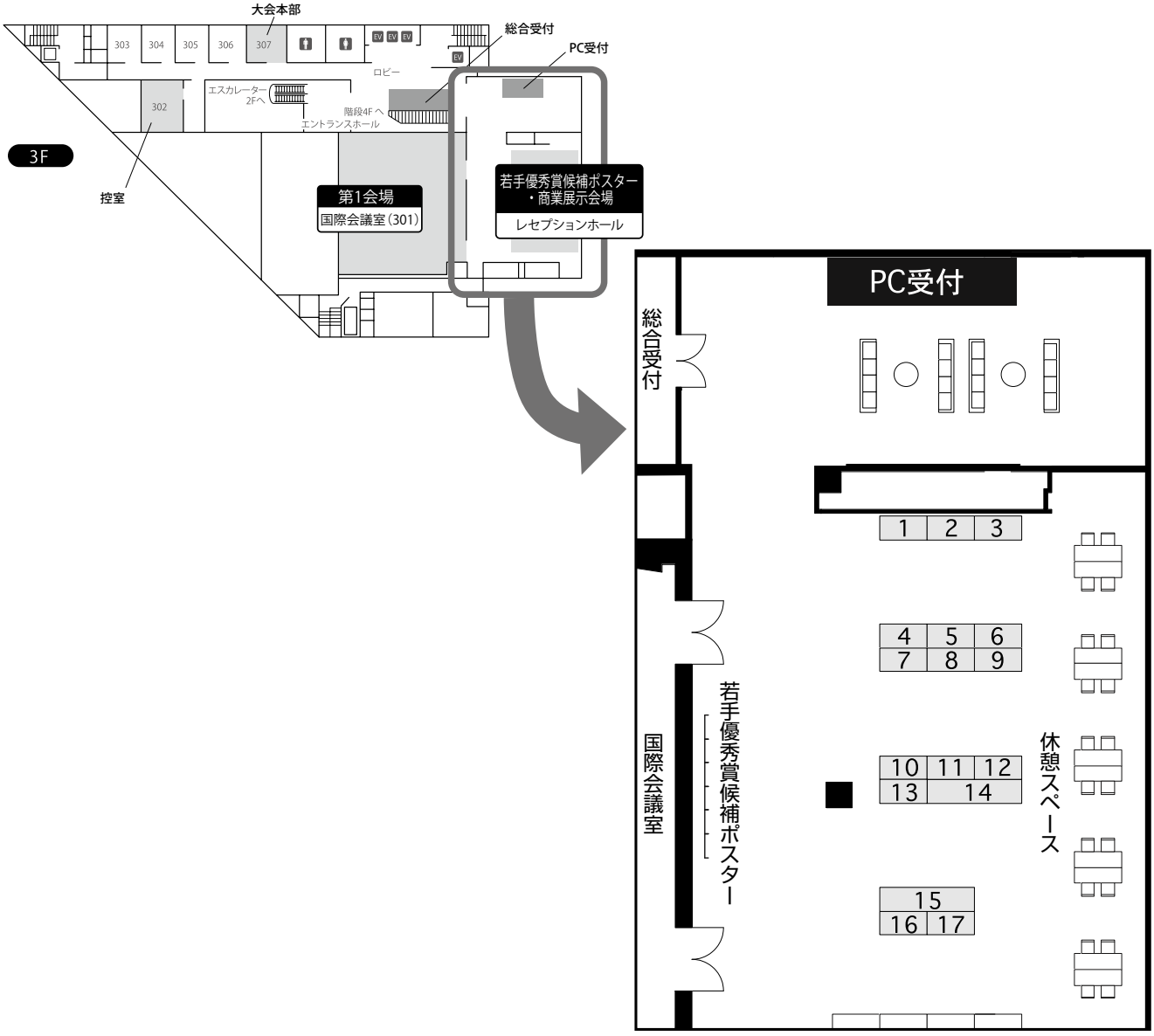

大会本部
総合受付
PC受付
303
304
305
306
307
EV EV EV
EV
ロビー
エスカレーター
2Fへ
302
階段4F へ
エントランスホール
3F
控室
第1会場
国際会議室（301）
若手優秀賞候補ポスター
・商業展示会場
レセプションホール


404
405
406
407
EV EV EV
EV
EV
階段3F へ
403
第2会場
401+ 402
4F

商業展示

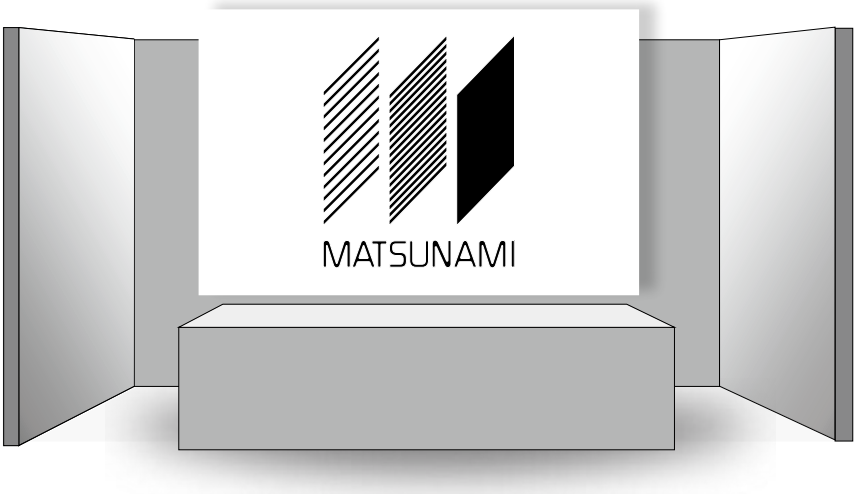
商業展示会場（レセプションホール）

ブース番号		ブース番号	
1	実験病理組織技術研究会	10	サクラファインテックジャパン株式会社
2	株式会社ボゾリサーチセンター	11	株式会社 DIMS 医科学研究所
3	Charles River	12	株式会社新日本科学
4	株式会社イナリサーチ	13	コージンバイオ株式会社
5	Instem	14	松浪硝子工業株式会社
6	日本エスエルシー株式会社	15	PHC 株式会社
7	インラボテックジャパン合同会社	16	株式会社スクラム /10x Genomics
8	アズワン株式会社	17	ライカ マイクロシステムズ株式会社
9	アドバンテック株式会社		



WEB 商業展示

PHC 株式会社



松浪硝子工業株式会社

アドバンテック株式会社

株式会社スクラム /10x Genomics

※イラストはイメージです

新型コロナウイルス等感染症予防及び拡散防止対策について

第 38 回日本毒性病理学会総会及び学術集会・第 1 回アジア毒性病理学連盟学術集会は、神戸市および日本コンベンション協会の感染予防対策ガイドラインに沿って開催の準備を進めております。
現地開催におきましては、下記の感染対策を実施いたします。ご理解・ご協力をお願い申し上げます。

- 会場入口での検温実施および健康状態申告書のご提出
  （37.5℃以上が検知された場合、入場をご遠慮いただく場合がございます。）
- 会場内でのマスク着用
- 入場時のアルコールによる手指消毒（会場各所に手指消毒剤の設置いたします）
- 会場内などソーシャルディスタンスの確保
- 会場内の席数削減と参加人数制限および立ち見の禁止
- 会場内の換気の強化
  （会場によってはドアを開放した状態でプログラムを進行いたします。）
- 「新型コロナウイルス接触確認アプリ（COCOA）」および「兵庫県新型コロナ追跡システム」のインストールをお願いいたします。

新型コロナウイルス接触確認アプリ（COCOA）

App Store または Google Play で「接触確認アプリ」で検索してインストールしてください。

iPhone の方はこちら　App Store からダウンロード

Android の方はこちら　Google Play で手に入れよう

兵庫県新型コロナ追跡システム

会場内に掲示いたします QR コードを読み取ってください。

- 感染拡大防止のため、クロークおよびドリンクサービスは中止いたします。
- 会場を離れてからも、感染症対策を各自おこなってください（大人数での会食を控える等）。
- 感染者発生時には、感染経路特定等の理由により政府機関・自治体の要請により、個人情報を開示することをあらかじめご了承ください。

参加者へのご案内

第 38 回日本毒性病理学会学術年会・第 1 回アジア毒性病理学連盟学術集会は、新型コロナウイルス感染症対策を徹底し、会場開催＋ WEB 開催のハイブリット形式で開催いたします。
1 月 26 日（水）～ 1 月 28 日（金）の開催期間中、会場のセッションをライブ配信いたします。

	開催方法
特別講演 シンポジウム パネルディスカッション 若手ワークショップ IATP Maronpot Guest Lecture	現地開催＋ライブ配信
1st JSTP-CPA-STP Joint Education Seminar	ライブ配信のみ
一般演題（ポスター発表）*	オンデマンド配信 （WEB 開催システム内で PDF データを閲覧） （1/20（木）正午～ 2/13（日）23:59）

＊若手優秀賞候補ポスターは現地にて掲示いたします。

●参加者の方々へ

1. 新型コロナウイルス感染予防のため、当日登録は行いませんので、学術集会ホームページより、事前参加登録を行ってください。
   後期参加登録期間：2021 年 12 月 21 日（火）～ 2022 年 1 月 28 日（金）
2. 事前登録者はあらかじめ講演要旨集とともに送付された参加証（ネームカード）を持参し、会期中は必ず着用ください。
   ネームホルダーは総合受付にご用意いたしますので、ご利用ください。
3. 講演要旨集は事前に郵送いたしますので、忘れずにご持参ください。
   お忘れの場合は一般会員・学生会員：2,000 円、非会員：5,000 円での販売となります。
4. 質問・討論される方は、マイクの前に並んだ上、座長の指示に従って所属と氏名を述べてから発言してください。
5. 館内はすべて禁煙です。
6. 場内では携帯電話の電源を OFF またはマナーモードにしてください。
7. 無線 LAN によるインターネット接続をご提供しますのでご利用ください。
8. 昼食はランチョンセミナー、あるいは隣接している神戸ポートピアホテルのレストランをご利用ください。
9. 新型コロナウイルス感染予防のため、クロークおよびドリンクサービスは行いません。
10. 会場内での呼び出しは緊急時以外にはいたしませんのでご了承ください。
11. 会場内での写真撮影・録画・録音は禁止させていただきます。

● WEB での参加について

1. 学術集会ホームページから、WEB 開催会場へお入りいただけます。参加受付 ID と参加申込時にご自身で登録されたパスワードで、ログインしていただくと、視聴画面にお入りいただけます。
2. ライブ配信のプログラムについては、コメント機能で質疑応答が可能です。音声での質問はできません。
   ポスター発表はオンデマンドのみとなります。
   視聴方法の詳細は、学術集会ホームページをご覧ください。

●総会のご案内

日本毒性病理学会 会員各位

拝啓

新春の候　ますますご清祥のこととお慶び申し上げます。

さて、第 38 回日本毒性病理学会では、社員総会（以下、総会）を下記のとおり開催いたします。

本総会は、事業報告及び決算、名誉・功労会員、役員などをご承認いただく重要な会議となりますので、ご出席の程何卒よろしくお願い申し上げます。

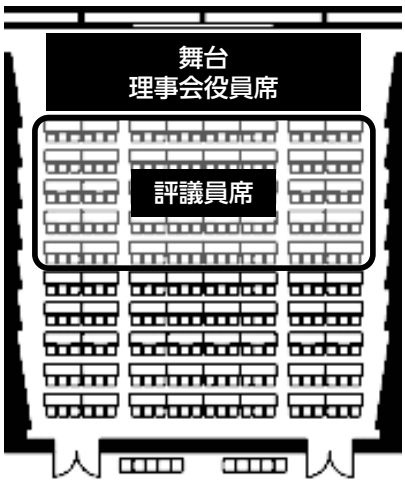
総会に参加いただくには、学術集会への参加登録が必要です。なお、評議員の皆様には、ご出欠を確認させていただきます。

敬具

日本毒性病理学会　理事長　鰐渕　英機

日　　時：2022 年 1 月 28 日（金）15:35 ～ 17:05
開催形式：現地 + ライブ配信
開催場所：国際会議室
主な議題：・2021 年度事業報告及び決算の承認
・2022 年度事業計画及び収支予算の報告
・名誉会員・功労会員の承認
・理事・監事の選任
・評議員の選任
・2024 年度学術年会長の選任

国際会議室



●座長の方々へ

特別講演・シンポジウム・パネルディスカッション・若手ワークショップ・IATP レクチャー

1. ご担当セッション開始時間の遅くとも 20 分前までには、3 階総合受付にお越しください。
2. セッション開始 10 分前には、会場内の次座長席にご着席ください。
3. ライブ配信で参加されている方からの質問は、座長席にご用意しますモニターに表示されます。集約していただき、演者へご質問ください。

●発表者の方々へ

利益相反について

発表者の皆様は可能な限り COI（利益相反）の開示をお願いいたします。企業に所属の場合は別企業と COI 状態にある場合に開示してください。
講演者は発表スライドの 2 枚目（表題の次のスライド）に、ポスター発表者は一番最後に記載してください。

Sample 1

COI Disclosure Information

Taro Dokusei

In connection with this presentation, there is

no COI to be disclosed with any companies.

本演題に関連して開示すべき利益相反はありません。

Sample 2

COI Disclosure Information

Hanako Dokusei

In connection with the presentation, we

disclose COI with following companies.

本演題に関連して開示すべき利益相反は以下の通りです。

Executive / Advisory Position:	(○○Company)
Funded research / Collaborative research:	(○○Company)
Lecture Honorariums, etc.:	(○○Company)

特別講演・シンポジウム・パネルディスカッション・若手ワークショップ・IATP レクチャー

1. 発表時間の遅くとも 30 分前までに、3 階 PC 受付にお越しいただき、発表データを提出してください。動作確認を行っていただきます。パソコンをお持ち込みの場合は、ミニ D-Sub15 ピンの端子が必要となりますので、変換コネクター等をご準備ください。
2. 発表機材は PC 液晶プロジェクターを使用します。スライド・ビデオは使用できませんのでご注意ください。
3. 発表は、演壇におかれたパソコン画面を見ながら、ご自身で画面操作をしてください。
4. 前演者の発表が始まりましたら、次演者席にお着きください。
5. 発表データは、会場のパソコンに一時保存いたしますが、これらのデータは本学会終了後、責任を持って廃棄します。

プレゼンテーションデータ作成時の注意

●環境の違いにより、画面レイアウトが乱れるなどの不具合が発生する可能性があります。
会場のパソコン使用環境は以下の通りですので、ご留意ください。

パソコン：Windows PC（Macintosh は用意しておりません）
OS　　：Windows 10
解像度　：1920 × 1080
プレゼンテーション用ソフト：PowerPoint 2016 / 2019
フォント：OS（Windows10）標準

● USB メモリに保存してご提出ください。
●スライドは、16:9 での作成を推奨いたします。

ポスター発表

1. ポスター発表はオンデマンド配信となります。WEB 開催システムから閲覧が可能です。
WEB 閲覧用に PDF データを作成いただき、指定のサーバーにアップロードしていただきます。
2. オンデマンド配信期間は、1 月 20 日（木）正午 ～ 2 月 13 日（日）23:59 です。
3. 若手優秀賞候補ポスターはレセプションホールにて掲示いたします。
4. 質疑応答について
ポスター閲覧画面に、参加者は質問を書き込みいただけます。書き込みがありましたら、投稿時に登録されたメールアドレスに通知が届きますので、WEB 開催システムにお入りいただき、回答を追記してください。書き込みは参加者全員が閲覧できます。詳細は学術集会ホームページの操作マニュアルをご覧ください。

●ランチョンセミナー・イブニングセミナー・モーニングセミナーのご案内

現地およびライブ配信にて開催いたします。
なお、現地会場ではチケット配布は行わず先着順となりますので、あらかじめご了承ください。

第1日目　1月27日（木）

ランチョンセミナー　L1

12:00 ～ 13:00　第 1 会場（国際会議室）

タイトル：AI Decision Support Tool Development in Toxicologic Pathology
演　　者：Esther Crouch（Veterinary Pathologist, Global Digital Pathology, Charles River）
座　　長：上西　将路（Charles River）
共　　催：Charles River

ランチョンセミナー　L2

12:00 ～ 13:00　第 2 会場（401+402）

タイトル：実験動物を用いたサイトカインおよび生体材料の歯周組織再生能評価
演　　者：白方　良典（鹿児島大学 大学院医歯学総合研究科 顎顔面機能再建学講座 歯周病学分野）
座　　長：小林　欣滋（株式会社新日本科学 安全性研究所 病理研究部）
共　　催：株式会社新日本科学

イブニングセミナー

18:35 ～ 19:35　第 1 会場（国際会議室）

タイトル：Quanticell の臨床検体への応用
演　　者：蔦　幸治　（関西医科大学 病理学講座）

タイトル：高感度・定量的かつ局在解析可能な免疫組織染色受託サービス Quanticell のご紹介
演　　者：西川　賢司（コニカミノルタ REALM 株式会社　ファーマ事業開発部）

共　　催：コニカミノルタ REALM 株式会社

第2日目　1月28日（金）

モーニングセミナー

8:00 ～ 8:40　第 2 会場（401+402）

タイトル：Microscopic Observations for Infectious Disease Models
–新型コロナウイルス（COVID-19）など感染モデルにおける病理組織学的検査–（仮）
演　　者：Carson Sakamoto（Anatomic Pathologist, Southern Research）
座　　長：林　俊英（株式会社イナリサーチ）
共　　催：株式会社イナリサーチ

ランチョンセミナー　L3

12:00 ～ 13:00　第 1 会場（国際会議室）

タイトル：Visium 空間解析によって可能になった組織位置情報と全遺伝子発現の統合解析
演　　者：雨貝　陽介（Science & Technology Advisor　10x Genomics）
座　　長：大崎　研　（Regional Marketing Manager, North Asia Pacific　10x Genomics）
共　　催：株式会社スクラム /10x Genomics

後援・協賛法人・企業一覧

第 38 回日本毒性病理学会総会及び学術集会・第 1 回アジア毒性病理学連盟学術集会を開催するにあたり、多くの企業・団体様よりご支援ご協力を賜りました。
ここにお名前を掲載して厚く御礼申し上げます。

第 38 回日本毒性病理学会総会及び学術集会・第 1 回アジア毒性病理学連盟学術集会
年会長　鰐渕　英機

後援

一般財団法人 神戸観光局
公益財団法人 中内力コンベンション振興財団
公益財団法人 日本食品化学研究振興財団

協賛

一般社団法人 日本毒性学会
日本食品化学学会
安全性評価研究会
実験病理組織技術研究会

寄付

旭化成ファーマ株式会社
旭化成メディカル株式会社
味の素株式会社
アステラス製薬株式会社
株式会社東屋医科器械
アピ株式会社
株式会社安評センター
石原産業株式会社
エーザイ株式会社
株式会社 LSIM 安全科学研究所
小野薬品工業株式会社
株式会社カネカ
杏林製薬株式会社
株式会社札幌総合病理研究所
三栄源エフ・エフ・アイ株式会社
一般財団法人残留農薬研究所
株式会社三和化学研究所
住友化学株式会社
ゼリア新薬工業株式会社
第一三共株式会社
大日本住友製薬株式会社
大鵬薬品工業株式会社
武田薬品工業株式会社
田辺三菱製薬株式会社
中外製薬株式会社
帝人ファーマ株式会社
日産化学株式会社
日本香料工業会
日本たばこ産業株式会社　医薬総合研究所
日本農薬株式会社
パルテノンジャパン株式会社
Pfizer

バナー広告

株式会社アーガス・サイエンス
Charles River

ランチョンセミナー

株式会社新日本科学
株式会社スクラム /10x Genomics
Charles River

モーニングセミナー

株式会社イナリサーチ

イブニングセミナー

コニカミノルタ REALM 株式会社

商業展示

アズワン株式会社
アドバンテック株式会社
株式会社イナリサーチ
Instem
インラボテックジャパン合同会社
コージンバイオ株式会社
サクラファインテックジャパン株式会社
実験病理組織技術研究会
株式会社新日本科学
株式会社スクラム /10x Genomics
Charles River
株式会社 DIMS 医科学研究所
日本エスエルシー株式会社
PHC 株式会社
株式会社ボゾリサーチセンター
松浪硝子工業株式会社
ライカ マイクロシステムズ株式会社

広告

Instem
オリエンタル酵母工業株式会社
キコーテック株式会社
三栄源エフ・エフ・アイ株式会社
白井松器械株式会社
株式会社新日本科学
株式会社スクラム /10x Genomics
内閣府　食品安全委員会
株式会社ニコンソリューションズ
日本クレア株式会社
メドメイン株式会社
八洲薬品株式会社

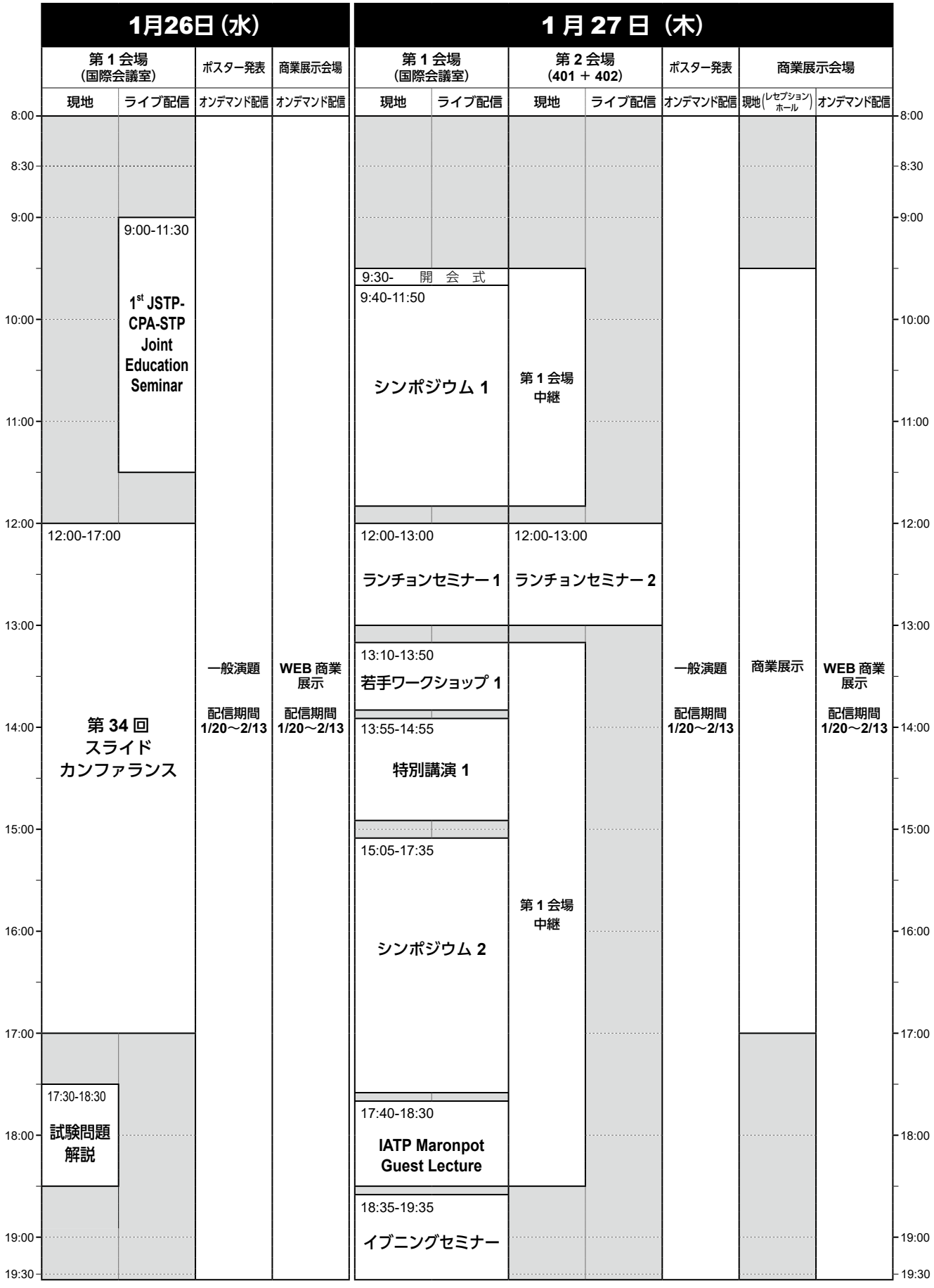
（五十音順）

日本毒性病理学会のあゆみ

回	開催地	会　長（所　属）	会　期	特別講演	シンポジウム ワークショップ その他	一般演題
1	東　京	西山　保一（北里学園）	1985. 3. 25	2	0	0
2	東　京	藤原　公策（東京大学）	1986. 2. 7-8	1	5	29
3	名古屋	伊東　信行（名古屋市立大学）	1987. 2. 6-7	1	8	47
4	浜　松	榎本　　眞（安評センター）	1988. 2. 5-6	1	7	55
5	横　浜	蟹澤　成好（横浜市立大学）	1989. 1. 27-28	1	6	53
6	札　幌	板倉　智敏（北海道大学）	1990. 2. 13-14	1	6	80
7	東　京	林　　裕造（国立衛試）	1991. 1. 17-18	1	20	53
8	奈　良	小西　陽一（奈良医科大学）	1992. 1. 23-24	1	19	71
9	東　京	土井　邦雄（東京大学）	1993. 1. 21-22	2	4	126
10	広　島	伊藤　明弘（広島大学）	1994. 1. 27-29	1	18	136
11	大　阪	佐久間貞重（大阪府立大学）	1995. 1. 26-27	2	10	151
12	東　京	高橋　道人（国立衛試）	1996. 1. 24-25	0	16	147
13	鳥　取	梅村　孝司（鳥取大学）	1997. 1. 23-24	1	11	151
14	東　京	前川　昭彦（佐々木研）	1998. 2. 3-4	1	9	143
15	水　戸	真板　敬三（残農研）	1999. 1. 28-29	0	7	142
16	岐　阜	森　　秀樹（岐阜大学）	2000. 1. 26-27	1	12	125
17	淡　路	奈良間　功（摂南大学）	2001. 1. 25-26	1	10	146
18	東　京	津田　洋幸（国立がんセンター）	2002. 1. 24-25	0	2	119
19	東　京	布谷　鉄夫（日生研）	2003. 1. 23-24	1	5	102
20	神　戸*	福島　昭治（大阪市立大学）	2004. 2. 15-18	2	31	172
21	浜　松	今井　　清（安評センター）	2005. 1. 20-21	1	23	100
22	鹿児島	吉田　浩己（鹿児島大学）	2006. 1. 26-27	1	15	109
23	東　京	三森　国敏（東京農工大学）	2007. 1. 30-31	0	15	107
24	名古屋	白井　智之（名古屋市立大学）	2008. 2. 6-7	1	13	106
25	浜　松	真鍋　　淳（第一三共（株））	2009. 1. 27-28	2	17	124
26	金　沢	田中　卓二（金沢医科大学）	2010. 2. 3-4	2	10	125
27	大　阪	大石　裕司（アステラス製薬（株））	2011. 1. 27-28	2	13	144
28	東　京	西川　秋佳（国立衛研）	2012. 2. 2-3	2	21	108
29	つくば	原田　孝則（残農研）	2013. 1. 31-2. 1	1	8	107
30	徳　島	泉　　啓介（徳島大学）	2014. 1. 30-31	2	15	114
31	東　京	中山　裕之（東京大学）	2015. 1. 29-30	1	11	96
32	香　川	今井田克己（香川大学）	2016. 1. 28-29	2	13	101
33	大　阪	山手　丈至（大阪府立大学）	2017. 1. 26-27	1	22	83
34	沖　縄	吉見　直己（琉球大学）	2018. 1. 25-26	2	17	108
35	東　京	鈴木　雅実（中外製薬（株））	2019. 1. 31-2. 1	2	18	87
36	東　京	中江　　大（東京農業大学）	2020. 2. 13-14	5	14	86
37	浜　松**	岩田　　聖（ルナパス毒性病理研究所）	2021. 1. 28-29	3	18	68
38	神　戸***	鰐渕　英機（大阪市立大学）	2022. 1. 26-28	2	30	121

*：国際毒性病理学会連合（The International Federation of Societies of Toxicologic Pathology）との共同開催　　**：Web 開催
***：アジア毒性病理学連盟（Asian Union of Toxicologic Pathology）との共同開催、現地及び WEB 開催

日　程　表


1月26日（水）
1月27日（木）
第1会場（国際会議室）
第2会場（401＋402）
ポスター発表
商業展示会場
現地
ライブ配信
オンデマンド配信
現地（レセプションホール）
9:00-11:30
1st JSTP-CPA-STP Joint Education Seminar
12:00-17:00
第34回スライドカンファランス
17:30-18:30
試験問題解説
一般演題
配信期間1/20〜2/13
WEB商業展示
9:30- 開会式
9:40-11:50
シンポジウム1
第1会場中継
12:00-13:00
ランチョンセミナー1
ランチョンセミナー2
13:10-13:50
若手ワークショップ1
13:55-14:55
特別講演1
15:05-17:35
シンポジウム2
17:40-18:30
IATP Maronpot Guest Lecture
18:35-19:35
イブニングセミナー
商業展示
8:00
8:30
9:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
18:00
19:00
19:30

日　程　表

1月28日（金）

第1会場（国際会議室）		第2会場（401 + 402）		ポスター発表	商業展示会場	
現地	ライブ配信	現地	ライブ配信	オンデマンド配信	現地（レセプションホール）	オンデマンド配信
		8:00-8:40 モーニングセミナー		一般演題 配信期間 1/20〜2/13		WEB商業展示 配信期間 1/20 〜 2/13
9:00-9:50 特別講演 2					商業展示	
9:55-11:55 シンポジウム 3		第1会場中継				
12:00-13:00 ランチョンセミナー 3						
13:10-13:50 若手ワークショップ 2						
13:55 〜 15:25 パネルディスカッション		第1会場中継				
15:35 〜 17:05 総会及び表彰式 閉会式						

8:00 / 8:30 / 9:00 / 10:00 / 11:00 / 12:00 / 13:00 / 14:00 / 15:00 / 16:00 / 17:00 / 18:00 / 19:00

司会・座長一覧

セッション名	日　　時	司会・座長（所属）
特別講演 1	1 月 27 日（木）13：55 ～ 14：55	鰐渕　英機（大阪市立大学）
特別講演 2	1 月 28 日（金）　9：00 ～　9：50	髙橋　　智（名古屋市立大学）
シンポジウム 1	1 月 27 日（木）　9：40 ～ 11：50	小川久美子（国立医薬品食品衛生研究所） 小林　欣滋（株式会社新日本科学）
シンポジウム 2	1 月 27 日（木）15：05 ～ 17：35	中江　　大（東京農業大学） 義澤　克彦（武庫川女子大学）
シンポジウム 3	1 月 28 日（金）　9：55 ～ 11：55	太田恵津子（エーザイ株式会社） 桑村　　充（大阪府立大学）
パネル ディスカッション	1 月 28 日（金）13：55 ～ 15：25	加藤　淳彦（中外製薬株式会社） 下井　昭仁（株式会社イナリサーチ）
IATP Maronpot Guest Lecture	1 月 27 日（木）17：40 ～ 18：30	林　　新茂（国立医薬品食品衛生研究所）
若手 ワークショップ 1	1 月 27 日（木）13：10 ～ 13：50	内木　　綾（名古屋市立大学） 鈴木　周五（大阪市立大学）
若手 ワークショップ 2	1 月 28 日（金）13：10 ～ 13：50	豊田　武士（国立医薬品食品衛生研究所） 吉田　敏則（東京農工大学）
1st JSTP-CPA-STP Joint Education Seminar	1 月 26 日（水）　9：00 ～ 11：30	Jin Ren (Shanghai Institute of Material Medica, Chinese Academy of Science) Min Gi (Osaka City University Graduate School of Medicine)

プログラム

特別講演 1

第 1 日目　1 月 27 日（木）13:55 - 14:55　　第 1 会場（国際会議室）

座長：鰐渕　英機（大阪市立大学）

SL-1　腸内細菌叢の異常を伴う疾患に対する新規治療法の開発

○植松 智 [1,2]

[1]大阪市立大学　大学院医学研究科　ゲノム免疫学
[2]東京大学　医科学研究所　ヒトゲノム解析センター　メタゲノム医学分野

特別講演 2

第 2 日目　1 月 28 日（金）9:00 - 9:50　　第 1 会場（国際会議室）

座長：髙橋　智（名古屋市立大学）

SL-2　Contribution of toxicologic pathology to occupational health

○福島 昭治 [1,2]

[1]独立行政法人労働者健康機構 日本バイオアッセイ研究センター
[2]一般社団法人化学物質安全性評価研究推進機構

シンポジウム 1
Toxicologic pathology and beyond ～可視化技術で読み解く病理組織標本の深層～

第 1 日目　1 月 27 日（木）9:40 - 11:50　　第 1 会場（国際会議室）

座長：小川　久美子（国立医薬品食品衛生研究所）
小林　欣滋　（株式会社新日本科学）

S1-1　脱離エレクトロスプレーイオン化法による質量分析イメージング－組織切片上における化学物質及び代謝物の局在解析

○石井 雄二

国立医薬品食品衛生研究所　病理部

S1-2　病理組織形態の人工知能による構造化

○石川 俊平

東京大学　医学部・大学院医学系研究科　衛生学教室

S1-3　OCT（光干渉断層計）検査の基礎及び OCT 画像と病理組織像との関連

○荒木 智陽

（株）新日本科学　安全性研究所

S1-4　AI ホスピタル計画における病理業務のデジタル化と AI 活用

○高松 学

公益財団法人がん研究会　がん研究所　病理部

シンポジウム 2　JSTP 毒性病理学専門家認定制度の国際化

第 1 日目　1 月 27 日（木）15:05 - 17:35　　第 1 会場（国際会議室）

座長：中江　　大　（東京農業大学）
義澤　克彦　（武庫川女子大学）

S2-1　The current status and future plans for the globalization of JSTP's certification system for toxicologic pathology

○義澤 克彦[1,2)]

[1)]武庫川女子大学　食物栄養科学部　食創造科学科、[2)]日本毒性病理学会　資格認定委員会

S2-2　Establishment of accreditation procedures in toxicologic pathology for trainees

○Kevin Keane

International Academy of Toxicologic Pathology (IATP)

S2-3　規制当局の認識について

○三枝 由紀恵

（独）医薬品医療機器総合機構

S2-4　欧州での実情

○岡崎 欣正

アナパス・サービス・ゲーエムベーハー

S2-5　Current status and future prospects of pharmaco-toxicologic pathology in China

○Jin Ren

Chinese Pharmaceutical Association-Society of Toxicologic Pathology

S2-6　Korean society of toxicologic pathology and board certification

○Jin Seok Kang

Korean Society of Toxicologic Pathology

S2-7　Overview on society of toxicologic pathology India (STPI) and Indian board of toxicologic pathology (IBTP)

○Venkatesha Udupa[1)], SK Vijayasarathi[2)], Narendra Deshmukh[3)], Shekar Chelur[4)], Kamala Kanan[2)], Jomy Jose[5)], PC Prabu[6)], GJ Nataraju[7)], Geeta Nirody[8)] , Madhav Marathe[9)]

[1)]Vice President & Head Toxicology, Glenmark Pharmaceuticals Ltd
[2)]Expert Pathologist, Eurofins Advinus Limited
[3)]Co-Founder and Director, Intox Pvt Ltd
[4)]Director, Preclinical Safety Evaluation, Aurigene Discovery Technologies Ltd, Bengaluru, India; 2Head Pathology, Eurofins Advinus Limited
[5)]Head of the Department, Pathology, Sai Lifesciences
[6)]Assistant Professor, Department of Pathology, Veterinary College & Research Institute
[7)]Head Pathology, Bioneeds India Private Ltd
[8)]Consultant Pathologist
[9)]Vice President Toxicology, Sun Pharma Advanced Research Company Ltd

シンポジウム 3
Toxicologic pathology and beyond　～先端技術で拓く新毒性病理学～

第 2 日目　1 月 28 日（金）9:55 - 11:55　　第 1 会場（国際会議室）

座長：太田　恵津子（エーザイ株式会社）
桑村　　充　（大阪府立大学）

S3-1　ゲノム編集技術とその医療応用

○真下 知士

東京大学医科学研究所

S3-2　がん細胞とがん微小環境の相互作用によるがん組織の形態形成

○中野 清孝[1)]、山崎 雅輝[1)]、川合 重人[1)]、藤井 悦子[1)]、油谷 浩幸[2)]、鈴木 雅実[3)]

[1)]中外製薬株式会社、[2)]東京大学　先端科学技術研究センター、[3)]公益財団法人　実験動物中央研究所

S3-3　Establishment of a dual organ carcinogenicity model in rats for application in cancer chemopreventive studies on natural product and functional food

○Rawiwan Wongpoomchai[1,2)], Charatda Punvittayagul[3)], Sirinya Taya[2)], Arpamas Chariyakornkul[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University
[3)]Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University

S3-4　NAFLD/NASH 肝発がんの促進機序への最近の洞察

○梯 アンナ、鰐渕 英機

大阪市立大学大学院医学研究科　分子病理学

パネルディスカッション

第 2 日目　1 月 28 日（金）13:55 - 15:25　　第 1 会場（国際会議室）

座長：加藤　淳彦（中外製薬株式会社）
下井　昭仁（株式会社イナリサーチ）

PD　Post コロナ時代の毒性病理学　～リモート病理評価、リモート Peer review の実際と課題～

パネリスト：　小林　欣滋（株式会社新日本科学）
松本　泉美（大日本住友製薬（株）前臨床研究ユニット安全性第 2 グループ）
穴山　久志（武田薬品工業 リサーチ薬剤安全性研究所）
太田恵津子（エーザイ株式会社 グローバル安全性研究部）
爰島　洋子（株式会社 LSIM 安全科学研究所）
岩田　　聖（ルナパス合同会社 毒性病理研究所）
山口　裕子（株式会社ボゾリサーチセンター）
オブザーバー：中野　賢司（独立行政法人医薬品医療機器総合機構）

若手ワークショップ 1

第 1 日目　1 月 27 日（木）13:10 - 13:50　　第 1 会場（国際会議室）

座長：内木　　綾（名古屋市立大学）
鈴木　周五（大阪市立大学）

W-1＊　炭酸脱水素酵素阻害剤 Acetazolamide の Wnt/β カテニンシグナル経路抑制を介した膀胱癌浸潤抑制効果

○松江 泰佑[1,2)]、魏 民[1,3)]、塩田 正之[4)]、鈴木 周五[1)]、藤岡 正喜[1)]、梯 アンナ[1)]、内田 潤次[2)]、鰐渕 英機[1)]

[1)]大阪市立大学大学院医学研究科　分子病理学、[2)]大阪市立大学大学院医学研究科　泌尿器病態学
[3)]大阪市立大学大学院医学研究科　環境リスク評価学、[4)]大阪市立大学大学院医学研究科　分子制御生物学

W-2＊　カニクイザル子宮内膜の性周期におけるエストロジェン及びプロジェステロンレセプターの免疫組織化学的解析

○栗津原 優美、爰島 洋子、友成 由紀、霜山 奈津美、中原 豊、涌生 ゆみ、佐藤 順子、土居 卓也
（株）LSIM 安全科学研究所　病理研究部　鹿島病理部

W-3＊　Rubiadin の腎臓における局在と病理組織学的変化が示す部位特異的な遺伝毒性

○満元 達也[1,2]、石井 雄二[1]、滝本 憲史[1,3]、並木 萌香[1]、高須 伸二[1]、能美 健彦[1]、小川 久美子[1]
[1]国立医薬品食品衛生研究所　病理部、[2]ヤマザキ動物看護大学　動物看護学科
[3]東京農工大学　獣医病理学研究室

W-4＊　コリン欠乏メチオニン低減高脂肪アミノ酸食（CDAA-HF-T(-)）によるマウス NASH 誘発における interleukin-21 受容体（IL-21R）の関与

○煙山 紀子[1]、渡邉 颯人[2]、中根 冴[2]、桐ケ窪 彩[1]、佐々木 夏純[1]、田中 大揮[1]、吉瀬 優[1]、政所 陽菜[2]、宇野 絹子[3]、美谷島 克宏[1,2]、中江 大[1,2]
[1]東京農大・応生・食品安全健康、[2]東京農大院・農学研究・食品安全健康、[3]東京農大院・農学研究・食品栄養

若手ワークショップ 2

第 2 日目　1 月 28 日（金）13:10 - 13:50　　第 1 会場（国際会議室）

座長：豊田　武士（国立医薬品食品衛生研究所）
吉田　敏則（東京農工大学）

W-5＊　有機粉じん吸入による労働災害事例を端にした新規肺疾患の紹介

○山野 荘太郎[1]、武田 知起[1]、高信 健司[1]、妹尾 英樹[1]、甲田 茂樹[2]、岡本 賢三[3]、岸本 卓巳[4]、梅田 ゆみ[1]
[1]（独）労働者健康安全機構日本バイオアッセイ研究センター
[2]（独）労働者健康安全機構労働安全衛生総合研究所、[3]（独）労働者健康安全機構北海道中央労災病院
[4]（独）労働者健康安全機構アスベスト疾患研究・研修センター

W-6＊　気管内投与法によるカーボンナノホーン (CNH) およびカーボンナノブラシ (CNB) の肺および胸膜における短期毒性試験

○Saleh Dina[1,2,3]、アーメッド オムニア[1,2,4]、アレクサンダー デービッド[1]、アレクサンダー ウィリアム[1]、グナセカラン シバガミ[1,2]、沼野 琢旬[1]、高瀬 弘嗣[5]、大西 誠[6]、高橋 智[2]、湯田坂 雅子[7]、弓削 亮太[8]、津田 洋幸[1]
[1]名古屋市立大学　津田特任教授研究室、[2]名古屋市立大学大学院　医学研究科　実験病態病理学分野
[3]Assuit 大学　医学部　法医学・臨床毒物学教室、[4]Aswan 大学　医学部　法医学・臨床毒物学教室
[5]名古屋市立大学大学院　医学研究科　共同研究教育センター
[6]（独）労働者健康安全機構　日本バイオアッセイ研究センター　試験管理部
[7]（独）産業技術総合研究所　ナノチューブ応用研究センター　高度機能 CNT チーム
[8]NEC（株）システムプラットフォーム研究所

W-7＊　Generation of cerebral organoids from human embryonic stem cells

○Ke Chen[1]、Shuang Qiu[1]、Haoan Wang[1]、Qingxi Kong[2]、Qian Bu[1,3]、Qian Liu[1]、Xiaobo Cen[1,4]、Chunyan Hu[1]
[1]Westchina-Frontier Pharma Tech Co., Ltd (WCFP), [2]Pharmaron
[3]Healthy Food Evaluation Research Center, Department of Food Science and Technology, College of Light Industry, Textile and Food Engineering, Sichuan University
[4]National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, and Collaborative Innovation Center for Biotherapy

W-8＊　*Ex vivo/in vivo* MRI によるラットの薬物誘発性動脈炎の検出

○藤井 雄太[1,2]、吉野 有香[1,2]、千原 和弘[1]、中江 文[2,3]、圓見 純一郎[2,3]、吉岡 芳親[2,3]、宮脇 出[1]
[1]大日本住友製薬　前臨床研究ユニット、[2]大阪大学大学院　生命機能研究科
[3]情報通信研究機構及び大阪大学　脳情報通信融合研究センター

IATP Maronpot Guest Lecture

第 1 日目　1 月 27 日（木）17:40 - 18:30　　**第 1 会場（国際会議室）**

座長：林　新茂（国立医薬品食品衛生研究所）

IATP　Digital pathology and tissue image analysis - how did we start and where are we now

○Aleksandra Zuraw

Charles River Laboratories

1st JSTP-CPA-STP Joint Education Seminar

1 月 26 日（水）9:00 - 11:30　　**ライブ配信**

Understanding, detection, and diagnosis of background and induced lesions in toxicity and carcinogenicity studies

Chairperson：Jin Ren (Shanghai Institute of Material Medica, Chinese Academy of Science)
Min Gi　(Osaka City University Graduate School of Medicine)

ES-1　Chemically induced nonproliferative and proliferative lesions in rat and mouse urinary bladder

Min Gi

Osaka City University Graduate School of Medicine

ES-2　Nonproliferative and proliferative lesions observed in the short-term carcinogenicity studies in rasH2 mice

Hemei Wang

Jiangsu ChemPartner

ES-3　Proliferative lesions of the rodent endocrine system

Toko Ohira

Shanghai InnoStar Bio-tech Co., Ltd.

ES-4　Spermatogenesis and testicular staging in rats

Chunyan Hu

WestChina-Frontier PharmaTech

ES-5　Preclinical toxicologic pathology evaluation of cellular therapy products

Jianjun Lyu

Shanghai InnoStar Bio-tech Co., Ltd.

※演題番号に＊の表記があるものは、筆頭演者が 40 歳未満の演題です。

一般演題

オンデマンド配信　配信期間 1 月 20 日（木）～ 2 月 13 日（日）終日

P-01＊　ラットにおける海馬神経伝達関連遺伝子のメチル化制御破綻に着目した発達神経毒性指標の探索

○高橋 康徳[1,2]、尾城 椋太[1,2]、山下 理紗子[1]、清水 沙織[1]、前田 夏乃[1]、岡野 拡[1,2]、高嶋 和巳[1,2]、唐 倩[1,2]、小澤 俊介[1,2]、吉田 敏則[1,2]、渋谷 淳[1,2]
[1]東京農工大学　獣医病理学研究室、[2]東京農工大学　大学院　共同獣医学専攻

P-02＊　アクリルアミドのラット嗅球 - 脳室下帯神経新生への影響

○小川 文一朗[1,2]、中西 豊[1]、若松 正樹[1]、高橋 康徳[2,3]、渋谷 淳[2,3]
[1]大正製薬（株）　安全性研究室、[2]東京農工大 獣医病理学研究室、[3]東京農工大 院 共同獣医学専攻

P-03＊　Histopathologcial evaluation in SD rat model of optic nerve injury

○Liu Xiangjiang、Du Mu、Qi Wei、Guo Jin、Zhang Rui、Guo Hui、廣内 康彦
昭衍（蘇州）新薬研究中心有限公司

P-04　1 型糖尿病ラットへの軽度の高血圧負荷は表皮感覚神経密度に影響を及ぼさない

○尾崎 清和、松浦 哲郎
摂南大学　薬学部　病理学研究室

P-05　ラット母体への核酸投与による免疫活性化に起因した発達神経障害に対するα-glycosyl isoquercitrin の保護効果

○高嶋 和巳[1,2]、岡野 拡[1,2]、唐 倩[1,2]、高橋 康徳[1,2]、尾城 椋太[1,2]、小澤 俊介[1,2]、小柳 美穂子[3]、吉田 敏則[1,2]、渋谷 淳[1,2]
[1]東京農工大・獣医病理学研究室、[2]東京農工大・院・共同獣医学専攻、[3]三栄源エフ・エフ・アイ株式会社

P-06＊　Role of CCDC85C, a causative protein for hydrocephalus, and intermediate filament proteins (IFs) during lateral ventricle development in rat brain

○Hasan Md. Mehedi、Konishi Shizuka、Tanaka Miyuu、Izawa Takeshi、Yamate Jyoji、Kuwamura Mitsuru
Laboratory of Veterinary Pathology, Osaka Prefecture University

P-07＊　遺伝性ミエリン変性モデル VF ラットの振戦症状への *Hcn1* 遺伝子変異の関与

○田中 美有[1,2]、磯谷 星佳[1]、小島 瑳希子[1]、井澤 武史[1]、庫本 高志[2,3]、桑村 充[1]
[1]大阪府立大学　獣医病理、[2]京都大学　医　動物実験施設、[3]東京農業大学　農　動物科学

P-08　マウスの脊髄における運動ニューロンの評価について

○田中 雅治、小川 靖子、本間 謙吾、副島 亜紀
田辺三菱製薬（株）

P-09＊　ラットの海馬における神経突起伸展及びシナプス可塑性関連遺伝子のメチル化制御破綻に着目した発達神経毒性指標の探索

○尾城 椋太[1,2]、高橋 康徳[1,2]、山下 理紗子[1]、清水 沙織[1]、前田 夏乃[1]、岡野 拡[1,2]、高嶋 和巳[1,2]、唐 倩[1,2]、小澤 俊介[1,2]、吉田 敏則[1,2]、渋谷 淳[1,2]
[1]東京農工大学　獣医病理学研究室、[2]東京農工大学大学院　共同獣医学専攻

P-10＊　Davidson 固定・改変 Davidson 固定ラット眼球標本におけるアーティファクト所見と固定時間の関係性に関する詳細な検討

○中川 明都、松尾 沙織里、林 修次、加藤 淳彦
中外製薬株式会社　トランスレーショナルリサーチ本部

P-11＊　染色及びバイオマーカー測定による中枢神経毒性プロファイリング及び検出感度向上についての検討

○後藤 彩[1)]、石川 玲奈[1)]、中島 康太[1)]、関 由妃[1)]、中野 健二[2)]、太田 恵津子[1)]
[1)]エーザイ（株）メディスン開発センター　BA 機能ユニット グローバル安全性研究部
[2)]株式会社サンプラネット　筑波研開支援事業部　安全性・支援ユニット

P-12＊　パラフィン切片の 3 次元解析への応用

○岩下 直樹[1,2)]、小澤 秋沙[3)]、坂上 元栄[3)]
[1)]Bioalchemis、[2)]麻布大学　獣医学部　薬理学研究室、[3)]麻布大学　獣医学部　解剖学第二研究室

P-13＊　ラットの胎生期ないし新生児期での lipopolysaccharide 曝露によるオリゴデンドロサイト傷害性とα-glycosyl isoquercitrin の保護効果

○岡野 拡[1)]、高嶋 和巳[1,2)]、高橋 康徳[1,2)]、尾城 椋太[1,2)]、唐 倩[1,2)]、小澤 俊介[1,2)]、小柳 美穂子[3)]、吉田 敏則[1,2)]、渋谷 淳[1,2)]
[1)]東京農工大・獣医病理、[2)]東京農工大・院・共同獣医学専攻、[3)]三栄源エフ・エフ・アイ株式会社

P-14＊　幼若期ラット /Crl:CD（SD）における脊髄の病理組織学的背景データ

○佐藤 弘昌[1)]、渡辺 純[1)]、畠山 洋文[1)]、黒滝 哲郎[1)]、小泉 治子[1)]、梶村 哲世[1)]、佐藤 伸一[1)]、岩田 聖[2)]
[1)]（株）イナリサーチ、[2)]株式会社ルナパス毒性病理研究所

P-15＊　8-Methoxypsoralen のラット網膜光毒性における経時的な病理組織学的変化

○吉野 有香、池田 圭吾、森脇 さや香、岡田 久実代、栃谷 智秋、三瀬 いずる、藤井 雄太、河内 眞美、松本 泉美、稲田 拓、千原 和弘、宮脇 出
大日本住友製薬株式会社　前臨床研究ユニット

P-16＊　Laser induced acute ocular hypertensive damage in cynomolgus monkey

○Guo Hui、Du Mu、Qi Wei、Guo Jin、Zhang Rui、Liu Xiangjiang、Guo Hongnian、廣内 康彦
昭衍（蘇州）新薬研究中心有限公司

P-17　マウス乳癌転移モデルにおける転移前センチネルリンパ節の腫瘍免疫応答

○柴田 雅朗[1)]、竹下 篤[2)]、白岡 千夏[1)]、廣瀬 善信[2)]、近藤 洋一[1)]
[1)]大阪医科薬科大学　医学部　解剖学教室、[2)]大阪医科薬科大学　医学部　病理学教室

P-18＊　Burkitt lymphoma 移植 mice に観察された類上皮細胞肉芽腫

○Zhang Rui、Du Mu、Qi Wei、Guo Jin、Guo Hui、Liu Xiangjiang、Li Zheng、廣内 康彦
昭衍（蘇州）新薬研究中心有限公司

P-19＊　免疫チェックポイント阻害剤等の新規 *in vivo* 抗腫瘍評価モデル構築に向けての検討

○堀田 佳資、萩原 顕昭、杉山 大揮、河部 真弓、宮田 裕人、米良 幸典
（株）DIMS 医科学研究所

P-20＊　Early diagnostic and prognostic role of micro RNAs during 2-amino-3-methylimidazo[4,5-*f*] quinoline- induced liver and colon carcinogenicity in rat

○Elham M. Yousef[1)], Mona M. Hegazi[1)], Doha M. Beltagy [2)], Elsayed I. Salim[1)]
[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Department, Faculty of Science, Damanhour University

P-21＊　The extract of *Houttuynia cordata hunb.* fermented leaf inhibits carcinogenesis via modulates xenobiotic-metabolizing enzymes and cell proliferation

○Chonikarn Singai[1)], Sirinya Taya[2)], Rawiwan Wongpoomchai[1)]
[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University

P-22＊ Cancer chemopreventive effect of hesperidin and mixed extract of sesame and orange seed on diethylnitrosamine-induced hepatocarcingenesis in rats

○Napaporn Khuanphram[1)], Sirinya Taya[2)], Prachya Kongtawelert[1)], Rawiwan Wongpoomchai[1)]

[1)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)] Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University

P-23＊ Protective effect of color rice bran protein and hydrolysates on carcinogens induced early stage of liver and colon carcinogenesis in rats

○Aroonrat Pharapirom, Arpamas Chariyakornkul, Warunyoo Phannasorn, Kwanchanok Parseatsook, Rawiwan Wongpoomchai

Department of Biochemistry, Faculty of Medicine, Chiang Mai University

P-24＊ Chemopreventive effects of cooked glutinous purple rice on the early stages of rat hepatocarcinogenesis

○Huina Guo, Arpamas Chariyakornkul, Warunyoo Phannasorn, Rawiwan Wongpoomchai

Department of Biochemistry, Faculty of Medicine, Chiang Mai University

P-25＊ Chronic toxicity of calcium disodium EDTA on pregnant rats and fetuses

○Mona E. El-Maghawry, Fouad A. Abou-Zaid, Sabry A. El-Naggar, Elsayed I. Salim

Zoology Department, Faculty of Science, Tanta University

P-26＊ 8-Hydroxydeoxyguanosine levels and histopathological evaluation during placental transfer of zinc oxide nanoparticles in pregnant rats

○Naira M. Al-Fiky, Fouad A. Abou-Zaid, Khalid Y. Abdul-Halim, Elsayed I. Salim

Zoology Department, Faculty of Science, Tanta University

P-27＊ Tissue distribution, placental transfer and excretion of silver nanoparticles in pregnant rats after a single oral dose

○Ahmed S. Abdel-Latif[2)], Khaled Y. Abdel-Halim[2)], Elsayed I. Salim[1)]

[1)] Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)] Mammalian & Aquatic Toxicology department, Central Agricultural Pesticides Laboratory (CAPL)

P-28 F344 ラットを用いたナノサイズ酸化チタン (IV) の 28 日間反復経口投与毒性試験

○赤木 純一、水田 保子、赤根 弘敏、豊田 武士、小川 久美子

国立衛研　病理

P-29＊ Safety assessment of red yeast (*Sporidiobolus pararoseus*) powder : acute and subchronic toxicity studies in Wistar rats

○Sirinya Taya[1)], Charatda Punvittayagul[2)], Thanongsak Chaiyaso[3)], Rawiwan Wongpoomchai[1,4)]

[1)] Functional Food Research Unit, Science and Technology Research Institute
[2)] Research Affairs, Faculty of Veterinary Medicine, [3)] Division of Biotechnology, Faculty of Agro-Industry
[4)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University

P-30＊ Acute and subchronic toxicity of isomaltooligosaccharide and its effect of gut microbiota

○Arpamas Chariyakornkul[1)], Charatda Punvittayagul[2)], Sirinya Taya[3)], Atigan Thongtharb[4)], Santad Wichienchot[5)], Rawiwan Wongpoomchai[1)]

[1)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)] Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University
[3)] Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University
[4)] Department of Companion Animal, Faculty of Veterinary Medicine, Chiang Mai University
[5)] Center of Excellence in Functional Foods and Gastronomy, Faculty of Agro-Industry, Prince of Songkla University

P-31 Pathological changes of spontaneous tumors in Sprague-Dawley and Wistar rats

○Yanan He、Du Mu、Beibei Wang、Jun Yin、Wenyu Wu、Rui Zhang、Sucai Zhang、Huiming Zhang

JOINN LABORATORIES (Beijing) Inc.

P-32＊　伝播性 AA アミロイドーシスにおけるアミロイド沈着初発部位の探索

○岩出 進、村上 智亮
東京農工大学　農学府　共同獣医学専攻

P-33　マウス腹腔内投与におけるポリビニルピロリドンでコートされた銀ナノ球と銀ナノプレートの急性毒性の差異

○水田 保子、Cho Young-Man、赤木 純一、井手 鉄哉、小川 久美子
国立医薬品食品衛生研究所　病理部

P-34＊　Incidence and types of spontaneous tumors in young Sprague-Dawley rats in 4-week toxicity studies

○Hou Minbo, Jianjun Lyu, Yan Jianyan, Cui Tiantian, Qian Zhuang, Wang Xijie, Toko Ohira
Shanghai Innostar Bio-tech Co., Ltd (Innostar)

P-35　Differentially expressed genes induced by metformin and *d*-limonene as potential effective anticancer agents for HepG2 and MCF-7 cells

○Elsayed I. Salim[1)], Mona M. Alabasy[1)], Doha M. Beltagy[2)], Zihu Guo[3)], Mohamed Shahen[1)]
[1)] Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)] Biochemistry Department, Faculty of Science, Damanhour University
[3)] College of Life Science, Center of Bioinformatics, Northwest A & F University

P-36　New biomarkers of drug-induced liver and heart injury in preclinical studies

○Zhou Fei, Zhao Xixing, Zhou Tiansheng
WuXi AppTec (Suzhou) Co., Ltd.

P-37＊　LNA 修飾アンチセンスオリゴヌクレオチド検出における TUNEL 染色の有用性

○見鳥 光、梶川 悟、高橋 美和、小野 美穂子
アステラス製薬（株） 安全性研究所

P-38　SD ラットとビーグル犬の臨床病理参照データベースの構築について

○孔 慶喜[1)]、金 美蘭[2)]、邱爽[3)]、陈珂[3)]、乔 俊文[4)]
[1)] Pharmaron, [2)] Laboratory Animal Center, Southwest University
[3)] WestChina-Frontier Pharma Tech Co., Ltd, [4)] Insilico Medicine

P-39　INHAND: International harmonization of nomenclature and diagnostic criteria for lesions - An Update - 2022

○林 新茂[1)]、Keenan CM[2)]、Bradley A[3)]、Goodman DG[4)]、原田 孝則[5)]、Herbert R[6)]、岩田 聖[7)]、Jacobsen M[8)]、Kellner R[9)]、Mahler B[6)]、Meseck E[10)]、Nolte T[11)]、Rittinghausen S[9)]、Vahle J[12)]、義澤 克彦[13)]
[1)]国立医薬品食品衛生研究所、[2)]CM Keenan ToxPath Consulting、[3)]Charles River、[4)]Independent Consultant
[5)]残留農薬研究所、[6)]National Institute of Environmental Health Sciences、[7)]ルナパス毒性病理研究所
[8)]Astra Zeneca、[9)]Fraunhofer ITEM、[10)]Novartis、[11)]Boehringer Ingelheim、[12)]Eli Lily、[13)]武庫川女子大学

P-40　試験施設と SEND 作成者が異なる場合における病理組織所見の SEND 化の課題と対策

○飯高 健[1,6)]、石本 明宏[1,6)]、堀川 真一[2,6)]、飯野 好美[2,6)]、佐藤 伸一[2,6)]、中江 大[3,6)]、岩田 聖[4,6)]、安齋 享征[5,6)]
[1)]日精バイリス（株）、[2)]（株）イナリサーチ、[3)]東京農業大学、[4)]ルナパス毒性病理研究所、[5)]昭和大学 医学部
[6)]G-SEND

P-41＊　Comparative anatomy and histology of lacrimal gland in rat, rabbit, dog and monkey

○Qiu Shuang[1)], Chen Ke[1)], Hu Chunyan[1)], Wang Haoan[1)], Kong Qingxi[2)]
[1)] WestChina-Frontier PharmaTech, [2)] Pharmaron

P-42　SEND を意識した病理組織所見辞書の最適化とは

○畠山 洋文[1)]、堀川 真一[1)]、飯野 好美[1)]、佐藤 伸一[1)]、安齋 享征[2,3)]、岩田 聖[4)]
[1)](株) イナリサーチ、[2)]昭和大学　医学部、[3)]PDS パソロジー・データシステムズ・リミテッド
[4)]ルナパス毒性病理研究所

P-43＊　Evaluation of lung carcinogenicity of single-walled carbon nanotube (SWCNT) compared with MWCNT-7 and MWCNT-N

○Sheema Asraful Nahar[1)], Aya Naiki-Ito[1)], Hiroyuki Kato[1)], Masayuki Komura[1)], Hiroyuki Tsuda[2)], Satoru Takahashi[1)]
[1)]Department of Experimental Pathology and Tumor Biology, Nagoya City University Graduate School of Medical Sciences
[2)]Nanotoxicology Project, Nagoya City University

P-44＊　Balanitoside as a natural adjuvant to gemcitabine in lung cancer experimental model

○Sara S. Aboueisha[1)], Abeer A. Khamis[2)], Elsayed I. Salim[1)]
[1)]Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Division, Chemistry Department. Faculty of Science, Tanta University

P-45＊　肺組織におけるタバコの短期曝露による初期反応バイオマーカーの探索

○西土井 悠作[1)]、鈴木 周五[1)]、魏 民[1,2)]、梯 アンナ[1)]、松江 泰佑[1)]、鰐渕 英機[1)]
[1)]大阪市立大学大学院医学研究科　分子病理学、[2)]大阪市立大学大学院医学研究科　環境リスク評価学

P-46　有機粉じん吸入によるラット肺病変の病理組織学的特徴

○梅田 ゆみ
（独）労働者健康安全機構　日本バイオアッセイ研究センター

P-47　マウス肺化学発がんモデルを用いた抗腫瘍効果の予測
－ 免疫チェックポイント阻害剤と化学療法剤併用での検討

○萩原 顕昭、沼野 琢旬、土井 悠子、今井 則夫、原 智美、宮田 裕人、米良 幸典
（株）DIMS 医科学研究所

P-48＊　糖尿病モデル動物を用いた ACE2 発現による COVID-19 重症化モデルとしての検討

○畑中 悠里[1)]、美谷島 克宏[1,6)]、宇野 絹子[2)]、当摩 茉莉花[6)]、グエン ハンニユン[1)]、煙山 紀子[1)]、渡辺 寿久[3)]、伊藤 秀樹[3)]、篠原 雅巳[4)]、笹瀬 智彦[5)]、太田 毅[5)]、中江 大[1,6)]
[1)]東京農業大学・応生・食品安全健康学科、[2)]東京農業大学・院・食品栄養学専攻
[3)]日本クレア株式会社 富士生育場、[4)]日本クレア株式会社 業務推進部
[5)]京都大学・院・農学研究科 応用生物学専攻 生体機能学分野
[6)]東京農業大学大学院　応用生物科学研究科　食品安全健康学専攻

P-49＊　Bee pollen and its encapsulated nanoproduct loaded with folic acid as antitumor agents against lung cancer cells

○Eman A. Eltonoby[1)], Magdy E. Mahfouz[2)], Nemany A. N. Hanafy[3)], Ezar H. Hamed[1)], Elsayed I Salim[1)]
[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Zoology Department, Faculty of Science, Kafrelsheikh University
[3)]Nanomedicine Division, Institute of Nanoscience and Nanotechnology, Kafrelsheikh University

P-50＊　アクリルアミド反復暴露によるマウス肺由来オルガノイドの形態変化の解析

○田邉 健斗[1)]、平田 暁大[1)]、入澤 祐太[1,2)]、今井 俊夫[3)]、酒井 洋樹[1)]
[1)]岐阜大学　応用生物科学部　共同獣医学科 獣医病理学研究室
[2)]あすか製薬株式会社　薬物動態・安全性研究部　安全性研究課
[3)]国立がん研究センター　研究所　がんモデル開発部門

P-51＊　食餌性鉄過剰モデルラットの出血傾向に関わるビタミン K の影響

○稲井 洋平、井澤 武史、藤原 奨、田中 美有、桑村 充
大阪府立大学　獣医病理学教室

P-52＊　ラットを用いた一般毒性試験におけるマイクロサンプリングの毒性評価項目への影響

○栃谷 智秋、佐々木 靖弘、西村 直恵、藤井 雄太、祝迫 隆行、梅屋 直久、橋本 雅世、稲田 拓、千原 和弘、宮脇 出

大日本住友製薬（株） 前臨床研究ユニット

P-53　Toxicity assessment of a recombinant humanized antibody-drug Conjugate (rhADC) in *cynomolgus* monkeys

○Xueyan Pu, Lu Peng

Pathology Department, Jiangsu Tripod Preclinical Research Labortory Co., LTD

P-54＊　下肢 DES 評価モデルとしての糖尿病・高コレステロール血症ブタモデルの有用性検討

○佐藤 晶子、岩崎 泰造、小路 由佳、菊地 亮介、市村 夏穂、佐藤 秀樹

テルモ株式会社

P-55　植物芭蕉 (*Musa basjoo*) 抽出物のヒト大腸がん細胞株に対する増殖抑制効果および細胞周期制御分子発現への作用

○松本 晴年、Sultana Nahida、深町 勝巳、酒々井 眞澄

名古屋市立大学大学院　医学研究科　神経毒性学分野

P-56＊　Riceberry bran oil ameliorates carcinogens-induced liver and colon carcinogenesis through the mechanism of cell apoptosis, anti-inflammation, and gut microbiota

○Warunyoo Phannasorn[1)], Aroonrat Pharaphirom[1)], Parameth Thiennimitr[2)], Rawiwan Wongpoomchai[1)]

[1)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)] Department of Microbiology, Faculty of Medicine, Chiang Mai University

P-57＊　Vanillic acid attenuates rat hepatocarcinogenesis induced by diethylnitrosamine and 1,2-dimethylhidrazine

○Charatda Punvittayagul[1)], Arpamas Chariyakornkul[2)], Kanokwan Jarukamjorn[3)], Rawiwan Wongpoomchai[2)]

[1)] Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University
[2)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[3)] Research Group for Pharmaceutical Activities of Natural Products using Pharmaceutical Biotechnology, Faculty of Pharmaceutical Sciences, Khon Kaen University

P-58　唾液分泌機能が低下したアロキサン誘発 1 型糖尿病ラットでは、耳下腺における腺房細胞の異常のみならず筋上皮細胞の肥大が出現する

○兒玉 安史 [1)]、寺山 由依 [2)]、松浦 哲郎 [2)]、松田 美和 [3)]、尾崎 清和 [2)]

[1)]広島国際大学　薬学部　病態薬理学研究室、[2)]摂南大学　薬学部　病理学研究室
[3)]広島国際大学　保健医療学部　医療技術学科

P-59＊　Palmitoyl piperidineopiperidine induces selective anticancer activity against human colon carcinoma cell lines

○Sultana Nahida、深町 勝巳、松本 晴年、酒々井 眞澄

名古屋市立大学大学院　医学研究科　神経毒性学分野

P-60　ラット非アルコール性脂肪肝炎に対する紫米抽出物の化学予防効果

○内木 綾、加藤 寛之、小村 理行、高橋 智

名古屋市立大学　大学院医学研究科　実験病態病理学

P-61＊　有機ヒ素化合物 DPAA のマウス経胎盤曝露による次世代に対する発がん影響及びその機序の検討

○藤岡 正喜 [1)]、魏 民 [2)]、鈴木 周五 [1)]、梯 アンナ [1)]、大石 裕司 [1)]、山口 貴嗣 [1)]、鰐渕 英機 [1)]

[1)]大阪市立大学大学院　医学研究科　分子病理学、[2)]大阪市立大学大学院　医学研究科　環境リスク評価学

P-62　1,4- ジオキサンの *in vivo* 変異原性及び発がん性の定量解析

○魏 民 [1,2)]、鈴木 周五 [2)]、藤岡 正喜 [2)]、梯 アンナ [2)]、鰐渕 英機 [2)]

[1)]大阪市立大学大学院医学研究科　環境リスク評価学、[2)]大阪市立大学大学院医学研究科　分子病理学

P-63　ラット早期肝癌発生に対する Bear Bile Powder の予防治療作用

○金 美蘭[1,2]、董 鋭[2]、洪 澤宣[2]、賈 貴楊[2]

[1]中國　西南大学　実験動物センター、[2]中國　西南大学　動物医学院　獣医病理研究室

P-64＊　肝発がん物質フランの葉特異的毒性発現

○相馬 明玲[1]、日比 大介[2,3]、高須 伸二[3]、石井 雄二[3]、梅村 隆志[1,3]

[1]ヤマザキ動物看護大学　動物看護学研究科　動物看護学専攻修士課程、[2]小野薬品工業（株）
[3]国立医薬品食品衛生研究所

P-65＊　細胞質内封入体が示す methyl carbamate の染色体異常と肝発がんへの関与

○瀧本 憲史[1,2]、石井 雄二[1]、満元 達也[1,3]、並木 萌香[1]、高須 伸二[1]、能美 健彦[1]、渋谷 淳[2]、小川 久美子[1]

[1]国立医薬品食品衛生研究所　病理部、[2]東京農工大学大学院　獣医病理学研究室
[3]ヤマザキ動物看護大学　動物看護学科

P-66＊　Aristolochic acid I promotes clonal expansion but did not induce hepatocellular carcinoma in adult rats

○Lu Henglei、Tan Rongrong、Xiu Xiaoyu、Zhu Huaisen

Centre for Drug Safety Evaluation and Research (CDSER), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences (CAS)

P-67＊　マウスにおける食餌性非アルコール性脂肪肝炎（NASH）病態の進展過程における Sox9 の役割

○中根 冴[1]、煙山 紀子[2]、阿部 有加里[3]、渡邉 颯人[1]、結城 恵美[4]、美谷島 克宏[1,2,3]、梅村 隆志[5,6]、中江 大[1,2,3]

[1]東京農業大学大学院　応用生物科学研究科　食品安全健康学専攻
[2]東京農業大学　応用生物学部　食品安全健康学科、[3]東京農業大学大学院　農学研究科　食品安全健康学専攻
[4]アドバンテック株式会社病理委託事業部、[5]国立医薬品食品衛生研究所　病理部
[6]ヤマザキ動物看護大学　動物看護学部　動物看護学科

P-68＊　Tumor promoting effect of iron(III)-tannic acid nanoparticles in diethylnitrosamine-induced hepatocarcinogenesis in rats

○Chi Be Hlaing[1], Arpamas Chariyakornkul[1], Chalermchai Pilapong[2], Rawiwan Wongpoomchai[1]

[1]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2]Center of Excellence for Molecular Imaging (CEMI), Department of Radiologic Technology, Faculty of Associated Medical Sciences, Chiang Mai University

P-69＊　ラットにおけるジンクマルトール誘発膵臓病変の病理学的解析

○藤原 咲春、諸木 孝泰、人見 将也、佐藤 亮、寺山 由依、吉川 剛

大塚製薬株式会社 徳島研究所 前臨床研究センター 安全性研究部

P-70　*gpt* delta ラットを用いた 3-acetyl-2,5-dimethylfuran の一般毒性・遺伝毒性・発がん性包括的毒性評価

○高須 伸二、石井 雄二、並木 萌香、中村 賢志、能美 健彦、小川 久美子

国立医薬品食品衛生研究所　病理部

P-71　ジフェニルアルシン酸の C57BL6/J マウスにおける慢性毒性試験及び発がん性試験

○山口 貴嗣[1]、魏 民[2]、藤岡 正喜[1]、鈴木 周五[1]、大石 裕司[1]、鰐渕 英機[1]

[1]大阪市立大学大学院　医学研究科　分子病理学、[2]大阪市立大学大学院　医学研究科　環境リスク評価学

P-72＊　28-day repeated inhalation toxicity study of 1,2-dichlorobenzene in Fischer 344 rats

○Hee-Seon Park, Hye-Yeon Choi, Yong-Soon Kim, Mi-Ju Lee

Pathology Department, Inhalation Toxicity Research Center, Chemical Research Bureau, Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency

P-73　四塩化炭素 (CCl4) 皮下注射によるラット非アルコール性脂肪肝モデルの病理特徴とバイオマーカーの研究

○金 毅[1]、李 静[2]、呂 愛貞[2]、李 明[2]、金 志虎[2,3]

[1]深セン市薬品検験研究院、[2]広東東陽光薬業株式会社、[3]深セン金質科技株式会社

P-74　Establishment of mouse orthotopic transplantation tumor models of human hepatoma and comparison of their characteristics

○Jun Yin[1)]、Du Mu[3)]、Dingsha Lijing[1)]、Huiming Zhang[2)]、Ruiping She[2)]、Conglin Zuo[2)]
[1)]北京昭衍新薬研究中心有限公司、[2)]中国農業大学動物医学院、[3)]昭衍（蘇州）新薬研究中心有限公司

P-75＊　ヒト化マウスを用いた薬物性肝障害モデル作出の試み

○藤原 奨、井澤 武史、田中 美有、桑村 充
大阪府立大学　獣医病理

P-76　NAFLD モデルラットにおける糖尿病誘発の影響

○井澤 武史、水口 恵理、山手 丈至、桑村 充
大阪府大　獣医病理

P-77＊　ラットにおける非アルコール性脂肪性肝炎（NASH）病態の肝線維化への CD44 の関与

○宇野 絹子[1)]、美谷島 克宏[2,3)]、当摩 茉莉花[3)]、煙山 紀子[2)]、中江 大[2,3)]
[1)]東京農大院 農学研究科 食品栄養学専攻、[2)]東京農大　食品安全健康学科
[3)]東京農大院　応用生物科学研究科　食品安全健康学専攻

P-78＊　hL-FABP tg マウスを用いた L-FABP の早期 NAFLD バイオマーカーとしての有用性に関する検討

○当摩 茉莉花[1)]、美谷島 克宏[1,2)]、大畑 敬一[3)]、宇野 絹子[4)]、堀内 彩花[2)]、煙山 紀子[2)]、中江 大[1,2)]
[1)]東京農業大学大学院　応用生物科学研究科　食品安全健康学専攻
[2)]東京農業大学 応用生物科学部 食品安全健康学科
[3)]シミックホールディングス株式会社　L-FABP 事業部　研究開発グループ
[4)]東京農業大学大学院 農学研究科 食品栄養学専攻

P-79＊　2 型糖尿病動物モデルの病態におけるグルカゴンの関与

○万代 康平[1)]、美谷島 克宏[1,2,3)]、渡邉 果奈[1)]、石塚 佳菜[1)]、宇野 絹子[4)]、煙山 紀子[2)]、篠原 雅美[5)]、笹瀬 智彦[5)]、渡辺 寿久[6)]、伊藤 秀樹[6)]、篠原 雅巳[7)]、太田 毅[5,8)]、中江 大[1,2,4)]
[1)]東京農業大学　応用生物科学部　食品安全健康学専攻、[2)]東京農業大学　応用生物科学部　食品安全健康学科
[3)]東京農業大学　農学研究科　食品安全健康学専攻、[4)]東京農業大学大学院　農学研究科　食品栄養学専攻
[5)]日本クレア株式会社　東京 AD 部、[6)]日本クレア株式会社　富士生育所、[7)]日本クレア株式会社　業務推進部
[8)]京都大学大学院　農学研究科　応用生物科学専攻　生体機能学分野

P-80　膵癌モデルラットを用いた膵癌の血清診断マーカ LRG-1 の同定

○深町 勝巳[1)]、Sultana Nahida[1)]、松本 晴年[1)]、津田 洋幸[2)]、酒々井 眞澄[1)]
[1)]名古屋市立大学大学院医学研究科、[2)]名古屋市立大学

P-81＊　肝毒性評価モデルとしての肝スライス培養法

○加藤 由隆、高橋 尚史、藤原 千夏、宮崎 新也、伊藤 強、小山 彩、志賀 敦史、大塚 亮一、武田 眞記夫、原田 孝則
（一財）残留農薬研究所

P-82＊　Deep learning-based Image analysis algorithm for classification and quantification of multiple histopathological lesions of the rat liver

○島嵜 大志[1)]、牟田 恭孝[1)]、山田 直人[1)]、安井 雄三[1)]、Deshpande Ameya[2)]、Hajra Anindya[2)]、Thomas Tijo[2)]、正田 俊之[1)]
[1)]日本たばこ産業株式会社　医薬総合研究所　横浜リサーチセンター、[2)]AiraMatrix

P-83　Quantification of hepatic fibrosis in Sprague-Dawley rats using deep learning instance segmentation focused on H&E staining whole slide level

○Ji-Hee Hwang[1)], Hyun-Ji Kim[1,2)], Heejin Park[1)], Byoung-Seok Lee[1)], Hwa-Young Son[2)], Yong-Bum Kim[3)], Sang-Yeop Jun[4)], Jong-Hyun Park[4)], Jaeku Lee[4)], Jae-Woo Cho[1)]

[1)] Toxicologic Pathology Research Group, Toxicology Mechanism Research Divison, Department of Advanced Toxicology Research, Korea Institute of Toxicology
[2)] College of Veterinary Medicine, Chungnam National University
[3)] Department of Advanced Toxicology Research, Korea Institute of Toxicology
[4)] Research & Development team, LAC Inc

P-84＊　膵癌における DPYD 発現の寄与と発現抑制機序の検討

○加藤 寛之、内木 綾、小村 理行、高橋 智
名古屋市立大学　大学院医学研究科　実験病態病理学

P-85　職業性膀胱がん関連芳香族アミンの膀胱尿路上皮への影響及び尿中代謝物との関係

○鈴木 周五、魏 民、藤岡 正喜、梯 アンナ、鰐渕 英機
大阪市大　院医　分子病理学

P-86　オルト - トルイジンおよびオルト - アニシジン代謝物の 28 日間反復経口投与によるラット膀胱への影響

○豊田 武士[1)]、小林 琢磨[2)]、三好 規之[2)]、松下 幸平[1)]、赤根 弘敏[1)]、森川 朋美[1)]、小川 久美子[1)]
[1)]国立医薬品食品衛生研究所　病理部、[2)]静岡県立大学　生化学研究室

P-87＊　The potential effect of thymoquinone and *Nigella sativa* crude oil extract on experimental urinary bladder cancer model

○Areeg M. Khalifa, Elsayed I. Salim
Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University

P-88＊　アシクロビル結晶誘発性腎症に関連した心血管病変の解析

○杉山 淳一、田中 英樹、吉田 翔太、蟹江 尚平、別枝 和彦
大鵬薬品工業株式会社　安全性研究所

P-89　薬剤性腎障害の慢性化を予測するバイオマーカーとしての CD44 の有用性の検証

○松下 幸平、豊田 武士、赤根 弘敏、森川 朋美、小川 久美子
国立医薬品食品衛生研究所　病理部

P-90＊　高ショ糖 / 高脂肪食給餌が肥満 2 型糖尿病モデル SDT fatty ラットの腎臓に及ぼす影響について

○渡邉 果奈[1)]、美谷島 克宏[1,2)]、万代 康平[1)]、関口 敬大[2)]、宇野 絹子[3)]、煙山 紀子[2)]、笹瀬 智彦[6)]、渡辺 寿久[4)]、伊藤 秀樹[4)]、篠原 雅巳[5)]、中江 大[1,2)]、太田 毅[6)]
[1)]東京農大院　応用生物科学研究科　食品安全健康学専攻、[2)]東京農大、食品安全健康学科
[3)]東京農大院　農学研究科　食品栄養学専攻、[4)]日本クレア株式会社　富士生育場
[5)]日本クレア株式会社　業務推進部、[6)]京都大学院　農学研究科　応用生物科学専攻　生体機構学分野

P-91＊　DIC 発症モデルにおける尿中 L-FABP の COVID19 重症化の早期バイオマーカーとして検証

○グエン ハン・ニユン[1)]、美谷島 克宏[1,2)]、大畑 敬一[3)]、河口 友香[1)]、畑中 悠里[1)]、堀内 彩花[1)]、宇野 絹子[4)]、当麻 茉莉花[2)]、新井 かりん[1)]、上地 哲平[1)]、煙山 紀子[1)]、中江 大[1,2)]
[1)]東京農業大学・応生・食品安全健康学科、[2)]東京農業大学
[3)]東京農業大学大学院・応用生物科学研究科・食品安全健康学専攻
[4)]シミックホールディングス株式会社　L-FABP 事業部 研究開発グループ
[5)]東京農業大学大学院・農学研究科・食品栄養学専攻

P-92＊　Karnovsky 固定液のアンチセンス核酸投与時にみられる空胞化アーチファクト防止に対する有用性検討

○仁科 嘉修、西川 智美、樫村 茜、水川 真緒、坂入 鉄也
田辺三菱製薬（株）　安全性研究所

P-93　Pathological study for chronic progressive nephropathy in rats

○Beibei Wang、Du Mu、Yanan He、Jun Yin、Wenyu Wu、Rui Zhang、Sucai Zhang、Huiming Zhang
北京昭衍新薬研究中心有限公司

P-94　Halo AI を用いた抗糸球体基底膜腎炎モデルマウスの糸球体硬化の検出

○村井 厚子[1)]、松尾 沙織里[1)]、宇佐美 晶子[2)]、羽田 奈津子[2)]、金森 正和[2)]、山崎 雅輝[1)]、大西 慎一[1)]、加藤 淳彦[1)]
[1)]中外製薬株式会社　TR 本部　安全性研究部、[2)]中外製薬株式会社　研究本部　創薬薬理研究部

P-95　ラットモデルを用いたキトサンオリゴ糖の乳癌抑制効果の検証

○吉岡 正浩[1)]、茶谷 桃花[2)]、又間 梨央[3)]、三好 真由[3)]、木下 勇一[4)]、岡本 芳晴[5)]、義澤 克彦[2,3)]
[1)]甲子園大学　栄養学部　栄養学科、[2)]武庫川女子大学大学院　生活環境学研究科
[3)]武庫川女子大学　食物栄養科学部　食創造科学科、[4)]和歌山県立医科大学附属病院
[5)]鳥取大学　農学部　共同獣医学科

P-96＊　RNA シーケンス解析を利用した放射線誘発ラット乳がんにおける融合遺伝子の同定

○渡辺 光[1,2)]、臺野 和広[1)]、石川 敦子[1)]、今岡 達彦[1,2)]、西村 まゆみ[1)]、高畠 賢[1,2)]、井上 一雅[2)]、福士 政広[3)]、柿沼 志津子[1)]
[1)]量研　放医研　放射線影響、[2)]東京都立大院　人間健康科学　放射線、[3)]つくば国際大　診療放射線

P-97　テストステロンのラット胎盤発生に対する影響

○古川 賢[1)]、辻 菜穂[1)]、林 清吾[1)]、黒田 雄介[1)]、木村 真之[1)]、早川 知里[1)]、竹内 和也[1)]、杉山 晶彦[2)]
[1)]日産化学株式会社　生物科学研究所、[2)]岡山理科大学　獣医学部

P-98＊　AI 画像解析プラットフォーム IBM® Visual Insights を用いたラット性周期自動分類モデルの構築

○大西 慎一[1)]、江上 陸[2)]、長島 慶宜[2)]、中村 祐哉[2)]、西原 香織[1)]、松尾 沙織里[1)]、村井 厚子[1)]、林 修次[1)]、山崎 雅輝[1)]、水野 英明[2)]、加藤 淳彦[1)]
[1)]中外製薬株式会社 トランスレーショナルリサーチ本部、[2)]中外製薬株式会社 研究本部

P-99＊　ACTH-induced stress in weaned sows impairs LH receptor expression steroidogenesis capacity in the ovary

○Zhu Huaisen[1,2)]、Tan Rongrong[1)]、Xiu Xiaoyu[1)]、Lu Henglei[1)]
[1)]AnLing Biomed (ShenZhen) Co., Ltd
[2)]Centre for Drug Safety Evaluation and Research (CDSER), Shanghai Institute of MateriaMedica (SIMM), Chinese Academy of Sciences (CAS)

P-100　マウス正常組織由来オルガノイドを用いる新たな DMBA 誘発性乳腺発がん機序の解明

○今井 俊夫[1,2)]、石ケ守 里加子[1)]、中西 るり[1)]、町田 雪乃[3)]、成瀬 美衣[1)]
[1)]国立がん研究センター　研究所　動物実験施設、[2)]国立がん研究センター　研究所　がんモデル開発部門
[3)]日本獣医生命科学大学　獣医病理学研究室

P-101＊　Assessment of the molecular and physiological role of micro RNA in chemically-induced mammary gland carcinoma in rats

○Fatma A. Elmalah[1)], Mona M. Hegazi[1)], Doha M Beltagy[2)], Elsayed I. Salim[1)]
[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Department, Faculty of Science, Damanhour University

P-102＊　Promoting effect of sunset yellow at low doses on *N*-methyl *N*-nitrosourea-induced rat mammary gland carcinogenesis

○Malak I. Elbassuny[1)], Magdy E. Mahfouz[2)], Elsayed I. Salim[1)]
[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis. Faculty of Science, Tanta University
[2)]Zoology Department, Faculty of Science, Kafrelsheikh University

P-103　The histopathologic changes in lungs of mice and cynomolgus monkeys administrated intravenously with human umbilical cord-derived mesenchymal stem cells

○Yanjun Cui, Xu Zhu, Yi Zhou, Xuezhou Cai, Yichao Tian, Li Zhou
Hubei Topgene Biotechnology Co. Ltd Wuhan Branch

P-104　Histopathological investigation of islets in SD rat by subcutaneous injection with a repeat dose new hypoglycemic compound

○Du Mu、Qi Wei、Guo Jin、Zhang Rui、Guo Hui、Liu Xiangjiang、Wang Beibei、He Yanan、Yin Jun、廣内 康彦
昭衍（蘇州）新薬研究中心有限公司

P-105＊　ラットにおける化学物質誘発抗甲状腺作用検出における病理組織学的及び免疫組織化学的手法と血中ホルモン値との比較

○赤根 弘敏[1)]、豊田 武士[1)]、松下 幸平[1)]、森川 朋美[1)]、小坂 忠司[2)]、田島 均[2)]、青山 博昭[2)]、小川 久美子[1)]
[1)]国立医薬品食品衛生研究所　病理部、[2)]一般財団法人残留農薬研究所　毒性部

P-106　両生類変態試験（AMA）の陽性対象物質処理区でみとめられた甲状腺の病理組織学的変化

○永池 美香、山本 格、馬場 雄大、池田 瑛人、岡田 亜季子、本郷 直子、乾 公正
石原産業（株） 中央研究所　安全科学研究室

P-107＊　脳底部に観察された神経節起源と考えられる腫瘍性塊

○Qi Wei、Du Mu、Guo Jin、Guo Hui、Zhang Rui、Liu Xiangjiang、廣内 康彦、Li Zheng
昭衍（蘇州）新薬研究中心有限公司

P-108　A spontaneous benign meningioma in an ICR mouse

○Hu Yiwen、Kong Qingxi、Lv Ai
Pharmaron Inc.

P-109＊　強膜に軟骨化生がみられた Kbs:JW ウサギの 1 例

○山田 康太郎、山際 慶典、政次 美紀、原ノ園 祐、倉田 昌明
千寿製薬株式会社　研究開発本部　総合研究所

P-110＊　ビーグル犬にみられた肺の低形成の 1 例

○等々力 舞、増田 湊介、吉見 直、古屋 真、森 重之
全薬工業株式会社　創薬研究部　安全性研究室

P-111＊　ICR マウスの心冠状動脈の血管炎

○安野 恭平[1)]、今岡 尚子[1)]、大澤 徹也[1)]、岡戸 恵子[2)]、甲斐 清徳[1)]、土屋 由美[1)]
[1)]第一三共（株）、安全性研究所、[2)]第一三共 RD ノバーレ（株）、トランスレーショナル研究部

P-112＊　若齢 SD ラットにおける自然発生性のリンパ管腫の一例

○石川 玲奈、後藤 彩、関 由妃、中島 康太、太田 恵津子
エーザイ（株） メディスン開発センター　BA 機能ユニット　グローバル安全性研究部

P-113　Gastric carcinoid tumors in rats with parietal cell atrophy in a long-term carcinogenicity study

○Shirai Norimitsu、Choudhary Shambhunath、Houle Christopher
Pfizer Inc. Drug Safety R&D, Pathology

P-114　SD ラットにみられた胸腔内に充満する巨大食道憩室の 1 例

○藤島 純子、山下 弘貴、笹木 祐司、小林 欣滋、前田 博
（株）新日本科学　安全性研究所

P-115＊ ラット空腸に認められた嚢胞状結節性病変の 1 例

○馬場 雄大、池田 瑛人、岡田 亜季子、本郷 直子、乾 公正、永池 美香
石原産業株式会社　中央研究所　安全科学研究室　安全性グループ

P-116 Study on pathomorphological changes of liver in Beagle dog with spontaneous hepatocirrhosis

○Hu Jian-ting、Qiu Bo、Ying Yong
New Drug Evaluation Center of Shandong Academy of Pharmaceutical Sciences

P-117＊ 腎臓に観察された腎間葉系腫瘍と考えられる一例

○Guo Jin、Du Mu、Qi Wei、Zhang Rui、Guo Hui、Liu Xiangjiang、廣内 康彦
昭衍（蘇州）新薬研究中心有限公司

P-118＊ 卵巣の絨毛癌により死亡した 9 週齢の雌性 CBA/J マウスの一例

○小林 俊夫、大嶋 浩、山本 季美花、森岡 久子、堀内 雅史、坪倉 靖祐、宮田 克己、寶珠山 五月
（一財）化学物質評価研究機構

P-119＊ Malignant tumour of ovary in a young Rhesus monkey - Case Report

○Wang Haoan[1)]、He Yang[1)]、Chen Ke[1)]、Qiu Shuang[1)]、Yang Kaixuan[2)]、Cen Xiaobo[1,3)]、Hu Chunyan[1)]
[1)] Westchina-Frontier Pharma Tech Co., Ltd (WCFP)
[2)] West China Second University Hospital, Sichuan University
[3)] National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, and Collaborative Innovation Center for Biotherapy

P-120 A case of spontaneous pituitary gland adenocarcinoma in a nineteen-week-old female Sprague-Dawley rat

○Duyeol Kim, Jong-Il Shin, Hyun Kyung Song, Byung-Woo Lee, Hyun-Woo Kim, Han Kyul Lee, Sun-Hee Park
Biotoxtech Co

P-121＊ ヒトの clear cell sarcoma に類似する雌 SD ラットの足蹠部自然発生腫瘍

○斎藤 翼、岡野 拡、青木 萌子、神谷 有美子、藤原 史織、橋口 収、山口 裕子
（株）ボゾリサーチセンター

講演要旨

特別講演

シンポジウム

パネルディスカッション

若手ワークショップ

IATP Maronpot Guest Lecture

1st JSTP-CPA-STP Joint Education Seminar

SL-1

腸内細菌叢の異常を伴う疾患に対する新規治療法の開発

○植松 智[1,2)]

[1)]大阪市立大学　大学院医学研究科　ゲノム免疫学、[2)]東京大学　医科学研究所　ヒトゲノム解析センター　メタゲノム医学分野

次世代シークエンサーの開発によって、腸内細菌叢の解析は、古典的な培養法からゲノム解析に変化しました。それに伴い、感染症、炎症性腸疾患、肥満、糖尿病、そして精神疾患などの様々な疾患において腸内細菌叢の構成異常である dysbiosis が認められることが分かってきました。dysbiosis では、微生物の多様性の変化や菌交代現象が観察され、その結果、腸内細菌叢が宿主にもたらす有益な効果が損なわれ、ホメオスタシスが崩壊します。さらに、炎症性腸疾患や糖尿病などでは、疾患の発症に直接関わる共生常在菌 (pathobiont) の存在も明らかになりました。疾患の新しい制御法として、dysbiosis を是正したり、pathobiont を特異的に制御、排除する方法が求められています。私たちの研究室では全ゲノムシークエンスによるメタゲノム解析を実施しています。高速での解析を可能とする相同検索ソフト GHOST-MP をスーパーコンピュータ上で駆動させ、超高速でメタゲノム解析を行うパイプラインを構築しました。本講演では、構築した超高速パイプラインの概要、それを用いた腸内細菌解析、さらに腸内ウイルス叢の解析を紹介します。さらに、dysbiosis の是正と pathobiont の特異的排除を目的とした粘膜ワクチンの開発及びファージ治療の基盤構築に関してもご報告します。

略歴

植松　智

大阪市立大学大学院医学研究科ゲノム免疫学　教授

略歴：
・1991-1997　大阪市立大学医学部
・1997-1999　大阪市立大学医学部附属病院第 2 内科研修医（森井浩世教授）
・1999-2000　大阪市立大学大学院医学研究科博士課程　中退
・2000-2004　大阪大学大学院医学系研究科博士課程（審良静男教授）
・2003-2004　日本学術振興会特別研究員（DC2）
・2004-2009　大阪大学微生物病研究所　助教（審良静男教授）
・2009-2012　大阪大学 WPI 免疫学フロンティア研究センター　特任准教授（審良静男教授）
・2012-2020　東京大学医科学研究所国際粘膜ワクチン研究センター自然免疫制御分野　特任教授
・2014-2018　千葉大学大学院医学研究院粘膜免疫学　教授
・2018- 現在　大阪市立大学大学院医学研究科ゲノム免疫学　教授
・2020- 現在　東京大学医学研究所ヒトゲノム解析センターメタゲノム医学分野　特任教授

学会活動：
・日本免疫学会：評議員

受賞 / その他：
・2009 年 第 4 回日本免疫学会研究奨励賞

SL-2

Contribution of toxicologic pathology to occupational health

○福島 昭治 [1,2)]

[1)]独立行政法人労働者健康機構 日本バイオアッセイ研究センター、[2)]一般社団法人化学物質安全性評価研究推進機構

In general, the toxicity of chemical substances to humans is evaluated based on toxicity tests using test animals. It is particularly important to determine if genotoxicity is involved in the harmful effects, e.g., carcinogenicity and reproductive toxicity, elicited by the tested chemical. Toxic substances are divided into genotoxic and non-genotoxic substances. The non-genotoxic substances are considered to have threshold exposure levels below which no toxic effects are produced. The substances have S-shaped dose-response curves from which NOAEL and LOAEL values can be obtained. This allows the generation of permissible exposure values that can be applied to occupational health. In contrast, the genotoxic substances are considered to not have threshold levels below which they do not exert harmful effects, and therefore, to lack permissible exposure levels. However, in reality, various situations do need to set permissible exposure values for substances that are considered genotoxic. It is well known that workers exposed to solid substances have respiratory diseases such as lung cancer and mesothelioma. The JBRC has investigated the inhalation carcinogenicity of numerous chemical substances using rats and mice. In this talk, I will focus on the rat pulmonary carcinogenicity of the solid substances, e.g. fibrous multi-walled carbon nanotube and indium tin oxide. I will then discuss using BMD or NOAEL as points of departure to derive occupational health guidance values.

略歴

Shoji Fukushima, MD., Ph.D.

Current position
President, Association for Promotion of Research on Risk Assessment
Advisor, Japan Bioassay Research Center, Japan Organization of Occupational Health and Safety
Visiting Professor, Kitasato University School of Medicine

School Education
1961-1967 Nagoya City University Medical School

Employment History
1977-1979 University of Massachusetts, School of Medicine, USA, Research Associate
1980-1990 Nagoya City University Medical School, Department of Pathology, Associate Professor
1990-2006 Osaka City University Medical School, Department of Pathology, Professor
2002-2006 Osaka City University Medical School, Dean
2006-2016 Japan Bioassay Research Center, Director
2016- Association for Promotion of Research on Risk Assessment, President

Honors and Prizes
Minister of Health, Labor and Welfare Achievement Award
Yasuda Memorial Medical Award
Mochizuki Kitashi Memorial Award Achievement Award
Osaka City Medical Association Award
Kenkou Award

Main research
Chemical carcinogenesis
Carcinogenic risk assessment of environmental factors
Toxicologic pathology
Pathology of human bladder cancer

S1-1

脱離エレクトロスプレーイオン化法による質量分析イメージング－組織切片上における化学物質及び代謝物の局在解析

○石井 雄二

国立医薬品食品衛生研究所　病理部

近年、質量分析イメージングの登場により組織切片上で化合物や生体分子の分布を可視化することが可能になった。質量分析イメージングでは既知の分子だけでなく未知の分子についてもその位置情報とともに構造情報を得られるため、毒性病理学分野における新たな研究ツールとして期待される。現在の質量分析イメージングの主流であるマトリックス支援レーザー脱離イオン化法（MALDI）は、タンパクを効率良くイオン化し高解像度なイメージングを達成している。しかし、本法はマトリックスと呼ばれるイオン化促進剤を必要とし、標的分子に適したマトリックスの選択とその塗布には経験と熟練を要することから未だ汎用性の高い方法とは言い難い。また、イオン化の特性上、MALDI は低分子よりも高分子の検出に適している。一方、脱離エレクトロスプレーイオン化法（DESI）は電化を帯びた液滴を組織表面に噴霧することで分子を抽出する。それ故、マトリックス塗布などの複雑な前処理が不要であり、厚さ十数μ m の凍結切片をスライドグラス上で乾燥させた後、ステージにセットするだけで解析を始められる。また、DESI の機構は質量分析装置で一般的に用いられるエレクトロスプレーイオン化法（ESI）と類似していることから、ESI でイオン化する低分子は本法により比較的容易に質量分析イメージングを得られる。さらに、MALDI と異なりレーザーを使用しない DESI は非破壊的であることから、イメージング後の試料を染色して病理組織学的に解析できることも大きな利点である。本講演では DESI の原理や特徴についてまとめ、実際に DESI-MSI を使用した我々の解析データを紹介し、本法の利点と問題点、今後の展望について考察する。

略歴

石井　雄二

国立医薬品食品衛生研究所　病理部第一室長

略歴：
・1998-2002　星薬科大学薬学部衛生薬学科
・2002-2004　星薬科大学大学院修士課程
・2004-2007　星薬科大学大学院博士課程
・2007-2009　国立医薬品食品衛生研究所　安全性生物試験研究センター　病理部　流動研究員
・2009-2012　国立医薬品食品衛生研究所　安全性生物試験研究センター　病理部　研究員
・2012-2017　国立医薬品食品衛生研究所　安全性生物試験研究センター　病理部　主任研究官
・2017-　国立医薬品食品衛生研究所　安全性生物試験研究センター　病理部　第一室長

学会活動：
・日本毒性学会：評議員
・日本環境変異原ゲノム学会：評議員

受賞 / その他：
・2019 年度日本環境変異原学会研究奨励賞 : 日本環境変異原学会
・2016 年度日本毒性学会ファイザー賞
・2014 年度第 30 回日本毒性病理学会学術会会長賞
・2012 年度第 27 回日本毒性病理学会学術会会長賞

S1-2

病理組織形態の人工知能による構造化

○石川 俊平

東京大学　医学部・大学院医学系研究科　衛生学教室

病理診断や毒性評価に使われる病理組織像はその客観的もしくは定量的表現が難しく、他の症例との直接比較や多数の症例情報の蓄積、他のモダリティのデータとの定量的相関関係などを調べることが一般的に困難であった。我々はニューラルネットワークの中層から得られるディープテクスチャ情報が、がんの病理組織像をうまく表現し、ユニバーサルに病理組織像を数値ベクトルとして構造化できる手段であることを見いだした。構造化されたがんの病理組織像は、発現プロファイルなどのゲノミクスデータや臨床検査値データと同様に数値として扱うことができ、さまざまな用途に広く応用可能である。たとえば、病理組織学的多様性の全体像を把握することによりまれなサブタイプを特定することや、多くの画像データベースからの病理組織学的に類似した画像の検索（いわゆる Contents Based Image Retrieval）、がんゲノムの変異の予測などが可能となる。病理組織像を構造化することで、組織病理学にゲノム科学のようなデータサイエンスの特性を持たせることができ、医学および医療に高いエビデンスをもたらす体系に変えることができると考えられる。

略歴

石川　俊平

東京大学 医学系研究科　衛生学分野 教授

略歴：
・1994-2000　東京大学 医学部 卒業
・2000-2004　東京大学 大学院医学系研究科 人体病理学・病理診断学 修了
・2004-2007　東京大学 先端科学技術研究センターゲノムサイエンス部門 特任助手
・2007-2012　東京大学 大学院医学系研究科 人体病理学・病理診断学 助教のち准教授
・2013-2018　東京医科歯科大学 難治疾患研究所 ゲノム病理学分野 教授
・2018 年～　東京大学 大学院医学系研究科 衛生学分野 教授

学会活動：
・日本癌学会：監事 / 評議員
・日本病理学会：評議員

受賞 / その他：
・第 2 回ヤマト科学賞
・第 34 回日本癌学会学術奨励賞
・第 61 回日本病理学会学術研究賞
・日本癌学会 JCA-Mauvernay Award 2021

S1-3

OCT（光干渉断層計）検査の基礎及び OCT 画像と病理組織像との関連

○荒木 智陽

（株）新日本科学　安全性研究所

ヒトは外界から入る情報の約 80％を視覚から得ており、視覚の喪失は QOL を著しく損なう。そのため、医薬品の非臨床安全性試験における視覚器に及ぼす影響の評価は非常に重要である。しかし、動物は視覚に関する異常や症状を検査者に伝えることはできない。また、視覚機能に生じた変化を一般状態観察のみで捉えるには限界があり、眼科学的検査や病理組織学的検査から得られる網膜・視神経の形態変化の有無を併せて、総合的に評価する必要がある。近年、網膜の形態変化を精査するために光干渉断層計（Optical Coherence Tomography，以下 OCT）を用いた OCT 検査が汎用されるようになってきた。OCT は、病理組織像のような眼底組織の断層像を非侵襲的に撮影できるため、動物種を問わず生きた状態での網膜各層の形態を立体的に知ることが可能である。また、眼底に異常がみられた際には、その断層像を経時的に観察することで、異常の有無、原発部位及び変化の特徴を捉えることが可能であり、その発現機序を考察する上でも重要な手掛かりが得られる。しかし、OCT 検査の知見は病理組織学的検査ほど、その蓄積がない。OCT 画像が捉える網膜の変化とその病理組織学的な変化・状態との関連性について、情報を蓄積・理解することは、的確な眼毒性評価へとつながる。本講演では、弊社で非臨床安全性試験の一環として実施している網膜 OCT 検査について紹介するとともに、実験動物の眼底にみられた薬物起因性の変化や自然発生病変について OCT 画像と病理組織像を比較し、それぞれが示す網膜の変化・状態や相互の関連について解説する。

略歴

荒木　智陽

株式会社 新日本科学 安全性研究所 安全性評価一部 眼科検査研究室 室長

略歴：
・1998-2002　福山大学工学部生命工学科
・2002-　株式会社新日本科学 安全性研究所入社
・2013-　株式会社新日本科学 安全性研究所 実験研究部 機能検査グループ グループリーダー
・2018-　株式会社新日本科学 安全性研究所 安全性評価一部 第二毒性評価室 室長
・2020-　株式会社新日本科学 安全性研究所 安全性評価一部 眼科検査研究室 室長

学会 / 研究会活動：
・比較眼科学会：基礎部会事務局 / 評議員
・日本毒性学会：会員
・日本臨床視覚電気生理学会：会員
・サル類の疾病と病理のための研究会：幹事

資格：
・比較眼科学会認定基礎眼科学専門家
・実験動物 1 級技術者

S1-4

AI ホスピタル計画における病理業務のデジタル化と AI 活用

○高松 学

公益財団法人がん研究会　がん研究所　病理部

現代では診療活動により生み出されるデータの大半がデジタル化され、病院のサーバ等で管理、運用されている。デジタル化されていることのメリットは、病院内ネットワークに接続している端末から、各種情報を直ちに取り出して、診療の実務を行えるということである。病理業務については、病理オーダ情報や診断書情報はデジタルデータでやりとりされている病院が多いが、診断業務そのものをデジタル化している施設はごく一部に限られる。病理部門で扱う固有の情報は、マクロ（肉眼、写真）とミクロ（スライドガラス上の染色切片）であり、それらに含まれる高次元の情報を収集・分析することで、病変の認識や疾患分類を経て最終的に診断を行っている。これらの業務は専門性が高く複雑であるため、たとえ熟練した人間であっても精度限界がある。情報を可能な限りデジタル処理し、人工知能 (AI) を取り入れることができれば、医療の効率化・安定化・質向上に繋げられるはずである。がん研は内閣府の AI ホスピタル計画に参画し、特に病理部門のデジタル化を推し進めている。マクロ写真については、撮影した検体の写真において切り出し位置を正確に記録し、ミクロ画像との対比により病変範囲を推定し業務を支援する AI を開発した。ミクロ画像については、全症例数の約７割にあたるスライドガラスを日々デジタル化し、コンピュータ画面上で病理医が診断を行うことに加え、事前に組織画像を学習した AI による病変範囲の推定や、教師データ作成用の組織分類アノテーションツールの開発を行っている。既存の病理学にとらわれない、次世代の病理を担うシステムを構築すべく、産学連携を活用し、多くの施設で取り入れられるような汎用性の高いものづくりを目指す、がん研の取り組みを紹介する。

■ 略歴

高松　学

公益財団法人がん研究会　がん研究所病理部　研究員

略歴：
・2002-2008　岐阜大学医学部医学科
・2008-2010　初期臨床研修
・2010-2014　岐阜大学大学院医学系研究科腫瘍病理
・2014-2018　公益財団法人がん研究会がん研究所病理部　特任研究員
・2018-　　同　研究員

学会活動：
・日本病理学会：専門医・研修指導医
・日本癌学会

受賞 / その他：
・2020 年度国際病理アカデミー (IAP) 学術奨励賞

S2-1

The current status and future plans for the globalization of JSTP's certification system for toxicologic pathology

○義澤 克彦[1,2)]

[1)]武庫川女子大学　食物栄養科学部　食創造科学科、[2)]日本毒性病理学会　資格認定委員会

The Japanese Society of Toxicologic Pathology (JSTP) aims to promote the advancement and development of toxicologic pathology sciences by sharing the common goals of promoting education, scientific research, and dissemination of information. In 1994 the JSTP developed a toxicologic pathology certification system. The examinee's practical skills in macro- and microscopic pathology are assessed by examinaton of pathology slides and also includes a written examination to test knowledge of toxicological pathology. The recent passing rate is 30 to 50%. As of September 2021, the number of certified diplomates was 371, including 6 foreigners. The microscopic examination consists of 30 microscopic slides of neoplastic and non-neoplastic lesions including many slides with drug-induced lesions. Starting in 2022, the microscopic examination will be carried out using virtual slides. All examination questions are prepared in English for the benefit of foreign candidates.The JSTP relaxed the qualification of candidacy for the certification examination in order to give talented young pathologists and international candidates an early opportunity to qualify for the examination. As part of JSTP's global strategy, JSTP would like to contribute to the development of toxicologic pathology professionals by making the certification available to toxicologic pathologists in each country, especially in the Asian region.

略歴

義澤　克彦

武庫川女子大学　食物栄養科学部　食創造科学科

略歴：
・1984-1987　鳥取大学農学部獣医学科
・1987-1989　鳥取大学大学院農学研究科獣医学専攻修士課程
・1989-2009　アステラス製薬（藤沢薬品工業）株式会社　安全性研究所入社
・2009-2017　関西医科大学医学部病理学第二講座　講師
・2017-　武庫川女子大学食物栄養科学部食創造科学科　教授
・2018-　大阪市立大学医学部　客員教授

学会活動：
・日本毒性病理学会：理事 / 評議員
・日本毒性学会：評議員
・日本獣医病理学専門家協会：監事 / 評議員
・日本病理学会：学術評議員
・International Academy of Toxicologic Pathology：フェロー
・浜松毒性試験フォーラム：幹事
・日本食品化学学会：評議員

受賞 / その他：
・2018 年度年 JTP 業績賞 : 日本毒性病理学会
・2015 年 JTP 症例報告賞 : 日本毒性病理学会
・2012 年 JTP 最優秀論文賞 : 日本毒性病理学会
・2005 年望月喜多司記念賞奨励賞：（財）食品農医薬品安全性評価センター
・2000 年プレナリーセッション賞：第 130 回日本獣医学科学術集会

S2-2

Establishment of accreditation procedures in toxicologic pathology for trainees

○Kevin Keane

International Academy of Toxicologic Pathology (IATP)

Toxicologic pathology has evolved and grown over the years from a niche, poorly defined, sub-specialty into a distinct, scientific discipline with a well-developed set of best practice in methods, procedures, and terminology that are expected of its practitioners. The training and experiences required of experts in this field have not been uniformly established within this profession and these are generally gained on ad hoc basis after completion of formal educational programs. The IATP was established to create an accreditation program that is flexible in recognizing the various educational pathways and experiences one might accomplish to become an expert in this field and thus recognized as a Fellow. Recently, the IATP has approved an associate Fellow membership category with the express purpose encouraging young trainees to participate in a formal mentorship program that will guide them through activities that will optimize their acquisition of expertise in toxicologic pathology.

略歴

Kevin Keane, DVM, Ph.D. Fellow IATP

Current full-time position: Senior Director of Pathology, Blueprint Medicines, Cambridge, Massachusetts USA
Current part-time position: Editor-in-Chief, Toxicologic Pathology (official journal of STP, BSTP, & ESTP)
Current part-time position: President, International Academy of Toxicologic Pathology (Term: Jan 2021 – Dec 2022)

Education
- 1986-1990 Bachelor Arts, Cornell University, Ithaca, New York USA
- 1992-1995 Doctor Veterinary Medicine, University of Tennessee, Knoxville, Tennessee, USA
- 1995-1998 Resident in Anatomical Pathology, Colorado State University, Fort Collins, Colorado, USA
- 1995-2001 Ph.D. Pathology, Colorado State University, Fort Collins, Colorado, USA

Professional experience
- 2001- 2002 ICOS Corporation, Bothell, Washington, USA
- 2003- 2010 Schering Plough /Merck, Lafayette, New Jersey, USA
- 2011- 2012 Huntingdon Life Sciences, Princeton, New Jersey, USA
- 2011- 2013 Consultant, Hopewell, New Jersey, USA / Beijing, China
- 2013- 2021 Novo Nordisk, Beijing, China / Copenhagen, Denmark
- 2021- Present Blueprint Medicines, Cambridge, Massachusetts, USA

Memberships
- Society of Toxicologic Pathology
- European Society of Toxicologic Pathology
- International Academy of Toxicologic Pathology
- Boston Area Pharmacology Toxicology Group
- Davis-Thompson Foundation for Comparative Veterinary Pathology

S2-3

規制当局の認識について

○三枝 由紀恵

（独）医薬品医療機器総合機構

毒性病理学専門家の認定制度は、わが国の安全性試験における病理学的検査成績の信頼性向上と毒性病理学進歩に寄与するために 1992 年に設立され、2022 年に満 30 年を迎えようとしている。その間、371 名のパソロジストが毒性病理学専門家として認定（2021 年 4 月時点）され、アカデミア、医薬品や農薬等の産業界及び規制当局等の様々な分野において専門家として携わっている。一方、各国においては、毒性病理学に特化した専門家の認定制度を有する国・地域は限定的であり、アジア領域では、唯一、日本毒性病理学会が当該専門家の認定制度を設けている。毒性病理学専門家は、これまで我が国で実施された GLP 適用の非臨床安全性試験における病理学的検査成績の信頼性の確保、及び製造販売承認申請資料の質の向上等に大きな貢献を果たしてきた。さらに、近年、世界的にグローバル化が急速に発展する中で、病理学的な用語・診断基準におけるグローバル統制用語の確立が進んでいること、またデジタルパソロジーや人工知能の導入が進むことにより、毒性病理学専門家が担う役割や分野は今後益々拡大していくことが考えられる。本発表では、毒性病理学専門家及び当該認定制度の国際化に向けての期待や将来像等について、規制当局側の視点から、個人的な見解を述べる予定である。

略歴

三枝　由紀恵

独立行政法人　医薬品医療機器総合機構　新薬審査第五部　主任専門員

略歴
・1994　　日本大学生物資源科学部獣医学科卒業
・1994-2005　山之内製薬株式会社　安全性研究所
・2010　　岐阜大学大学院　連合獣医学研究科　獣医学専攻（病態連合講座）博士課程修了
・2010-　　独立行政法人　医薬品医療機器総合機構

学会活動
・日本毒性病理学会
・日本毒性学会
・日本獣医病理学会
・日本獣医学会

資格・認定
・獣医師
・日本毒性病理学会認定毒性病理学専門家
・日本獣医病理学専門家
・日本毒性学会認定トキシコロジスト

受賞 / その他
・2009 年度　第 25 回日本毒性病理学会総会及び学術集会会長賞

S2-4

欧州での実情

○岡崎 欣正

アナパス・サービス・ゲーエムベーハー

欧州のいくつかの国では毒性病理分野を対象とする団体を独自に有しているものの、ヨーロッパ諸国一体となったより強力な活動を推進するために、2002 年に、その前身となる Gesellschaft fuer Toxikologische Pathologie を発展させる形で European Society of Toxicologic Pathology (ESTP) が設立された。ESTP は毒物病理分野で活動する全ての科学者に様々な継続教育プログラムを提供しているが、認定制度は設けられていない。一方、ESTP は ESVP (European Society of Veterinary Pathology) や ECVP (European college of Veterinary Pathologists) との共同プログラムにも積極的に取り組んでいる。ECVP は、ヨーロッパにおける獣医病理学教育を調和させるとともに、認定制度確立に対する高い要望を受けて 1995 年に設立された。最初の認定試験は 1999 年に行われ、試験による認定者は 2020 年 7 月時点で 238 名になっている。ECVP 認定試験は、ミクロおよびマクロの実技試験、筆記問題として総論、獣医病理学ならびに毒性病理に関する問いを少なくとも 1 件含む包括病理学の 5 つのセクションで構成されている。これまで、獣医病理学セクションの選択分野として毒性病理に関する問題が含まれていたが、この分野を選択する受験者が少ないことから現在は主要選択項目から除外されている。本シンポジウムでは、ECVP 認定試験の一端と、ドイツにおける独自の国家病理認定制度を例にあげながら、欧州における毒性病理専門家認定制度の現状について話題提供しようと思う。

略歴

岡崎　欣正

アナパス・サービス・ゲーエムベーハー　毒性病理研究員

略歴：
・1983-1987　宮崎大学農学部獣医学科
・1987-1989　宮崎大学大学院農学研究科獣医学専攻修士課程
・1998-2002　山口大学大学院連合獣医学研究科博士課程

・1989-1994　大日本製薬株式会社　総合研究所 安全性研究部　研究員
・1994-2003　株式会社三菱化学安全科学研究所　鹿島研究所病理グループ　副主任研究員
・2003-2010　藤沢薬品工業株式会社 / アステラス製薬株式会社 安全性研究所　毒性病理担当研究員
・2010-2011　ハーランラボラトリーズ株式会社　スイス研究所　病理研究員
・2011-2016　アナパス・ゲーエムベーハー　毒性病理研究員
・2016-2018　一般財団法人残留農薬研究所　毒性部　病理研究室　室長
・2019-　　アナパス・サービス・ゲーエムベーハー　毒性病理研究員

学会活動：
・日本毒性病理学会：評議員
・日本獣医学会：評議員
・日本獣医病理学専門家協会：評議員

S2-5

Current status and future prospects of pharmaco-toxicologic pathology in China

○Jin Ren

Chinese Pharmaceutical Association-Society of Toxicologic Pathology

Chinese Pharmaceutical Association-Specialty group of Toxicologic Pathology (CPA-STP) was established on 19th March 2015 in Beijing, which is the first STP Committee in China, representing a new milestone in this field. The committee was composed 38 members. The total number of professional staffs in the field has been expanding, from about 200 to over 700, of which more than 70% members are young.

The CPA-STP has held four conferences since its establishment in 2015. Each it had a different theme and 40 overseas or domestic experts have been invited to give lectures. Also 40 online or offline slide-reading symposiums have been conducted in the different areas in China. So far, the participants have reached over 1000. CPA-STP completed the "Terminology of Toxicologic Pathology (First Edition)", which was officially released at the CPA last year. It is of benefit to promote the professionalization, harmonization and standardization.

In Nov. 2019, the CPA-STP invited Prof. Hideki Wanibuchi, the president of JSTP, to attend the 3rd academic symposium in Suzhou China, and to give a lecture. Consensus and preliminary framework of agreements were reached, and it was an important foundation for China-Japan in-depth cooperation in future.

I would like to express my sincere gratitude to Professor Hideki Wanibuchi for his great efforts in advancing the friendly China-Japan cooperation and promoting the development in the field of toxicologic pathology in China.

略歴

Jin Ren, MD. Ph.D.

Current position President of Chinese Pharmaceutical Association-Specialty group of Toxicologic Pathology (CPA-STP)
Director and Test Facility Manager of CDSER, SIMM, CAS, China

Education

- 1977-1982 B.M. China Medical University, China
- 1982-1985 Master's degree, in Medical Pathology, China Medical University, China
- 1986-1991 Doctoral degree, in Medical Pathology, Hokkaido University School of Medicine, Sapporo, Japan

Professional experience

- 1990-1992 Postdoctoral, Roswell Park Memorial Institute, Buffalo, New York, U.S.A
- 1997-2001 Dept. of Neuropathology, School of Medicine, The University of Tokyo, Tokyo City, Japan (JST, CREST Program)
- 2001- present Center for Drug Safety Assessment and Research in SIMM, CAS, China

Memberships

- The Japanese Society of Toxicological Pathology (member)
  The British Royal College of Pathology (FRCPath Fellow)
  The International Academy of Toxicity Pathology (IATP Fellow)

Honors and Prizes

Cancer Research Award of IWAZAWARUI by Japanese Cancer Research Foundation
Second Prize of National Scientific and Technological Progress, China (first listed owner)
First prize in Science and Technology by Chinese Pharmaceutical Association (first listed owner)
Ho Liang Ho Lee Foundation for scientific and Technological Progress Award, Hong Kong

S2-6

Korean society of toxicologic pathology and board certification

○Jin Seok Kang

Korean Society of Toxicologic Pathology

Korean Society of Toxicologic Pathology (KSTP) is a professional society of experts in the fields of toxicopathology and related sciences. The KSTP has accomplished remarkable progress over the years, gaining strong reputation since it was established in 2002. The KSTP aims to promote the academic development of toxicopathology and to serve as a platform for its utmost interaction with related societies and organizations, that are actively making contributions to the development of toxicopathology. The KSTP supports research activities that encompass the whole areas of toxicopathology matters including toxicological and carcinogenicity studies. The KSTP also provides a fundamental scientific view and takes an initiative in solving problems related to safety issues and risk assessment of foods, medicines, cosmetics, insecticides, medical devices and so on. The KSTP holds annual conference and educational program. In general, the conference consists of several plenary lectures, symposia and poster presentations focusing on the latest research breakthroughs. And the educational programs function as continuing education for practicing toxicologic pathologists and trainees. Each education program covers a target organ or system. Korean Board of Toxicologic Pathology was founded in 2002 to facilitate the education of toxicologic pathologists and certification exam, that is required to get a diploma of Korean Board of Toxicologic Pathology. The education program is offered in May every year. And the certification examination is given every three years on average, and is composed of two parts, a written test and a practical test of toxicopathology.

略歴

Jin Seok Kang, D.V.M., Ph.D.

Director of Student Affair, Namseoul University
Professor, Department of Biomedical Laboratory Science, Namseoul University
President, Korean Society of Toxicologic Pathology

Education

- 1986-1990 Doctor of Veterinary Medicine, Seoul National University, Republic of Korea
- 1990-1992 Master's degree, Seoul National University, Republic of Korea
- 2002-2006 Doctoral degree, Osaka City University, Japan

Professional experience

- 1990- 1998 Daewoong Pharmaceutical Co. Ltd, Republic of Korea
- 1998- 2008 Korea Food and Drug Administration, Republic of Korea
- 2008- present Namseoul University, Republic of Korea
- 2017- 2018 University of Missouri, USA

Memberships

- The Korean Society of Toxicologic Pathology
- The Japanese Society of Toxicologic Pathology
- The Korean Society of Toxicology
- The Korean Society of Laboratory Animal Science

Honors and Prizes

- Science Good Paper Award from Ministry of Science and Technology of Korea Government, Republic of Korea (2017)
- Good Teacher Award from Ministry of Education of Korea Government, Republic of Korea (2019)

S2-7

Overview on society of toxicologic pathology India (STPI) and Indian board of toxicologic pathology (IBTP)

○Venkatesha Udupa[1)], SK Vijayasarathi[2)], Narendra Deshmukh[3)], Shekar Chelur[4)], Kamala Kanan[2)], Jomy Jose[5)], PC Prabu[6)], GJ Nataraju[7)], Geeta Nirody[8)], Madhav Marathe[9)]

[1)] Vice President & Head Toxicology, Glenmark Pharmaceuticals Ltd
[2)] Expert Pathologist, Eurofins Advinus Limited
[3)] Co-Founder and Director, Intox Pvt Ltd
[4)] Director, Preclinical Safety Evaluation, Aurigene Discovery Technologies Ltd; 2Head Pathology, Eurofins Advinus Limited
[5)] Head of the Department, Pathology, Sai Lifesciences
[6)] Assistant Professor, Department of Pathology, Veterinary College & Research Institute
[7)] Head Pathology, Bioneeds India Private Ltd
[8)] Consultant Pathologist
[9)] Vice President Toxicology, Sun Pharma Advanced Research Company Ltd

IBTP is an affiliate of STP-I established in 2011 to encourage the study of Toxicologic Pathology and its allied fields to stimulate the advancement of existing standards in Industry for professional practice to prepare and administer procedures, including testing, for the recognition of such standards by certification for those members of the profession who demonstrates competence deserving recognition as Diplomats of the IBTP (DIBTP). The IBTP consists of members who are primarily a Diplomate of IBTP involved in setting up the eligibility criteria, evaluating applicants, and conducting examinations. IBTP ensures running at least two training programs in a year involving practical slide reading, lecture on various topics, before they appear for examination in line with other International Certifying Boards. IBTP gathers questions from Board members and Resource matter specialists, and has a question bank. IBTP, in association with STPI, has collected thousands of glass slides, CDs, teaching materials to train DIBTP aspirants. IBTP certification examination involves theory, practical (glass slide and image) and objective type questions running over nearly 6 hours. Candidates must pass all the 3 sections to obtain DIBTP. The certification is valid for 5-years, and the status has to be renewed by appearing for a recertification examination. Starting October 2012, the board examination is conducted annually with 43 Diplomates to date and are increasingly recognized in the Indian toxicology industry.

略歴

Venkatesha Udupa MVSc (Path), MSc (Tox, UK), DABT, ERT (UK), DIBTP, DSP, PhD

Dr. Venkatesha Udupa is currently working as Vice President and Head – Toxicology at Glenmark Pharmaceuticals Ltd, Mumbai. In this role, Dr. Udupa supports drug discovery and development for several unprecedented targets by providing scientific input in the design and execution of early discovery and nonclinical toxicology experiments that focus on characterizing the safety of the candidates and/or understanding potential mode of action for toxicity in pre-clinical studies. Prior to joining Glenmark Pharmaceuticals, he worked at Ranbaxy Laboratories Ltd (Gurgaon, India), Maccine Pvt Ltd (Singapore) and Himalaya Drug Company (Bangalore, India) in the area of toxicology and pathology.
Dr. Udupa completed his Masters in Veterinary Pathology and PhD in Biochemistry. He is a recipient of Commonwealth Scholarship for Master's program in Toxicology at University of Surrey, UK. He is a Diplomate of American Board of Toxicology (DABT), Diplomate of Safety Pharmacology (DSP), European Registered Toxicologist (ERT, UK) and Diplomate of Indian Board of Toxicological Pathologists (IBTP) and actively involved in various professional activities of STPI, IBTP, IFSTP, STP, ESTP and SOT. He has 20 international publications in peer reviewed journals and 18 national publications, co-inventor in couple of patents and a coauthor for a book chapter on topics in 'Discovery and Regulatory Toxicology in Pharmaceutical Industry' and 'Regulatory Toxicology in Pharmaceuticals' published in 2021 by Springer Nature.

SK Vijayasarathi, MVSc, PhD, Fellow STP-I, Fellow IATP

Dr SK Vijayasarathi has ~50 years of experience in the field of Veterinary Pathology. Dr Vijayasarathi worked at Veterinary College, University of Agricultural Sciences, Bangalore, India in 1969 and served in various capacities till 2004. During this period, he was involved in teaching and also lead supervisor for 25 Master's and 4 Doctoral students, and advisor for more than 150 graduate students (MVSc/PhD). He was the principal investigator for several federal and private funded research projects. Has visited various veterinary and Medical academic institutions as an external examiner to evaluate Masters and Doctoral thesis and to conduct final examinations. He has over 95 scientific publications to his credit and has presented several research paper/ abstracts at various National and international forums. Dr. Vijayasarathi has received several awards for scientific/professional achievements. He is actively involved in the field of regulatory toxicology for more than 28 years for histopathological evaluation to understand the toxicological potential of pharmaceuticals, agrochemicals and biologics in a variety of animal models. He is the author of nearly 700 safety evaluation GLP study reports, including more than 28 carcinogenicity studies. Further, he has peer reviewed nearly 100 GLP studies.

S3-1

ゲノム編集技術とその医療応用

○真下 知士

東京大学医科学研究所

ゲノム編集はバイオサイエンスや医薬開発研究の‘革命’的技術である。ゲノム編集ツールの開発、エピゲノム編集、遺伝子転写調節、細胞スクリーニングなどに、次々と研究開発利用がなされている。大学、研究機関や製薬企業、ベンチャーによる、ゲノム編集を使った遺伝子治療、細胞治療、創薬の開発競争が激しくなっている。一方で、ゲノム編集に関する規制やガバナンス、リスクマネジメントなども重要な検討課題である。本シンポジウムでは、我々が最近開発した日本発の新規ゲノム編集ツール CRISPR-Cas3 について紹介する。また、CRISPR-Cas3 を使った新型コロナウイルスの迅速診断法 CONAN についても紹介したい。CRISPR-Cas3 は、生命科学分野の基盤技術になり得る成果として、農水産業における品種改良、遺伝子治療、再生医療での新規治療法開発など、幅広い産業分野においての活用が期待されている。

略歴

真下　知士

東京大学医科学研究所　実験動物研究施設先進動物　ゲノム研究分野　教授

略歴：
・1990-1994　京都大学農学部畜産学専攻
・1995-1997　京都大学大学院人間環境学研究科文化地域環境学専攻修士課程
・1997-2000　京都大学大学院人間環境学研究科文化地域環境学専攻博士課程
・2000–2002　フランス・パスツール研究所免疫学講座ポスドク研究員
・2003–2015　京都大学大学院医学研究科附属動物実験施設特定准教授
・2015–2020　大阪大学大学院医学系研究科附属動物実験施設准教授
・2016–2020　大阪大学大学院医学系研究科附属共同研ゲノム編集センター長
・2019– 現在　東京大学医科学研究所実験動物研究施設先進動物ゲノム研究分野教授
　　同　システム疾患モデル研究センターゲノム編集研究分野（兼）

学会活動：
・日本ゲノム編集学会：副会長
・日本実験動物学会：常務理事
・SHR 等疾患モデル共同研究会：理事
・高血圧関連疾患モデル学会：評議員

受賞 / その他：
・平成 15 年度（社）日本実験動物学会奨励賞
・平成 19 年度岡本研究奨励賞

S3-2

がん細胞とがん微小環境の相互作用によるがん組織の形態形成

○中野 清孝[1)]、山崎 雅輝[1)]、川合 重人[1)]、藤井 悦子[1)]、油谷 浩幸[2)]、鈴木 雅実[3)]

[1)]中外製薬株式会社、[2)]東京大学　先端科学技術研究センター、[3)]公益財団法人　実験動物中央研究所

腫瘍組織は癌細胞に加え線維芽細胞や免疫細胞など多様な細胞から構成されており、近年腫瘍環境についての研究が活発に進められている。臨床組織の病理解析は重要な知見を与える一方、スナップショットであるため各細胞の役割の理解は容易ではない。我々は xenograft モデルや癌オルガノイドを用いた経時的な実験病理学的解析を通じて、腫瘍環境が癌進展、形態形成に与える影響について検討を行った。臨床大腸癌より樹立した細胞株 PLR123 をマウスに皮下移植し病理解析を行った結果、がん幹細胞マーカー LGR5 陽性細胞を含む小型構造体が癌進展の起点となっていると考えられた。single cell RNA シークエンス解析を実施した結果、腫瘍近傍の線維芽細胞やマクロファージは、臨床腫瘍組織で認められるような多様な状態で存在していた。小型構造体の形成メカニズムを理解するため癌オルガノイドを用いた解析を行い、線維芽細胞が小型構造体形成に関わることが示唆された。また、PLR123 細胞のマウス転移モデルの病理解析の結果、肺転移巣と肝転移巣で腫瘍の形態が異なる事が判明した。腫瘍環境の影響について癌オルガノイドを用いた検証を行い、酸素分圧や増殖因子が形態形成に影響する事を示した。次に、スキルス胃がんにおける変異型 RHOA の役割を理解するため、同所移植 xenograft モデルの病理解析を行った。変異 RHOA 発現細胞株を移植した組織では、浸潤性増殖の亢進が認められた。in vitro の解析においても細胞骨格の変化や運動性向上が認められ、癌進展における変異 RHOA の影響を実験的に明らかにする事ができた。以上のように、実験病理学的解析と癌オルガノイドならびに single cell RNA シークエンス解析等先端技術との融合は、癌微小環境を理解する上で有用であると考えられた。

略歴

中野　清孝

中外製薬株式会社　医科学薬理部　ヒト予測基盤研究グループ　グループマネージャー

略歴：
・1991-1995　九州大学薬学部
・1995-1997　九州大学大学院約学研究科　修士課程
・1997-　中外製薬株式会社　富士御殿場研究所入社
・2012-2013　筑波大学　生命環境科学研究科生物科学専攻　博士課程
・2021-　中外製薬株式会社　医科学薬理部　ヒト予測基盤研究グループ　グループマネージャー

S3-3

Establishment of a dual organ carcinogenicity model in rats for application in cancer chemopreventive studies on natural product and functional food

○Rawiwan Wongpoomchai[1,2], Charatda Punvittayagul[3], Sirinya Taya[2], Arpamas Chariyakornkul[1]

[1] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2] Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University
[3] Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University

[Background] The anticarcinogenic properties of natural products and functional food are usually evaluated in a single organ-specific test. [Aim] To reduce the cost and time of analysis, a dual organ carcinogenicity test using diethylnitrosamine (DEN) and 1,2-dimethylhydrazine (DMH) was developed.

[Materials and Methods] Triple intraperitoneal administrations of DEN were made before, during or after double subcutaneous injections of DMH. At the end of the experiment, the preneoplastic hepatic glutathione-S-transferase placental form (GST-P) positive foci and colonic aberrant crypt foci (ACF) were analyzed.

[Results] The combined treatment of these carcinogens increased toxicity to rats. Administration of DMH alone did not induce hepatic GST-P positive foci, while co-treatment with DMH enhanced GST-P positive foci formation. However, DEN did not influence the size or number of colonic ACF. The treatment with DMH alone induced CYP2E1, demonstrating that DMH enhanced DEN metabolism in DEN-and DMH-treated rats. These findings were related to increases in hepatic O6-methylguanine DNA adducts and hepatotoxicity, associated with the induction of cell proliferation and liver cancer development. DEN-induced early stages of rat hepatocarcinogenesis was synergistically promoted by DMH via metabolic enzyme induction leading to enhanced DNA mutation and hepatocarcinogenicity.

[Conclusion] The dual organ carcinogenicity model might be an alternative model for anticarcinogenicity testing.

略歴

Rawiwan Wongpoomchai

Current position：
- Associated Professor, Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Thailand
- Head of Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University, Thailand

Employment History:
- 1997- until now: Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Thailand

Commitee Memberships：
- Thai Society of Toxicology (2006~)
- Thai Environmental Mutagen Society (2006~)
- Thai Association for Laboratory Animal Science (2006~)
- The Science Society of Thailand (2007~)
- The Biochemical and Molecular Biology Society of Thailand (2007~)

Honors and Prizes：

2006 Young Scientist Award, The 3rd Regional Meeting of Asian Pacific Organization for Cancer Prevention, January 20-21, 2006, Nagoya, Japan
2010 The Best Award for Thesis Advisor in Health Science, Graduate School of Chiang Mai University
2010 Bo Holmstedt Memorial Foundation Travel Award. The XII International Congress of Toxicology, July 19-23, 2010, Barcelona, Spain
2011 Travel Grant Award. The 70th Annual Meeting of the Japanese Cancer Association, October 3-5, 2011, Nagoya, Japan
2013 Travel Grant Award. The 72nd Annual Meeting of the Japanese Cancer Association, October 3-5, 2013, Kanagawa, Japan
2014 The Best Research Award on Supra Cluster of Agriculture and Food. The 3rd Thailand National Research Universities Summit. July 31-August 1, 2014, Bangkok, Thailand.
2018 The Best Award for Thesis Advisor in Health Science, Graduate School of Chiang Mai University
2019 The 1st Price on the 2019 winner of the Flash Talk Session 2 Competition in The 7th International Conference on Food Factors and The 12th International Conference and Exhibition on Nutraceutials and Functional Food organized by The International Society for Nutraceutials and Functional Food. Dec 1-5, 2019, Kobe Convention Center, Japan.

S3-4

NAFLD/NASH 肝発がんの促進機序への最近の洞察

○梯 アンナ、鰐渕 英機

大阪市立大学大学院医学研究科　分子病理学

非アルコール性脂肪性肝疾患（NAFLD）と脂肪性肝炎（NASH）は、現在、肝細胞癌（HCC）の発症の素因となる一般的な慢性肝疾患として知られている。現在成因の主流となっている「多重並行ヒット仮説」によると、NASH は肥満の有無に関わらず認められる可能性があり、異常な代謝と脂質の蓄積、ミトコンドリア機能障害、酸化的及び小胞体ストレス等の複数の要因によって引き起こされると考えられている。過去 10 年間で、トランスレーショナルリサーチの研究により脂肪肝の発症だけでなく、NASH や肝硬変、肝細胞癌への進行にも関与する新規蛋白質とシグナル伝達経路が特定された。それにもかかわらず、前癌病変から肝細胞癌が発生するメカニズムは未だ解明されていない。肝臓での脂肪蓄積の原因として脂質およびグルコース代謝の変化を媒介する根本的な分子経路を説明する研究が進んで、この点に関して、近年では肝臓での脂肪蓄積の原因として脂質およびグルコース代謝の変化を媒介する根本的な分子経路を説明する研究が進んでおり、肝細胞癌への NASH の進行における mTOR シグナル伝達の役割が注目されている。我々の研究の目標は、1) NAFLD/NASH への新しい遺伝的及び蛋白質の寄与の探索、2) NASH 関連 HCC の主要な分子機序の解明と 3）NASH/HCC バイオマーカーの開発である。

略歴

梯　アンナ

大阪市立大学大学院医学研究科　分子病理学　講師

略歴：
・1989-1993　サンクト・ペテルブルグ国立大学生物学部
・1993-1995　サンクト・ペテルブルグ国立大学生物学部生化学専攻修士課程
・1999-2003　大阪市立大学大学院医学研究科医学専攻博士課程
・2003-2006　大阪市立大学大学院医学研究科　都市環境病理学　厚生労働科学研究費補助金
　　食品の安全性高度化推進研究推進事業 若手研究者育成活用事業リサーチレジデント
・2006-2011　大阪市立大学大学院医学研究科 分子病理学 助教
・2011-　　大阪市立大学大学院医学研究科 分子病理学 講師

学会活動：
・日本毒性病理学会：評議員
・日本癌学会：評議員
・日本病理学会：評議員
・日本がん予防学会：評議員

受賞 / その他：
・2002 年度　　学会発表賞・会長賞 : 第 18 回日本毒性病理学会
・2003 年 7 月　若手優秀研究発表賞 : 第 30 回日本トキシコロジー学会
・2018 年 3 月　学会賞 : 大阪市医学会
・2018 年 3 月　医学部長賞優秀賞 : 大阪市立大学大学院医学研究科

PD

Post コロナ時代の毒性病理学
～リモート病理評価、リモート Peer review の実際と課題～

パネリスト：小林　欣滋（株式会社新日本科学）
松本　泉美（大日本住友製薬（株）前臨床研究ユニット安全性第 2 グループ）
穴山　久志（武田薬品工業 リサーチ薬剤安全性研究所）
太田恵津子（エーザイ株式会社 グローバル安全性研究部）
爰島　洋子（株式会社 LSIM 安全科学研究所）
岩田　　聖（ルナパス合同会社 毒性病理研究所）
山口　裕子（株式会社ボゾリサーチセンター）
オブザーバー：中野　賢司（独立行政法人医薬品医療機器総合機構）

Covid19 pandemic を受けて、様々な業種、職種でこれまでの「働き方」を改革しようという機運が高まっている。このような Post コロナ時代を生きる毒性病理学専門家である我々にとっても、より働きやすく、より効率的で、より信頼性の高いデータ創出が可能な「働き方」を手にするために、その姿を自ら描き、そこに向けた課題を抽出して、解決に近づけていく絶好の機会が訪れていると考えられる。
そこで今回のパネルディスカッションでは、コンサルタント、医薬品メーカー、CRO の一線でそれぞれ活躍中の専門家にパネリストとして登壇いただき、理想の「働き方」のイメージ作りとそこに向けた wish list の作成をゴールとできればと考えた。今後、このリストが、何らかの提言につながっていけば幸甚である。

W-1＊

炭酸脱水素酵素阻害剤 Acetazolamide の Wnt/ βカテニンシグナル経路抑制を介した膀胱癌浸潤抑制効果

○松江 泰佑[1,2]、魏 民[1,3]、塩田 正之[4]、鈴木 周五[1]、藤岡 正喜[1]、梯 アンナ[1]、内田 潤次[2]、鰐渕 英機[1]

[1]大阪市立大学大学院医学研究科　分子病理学、[2]大阪市立大学大学院医学研究科　泌尿器病態学
[3]大阪市立大学大学院医学研究科　環境リスク評価学、[4]大阪市立大学大学院医学研究科　分子制御生物学

【背景】我々は浸潤性膀胱癌ラットモデルの膀胱癌プロテオーム解析により、新規癌関連蛋白として炭酸脱水素酵素 2 (carbonic anhydrase 2 : CA2) を同定してきた。【目的】本研究は N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) 誘発マウス膀胱癌に対する CA 阻害剤である Acetazolamide(Ace) の抗腫瘍効果の検討と、ヒト膀胱癌細胞株に対する CA2 導入による影響と分子機序の探索を行った。【材料と方法】雄性 C57BL/6J マウスに 0.05%BBN を 10 週間飲水投与後、無処置、Ace 単独投与、Cisplatin(Cis) 単独投与、あるいは Ace・Cis 併用投与のいずれかの処置を 12 週間行った。実験開始 22 週間後に剖検、膀胱を採取し、病理組織学的検討を行った。ヒト膀胱癌細胞株 T24・UMUC3 に CA2 遺伝子導入し、遊走能・浸潤能アッセイ、遺伝子発現解析、ＥＭＴ関連蛋白の発現解析を行った。【結果】BBN 単独投与群と比較して、BBN → Ace 群および BBN → Ace・Cis 併用群で筋層浸潤癌の発生数の有意な減少を認めた。CA2 導入ヒト膀胱癌細胞株における遊走能・浸潤能の亢進を認めた。リン脂質キナーゼ PIP5K1B 発現上昇による Wnt/ βカテニンシグナル経路活性化を介した EMT との関連が示唆された。【結論】マウス膀胱癌に対する Ace の浸潤抑制効果が明らかになった。また、その機序として Wnt/ β - カテニンシグナル経路の活性化と EMT を抑制している可能性が示唆された。

W-2＊

カニクイザル子宮内膜の性周期におけるエストロジェン及びプロジェステロンレセプターの免疫組織化学的解析

○粟津原 優美、爰島 洋子、友成 由紀、霜山 奈津美、中原 豊、涌生 ゆみ、佐藤 順子、土居 卓也

（株）LSIM 安全科学研究所　病理研究部　鹿島病理部

【緒言】カニクイザルの雌の性ホルモン変動と，それに伴う子宮内膜の周期的な増殖・分泌・脱落はヒトに類似している．ヒトでは性周期によるエストロジェンレセプター（ER）及びプロジェステロンレセプター（PgR）の発現変動が報告されているがカニクイザルでは報告がない．カニクイザルのレセプター変動を把握することは，ヒトへの外挿性を考える上で重要である．そこで，カニクイザル正常子宮を用いて性周期ごとのレセプター発現について精査した．【材料と方法】3~7 歳の雌カニクイザル 24 例の卵巣及び子宮を用いた．ホルマリン固定・パラフィンブロックより HE 染色，さらに子宮は抗 ER 抗体及び抗 PgR 抗体を用いた免疫組織化学的染色を実施した．子宮は組織学的に月経期（M 期）2 例，増殖期初期～中期（EG 期）11 例，増殖期後期（LG 期）2 例，分泌期前期（ES 期）5 例，分泌期後期（LS 期）4 例に分類された．【結果】ER：EG 期初期に内膜全域が強陽性を示したが徐々に弱まり，LG 期には陰性であった．ES 期・LS 期では基底層のみ弱陽性を示す例が多かった．PgR：EG・LG 期に内膜全域が陽性を示したが，ES 期には部分的に弱陽性を示すのみで大部分が陰性であった．LS 期では間質細胞のみ再び陽性を示した．【結論】ヒトの ER は，増殖期でほぼ全ての細胞に発現し，分泌期中期に陰性化する．カニクイザルの ER も増殖期で発現し，後期には陰性化しておおむねヒトと同様の変動を示した．一方，ヒトの PgR は，増殖期にほぼ全ての細胞で発現し，分泌期中期で減少，後期で陰性化する．しかし，カニクイザルの PgR は，分泌期後期でも陽性を示し，ヒトとは異なっていたことから，性周期によってカニクイザル独自のレセプター発現が見られることが示唆される．

W-3＊

Rubiadin の腎臓における局在と病理組織学的変化が示す部位特異的な遺伝毒性

○満元 達也[1,2]、石井 雄二[1]、滝本 憲史[1,3]、並木 萌香[1]、高須 伸二[1]、能美 健彦[1]、小川 久美子[1]

[1]国立医薬品食品衛生研究所　病理部、[2]ヤマザキ動物看護大学　動物看護学科、[3]東京農工大学　獣医病理学研究室

【背景】我々はこれまでに腎発がん物質アカネ色素を単回投与したラット腎臓において、構成成分の一つである rubiadin（Rub）が髄質外層外帯（OSOM）に特異的に分布することを脱離エレクトロスプレーイオン化－質量分析イメージング（DESI-MSI）を用いて明らかにした。本物質は Ames 試験陽性であるが、ラット腎臓における変異原性は明らかになっていない。本研究では、レポーター遺伝子導入動物である *gpt* delta ラットに Rub を反復投与し、腎臓における Rub 及びその代謝物の分布解析に加え、病理組織学的変化及び突然変異誘発性を検索し、それらと局在との関連を検討した。【材料と方法】雄性 6 週齢の F344 系 *gpt* delta ラットに Rub を 0、0.01、0.03 又は 0.1% の用量で 4 週間混餌投与した後、腎臓を採取した。左腎の一部は DESI-QTOF/MS による MSI 用として 4% carboxy methylcellulose 溶液に包埋後凍結し、残りは病理検査及びγ -H2AX 免疫組織化学検査用として 10% 中性緩衝ホルマリン液にて固定した。右腎は皮質と髄質を分けて採取し、*gpt* assay による変異原性の検索に供した。【結果】MSI の結果、0.1% 投与群において Rub 及び硫酸抱合体のプロトン脱離イオン [M-H]-（m/z 253.050 及び 333.007）はいずれも OSOM に認められた。病理組織学検査では 0.1% 投与群で同部位に核の大小不同が認められ、γ -H2AX 免疫組織化学染色の結果、同部位に陽性細胞の増加が認められた。【結論】MSI の結果は、単剤の反復投与においても Rub とその代謝物が OSOM 特異的に分布することを示した。また、同部位で認められた組織学的変化は、Rub が OSOM 特異的に DNA 損傷を引き起こすことを示唆するものであった。今後、OSOM と皮質についてそれぞれ *gpt* assay を実施し、それらの結果についても併せて報告する。

W-4＊

コリン欠乏メチオニン低減高脂肪アミノ酸食（CDAA-HF-T(-)）によるマウス NASH 誘発における interleukin-21 受容体（IL-21R）の関与

○煙山 紀子[1]、渡邉 颯人[2]、中根 冴[2]、桐ケ窪 彩[1]、佐々木 夏純[1]、田中 大揮[1]、吉瀬 優[1]、政所 陽菜[2]、宇野 絹子[3]、美谷島 克宏[1,2]、中江 大[1,2]

[1]東京農大・応生・食品安全健康、[2]東京農大院・農学研究・食品安全健康、[3]東京農大院・農学研究・食品栄養

【目的】IL-21R はリンパ球およびマクロファージの成熟や増殖など免疫機能に関与するとされているが、これまでの我々の検討により、肝臓で多く発現が認められる脂質合成転写因子 SREBPs との関連性が示唆されている。本研究は、エネルギー代謝関連臓器である肝における IL-21R の（病態）生理学的意義について検討することを目的に、非アルコール性脂肪性肝炎（NASH）発生への関与を解析した。【方法】実験は、6 週齢の C57BL/ 6 J 系雄性の野生型または IL-21R 全身欠損マウスに、普通食（脂質 13 kcal%、麦芽、大豆油；メチオニン 0.44%）・CDAA-HF-T(-)（脂質 45 kcal%、トランス脂肪酸非含有ショートニング；メチオニン 0.1%）を 4 週間投与して解剖し、各種の解析を行った。【結果】野生型 CDAA-HF-T(-) 群では、血中 ALT・AST 活性の増加と共に、肝において著明な脂肪蓄積と、IL-21・IL-21R および炎症または線維化関連遺伝子発現の増加が認められた。IL-21R 欠損 CDAA-HF-T(-) 群では、肝脂肪蓄積が野生型と同様に観察され、血中 ALT 活性がさらに増加した。炎症関連遺伝子発現は野生型と同様に増加した一方、線維化関連遺伝子発現は野生型と比較して低下を示した。普通食群においては、いずれのマウスでも変化がみられなかった。【結論】CDAA-HF-T(-)4 週間投与により誘発されるマウス NASH の比較的早期においては、肝の IL-21 および IL-21R 発現が増加し、これらが病態の発生・進展に関わることが示唆された。また、IL-21R は、CDAA-HF-T(-) 投与による肝の脂肪化・炎症に関与せず、肝線維化の進行に特異的に関与する可能性が示唆された。

W-5＊

有機粉じん吸入による労働災害事例を端にした新規肺疾患の紹介

○山野 荘太郎[1)]、武田 知起[1)]、高信 健司[1)]、妹尾 英樹[1)]、甲田 茂樹[2)]、岡本 賢三[3)]、岸本 卓巳[4)]、梅田 ゆみ[1)]

[1)]（独）労働者健康安全機構日本バイオアッセイ研究センター、[2)]（独）労働者健康安全機構労働安全衛生総合研究所
[3)]（独）労働者健康安全機構北海道中央労災病院、[4)]（独）労働者健康安全機構アスベスト疾患研究・研修センター

【背景 / 目的】架橋型アクリル酸系水溶性高分子化合物（以下ポリマー）の高濃度粉じんにばく露された労働者 5 名に肺線維性疾患等を発症した事例が 2017 年 4 月に厚生労働省労働基準局よりプレスリリースされ、業務上外に関する検討会での意見を踏まえ、2019 年 4 月に労災認定された[1,2]。当該ポリマーの吸入性粉じんによる呼吸器の有害性は国際的にも報告されておらず、呼吸器疾患の発生機序等が不明であった。そこで我々は病態の把握等を目的に下記の研究を実施した。【材料と方法】F344 ラットを用いて当該ポリマーを全身吸入ばく露 (0-40 mg/m3, 1 or 5 day/week, 10 or 13 weeks) 等で投与し、投与開始後最大 26 週間までの肺組織等を採集し、各種解析に興じた。【結果と考察】上記労働者の HRCT 及び VATS 肺生検では、両側上肺野の中枢性肺線維症、細気管支閉塞による末梢性肺気腫及び多発ブラに起因する気胸等が見られたが、ラット肺では気管支病変は認められず線維性肥厚を伴う胞隔炎等が観察された。分子細胞生物学的検討より、病巣内では毛細リンパ管の増加及び TGF βシグナルの恒常的な活性化が認められた。胞隔炎の早期変化では、高度の好中球浸潤を伴った肺胞虚脱が認められた。以上の結果より、ポリマーの吸入ばく露はラットに肺胞傷害を誘発する事が認められた。本発表では、無機粉じんデータとの比較考察等についても報告し、有機粉じん吸入による新規肺疾患について議論したい。

1, https://www.mhlw.go.jp/stf/houdou/0000163568.html

2, https://www.mhlw.go.jp/stf/houdou/2r98520000035viv_00003.html

W-6＊

気管内投与法によるカーボンナノホーン (CNH) およびカーボンナノブラシ (CNB) の肺および胸膜における短期毒性試験

○Saleh Dina[1,2,3)]、アーメッド オムニア[1,2,4)]、アレクサンダー デービッド[1)]、アレクサンダー ウィリアム[1)]、グナセカラン シバガミ[1,2)]、沼野 琢旬[1)]、高瀬 弘嗣[5)]、大西 誠[6)]、高橋 智[2)]、湯田坂 雅子[7)]、弓削 亮太[8)]、津田 洋幸[1)]

[1)]名古屋市立大学　津田特任教授研究室、[2)]名古屋市立大学大学院　医学研究科　実験病態病理学分野
[3)]Assuit 大学　医学部　法医学・臨床毒物学教室、[4)]Aswan 大学　医学部　法医学・臨床毒物学教室
[5)]名古屋市立大学大学院　医学研究科　共同研究教育センター
[6)]（独）労働者健康安全機構　日本バイオアッセイ研究センター　試験管理部
[7)]（独）産業技術総合研究所　ナノチューブ応用研究センター　高度機能 CNT チーム
[8)]NEC（株）　システムプラットフォーム研究所

Use of carbon nanotubes (CNT) is expanding. Carbon nanohorns (CNH) are graphene-based tubular objects ended by a five-pentagon conical cap, and thousands of these tubular objects assemble into spherical aggregates. Carbon nanobrushes (CNB) are linear assemblies of CNH spherical aggregates. Their unique structures with high surface area make CNH and CNB promising materials for many high technology fields. We have been examining multi-walled carbon nanotubes (MWCNTs) for pulmonary and pleural hazards using intra-tracheal intra-pulmonary spraying (TIPS). Using this method, we examined the pulmonary and pleural toxicity of CNH (0.5 mg/rat and 1 mg/rat) and CNB (0.5 mg/rat and 1 mg/rat) with MWCNT-7 (0.5 mg/rat) as the reference material. Test materials were administrated every other day for 15 days and rats were observed without further treatment until sacrifice at week 6. Results: Histopathological analysis showed alveolar macrophages engulfing all 3 types of CNTs and formation of granulation tissue. Granulation tissue, macrophage count, and alveolar cells and pleural mesothelial cells positive for PCNA (cell proliferation index) were all significantly lower in the CNH and CNB groups compared to the MWCNT-7 group ($p<0.05$). Conclusion: Our results show that inflammatory lesion development is significantly less in CNH and CNB exposed lung tissue compared to MWCNT-7, and thus CNH and CNB are less harmful to the rat lung than MWCNT-7.

W-7＊

Generation of cerebral organoids from human embryonic stem cells

○Ke Chen[1)]、Shuang Qiu[1)]、Haoan Wang[1)]、Qingxi Kong[2)]、Qian Bu[1,3)]、Qian Liu[1)]、Xiaobo Cen[1,4)]、Chunyan Hu[1)]

[1)] Westchina-Frontier Pharma Tech Co., Ltd (WCFP), [2)] Pharmaron
[3)] Healthy Food Evaluation Research Center, Department of Food Science and Technology, College of Light Industry, Textile and Food Engineering, Sichuan University
[4)] National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, and Collaborative Innovation Center for Biotherapy

[Background] In traditional neurotoxicity research animal or human nerve cell lines are mostly used as models, both of them can't reflect the complexity of the human brain structure and function. **[Aim]** To provide a better model in vitro for studying cerebral development and neurotoxicity. **[Materials and Methods]** The cerebral organoids were generated from H1 hESC line. A 3D culture system was introduced to generate the hESC-derived cerebral organoids in Matrigel. **[Results]** During the 2D subculture of the hESCs in vitro, chromosome karyotyping, immunofluorescence, trilineage differentiation test and teratoma experiment showed that the hESCs maintained the normal human diploid karyotype with differentiation pluripotency. During the 3D culture process, the immunofluorescence showed that the cerebral organoids not only contained differentiated cell types, also self-assembled into cerebral cortex with complex morphology, including the human VZ-like area, organized horizontal multilayers structure, and synapse network. The multi-electrode arrays also recorded consistent increases in electrical activity in the cerebral organoids, as parametrized by burst frequency and firing rate, which indicated a continually evolving neural network. **[Conclusion]** A 3D culture systerm was successfully developed to generate cerebral organoids model from hESCs. This research provided a novel platform for developmental neurotoxicity studies in vitro.

W-8＊

Ex vivo/in vivo MRI によるラットの薬物誘発性動脈炎の検出

○藤井 雄太[1,2)]、吉野 有香[1,2)]、千原 和弘[1)]、中江 文[2,3)]、圓見 純一郎[2,3)]、吉岡 芳親[2,3)]、宮脇 出[1)]

[1)]大日本住友製薬　前臨床研究ユニット、[2)]大阪大学大学院　生命機能研究科
[3)]情報通信研究機構及び大阪大学　脳情報通信融合研究センター

【背景・目的】薬剤性動脈炎は、発生メカニズムがほとんど解明されておらず、特異的かつ鋭敏なバイオマーカーが存在せず、臨床試験におけるモニタリングが困難であることから、医薬品開発での大きな問題となっている。MRI は臨床にて 30 年以上使用されており、非臨床から臨床へ橋渡し可能な検査手法と期待される一方、げっ歯類の MRI の研究は、動物が小さいことを理由に発展が緩慢であった。しかし近年、超高磁場 MRI を含む *in vivo* イメージング技術の進展に伴い、げっ歯類の MRI 研究が進んできた。今回、薬剤誘発性のラットの動脈炎を 11.7T の MRI を用いて検出可能か否かを検討した。【方法】血管拡張作用により動脈炎を惹起する Fenoldopam mesylate（FM, 投与量：100 mg/kg/day）及び血管収縮作用により動脈炎を惹起する Midodrine hydrochloride（投与量：40 mg/kg/day）をそれぞれ SD 系ラットに 2 日間皮下投与し、腸間膜動脈を 11.7T の MRI にて評価した。gadolinium 含有 PBS 溶液に浸漬させた摘出腸間膜動脈（*ex vivo*）を評価した後（FM のみ）、麻酔下で腸間膜動脈（*in vivo*）を評価した。併せて、MRI 撮像後の腸間膜動脈の病理組織学的検査も実施した。【結果・結論】いずれの薬剤で誘発された動脈炎でも MRI では動脈周囲の高信号として検出され、高信号部位は病理組織学的に観察された動脈周囲の水腫と一致した。更に *ex vivo* での詳細画像では、血管壁の低信号を検出でき、低信号部位は病理組織学的に観察された赤血球の血管壁内への滲出と一致した。これらのことから、MRI は異なる作用メカニズムで誘発された薬剤性動脈炎を非侵襲的に検出することが可能であり、動脈周囲の高信号は臨床試験でのバイオマーカーの一つになり得ると推察された。

IATP

Digital pathology and tissue image analysis - how did we start and where are we now

○Aleksandra Zuraw

Charles River Laboratories

The field of digital pathology was born with the development of telepathology in the 1980's of the last century. It originated with the need of remote consultation, evolved over more than 30 years, and now allows us to serve patients and advance science from home during a global pandemic.

The aspects of current digital pathology span from classical telepathology and collaboration tools all the way to artificial intelligence-powered image analysis. Digital pathology is a cutting-edge discipline where pathology, computer science and computer vision meet and scientists collaborate.

To advance the field of digital pathology individuals specializing in each of those disciplines need to understand each other and work together efficiently. This presentation is an overview of the history and evolution of digital pathology as well as a source of background knowledge necessary for a pathologist to navigate and contribute to this rapidly evolving field.

略歴

Aleksandra Zuraw, DVM, Ph.D.

Charles River Laboratories, Veterinary Pathologist II, Digital Pathology

Education

・2003-2009 Master's degree, Veterinary Medicine, Wroclaw University of Environmental and Live Sciences, Poland
・2012-2016 Doctoral degree, Veterinary Pathology, Freie Universitaet Berlin, Germany

Professional experience

・2016-2018 Senior Pathologist, Definiens, Germany
・2018-present Veterinary Pathologist II, Charles River Laboratories, USA
・2019-present Founder and Publisher of Digital Pathology Place (www.digitalpathologyplace.com)

Memberships

・Society of Toxicologic Pathology (STP)
・American College of Veterinary Pathologists (ACVP)

Honors and Prizes

・Best Presentation Award at the Second Joint European Congress of the European Society of Veterinary Pathology, European Society of Toxicologic Pathology and the European College of Veterinary Pathologists (2014)

ES

1st JSTP-CPA-STP Joint Education Seminar
Understanding, detection, and diagnosis of background and induced lesions in toxicity and carcinogenicity studies

Chairperson：Jin Ren (Shanghai Institute of Material Medica, Chinese Academy of Science)
Min Gi (Osaka City University Graduate School of Medicine)

The Japanese Society of Toxicologic Pathology (JSTP) and the Chinese Pharmaceutical Association-Society of Toxicologic Pathology (CPA-STP) are proud to offer our first joint education seminar. This seminar brings together toxicopathology specialists from China and Japan to share their expertise in pathological examination. This seminar will cover basic and advanced toxicology topics with the aim of developing the abilities of younger pathologists in understanding, detection, and diagnosis of background and induced lesions in toxicity and carcinogenicity studies. Attendees will gain a solid understanding of induced non-proliferative and proliferative lesions of the rodent urinary bladder; proliferative lesions of the rodent endocrine system; background and non-proliferative and proliferative lesions in rasH2 mice; spermatogenesis and stages of the seminiferous epithelium cycle in rats; and the latest advances in preclinical assessment of cellular therapy products.

ES-1 Chemically induced nonproliferative and proliferative lesions in rat and mouse urinary bladder
Min Gi (Osaka City University Graduate School of Medicine)

ES-2 Nonproliferative and proliferative lesions observed in the short-term carcinogenicity studies in rasH2 mice
Hemei Wang (Jiangsu ChemPartner)

ES-3 Proliferative lesions of the rodent endocrine system
Toko Ohira (Shanghai InnoStar Bio-tech Co., Ltd)

ES-4 Spermatogenesis and testicular staging in rats
Chunyan Hu (WestChina-Frontier PharmaTech)

ES-5 Preclinical toxicologic pathology evaluation of cellular therapy products
Jianjun Lyu (Shanghai InnoStar Bio-tech Co., Ltd)

一般演題

※演題番号に＊の表記があるものは、筆頭演者が 40 歳未満の演題です。

P-01 ～ P-121

P-01＊

ラットにおける海馬神経伝達関連遺伝子のメチル化制御破綻に着目した発達神経毒性指標の探索

○高橋 康徳[1,2]、尾城 椋太[1,2]、山下 理紗子[1]、清水 沙織[1]、前田 夏乃[1]、岡野 拡[1,2]、高嶋 和巳[1,2]、唐 倩[1,2]、小澤 俊介[1,2]、吉田 敏則[1,2]、渋谷 淳[1,2]

[1]東京農工大学　獣医病理学研究室、[2]東京農工大学　大学院　共同獣医学専攻

【背景と目的】我々は発達神経毒性の不可逆影響指標を得る目的で、ラットへの発達期曝露により海馬の神経新生を不可逆的に障害するプロピルチオウラシル (PTU)、バルプロ酸 (VPA)、グリシドール (GLY) で過メチル化・発現抑制を示す多数の遺伝子を見出した。本研究では、その中で神経伝達・神経新生関連遺伝子に着目して、指標分子としての特性を解析した。【方法】PTU、VPA、GLY の各候補遺伝子について、曝露終了時の生後 21 日 (PND 21) と PND 77 における発現を qRT-PCR 解析し、不可逆的な発現抑制遺伝子を得て、メチル化特異的高解像度融解曲線法によるプロモーターメチル化解析を行った。各曝露例の候補分子について歯状回での免疫組織化学的解析 (IHC) を実施して発現変動分子を得て、ヒトに重要な発達神経毒性物質であるエタノール (EtOH)、塩化アルミニウム、酢酸鉛の発達期及び 28 日間曝露例で IHC を実施した。【結果】qRT-PCR では、PTU で 3 遺伝子、GLY で 1 遺伝子が不可逆的に発現抑制し、そのうち PND 21 で全ての遺伝子、PND 77 で PTU の 2 遺伝子の過メチル化が確認された。IHC では、GLY で見出された neurogranin (NG) の海馬歯状回腹側顆粒細胞層での不可逆的な陽性細胞数減少を認めた。NG は PTU の PND 21 でも減少し、ヒトで重要な EtOH で発達期曝露の PND 77 で陽性細胞数減少、28 日間曝露で減少傾向を認めた。二重免疫染色により、NG は成熟顆粒細胞に発現した。【考察】NG は CaMKII 経路を介したシナプス可塑性の調節に寄与する。我々は上記の PTU、GLY、EtOH の曝露例で成熟顆粒細胞のシナプス可塑性の低下を報告しており、それは NG の発現抑制に起因することが示唆された。以上より、NG 発現抑制の原因の一部に、本遺伝子のメチル化制御の破綻の関与が示唆され、NG はシナプス可塑性抑制の有効な評価指標であると考えられた。

P-02＊

アクリルアミドのラット嗅球 - 脳室下帯神経新生への影響

○小川 文一朗[1,2]、中西 豊[1]、若松 正樹[1]、高橋 康徳[2,3]、渋谷 淳[2,3]

[1]大正製薬（株）　安全性研究室、[2]東京農工大 獣医病理学研究室、[3]東京農工大 院 共同獣医学専攻

【背景及び目的】アクリルアミド（ACR）の神経毒性については軸索遠位端のシナプス障害が古くから知られており、我々も、発達期の曝露により海馬神経新生の神経突起伸展及びシナプス形成が盛んな type-3 前駆細胞～未熟顆粒細胞が傷害されることを報告した。嗅球 - 脳室下帯は、海馬と同様に生後も神経新生が継続する器官であるが、ACR による嗅球 - 脳室下帯神経新生への影響に関する報告は乏しい。本研究ではラット嗅球 - 脳室下帯の神経新生における ACR の影響について検討した。【方法】雄 SD ラットに 0, 5, 10, 20 mg/kg の ACR を 28 日間経口投与し、嗅球及び脳室下帯（n=10）の各発達段階の神経細胞マーカーについて免疫組織化学的解析を実施した。また、0 及び 20 mg/kg 群の嗅球顆粒層（n=6）について qRT-PCR により神経新生関連遺伝子の発現変動を検索した。【結果】嗅球の上衣層、顆粒層、糸球体層において、未熟ニューロンマーカーの PSA-NCAM または doublecortin（DCX）$^+$ 細胞数の減少が 10 mg/kg 群以上で認められた。その他の神経細胞マーカー（嗅球の CALB2 及び NeuN、脳室下帯の GFAP、SOX2、TBR2、PSA-NCAM、DCX）については変動が認められなかった。嗅球顆粒層の qRT-PCR ではシナプス関連マーカーの *Ncam2* 及び神経栄養因子の *Bdnf* の発現の低下が認められた。【結論】脳室下帯の PSA-NCAM 及び DCX$^+$ 細胞数に変化がなく、嗅球上衣層の PSA-NCAM 及び DCX$^+$ 細胞数が減少していたことから、ACR は脳室下帯から移動した吻側移動流～嗅球の未熟ニューロンを障害していると考えられ、その障害機序として、BDNF や NCAM2 の発現低下による神経突起伸展やシナプス形成の障害の可能性が示唆された。

P-03＊

Histopathologcial evaluation in SD rat model of optic nerve injury

○Liu Xiangjiang、Du Mu、Qi Wei、Guo Jin、Zhang Rui、Guo Hui、廣内 康彦

昭衍（蘇州）新薬研究中心有限公司

[Background] The establishment of an animal model of incomplete optic nerve injury is a prerequisite for the study of optic nerve injury. The existing models of optic nerve injury have poor repeatability due to the instability of injury degree. In this study, the model of optic nerve injury was induced by clamping the posterior optic nerve of SD rats, and histopathological evaluation was conducted. **[Materials and Methods]** Anesthetized the SD rats, cut the upper eyelid, separated the rectus muscle, fully exposed the optic nerve, removed the sheath of the optic nerve 1-3 mm behind the eyeballs, and clamped the sheath 2 mm behind the eyeballs with a vessel clip. The optic nerves and eyeballs were examined by HE stain. **[Results]** The main findings were swelling and degeneration of the optic nerve, and the arrangement of the optic nerve was disordered. Since the optic nerve is composed of axons of ganglion cells, the damage of the optic nerve will further affect the ganglion cells, which may eventually cause retinal findings. Disorder of retinal arrangement was seen in the retina, and retinal atrophy was seen in severe cases.

P-04

1 型糖尿病ラットへの軽度の高血圧負荷は表皮感覚神経密度に影響を及ぼさない

○尾崎 清和、松浦 哲郎

摂南大学　薬学部　病理学研究室

【目的】ヒトでは高血圧により、糖尿病性末梢神経症が増悪化することが示唆されている。我々はアロキサン (AL) 誘発糖尿病ラットへの高度高血圧の負荷により表皮内神経が減少することを報告した。今回、同糖尿病ラットへの長期間の軽度高血圧負荷が表皮内神経にどのような影響を及ぼすか検討した。【方法】10 週齢の雄 WBN/Kob ラットに AL を投与し早期に糖尿病を誘発させた AL 群、AL 誘発糖尿病ラットに 13 週齢から 36 週間 0.5% 食塩水を飲水投与した AN 群ならびに無処置で糖尿を自然発症させた C 群の計 3 群を設けた。49 週齢時に皮膚熱刺激試験、皮膚機械刺激試験、運動および感覚神経伝導速度測定を実施し、剖検後、足底皮膚表皮内神経を形態的に解析した。【結果】AN および AL 群の血糖・尿糖は AL 投与時から解剖時まで高値を維持し、C 群では 43 週齢以降に高血糖・尿糖が認められた。3 群の血圧はいずれも 33 週齢まで、ほぼ同程度に緩やかに上昇したが、その後ＡＮ群の血圧はさらに上昇し、49 週齢には AL および C 群（120 および 100mmHg）と比較し、有意な高値 (148 mmHg) を示した。AN 群の熱刺激による潜時は C 群より高い傾向であり、AL 群の潜時も C 群と比較し有意な高値を示したが、AN および AL 群間で差はみられなかった。機械刺激による反応閾値には、3 群間で差は認められなかった。AN および AL 群の運動および感覚神経伝導速度は、C 群と比較し低値傾向を示したが、AN および AL 群間で差は認められなかった。AN 群の表皮内神経密度は、C 群と比較し有意に低下し、AL 群でも C 群より低い傾向を示したが、AN および AL 群間で差は認められなかった。【結論】1 型糖尿病ラットへの長期間の軽度高血圧負荷は、表皮内末梢感覚神経密度には影響しないと考えられる。

P-05

ラット母体への核酸投与による免疫活性化に起因した発達神経障害に対するα-glycosyl isoquercitrin の保護効果

○高嶋 和巳[1,2]、岡野 拡[1,2]、唐 倩[1,2]、高橋 康徳[1,2]、尾城 椋太[1,2]、小澤 俊介[1,2]、小柳 美穂子[3]、吉田 敏則[1,2]、渋谷 淳[1,2]

[1]東京農工大・獣医病理学研究室、[2]東京農工大・院・共同獣医学専攻、[3]三栄源エフ・エフ・アイ株式会社

【背景】Polyinosinic-polycytidylic acid（poly (I:C)）のげっ歯類に対する妊娠期曝露は、ウイルス感染による母体免疫活性化に起因した発達神経障害モデルとして知られている。本研究では、ラット poly(I:C) 誘発母体免疫活性化モデルに対する抗酸化物質α -glycosyl isoquercitrin（AGIQ）の効果について、海馬神経新生を指標に検討した。【方法】妊娠ラットを溶媒対照群、poly(I:C) 単独群、poly(I:C)+0.25%AGIQ 群、poly(I:C)+0.5%AGIQ 群に分け、妊娠 15 日に poly(I:C) 4 mg/kg を静脈内投与した。AGIQ は妊娠 10 日から分娩後 21 日まで母動物に、以降は児動物に混餌投与した。生後 21 日（PND 21）及び PND 77 に雄児動物の海馬歯状回を対象に、顆粒細胞層下帯（SGZ）／顆粒細胞層（GCL）の顆粒細胞系譜指標及び歯状回門部の GABA 性介在ニューロン指標を免疫組織化学的に、関連遺伝子の発現を real-time RT-PCR 法により解析した。【結果】PND 21 では、溶媒対照群に比して poly(I:C) 単独群で SGZ の $TBR2^+$ 細胞数及び $PCNA^+$ 細胞数、歯状回門部の $reelin^+$ 細胞数が減少した。0.5% AGIQ 群ではこれらの変化が改善し、reelin シグナル及び Wnt/ β -catenin シグナル関連遺伝子の発現も増加した。PND 77 では、poly(I:C) による神経新生指標の変動はなかった。0.25% AGIQ 群で GCL の FOS^+ 細胞数が増加し、両 AGIQ 群で NMDA 型グルタミン酸受容体遺伝子の発現が増加した。【考察】妊娠期 poly(I:C) 投与は、幼若期の児動物に type-2b 神経前駆細胞を標的とした神経新生抑制を誘発し、reelin シグナルの低下及び神経前駆細胞の増殖抑制の関与が示唆された。AGIQ は poly (I:C) による神経新生障害を軽減し、reelin シグナルや Wnt/ β -catenin シグナルの増加による神経前駆細胞増幅の関与が示唆された。また、AGIQ による成熟後のシナプス可塑性の亢進が示唆された。

P-06＊

Role of CCDC85C, a causative protein for hydrocephalus, and intermediate filament proteins (IFs) during lateral ventricle development in rat brain

○Hasan Md. Mehedi、Konishi Shizuka、Tanaka Miyuu、Izawa Takeshi、Yamate Jyoji、Kuwamura Mitsuru

Laboratory of Veterinary Pathology, Osaka Prefecture University

Role of CCDC85C, a causative protein for hydrocephalus, and intermediate filament proteins (IFs) during lateral ventricle development in rat brainHasan MM, Konishi S, Tanaka M, Izawa T, Yamate J, and Kuwamura MLaboratory of Veterinary Pathology, Osaka Prefecture University **[Background & Aim]** Coiled-coil domain containing 85c (Ccdc85c) is a causative gene for hydrocephalus and subcortical heterotopia with frequent brain hemorrhage. A few is known on its role during brain development. Here we investigated the role of CCDC85C and IFs including nestin, vimentin, GFAP, and cytokeratin AE1/AE3 during lateral ventricle development in rats. **[Materials & Methods]** F344 wild type (WT) rats and Ccdc85c KO rats were maintained in our university, brains were collected on embryonic days 13 (E13) to E19 and postnatal days 0 (P0) to P30. Immunohistochemistry and immunoelectron microscopy were done. **[Results]** In WT rats, the expression of nestin and vimentin was decreased in the wall of the lateral ventricle in manner similar to CCDC85C, but GFAP expression started immediately after birth and became stronger with age; and had a strong relation with cytokeratin. But in KO rats, misexpression and ectopic expression of IFs was seen that indicates the ultra-expression of IFs at postnatal stages. **[Conclusion]** Expression of CCDC85C may be related to neurogenesis and ependymal cell differentiation. This CCDC85C model may be useful for evaluating the new pathway of neuronal and cell development.

P-07＊

遺伝性ミエリン変性モデル VF ラットの振戦症状への *Hcn1* 遺伝子変異の関与

○田中 美有[1,2]、磯谷 星佳[1]、小島 瑳希子[1]、井澤 武史[1]、庫本 高志[2,3]、桑村 充[1]

[1]大阪府立大学　獣医病理、[2]京都大学　医　動物実験施設、[3]東京農業大学　農　動物科学

【背景と目的】VF (vacuole formation) ラットは *Dopey1* 遺伝子のナンセンス変異を有し，生後 10 日齢前後からの振戦症状と，中枢神経系における軸索周囲の異常な空胞形成とミエリン低形成を特徴とするミエリンミュータントである．また，VF ラットは遺伝的背景として陽イオンチャネルである *Hcn1* 遺伝子のミスセンス変異を有する．この *Hcn1* 遺伝子変異は本態性振戦の原因遺伝子の 1 つとして報告されている．今回，VF ラットの振戦症状への *Hcn1* 遺伝子変異の関与を解析した．【材料と方法】VF ラットと亜系統（*Dopey1* および *Hcn1* 遺伝子が野生型で，振戦非発症）との交配で得られた F2 のうち，*Dopey1* ホモ型かつ *Hcn1* ヘテロ型または野生型の個体を選抜した．これらについて，振戦症状の観察と脊髄の病理組織学的検査（HE 染色およびエポン厚切りトルイジンブルー染色標本の観察）を行い，VF ホモ型ラットと比較した．【結果と考察】4 ～ 10 週齢の *Dopey1* ホモ型・*Hcn1* ヘテロ型または野生型ラットでは，後躯を中心としてわずかな振戦が観察されたが，その程度は同週齢の VF ホモ型ラットと比較して非常に軽度であった．これら個体の脊髄では，腹索を中心として VF ホモ型ラットと同程度の空胞形成とミエリン低形成が観察された．VF ラットの振戦症状の発症には、*Dopey1* 遺伝子のナンセンス変異だけでなく，遺伝的背景の *Hcn1* 遺伝子のミスセンス変異も関与していることが示唆され，毒性試験を含めた病態評価では，動物の遺伝的背景を考慮する必要があると考えられた．現在，VF ラットと F344 系統との戻し交配を進めており，さらなる解析を行う予定である．

P-08

マウスの脊髄における運動ニューロンの評価について

○田中 雅治、小川 靖子、本間 謙吾、副島 亜紀

田辺三菱製薬（株）

背景：脊髄における運動ニューロン (MN) の評価は、ChAT の免疫染色を行い、灰白質前角の陽性細胞をカウントすることが多い。しかし、ChAT 陽性細胞は灰白質前角以外にもみられることや形態学的に明らかな MN が陰性になることがあり、正確な評価法とは言い難い。目的：ChAT 免疫染色以外の方法で脊髄 MN の評価方法を検討する。材料と方法：ALS モデルとして汎用されている 7~21 週齢の雌雄 SOD1Tg マウスと WT マウス各 3 例の腰部脊髄を用い、以下の検討を行った。検討 1)MN の指標とされている SMI-32、Neogenin、HB-9、Islet-1 の免疫染色と Nissle 染色を行い、灰白質前角での陽性、陰性細胞の確認および灰白質以外での発現について ChAT 染色態度と比較した。検討 2) HE 染色標本を用いて灰白質前角における 25 μ m 以上の大きさのニューロン数をカウントした。結果：検討 1) 評価した全てのタンパクは灰白質前角で陽性反応を示したが、灰白質前角以外のニューロンでも陽性を示した。また、全てのタンパクは灰白質前角の一部の大型ニューロンで陰性を示した。Nissle 染色では MN が陽性となったが正常ニューロンと変性ニューロンの区別がつき難かった。検討 2) 雌雄ともに WT マウスでは評価期間を通して一定数の正常ニューロンがカウントされた。一方、Tg マウスにおける正常ニューロンは 7 週齢から有意に減少した。また、変性ニューロンを含む大型ニューロンは 21 週齢の Tg マウスで有意に減少した。結論：今回の検討から脊髄 MN の評価は HE 染色標本によるカウントが推奨される。また、正常ニューロンのみをカウントするか、あるいは変性ニューロンも含めてカウントするかについては評価する化合物の作用機序等を参考にするべきである。

P-09＊

ラットの海馬における神経突起伸展及びシナプス可塑性関連遺伝子のメチル化制御破綻に着目した発達神経毒性指標の探索

○尾城 椋太[1,2)]、高橋 康徳[1,2)]、山下 理紗子[1)]、清水 沙織[1)]、前田 夏乃[1)]、岡野 拡[1,2)]、高嶋 和巳[1,2)]、唐 倩[1,2)]、小澤 俊介[1,2)]、吉田 敏則[1,2)]、渋谷 淳[1,2)]

[1)]東京農工大学　獣医病理学研究室、[2)]東京農工大学大学院　共同獣医学専攻

【背景と目的】我々は不可逆的な発達神経毒性予測指標の同定を目的として、ラットへの発達期曝露により海馬神経新生の不可逆障害を示したプロピルチオウラシル (PTU)、バルプロ酸、グリシドールのそれぞれの発達期曝露例で、発現抑制・プロモーター過メチル化を示す多数の遺伝子を見出した。本研究では抗甲状腺剤である PTU を選択して、発達期甲状腺機能低下によりメチル化と発現の変動を示した神経突起伸展及びシナプス可塑性関連遺伝子に着目して指標分子を探索した。【方法】Methyl-Seq、RNA-Seq 解析により、PTU の発達期曝露終了時の生後 21 日 (PND 21) において過メチル化・発現抑制を示した遺伝子の中から、qRT-PCR 解析により PND 21 に引き続き PND 77 において mRNA 発現が不可逆的に低下した遺伝子を選抜し、メチル化特異的高解像度融解曲線法によりメチル化の検証解析を行った。不可逆的な過メチル化・発現抑制が確認された候補遺伝子については、免疫染色 (IHC) により海馬歯状回における発現を解析した。【結果】qRT-PCR では、PTU で 6 遺伝子が不可逆的に発現低下を示した。そのうち PND 21 で 3 遺伝子、PND 77 で 1 遺伝子の過メチル化が確認された。IHC では、PTU 発達期曝露例の歯状回顆粒細胞層において sodium voltage-gated channel beta subunit 1 (SCN1B) 陽性細胞の不可逆的な減少を認めた。【考察】SCN1B は電位依存性ナトリウムチャネルの構成蛋白であり、細胞興奮性のほか、神経突起伸展やシナプス可塑性など神経発達に関する多様なプロセスを調節する。本研究では発達期甲状腺機能低下により、成熟後にも持続した過メチル化と共に、mRNA 発現と発現細胞の不可逆的な減少が確認されたことから、SCN1B は発達神経毒性評価指標の有力な候補であると考えられた。

P-10＊

Davidson 固定・改変 Davidson 固定ラット眼球標本におけるアーティファクト所見と固定時間の関係性に関する詳細な検討

○中川 明都、松尾 沙織里、林 修次、加藤 淳彦

中外製薬株式会社　トランスレーショナルリサーチ本部

【背景･目的】眼球標本作製において STP position paper では、ブアン、Davidson 固定液（DF）、改変 Davidson 固定液（mDF）で 18 ～ 48 時間固定することを推奨している。また、mDF は精巣固定液として一般的に使用されており、眼球にも用いることで組織固定時の利便性向上が期待できる。DF や mDF を用いた眼球標本においても、一定のアーティファクト（AF）が生じることが報告されているが、AF と固定時間の関係を明確にした文献報告は限られる。そこで、ラットの眼球を用いて、DF、mDF の至適固定時間及び各眼球構成組織に対する AF 所見と固定時間との関係性を詳細に検索した。【方法】Crl:CD(SD) ラット 15 ～ 16 週齢の雄 21 例を用いて、各個体の左眼球を DF、右眼球を mDF で固定し、固定開始後 2 時間、5 時間、1 日、2 日、3 日、5 日、7 日経過後（各ポイント眼球 3 個ずつ使用）、10% 中性緩衝ホルマリン固定液で 2 日間後固定を実施した後に、常法に従い HE 染色標本を作製し、組織学的評価を行った。【結果・まとめ】ラットの眼球において、DF の最適な固定時間は 1 日であり、2 日及び 3 日間固定標本も許容範囲で形態良好であった。しかし、水晶体の割れ、水晶体の割れに伴う虹彩の角膜・水晶体への付着、視神経の空胞化といった AF は避けられなかった。mDF の最適な固定時間は 1 日であり、5 時間及び 2 日間固定標本も許容範囲であった。mDF で 5 時間～ 2 日間固定した標本では、網膜外顆粒層の核周囲の空隙や杆状体錐状体層の空胞化など一部の AF は軽減したものの、一定程度は残存し、加えて固定時間に影響されず発生する AF が、ほぼ全ての眼球構成組織において認められた。

P-11＊

染色及びバイオマーカー測定による中枢神経毒性プロファイリング及び検出感度向上についての検討

○後藤 彩[1)]、石川 玲奈[1)]、中島 康太[1)]、関 由妃[1)]、中野 健二[2)]、太田 恵津子[1)]

[1)]エーザイ（株）メディスン開発センター　BA 機能ユニット グローバル安全性研究部
[2)]株式会社サンプラネット　筑波研開支援事業部　安全性・支援ユニット

【背景・目的】中枢神経毒性の検出における適切な病理学的評価方法を模索するため，毒性標的の異なる複数の化合物を用いて，HE 染色に加え様々な染色方法およびバイオマーカーの検討を行った。【材料と方法】雄の SD ラットにクプリゾン，MK-801，トリメチルスズ，アクリルアミドをそれぞれ単回或いは短期反復投与し，神経症状が発現したタイミングで 10% 中性緩衝ホルマリン溶液で還流固定後，脳を採材した。常法に従いパラフィン切片を作製し，HE 染色に加え免疫染色（GFAP，Iba-1，MBP，リン酸化 Neurofilament heavy chain [NfH]，非リン酸化 NfH，Neurofilament light chain [NfL]，Caspase3），特殊染色（Klüver-Barrera 染色，LFB-HE 二重染色，LFB-NfL 二重染色，Fruolo-Jade C 蛍光染色）を実施した。また，剖検時に採材した脳脊髄液（CSF）及び血清中の GFAP，NfL を ELISA により測定した。【結果】いずれの化合物においても，HE 染色において脳に組織学的変化が認められた。各病変で染色法を検討した結果，病変の質にも依るが HE 染色と比べ検出感度が高い染色法の組み合わせがある一方，神経系の特殊染色として多用される染色法においても，HE 染色でみられた以上の情報が得られないものがあった。以上より，症状を呈してからのタイミングや HE 染色による組織学的特徴から，適切な評価に必要な染色の組み合わせを判断できる可能性が示唆された。今回は，臨床症状が認められた時点での各化合物の組織学的変化，組織化学的特徴，およびバイオマーカー（BM）の変化の関係について報告する。【結論】本検討結果より，ルーチンの HE 染色標本に加え，適切な染色や血清・CSF 中の BM 測定を組み合わせることで，中枢神経病変の検出感度を高め，各化合物の中枢神経への影響の特徴を明らかにすることが可能なことが示唆された。

P-12＊

パラフィン切片の 3 次元解析への応用

○岩下 直樹[1,2)]、小澤 秋沙[3)]、坂上 元栄[3)]

[1)]Bioalchemis、[2)]麻布大学　獣医学部　薬理学研究室、[3)]麻布大学　獣医学部　解剖学第二研究室

【背景】近年、共焦点レーザー顕微鏡や簡易 SEM の普及に伴い生体組織における 3 次元的解析のニーズが高まっており、病理組織学的解析において最も多く利用されるパラフィン切片を用いた 3 次元的解析が行われているが、それらの標本は薄いことから、効率的に情報を得るためには 3 次元的解析により適した「厚い組織片」の作成が必要である。従って、本研究は滑走式ミクロトームを使用してパラフィンブロックから 100 μ m 厚切片の採取法を確立し、3 次元的解析への応用について検討した。【目的】パラフィン切片の 3 次元的解析への応用【材料と方法】動物は正常な C57BL/6 wild マウスと Wistar ラットを使用し、麻酔下で安楽しした後に脳、鼻組織、蝸牛、腎臓、肺を摘出、10％中性緩衝ホルマリンにて固定した。各臓器は常法に従いパラフィン包埋し、X 液（本研究にて開発したパラフィン軟化液）を用いてＨＥ染色用切片および、低真空 SEM 用として 100 μ m 厚の切片を連続して採取した。肺では、免疫染色で HOPX の発現を共焦点レーザー顕微鏡で解析し、それぞれの組織の内腔面は低真空 SEM で解析した。【結果】共焦点レーザー顕微鏡で観察した HOPX の発現は組織表面より約 30 μ m ほどまで観察できた。低真空 SEM による観察は HE 標本と連続した脳室の線毛、鼻腔上皮、足細胞足突起、肺胞上皮、コルチ器の有毛細胞を倍率 3000 まで観察することができた。【結論】厚いパラフィン切片は病理組織学的な 3 次元的解析に有益である。

P-13＊

ラットの胎生期ないし新生児期でのlipopolysaccharide曝露によるオリゴデンドロサイト傷害性とα-glycosyl isoquercitrinの保護効果

○岡野 拡[1)]、高嶋 和巳[1,2)]、高橋 康徳[1,2)]、尾城 椋太[1,2)]、唐 倩[1,2)]、小澤 俊介[1,2)]、小柳 美穂子[3)]、吉田 敏則[1,2)]、渋谷 淳[1,2)]

[1)]東京農工大・獣医病理、[2)]東京農工大・院・共同獣医学専攻、[3)]三栄源エフ・エフ・アイ株式会社

【背景と目的】母体や新生児の感染症は脳発達に影響を与える。我々はラットへの胎生期からのα -glycosyl isoquercitrin（AGIQ）投与が、lipopolysaccharide（LPS）の胎生期ないし新生児期投与による免疫活性化を抑制し、脳発達障害を改善することを報告している。本研究ではLPSのオリゴデンドロサイト（OL）傷害性に着目し、AGIQの保護効果を検討した。【方法】LPSを妊娠15、16日のラットに50 μg/kg/day（実験1: 胎生期投与）或いは生後3日（PND 3）の児動物に1 mg/kg（実験2: 新生児期投与）、腹腔内投与した。AGIQは母動物に妊娠10日（実験1）或いは18日（実験2）から離乳時まで、続けて児動物に、0.5 %の濃度で混餌投与した。PND 6、21、77の脳梁における炎症、OL分化指標を免疫組織化学的に解析した。【結果】実験1の炎症指標は変動しなかった。OL分化指標はPND 6のLPS群で$NG2^+$細胞と$OLIG2^+$細胞が減少し、LPS+AGIQ群（AGIQ群）で回復した。PND 21のLPS群でも$NG2^+$細胞が減少、AGIQ群で回復し、更に$KLOTHO^+$細胞が増加した。PND 77は何れも変動しなかった。実験2の炎症指標はPND 6のLPS群で$Iba1^+$細胞、$CD68^+$細胞、$GFAP^+$細胞が増加し、AGIQ群で回復・回復傾向を示した。PND 21のLPS群で$Iba1^+$細胞、$CD68^+$細胞の増加が持続したが、AGIQ群で回復し、更に$CD163^+$細胞がLPS群と比較し有意に増加した。OL分化指標はPND 21のLPS群で$OLIG2^+$細胞が減少し、AGIQ群で回復した。また、LPS群で$KLOTHO^+$細胞が減少傾向を示した。PND 77のLPS群で$KLOTHO^+$細胞のみが増加した。【考察】胎生期或いは新生児期LPS投与は可逆的にOLの分化を障害し、これには一過性の神経炎症とOLの成熟に寄与するKLOTHOの減少が関与すると考えられた。胎生期からのAGIQ投与はLPSによる免疫活性化を抑制することでOLの分化障害を改善したと考えられた。

P-14＊

幼若期ラット /Crl:CD（SD）における脊髄の病理組織学的背景データ

○佐藤 弘昌[1)]、渡辺 純[1)]、畠山 洋文[1)]、黒滝 哲郎[1)]、小泉 治子[1)]、梶村 哲世[1)]、佐藤 伸一[1)]、岩田 聖[2)]

[1)]（株）イナリサーチ、[2)]株式会社ルナパス毒性病理研究所

【目的】若齢動物では器官が急速に発達するため，発達過程での正常組織の理解は毒性評価上重要である．ICH-S11 小児用医薬品開発の非臨床試験では，ラットの器官系発達での考慮事項の 1 つとして脊髄での髄鞘化の記載がある．そのため，本発表では幼若ラットを用い，各日齢の頸部，胸部及び腰部脊髄の特徴や髄鞘の変化について組織像の特徴をまとめた．【方法】Crl:CD（SD）ラット，生後 4，7，14 日齢の雄 2 匹以上を用いた．頸部，胸部，腰部の脊髄についてホルマリン固定後，椎骨とともに EDTA 脱灰液にて脱灰し，ヘマトキシリン・エオジン染色標本を作製し，病理組織学的に検討した．【結果】4 日齢から，頸部，胸部，腰部脊髄いずれにおいても脊髄中心管を取り囲む対称的な構造がみられ，白質と灰白質が区別されていた．いずれの部位においても白質ではグリア細胞，灰白質では神経細胞，グリア細胞がみられ，背角では感覚性神経細胞，腹角では運動神経細胞が分布していた．日齢が進むにつれ，白質は厚くなり，灰白質では H 形が明瞭になり細胞密度が減少していた．現在，ルクソールファストブルー染色による各日齢での髄鞘化の解析を進めており，その結果もあわせて報告する．

P-15＊

8-Methoxypsoralen のラット網膜光毒性における経時的な病理組織学的変化

○吉野 有香、池田 圭吾、森脇 さや香、岡田 久実代、栃谷 智秋、三瀬 いずる、藤井 雄太、河内 眞美、松本 泉美、
稲田 拓、千原　和弘、宮脇 出

大日本住友製薬株式会社　前臨床研究ユニット

【背景・目的】げっ歯類を用いた *in vivo* 光毒性試験では、陽性対照物質の投与により網膜変性、特に外顆粒層の萎縮が認められることが報告されているものの、その障害の進行や範囲は明らかになっていない。そこで我々は、初期の病理組織像や外顆粒層以外の網膜層における病理組織像を検討する目的で、Sprague-Dawley（以下、SD）系ラットに *in vivo* 光毒性試験の陽性対照物質として一般的に用いられる 8-Methoxypsoralen（以下、8-MOP）を単回投与した後、紫外線を照射し、網膜及び網膜以外の眼球への病理組織学的影響を経時的に評価した。
【材料と方法】6 週齢の SD 系雌性ラットに 8-MOP（10 mg/kg）又は媒体（0.5% メチルセルロース水溶液）を単回経口投与し、投与後 1 時間で紫外線（UVA: 約 10 J/cm^2）を照射した後、照射後 3、7 又は 10 日に安楽死させ、眼球の病理組織学的検査を実施した。
【結果】紫外線照射後 3 日で網膜の肥厚及び剥離、内顆粒層の変性 / 壊死及び細胞間空隙、杆体錐体層の変性などが、更に照射後 7 日及び 10 日では中心部網膜の外顆粒層の萎縮などが認められた。その他、照射後 3 日で媒体対照群ではみられない変化として、角膜上皮の変性、角膜固有層の水腫、水晶体線維の変性なども認められた。
【結論】本試験条件下では、8-MOP のラットにおける網膜光毒性として外顆粒層の萎縮が紫外線照射後 7 日以降に認められたが、網膜変性が照射後 3 日時点で既に発現していることがわかった。更に外顆粒層だけでなく、内顆粒層などにも網膜光毒性の影響が認められることがわかった。また、網膜のみならず、角膜、水晶体など眼球広範囲に病変が発現することもわかった。

P-16＊

Laser induced acute ocular hypertensive damage in cynomolgus monkey

○Guo Hui、Du Mu、Qi Wei、Guo Jin、Zhang Rui、Liu Xiangjiang、Guo Hongnian、廣内 康彦

昭衍（蘇州）新薬研究中心有限公司

[Background and Aim] Evaluation of optic axon decline and loss is key in non-human primate models of acute glaucoma that are used to define mechanisms of RGC and axonal degeneration, and potential neuroprotection. **[Materials and methods]** Experiment ocular hypertension was induced unilaterally in OD by laser photocoagulation of trabecular meshwork in 4 male cynomolgus monkeys. Intraocular pressure (IOP) measurement and automated optic nerve axon counting was conducted. The retinal ganglion cells (RGC) were ex vivo labeled with fluorescein conjugated RBPMS and counted automatically. The optic nerves were embedded in resin, and stained with toluidine blue. **[Results]** The IOP in the experimental eyes (OD) was significantly elevated (about 1.5-2.5 times over baseline) 2 weeks post model induction. The average RGC density in the experimental eyes (OD) was significantly reduced. Healthy nerves displayed regularly distributed glial cell somata across the entire cross section. The morphological changes of damaged optic nerve characterized by axonal loss/degeneration, nerve gliosis and scarring. **[Conclusion]** Acute ocular hypertensive damage characterized by progressive and subtle decline and loss of axons, which associates with increasing reactivity of glial cells and scarring of nerve areas depleted of axons. Our findings are consistent with studies in diverse experimental models of glaucoma.

P-17

マウス乳癌転移モデルにおける転移前センチネルリンパ節の腫瘍免疫応答

○柴田 雅朗[1)]、竹下 篤[2)]、白岡 千夏[1)]、廣瀬 善信[2)]、近藤 洋一[1)]

[1)]大阪医科薬科大学　医学部　解剖学教室、[2)]大阪医科薬科大学　医学部　病理学教室

【背景】癌は抗腫瘍免疫を抑制し、免疫監視機構を回避することで増殖・転移する。【目的】転移前センチネルリンパ節（SLN）と転移 SLN について、T 細胞を中心とした抗腫瘍免疫を解析した。また、免疫不全マウスを用いて、転移に対する T 細胞の影響をみた。【材料と方法】実験 1：Syngenic な系を用いて、転移性のマウス乳癌細胞（BJMC3879Luc2）を BALB/c 雌マウスに移植し、移植後の３～７週で経時的に屠殺した。病理組織学的に SLN を転移の有無によりに分類し、T 細胞とその活性化抑制に関わる分子について免疫組織染色を施し、画像解析ソフト HALO を用いて、定量的に解析した。実験 2：ヌードマウス雌（BALB/c-*nu/nu*）を用いて、同様の移植実験を行い、腫瘍の拡がりを定量的に解析した。【結果】実験 1：移植後 4 週の転移前 SLN において、非移植群と比較して、CD8 陽性 T 細胞の有意な減少が観察され、CD4/CD8 比でも CD8 陽性 T 細胞の活性は抑制されていることが示された。SLN の FOXP3 陽性細胞は、非移植群と比較して、転移前 4 週で増加が認められ、転移していない 5-6 週で有意な増加が示された。転移前 SLN に制御性 T 細胞（$FOXP3^{+}/CD4^{+}$）や免疫抑制性マクロファージ（$FOXP3^{+}/CD68^{+}$）が観察され、転移 SLN では PD-L1 陽性癌細胞が散見された。実験２：ヌードマウスに移植した群では、移植後 4 週において、免疫の正常な BALB/c マウスと比較して、リンパ節転移の有意な増加がみられた。【結論】転移性の BJMC3879Luc2 乳癌モデルにおいて、転移前より SLN での T 細胞活性は既に負に制御されており、転移に働く微小環境を整えているものと推測された。

P-18＊

Burkitt lymphoma 移植 mice に観察された類上皮細胞肉芽腫

○Zhang Rui、Du Mu、Qi Wei、Guo Jin、Guo Hui、Liu Xiangjiang、Li Zheng、廣内 康彦

昭衍（蘇州）新薬研究中心有限公司

目的 ヒトでは Burkitt lymphoma が発症すると、少数例だが類上皮細胞肉芽腫（Epithelioid cell granulomas）を併発する。我々はヒト化マウス（NPG 免疫不全マウス）に Burkitt lymphoma 株を皮下に移植した結果、脾臓、副腎、骨髄、肝臓等に類上皮肉芽腫が多発性に観察されたので報告する。　方法 ヒト化 CD34 stem cell をマウス（NOD-Cg.PrkdcSCID IL-2Rgcnull/vst）に移植 , さらに BL Raji 株を皮下に移植した。12 週後に病理解剖し、各臓器はホルマリン固定し、HE 染色および免疫組織化学的染色（CD68、CD163）などを施し病理組織学的に検討した。さらに生化学的検査およびリンパ球の分布、炎症性サイトカインを測定した。結果　類上皮細胞肉芽腫が脾臓に 7/10 例発現した。肉芽腫は脾臓、骨髄、肝臓、副腎などに観察され、類上皮細胞が融合して形成された多核巨細胞（ランゲルハンス巨細胞）が多数観察された。類上皮細胞の胞体は好酸性、泡沫状を呈し HCD68 強陽性を示した。一部の類上皮肉芽腫内に schaumann 体が観察され Sarcoidosis に見られる反応にも似る。結核に観察される類上皮細胞肉芽腫に類似するが乾酪壊死は見られない。免疫染色の結果、類上皮細胞肉芽腫はヒト由来の CD68 陽性、マウス由来の CD68 染色では陰性であった。結論　ヒト由来の組織球細胞が BL 移植により活性化され類上皮細胞肉芽腫に至ったと考えられた。

P-19＊

免疫チェックポイント阻害剤等の新規 *in vivo* 抗腫瘍評価モデル構築に向けての検討

○堀田 佳資、萩原 顕昭、杉山 大揮、河部 真弓、宮田 裕人、米良 幸典

（株）DIMS 医科学研究所

【背景及び目的】第 47 回日本毒性学会 (2020 年) にて、Tg-rasH2 マウスに ENU(N-nitroso-N-ethylurea) 及び BHT (Butylhydroxytoluene) を投与する二段階化学発がんモデルを用いたがん免疫療法の評価系において、実験開始後 5 週目から肺に腫瘍が形成されることを報告した。本研究は実験開始後 5 週目の肺腫瘍発現の再現性と肺がん患者の免疫チェックポイント阻害剤の効果予測因子 である腫瘍細胞上の PD-L1 の発現について検討した。
【方法】7 週齢の雌 Tg-rasH2 マウス 12 例に、ENU:120 mg/kg を 1 回腹腔内投与し、ENU 投与 1 週間後より BHT:400 mg/kg を 1 週間に 1 回、計 5 回強制経口投与した。実験開始後 5 週目に全例を剖検し、摘出した肺の各葉から一定部位を切り出し、常法に従って病理組織標本を作製した後、画像解析装置にて腫瘍の相対面積及び数の定量と免疫組織化学的に PD-L1 の発現について評価した。
【結果】剖検では、全例で肺腫瘍の発生が認められ、いずれも病理組織学的には細気管支肺胞上皮腺腫 であった。腫瘍発生部位は、胸膜に接するような肺野部または細気管支に接する部位に多い傾向がみられた。肺の腫瘍発生数の平均は、一個体あたり 5.50 ± 2.07 個であった。また、免疫組織化学的に腫瘍細胞に PD-L1 の発現は確認できたが、同一個体の腫瘍間での発現の有無に差異 がみられた。
【結論】本モデルは腫瘍形成と効果予測因子である PD-L1 の発現を実験開始後 5 週目で確認できたことから、免疫機構を保持した状態でがん免疫療法のみならず新規モダリティの抗がん剤の有効性を短期間で適切に評価できる *in vivo* 抗腫瘍評価モデルとなり得ることが示唆された。

P-20＊

Early diagnostic and prognostic role of micro RNAs during 2-amino-3-methylimidazo[4,5-*f*]quinoline- induced liver and colon carcinogenicity in rat

○Elham M. Yousef[1)], Mona M. Hegazi[1)], Doha M. Beltagy [2)], Elsayed I. Salim[1)]

[1)] Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)] Biochemistry Department, Faculty of Science, Damanhour University

[Background] Micro RNAs (*miRNAs*) are a new class of small non-protein-coding, regulatory RNAs in animals and plants. **[Aim]** This study evaluates the expression of *miR-21*, *miR-155*, *miR-122*, *miR-195* and *miR-17-3p* during early stages of rat colorectal (CRC) and hepatic-carcinogenesis induced by 2-amino-3-methylimidazo [4,5-*f*] quinoline (IQ), and after treatment with 5-fluorouracil (5-FU) or Thymoquinone (TQ) solely or in combination. **[Materials and Methods]** Two rat experiments: a short term (10 weeks), and a long term (40 weeks) with similar experimental design. Group1 (G1) control. G2 administered with IQ. G3 administered with IQ then treated with 5-FU. G4 were administered with IQ then treated with TQ until end. G5 were administered with IQ then treated with combination of 5-FU + TQ. **[Results]** In short-term, upregulation of oncogenic *miR-21*, *miR-155* and downregulation of *miR-122*, *miR-195* and *miR-17-3P* occurred at early stages of HCC and CRC. Combination therapy significantly modulated *miRNA* expression and antioxidative, cellular proliferation markers levels with a significant correlation ecoefficiency. In long term, 5-FU/TQ combination therapy resulted in a comprehensive modulation of numbers and distribution of preneoplastic lesions of HCC and CRC over than single treatments. **[Conclusions]** The studied *miRNAs* may have a role in prognosis of CRC and HCC. The synergistic interaction between TQ and 5-FU against carcinogenesis could be focused for cancer therapy.

P-21＊

The extract of *Houttuynia cordata hunb*. fermented leaf inhibits carcinogenesis via modulates xenobiotic-metabolizing enzymes and cell proliferation

○Chonikarn Singai[1)], Sirinya Taya[2)], Rawiwan Wongpoomchai[1)]

[1)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)] Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University

[Background] *Houttuynia cordata*, a native plant in Thailand, contains high amounts of bioflavonoids which significantly increase during fermentation. **[Aim]** This study aimed to investigate anticarcinogenicity of ethanolic extract of fermented *H. cordata* leaves (EFHC) in *in vitro* and *in vivo* models. **[Materials and Methods]** The mutagenicity and antimutagenicity of EFHC was analyzed using Ames test and rat liver micronucleus test. Moreover, the xenobiotic-metabolizing enzyme activities in murine hepatoma cells were measured. The anti-carcinogenicity of EFHC was further evaluated in rats treated by DEN and DMH injection. **[Results]** The result showed that EFHC exerted the antimutagenicity against aflatoxin B1 and MeIQ-induced mutagenesis. Moreover, EFHC showed mutagenic properties in *S. typhimurium*. However, it did not induce the formation of micronucleated hepatocytes in rats, suggesting non-clastogenicity. EFHC at 500 mg/kg bw significantly decreased phase I and increased phase II xenobiotic-metabolizing enzyme activities. Moreover, EFHC significantly reduced the number of preneoplastic lesion including glutathione *S*-transferase placental form positive foci in liver and aberrant crypt foci in colon of carcinogen-treated rats. Furthermore, EFHC significantly inhibited the expression of proliferating cell nuclear antigen in liver and colon of rats. **[Conclusion]** These findings indicated that EFHC displayed anticarcinogenic properties in both *in vitro* and *in vivo* models.

P-22＊

Cancer chemopreventive effect of hesperidin and mixed extract of sesame and orange seed on diethylnitrosamine-induced hepatocarcingenesis in rats

○Napaporn Khuanphram[1)], Sirinya Taya[2)], Prachya Kongtawelert[1)], Rawiwan Wongpoomchai[1)]

[1)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)] Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University

[Background] Plant extracts containing abundant phytochemicals and exposed greater chemopreventive effects than its single pure compounds. Hesperidin, mainly occurred in orange seed, and sesamin, a major active ingredient in sesame, possessed potent anti-cancer activities. **[Aim]** This study aimed to evaluate cancer chemopreventive effect of mixed extract of sesame and orange seed (MSO) compared with hesperidin and sesame extract (SE) on early stages of diethylnitrosamine (DEN)-induced hepatocarcinogenesis in rats. **[Materials and Methods]** Rats were intraperitoneal injection by 100 mg/kg bw of DEN for 3 times once a week. They were fed with low dose or high dose of all test compounds after the last injection for 10 weeks. Glutathione *S*-transferase placental form (GST-P) positive foci in the liver were used as the end-point marker of early phases of hepatocarcinogenesis in rats. **[Results]** MSO showed stronger inhibition of number and size of GST-P positive foci than hesperidin in DEN-initiated rats, while SE did not affect. MSO and hesperidin lessened number of cell proliferation and raised cell apoptosis in the livers. Furthermore, MSO, hesperidin and SE suppressed triglyceride content and fatty acid synthase expression in the liver. **[Conclusion]** Sesamin might promote chemopreventive effect of hesperidin in DEN-initiated hepatocarcinogenesis in rats. Their inhibitory mechanisms might involve the modulation of cellular homeostasis and hepatic lipogenesis during carcinogenesis.

P-23＊

Protective effect of color rice bran protein and hydrolysates on carcinogens induced early stage of liver and colon carcinogenesis in rats

○Aroonrat Pharapirom, Arpamas Chariyakornkul, Warunyoo Phannasorn, Kwanchanok Parseatsook, Rawiwan Wongpoomchai

Department of Biochemistry, Faculty of Medicine, Chiang Mai University

[Background] Plant proteins and hydrolysates are a source of bioactive compounds. Protein hydrolysates obtaining from color rice bran presented antioxidant activities and antimutagenicity. Among rice proteins, glutelin is a promising bran protein. **[Aim]** This study aimed to examine cancer chemopreventive effects of color rice bran hydrolysates in rats. **[Materials and Methods]** Glutelin (Glu) and various hydrolysates including glutelin hydrolysate (GH), all protein hydrolysate (AH), and non-glutelin hydrolysate (NGH) at the dose of 500 mg/kg bw were orally administrated for 10 weeks in diethylnitrosamine- and 1,2-dimethylhydrazine-initiated rats. The endpoint markers were hepatic GST-P positive foci and colonic aberrant crypt foci (ACF). Cell proliferation and apoptotic status in liver and colon were analyzed by immunohistochemistry, while inflammatory expression was detected using Real-time PCR. **[Results]** The treatment of Glu and GH reduced the formation of hepatic GST-P positive foci and ACF and decreased number of PCNA positive cells, a cell proliferation marker, in liver and colon tissues of carcinogens-initiated rats. Moreover, GH increased number of apoptotic hepatocytes and colonocytes and reduced some inflammatory gene expression in liver and colon tissues. However, the administration of AGH and NGH did not show any protective effect on carcinogen-induced preneoplastic lesions. **[Conclusion]** GH might be a source of cancer chemopreventive peptides of color rice bran.

P-24＊

Chemopreventive effects of cooked glutinous purple rice on the early stages of rat hepatocarcinogenesis

○Huina Guo, Arpamas Chariyakornkul, Warunyoo Phannasorn, Rawiwan Wongpoomchai

Department of Biochemistry, Faculty of Medicine, Chiang Mai University

[Background] Cooking process can alter chemical composition in plants. Our previous study showed heat could destroy some beneficial phytochemicals in purple glutinous rice but its biological functions using *in vitro* assays have still remained. **[Aim]** Here, we aimed to evaluate chemopreventive effects of methanol extract of purple glutinous rice (MR) and cooked rice (MC) in diethylnitrosamine (DEN)-induced early stages of hepatocarcinogenesis in rats. **[Materials and Methods]** Fifteen-week administration of MR and MC was started before triple DEN injection for 2 weeks. **[Results]** The results showed that MR and MC did not induce hepatic glutathione *S*-transferase placental form (GST-P) positive foci formation in rat hepatocarcinogenesis. MR and MC at 100 and 500 mg/kg bw significantly reduced the number and size of GST-P. There was no difference in inhibitory activity between MR and MC. In addition, MR and MC inhibited number of PCNA positive hepatocytes but enhanced number of apoptotic positive hepatocytes in DEN-initiated rats. MR and MC decreased iNOS gene expression level by RT-PCR analysis. **[Conclusion]** The heat stable anticarcinogens in purple glutinous rice might prevent the early stage of rat hepatocarcinogenesis through suppression of cell proliferation, enhancement of apoptosis, and decreased of NO production.

P-25＊

Chronic toxicity of calcium disodium EDTA on pregnant rats and fetuses

○Mona E. El-Maghawry, Fouad A. Abou-Zaid, Sabry A. El-Naggar, Elsayed I. Salim

Zoology Department, Faculty of Science, Tanta University

[Background] Calcium disodium ethylene diamine tetra acetic acid ($CaNa_2EDTA$) is regarded as one of the most common food additives. **[Aim]** Here we determine the possible effects of CaNa2EDTA on rats and their offspring upon chronic oral administration taking in consideration embryological, histopathological, biochemical and molecular developmental changes. **[Materials and Methods]** Rats were divided into four groups. Group 1: Control males. Group 2: Males administrated with 0.5 g/kg of $CaNa_2EDTA$ for 3 months. Group 3: Control females. Group 4: Females administrated with 0.5 g/kg CaNa2EDTA for 3 months. **[Results]** treated female rats showed a decrease in body weights, pregnancy percentage and number of pups in treated dams. Remarkable changes were recorded in foetus's livers and kidneys as well as histopathological alterations in liver, kidney and ovary of treated female rats. Moreover, mild deformation in skeletal system of fetuses from dams maternally treated with $CaNa_2EDTA$ including delayed ossification of inter-parietal, squamosal, humerus, radio-ulna, femur and tibia-fibula. Significant decrease in Zinc ion concentration in fetuses' tissues from dams maternally treated with $CaNa_2EDTA$. Down expression of peroxisome proliferator-activated receptor alpha and gamma genes (PPAR- α and PPAR-γ) in fetus's tissues. No changes in hematological parameters except increasing platelets count in treated male rats, increasing in W.B.Cs counts in treated female rats. Significant increase in luteinizing hormone level in treated female rats and superoxide dismutase level in treated male and female rats. **[Conclusions]** $CaNa_2EDTA$ is probably has toxic effects during pregnancy and on offspring.

P-26＊

8-Hydroxydeoxyguanosine levels and histopathological evaluation during placental transfer of zinc oxide nanoparticles in pregnant rats

○Naira M. Al-Fiky, Fouad A. Abou-Zaid, Khalid Y. Abdul-Halim, Elsayed I. Salim

Zoology Department, Faculty of Science, Tanta University

[Background] In recent years, ZnO-NPs are frequently used in several areas of technology as well as going interest in drug delivery applications. **[Aim]** The present study assesses the toxic effect of ZnO-NPs in pregnant rats at day 19th of gestation. Samples of target organs (serum, liver, spleen, fetus and placenta) are used for quantitative determination of 8-OHdG levels of genotoxicity. Trace metal accumulation levels were analyzed by (ICP-OS). Moreover, histopathological and TEM investigations were assessed. **[Materials and Methods]** ZnO-NPs were prepared through the hydrolysis and condensation of zinc acetate dihydrate by potassium hydroxide in alcoholic medium at low temperature, they were spherical at size 20 ± 5 nm. At the 19th day of gestation, female rats were intravenously administered by 3.1 and 7.75 mg/kg/b.wt of ZnO-NPs and sacrificed after 1, 6, 12 and 24 hrs. **[Results]** The two doses recorded significant high levels of 8-OHdG in fetuses and placenta as compared with controls. The blood showed highest accumulation level after one hour interval at the first dose while after 12 hours liver and uterus show high metal levels for the same dose. After 6 hours the second dose ZnO-NPs mainly accumulated in uterus. Prominent pathological changes are recorded in mothers and fetuses. **[Conclusions]** ZnO-NPs are toxic with evidence with genotoxicity in pregnant rats and fetuses. Greater attention needs to be paid to the toxic effects of ZnO-NPs and exposure to ZnO should be reduced.

P-27＊

Tissue distribution, placental transfer and excretion of silver nanoparticles in pregnant rats after a single oral dose

○Ahmed S. Abdel-Latif[2)], Khaled Y. Abdel-Halim[2)], Elsayed I. Salim[1)]

[1)] Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)] Mammalian & Aquatic Toxicology department, Central Agricultural Pesticides Laboratory (CAPL).

[Background] Silver nanoparticles (AgNPs) are used as antimicrobial coatings in medical devices and in many medical applications. **[Aim]** A quantitative assessment of silver nanoparticles in fluids and some organs of pregnant rats as well as their fetal blood was carried out in this study. **[Materials and Methods]** A single oral dose (1 mg kg^{-1}) of AgNPs with a size range (4-20 nm) was administered to pregnant rats on 19th of gestation. Five groups were euthanized after 10 min, 1, 6, 12 and 24 h as well as the control group. Silver (Ag^{+}) content was measured in Inductive Coupled Plasma Optical Emission Spectroscopy (ICP-OES). **[Results]** In maternal blood, AgNPs were found increased time dependently after 12 and 24 h into 0.135 and 0.224 µg ml^{-1}, but it was slightly high in fetal blood (0.32 and 0.31 µg ml^{-1}) after 10 min and 1 h. In other samples, the data indicated that NPs were rapidly absorbed from the dosing site (gastrointestinal tract) as evidenced by the detection of Ag^{+} in the analyzed samples. On the other hand, the percentages of urine excretion levels per applied dose at all the time points were higher in urine (8.25%) than those of the feces (4.77%) after 24 h. **[Conclusions]** These findings indicate the ability of AgNPs to accumulate in pregnant rats and transfer to their fetus imposing adverse outcomes and male formation. In fact, further investigations may be done on nanomaterials before recommending for human practices.

P-28

F344 ラットを用いたナノサイズ酸化チタン (IV) の 28 日間反復経口投与毒性試験

○赤木 純一、水田 保子、赤根 弘敏、豊田 武士、小川 久美子

国立衛研　病理

【背景】酸化チタン (IV)（TiO_2）は各国において食品添加物として認可されているが、ナノサイズ粒子（一辺が 100nm 以下）が含まれるものがあることから安全性に関する根強い懸念がある。これまでに我々はナノサイズ銀粒子の毒性が粒子径によって大きく異なり、直径 10nm の銀粒子の腹腔内投与では全例が 24 時間以内に死亡または瀕死状態に陥る重篤な毒性を示すことを見出していることから、本研究では結晶子径が極めて小さい 6 nm の TiO_2 の反復経口投与毒性について検討した。
【目的】結晶子径 6nm の TiO_2 をラットに 28 日間反復経口投与し、生体への影響を明らかにする。
【材料と方法】結晶子径 6 nm のアナターゼ型 TiO_2（テイカ株式会社、AMT-100）を 0.2% リン酸水素二ナトリウムに懸濁して投与液（50 パーセンタイル液中粒子径約 200nm）を調製し、6 週齢の F344/DuCrj ラット雌雄に 0、10、100、および 1000 mg/kg bw/day の用量で 28 日間強制経口投与を行った。
【結果】投与期間中全ての群で死亡はみられず、体重、一般状態、血液学的検査、臓器重量、および病理組織学的検査に毒性学的に有意な変化は見られなかった。血液生化学的検査では、雌の 1000mg/kg bw/day 群でトリグリセリド (TG) の有意な増加が見られた。肝臓中のチタン濃度測定では、全群で微量のチタンが検出され、雌の 1000 mg/kg bw/day 群ではきわめて微量（最終週の 1 日あたり平均投与量の 0.41ppm に相当）ではあるものの対照群と比較して統計学的に有意な高値を示した。
【結論】雌の 1000mg/kg bw/day 群で見られた TG の有意な増加の他に、投与に関連する可能性のある変化は認められなかったことから、本試験における NOAEL は 1000 mg/kg bw/day と結論した。

P-29＊

Safety assessment of red yeast (*Sporidiobolus pararoseus*) powder : acute and subchronic toxicity studies in Wistar rats

○Sirinya Taya[1)], Charatda Punvittayagul[2)], Thanongsak Chaiyaso[3)], Rawiwan Wongpoomchai[1,4)]

[1)] Functional Food Research Unit, Science and Technology Research Institute
[2)] Research Affairs, Faculty of Veterinary Medicine
[3)] Division of Biotechnology, Faculty of Agro-Industry
[4)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University

[Background] Oleaginous red yeasts were enriched in lipids for biodiesel production, antioxidant bioactive compounds such as carotenoids, and ß-glucan. Recently, there are increasing about lipids and carotenoids production using several types of oleaginous red yeast especially *Sporidiobolus pararoseus*. Our previous study reported about its antigenotoxicity using rat liver micronucleus test. However, there was no any studies on its systemic toxicity. **[Aim]** Thus, the scientific data of its safety were performed using acute oral and sub-chronic oral administration in rats. **[Materials and Methods]** RYP was prepared by spray drying. A single dose of 5,000 mg/kg bw of RYP was tested for acute toxicity while the repeated dose 90-day oral toxicity of 200, 600 and 2,000 mg/kg bw was performed. **[Results]** In the acute toxicity study, RYP did not show any signs of toxicity or mortality during the 14-day observation period. In subchronic toxicity test, no mortality or clinical signs of treatment was observed throughout the experimental period. RYP did not change in hematological and biochemical parameters of both sexes. Some histopathological changes in liver and epididymis were observed in high dose of RYP treatment. **[Conclusion]** Based on these results, the values of LD50 and NOAEL of RYP was estimated to be 5,000 and more than or equal to 2,000 mg/kg/day in rats, respectively.

P-30＊

Acute and subchronic toxicity of isomaltooligosaccharide and its effect of gut microbiota

○Arpamas Chariyakornkul[1)], Charatda Punvittayagul[2)], Sirinya Taya[3)], Atigan Thongtharb[4)], Santad Wichienchot[5)], Rawiwan Wongpoomchai[1)]

[1)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)] Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University
[3)] Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University
[4)] Department of Companion Animal, Faculty of Veterinary Medicine, Chiang Mai University
[5)] Center of Excellence in Functional Foods and Gastronomy, Faculty of Agro-Industry, Prince of Songkla University

[Background] Isomaltooligosaccharide (IMO) is one of prebiotic substances isolated from rice starch. It is considered as a potential prebiotic ingredient for dairy and medical food. **[Aim]** The present study determined acute and subchronic toxicity of IMO from rice starch. Furthermore, the gut microbiota profiles and short chain fatty acids (SCFAs) contents were investigated. **[Materials and Methods]** An orally single dosage of 5,000 mg/kg bw of IMO was given to female Wistar rats in an acute toxicity model. For subchronic toxicity test, the effect of daily oral administration of IMO at the dosages of 200, 600 and 2000 mg/kg bw for 90 days were evaluated. The blood biochemical and hematological parameters as well as histopathology of internal organs, gut microbial community and SCFAs contents were examined. **[Results]** IMO at a single high dose was safe in rat without any toxicity. The 90 days-treated with IMO did not induce mortality. Although, some haematological and biochemical parameters were different from those of control rats, these values also exist in normal range. Abnormal histopathology of various organs was not prominently observed. Moreover, the 600 mg/kg bw of IMO was modulated beneficial and pathogenic gut microbiota. SCFAs in feces of medium dose treated rats, particularly butyric acid was higher than normal rats. **[Conclusion]** IMO from rice starch was safety for acute and subchronic administration. It might be an effective prebiotic for food supplement.

P-31

Pathological changes of spontaneous tumors in Sprague-Dawley and Wistar rats

○Yanan He, Du Mu, Beibei Wang, Jun Yin, Wenyu Wu, Rui Zhang, Sucai Zhang, Huiming Zhang

JOINN LABORATORIES (Beijing) Inc.

[Background and Aim] To investigate the spontaneous neoplastic lesions and their incidences in SD and Wistar rats, and to accumulate background data for carcinogenicity studies. **[Materials and Methods]** Total 411 rats (176 SD and 235 Wistar) were used in this study. The rats were housed routinely and euthanized after 104 weeks. Histopathological examination was undertaken for all animals to evaluate the incidences of spontaneous tumors. **[Results]** The total tumor incidence in SD rats was 55.7% (benign 48.9%, malignant 15.9%). The total tumor incidence in Wistar rats was 59.1% (benign 51.5%, malignant 14.5%). The main benign tumors were pituitary adenoma (23.3% in SD, 12.3% in Wistar), breast fibroadenoma (21.4% in SD, 12.9% in Wistar) and breast adenoma (16.9% in SD, 9.5% in Wistar) in females; testis Leydig cell tumor (14.3% in Wistar) in males. The main malignant tumors were breast carcinoma (10.1% in SD, 3.5% in Wistar) and uterine leiomyosarcoma (2.6% in Wistar) in females; squamous cell carcinoma of skin (2.3% in SD, 0.9% in Wistar); subcutaneous fibrosarcoma (1.1% in SD, 2.1% in Wistar). **[Conclusion]** In this study, the incidence of benign tumors is higher than that of malignant rumors. The benign tumors mainly are pituitary adenoma, breast fibroadenoma and breast adenoma in females, and testis Leydig cell tumor. The malignant tumors mainly are breast carcinoma in females and some soft tissue sarcomas.

P-32＊

伝播性 AA アミロイドーシスにおけるアミロイド沈着初発部位の探索

○岩出 進、村上 智亮

東京農工大学　農学府　共同獣医学専攻

【目的】マウスに対しマウスの AA アミロイドを静脈内、腹腔内ないし経口投与することによって、AA アミロイドーシスの病態形成が促進されることが知られている。しかし、その病態の移行原理は正確に理解されていない。そこで、マウスに対して AA アミロイドを様々な経路・部位に投与し、アミロイド沈着の分布を経時的に評価した。【方法】６週齢の ICR マウスに対し、マウス AA フィブリル 30 μ g を肝臓内、脾臓内、腎臓内、胃壁、パイエル板内、静脈内、腹腔内もしくは皮下に単回投与し（各群 n=9）、同時に硝酸銀 10mg を皮下投与した。それぞれ 4, 7, 14 日後に各群 3 匹を剖検し、全身臓器を採材後、アミロイドの沈着の程度および分布を病理組織学的に評価した。【結果】肝臓、脾臓および腎臓内投与群では、4 日後から投与した局所にアミロイド沈着を認め、経時的に他臓器へと病態が顕著に広がった。胃壁投与群およびパイエル板内投与群では、4 日後から投与部位近位に沈着がみられたものの、以降の全身以降はあまりみられなかった。静脈内、腹腔内および皮下投与群ではいずれの時期においてもアミロイド沈着はほとんどみられなかった。【考察】局所臓器における AA アミロイドの沈着には、高濃度の AA アミロイドの曝露が重要であることが示唆された。また、静脈内投与群で全身臓器へのアミロイドの沈着がみられなかった点から、投与臓器以外へ沈着したアミロイドが投与した AA フィブリルに直接由来する可能性は低いと考えられる。本研究より、AA アミロイドが他臓器へと移行する際、血中に低濃度で分布するよりもむしろ、アミロイドがいずれかの臓器内で増幅され、一定の濃度に達する点が重要であると考えられる。

P-33

マウス腹腔内投与におけるポリビニルピロリドンでコートされた銀ナノ球と銀ナノプレートの急性毒性の差異

○水田 保子、Cho Young-Man、赤木 純一、井手 鉄哉、小川 久美子

国立医薬品食品衛生研究所　病理部

【背景と目的】我々は、クエン酸塩コート銀ナノ粒子のマウス腹腔内投与において、直径 10 nm の銀ナノ球は、60 及び 100 nm の銀ナノ球より毒性が強いことを報告した。本研究では、表面修飾の影響を見るため、ポリビニルピロリドン（PVP）コート銀ナノ球について、その毒性の差異を検討した。また、同じ PVP コートで形状の異なる銀ナノプレートについても同様に調べた。【方法】7 週齢の雌性 BALB/c マウスに（実験 1）直径 5、10、60、100 nm の PVP コート銀ナノ球を、（実験 2）約 10 nm 厚で長径 30、50、100 nm の PVP コート銀ナノプレートを、0.2 mg/ 匹の用量で単回腹腔内投与した。投与 1、3、6 時間後に一般状態の観察及び体温を測定した。投与 6 時間後に深麻酔下で採血・解剖し、血清生化学的検査及び病理組織学的検査を実施した。【結果】（実験 1）5 nm 投与群のみで、投与後 3 時間より活動低下、呼吸促拍及び体温の低下がみられた。さらに、尿素窒素、クレアチニン、無機リン、乳酸脱水素酵素、総ビリルビンの増加及び、クロール、グルコースの減少、肝臓のうっ血、類洞内細胞数増加、肝細胞の空胞化、胆嚢の浮腫及び胸腺皮質のアポトーシスが認められた。（実験 2）一般状態の異常はみられず、体温変化は対照群に比して軽微であった。100 nm 群でクロールの増加が、30 及び 100 nm 群で総コレステロールの低下が、50 nm 群でトリグリセリドの低下が認められた。肝臓に明らかな所見はみられなかったが、全投与群で腸間膜の血管周囲への好中球浸潤を伴う血管炎が認められた。【結論】ナノ銀は粒子のサイズや形状により組織への毒性に差が認められた。PVP コート銀ナノ球投与群でも先の研究のクエン酸塩コート銀ナノ球投与群と同様の肝毒性が認められたが、より小型粒子の投与群においてのみ観察された。

P-34＊

Incidence and types of spontaneous tumors in young Sprague-Dawley rats in 4-week toxicity studies

○Hou Minbo, Jianjun Lyu, Yan Jianyan, Cui Tiantian, Qian Zhuang, Wang Xijie, Toko Ohira

Shanghai Innostar Bio-tech Co., Ltd (Innostar)

[Background and Objective] Neoplastic lesions are less reported in young Sprague-Dawley rats in short-term toxicity studies. Incidence and types of spontaneous tumors in young Sprague-Dawley rats in 4-week toxicity studies can be extremely helpful to interpret data from short-term toxicity studies. **[Materials and Methods]** Spontaneous neoplastic lesion data from 76 4-week toxicity studies of Innostar in the past 5 years were collected and a total of 5632 rats were examined microscopically. The age of the animals at necropsy ranged from 12 to 20 weeks. All studies were performed according to Good Laboratory Practice. **[Results and Conclusion]** Spontaneous tumors were diagnosed in 9 animals from both control and treated animals in 9 different studies, including 2 cases (2/2816, 0.071%) of renal adenoma in males; 3 cases (3/2816, 0.107%) of nephroblastoma in females; 1 case (1/2816, 0.036%) of renal carcinoma in male and female respectively; and 2 cases (2/2816, 0.071%) of lymphoma in males. In the treated animals, the above-mentioned lesions were also considered spontaneous because of the low incidence and no dose-response relationship. The survey shows the incidence and type of early spontaneous tumors in young Sprague-Dawley rats (≤ 20 weeks) from studies performed in our facility, and can be used as useful background data for diagnosing spontaneous tumors in young Sprague-Dawley rats in short-term toxicity studies in the future.

P-35

Differentially expressed genes induced by metformin and *d*-limonene as potential effective anticancer agents for HepG2 and MCF-7 cells

○Elsayed I. Salim[1)], Mona M. Alabasy[1)], Doha M. Beltagy[2)], Zihu Guo[3)], Mohamed Shahen[1)]

[1)] Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)] Biochemistry Department, Faculty of Science, Damanhour University
[3)] College of Life Science, Center of Bioinformatics, Northwest A & F University

[Background] Recently, exploring strategies of biological mechanisms of many anticancer agents is progressing. **[Aim]** We evaluated the utility of metformin, a therapy for type II diabetes, and *d*-limonene, from citrus oils, for possible therapeutic potential either solely or in combination against HepG2 and MCF-7 cancer cells. **[Materials and Methods]** A systems-based analysis was applied for drug-target-pathway network using integrated systems pharmacology approach. This illustrates molecular correlations between metformin and *d*-limonene to identify genes associated with both drugs. **[Results]** DNA fragmentation assay clearly showed apoptosis induction after treatment especially with combination therapy vs. normal cells. mRNA expressions of *Bax* and *P53* were significantly up-regulated while *Bcl-2*, *iNOS* and *Cox-2* genes were significantly down-regulated in all treated groups vs. normal cells. The percentages of late apoptotic cells in HepG2 and MCF-7 cell lines were higher in all treatment groups particularly after combination treatment. The combination index (CI) revealed synergistic effect of both drugs on HepG2 cells (CI=0.12) and MCF-7 cells (CI=0.22). **[Conclusions]** Metformin, *d*-limonene and their combination exerted significant anticancer potential on HepG2 and MCF-7 cells, with synergistic potency via apoptosis induction and modulation of gene expression of target genes.

P-36

New biomarkers of drug-induced liver and heart injury in preclinical studies

○Zhou Fei, Zhao Xixing, Zhou Tiansheng

WuXi AppTec (Suzhou) Co., Ltd.

Hepatotoxicity and cardiac toxicity are the major causes for the drug discontinuation. Biomarker changes prior to the histopathology, which makes the biomarker as a forerunner in the toxicity. Traditional biomarkers had been used in toxicological studies for decades, while limitations of sensitivity, specificity and accuracy in clinical translation have been noted. For the reasons above, new biomarkers were discovered. During acute and chronic hepatocellular injury, Cytokeratin-18 (CK18, a type-I intermediate filament protein) and ccCK18 (caspase-cleaved CK18) were considered as the sensitive and clinically translational biomarkers of hepatocellular necrosis and apoptosis, and have received the letters of support from the FDA as well as EMA. Natriuretic peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), have been identified as predictors of drug-induced cardiac injury, such as hypertrophy or necrosis of the cardiomyocyte. In this presentation, we give a brief introduction of the new biomarkers of hepatotoxicity and cardiac toxicity. Combining the new biomarkers with the traditional ones, more accurate toxicity could be identified in the preclinical studies.

P-37＊

LNA 修飾アンチセンスオリゴヌクレオチド検出における TUNEL 染色の有用性

○見鳥 光、梶川 悟、高橋 美和、小野 美穂子

アステラス製薬（株） 安全性研究所

【目的】非臨床試験において，核酸医薬品の高曝露時にしばしば認められる所見として腎臓や肝臓における細胞質内の好塩基性顆粒があり，核酸医薬品が蓄積したものであることが示唆されている。また，細胞質内顆粒は両染性ないし好酸性を示すことがある。しかし，好塩基性顆粒が核酸医薬品の蓄積であることを病理組織学的に証明する方法としては，非市販抗体での免疫組織化学的手法を用いた報告があるのみである。核酸医薬品の 1 つである LNA 修飾アンチセンスオリゴヌクレオチド（以下 ASO）の基本構造は一本鎖 DNA であることから，TUNEL 染色が LNA 修飾 ASO の蓄積の証明に応用できる可能性を考え，その有用性を検討した。【材料及び方法】Neuro2a 細胞にビオチン標識 LNA 修飾 ASO を 20 μ M で 24 時間曝露し，FITC 標識 TUNEL 染色及び Alexa647 標識ストレプトアビジンによる蛍光染色を施した。また，LNA 修飾 ASO の ICR マウス単回静脈内投与試験において，近位尿細管の好塩基性顆粒が認められた腎臓のホルマリン固定パラフィンブロックを用いて TUNEL 染色を実施した。【結果】Neuro2a 細胞にビオチン標識 LNA 修飾 ASO を 20 μ M で曝露したところ，TUNEL 染色は細胞がび慢性に陽性を示し，Alexa647 の蛍光部位と一致した。また，マウス近位尿細管の好塩基性顆粒は TUNEL 染色陽性だった。【結論】TUNEL 染色は LNA 修飾 ASO を検出し，LNA 修飾 ASO 蓄積の証明に有用であることが示された。

P-38

SD ラットとビーグル犬の臨床病理参照データベースの構築について

○孔 慶喜[1)]、金 美蘭[2)]、邱爽[3)]、陈珂[3)]、乔俊文[4)]

[1)]Pharmaron, [2)]Laboratory Animal Center, Southwest University, [3)]WestChina-Frontier Pharma Tech Co., Ltd
[4)]Insilico Medicine

背景 : 血液の臨床病理学（血液学、臨床化学および凝固）は薬物毒性を予測する敏感な指標の一つであり、分析値の変化はいくつかの生物学的または毒性学的意義を反映する可能性があり、特に、時には病理組織学的潜在ターゲット臓器を示唆する。しかしながら、これらの臨床病理パラメータは、動物間の個体差または検出方法の違いのため実験室の間でかなり異なる結果が出る可能性がある。そのため、プレ臨床センターで歴代の対照群に対して独自の一貫した参照データベースを構築する必要がある。目的 : 康龍化成においての SD ラットとビーグル犬の臨床病理参照値の範囲を構築する方法を紹介する。材料と方法 : Vital River Laboratory Animal Technology からの 370 匹 SD ラット（雄 190 匹、雌 180 匹）と Marshall Biotechnology からの 240 頭ビーグル犬（雄 120 頭、雌 120 頭）の近 3 年間の対照群臨床病理データを解析した。SD ラットとビーグル犬の平均年齢は、それぞれ 10 ~ 12 週と 7 ~ 9 カ月である。結果 : SD ラットの歴代臨床病理データは、報告された背景データベース (Bruce D. Car, 2006, The Laboratory rat) と類似し、臨床病理指標の参照範囲にあることが示唆された。これらの結果は本社の臨床病理データが信頼性があることを示している。結論 : 康龍化成において臨床病理参照データベースを構築することが可能である。関鍵詞 : 参照範囲 , 確立 , 臨床病理。

P-39

INHAND: International harmonization of nomenclature and diagnostic criteria for lesions - An Update - 2022

○林 新茂[1)]、Keenan CM[2)]、Bradley A[3)]、Goodman DG[4)]、原田 孝則[5)]、Herbert R[6)]、岩田 聖[7)]、Jacobsen M[8)]、Kellner R[9)]、Mahler B[6)]、Meseck E[10)]、Nolte T[11)]、Rittinghausen S[9)]、Vahle J[12)]、義澤 克彦[13)]

[1)]国立医薬品食品衛生研究所、[2)]CM Keenan ToxPath Consulting、[3)]Charles River、[4)]Independent Consultant、[5)]残留農薬研究所
[6)]National Institute of Environmental Health Sciences、[7)]ルナパス毒性病理研究所、[8)]Astra Zeneca、[9)]Fraunhofer ITEM、[10)]Novartis
[11)]Boehringer Ingelheim、[12)]Eli Lily、[13)]武庫川女子大学

The INHAND Proposal in has been operational since 2005. A Global Editorial Steering Committee (GESC) helps coordinate overall objectives of the project. Development of harmonized terminology for each rodent organ system or non-rodent species is the responsibility of the Organ Working Groups or Non-rodent Working Groups respectively, drawing upon experts from North America, Europe and Japan.Great progress has been made with 15 rodent organ systems published in Toxicologic Pathology and Journal of Toxicologic Pathology as supplements and on a web site. A comprehensive review of all rodent systems to standardize terminology common to organ systems was completed and terminology updated in goRENI. Recommendations of the Apoptosis/Necrosis Working Group have been published. There are 5 non-rodent working groups. The mini-pig, dog, non-human primate and rabbit have been published in 2021. The manuscript on fish will be available for review in 2021. A new group has been formed to address terminology in non-rodent ocular toxicity studies. INHAND guides offer terminology, diagnostic criteria, differential diagnoses and guidelines for recording lesions in toxicity and carcinogenicity studies. The guides provide representative photo-micrographs of morphologic changes, information regarding pathogenesis, and key references.

P-40

試験施設と SEND 作成者が異なる場合における病理組織所見の SEND 化の課題と対策

○飯高 健[1,6)]、石本 明宏[1,6)]、堀川 真一[2,6)]、飯野 好美[2,6)]、佐藤 伸一[2,6)]、中江 大[3,6)]、岩田 聖[4,6)]、安齋 享征[5,6)]

[1)]日精バイリス（株）、[2)]（株）イナリサーチ、[3)]東京農業大学、[4)]ルナパス毒性病理研究所、[5)]昭和大学 医学部、[6)]G-SEND

米国 FDA による SEND データ提出の義務化以降，様々な施設で SEND データの作成が行われてきた．その中には，試験施設と SEND データ作成施設が異なるケースも多数存在し，数値データと共に病理組織所見などの所見（文字）データにおいてもそれは例外ではない．病理組織所見の SEND データ作成では，腫瘍・非腫瘍性所見を含めて基礎所見（Base Pathological process）を Controlled Terminology に集録された統制用語へマッピングする必要がある。加えて，拡張用語（Controlled Terminology に集録されていない用語）を用いた場合は，nSDRG でその用語の説明を記す必要があり，施設ごとにマッピングや拡張用語の説明文について異なる見解が生じる可能性がある．これらを関係者で調整し SEND データを最終化させることが重要な工程となり，いかに効率的に調整するかは SEND の課題と言える．このような状況から，我々が参加する G-SEND（Global SEND Alliance）※1 では，日精バイリス株式会社と株式会社イナリサーチの SEND データ作成シナリオを一つのケーススタディとして，CRO が受託した試験の病理組織所見を別の施設で SEND データを作成する際の課題を検討した．本発表では，検討に用いた基本フローとその課題に加え，最適化を意識し効率的に病理組織所見の SEND データ作成を行う方法について検討した結果を報告する．※ 1：G-SEND（Global SEND Alliance）とは，適正な SEND データ作成とその効率化を目指す非営利団体（現在 6 カ国 23 団体が加盟）であり，定期的に会合を開き，様々なテーマについて共有及び検討を行っている．

P-41＊

Comparative anatomy and histology of lacrimal gland in rat, rabbit, dog and monkey

○Qiu Shuang[1)], Chen Ke[1)], Hu Chunyan[1)], Wang Haoan[1)], Kong Qingxi[2)]

[1)]WestChina-Frontier PharmaTech, [2)]Pharmaron

[Background] The lacrimal gland is an exocrine gland. It plays such an essential role in secreting tear fluid. Therefore, histopathologic evaluation of lacrimal gland should be perform for some drugs with ocular administration or eye toxicity. **[Aim]** In this article, we attempted to describe the general anatomy and morphology features of lacrimal gland in rats, rabbits, dogs and monkeys. **[Materials and Methods]** Ten animals (five per sex) of each species were euthanized. All the lacrimal glands were macroscopically observed, collected and fixed in 10% NBF followed by HE staining and microscopic examination. **[Results]** By gross inspection, there are two pairs of lacrimal glands in the rats and rabbits. They are extraorbital and intraorbital lacrimal glands in rat, which are the counterparts of the orbital superior gland and inferior gland in the rabbits. In dogs and monkeys there is only one main gland, located at the supraorbital of lacrimal fossa.By microscopic examination, the lacrimal gland is organized according to the tubuloalveolar scheme. The predominant cell type comprising lacrimal gland acini is generally thought to be of the serous variety. However, different number of mucous cells are present within some acini as well in rat, rabbit, and monkey. The lacrimal gland in dog is mainly composed of mucous cells. **[Conclusion]** There are some different anatomical and histological characteristics among laboratory animals, such as rats, rabbits, dogs and monkeys.

P-42

SEND を意識した病理組織所見辞書の最適化とは

○畠山 洋文[1)]、堀川 真一[1)]、飯野 好美[1)]、佐藤 伸一[1)]、安齋 享征[2,3)]、岩田 聖[4)]

[1)]（株）イナリサーチ、[2)]昭和大学　医学部、[3)]PDS パソロジー・データシステムズ・リミテッド、[4)]ルナパス毒性病理研究所

毒性病理評価を行う上で、所見辞書（Glossary/Master Dictionary）や常用所見リスト（Common Finding List）は施設ごとに作成されることが一般的で、「新毒性病理組織学」、INHAND（International Harmonization of Nomenclature and Diagnostic Criteria）、SEND CT (Controlled Terminology)、goRENI（The standard reference for nomenclature and diagnostic criteria in toxicologic pathology）などを参考に作成されているものと考えられる。これら辞書や常用所見リストは，医薬品非臨床試験の FDA 電子申請のための SEND (Standard for Exchange of Nonclinical Data) データセットの作成を念頭に作成する必要がある。一方で、毒性評価上必要な用語は標準用語に収載されていない場合でも適宜使用する必要がある。今回我々は、常用所見リストを用いた効率的な SEND データ作成について事例をもとに報告する。病理 SEND データの作成は、原則、CT のリストから基礎所見の選択を行わなければならず、リストに無い場合は nSDRG (Nonclinical Study data Reviewer's guide) を用いて所見の定義を説明する必要がある。常用所見リストの維持、管理を含め CT か否かを明記しておくことは、効率的な鏡検をする上で重要であり、鏡検者間の統一的な所見登録も可能になる。このような所見辞書の最適化は SEND データセットの作成だけではなく、施設内の所見統一化においても有用な方法であると考えられる。

P-43＊

Evaluation of lung carcinogenicity of single-walled carbon nanotube (SWCNT) compared with MWCNT-7 and MWCNT-N

○Sheema Asraful Nahar[1)], Aya Naiki-Ito[1)], Hiroyuki Kato[1)], Masayuki Komura[1)], Hiroyuki Tsuda[2)], Satoru Takahashi[1)]

[1)] Department of Experimental Pathology and Tumor Biology, Nagoya City University Graduate School of Medical Sciences
[2)] Nanotoxicology Project, Nagoya City University

[Background and aims] Though carbon nanotubes (CNTs) have been fundamental for various developments in our current technology, it may cause lung carcinogenicity. For example, MWCNT-7 and MWCNT-N have already proven as carcinogenic for lung and pleura. In this study, we examined the effect of SWCNT on lung toxicities by comparison with those of MWCNT-7 or MWCNT-N. **[Materials and methods]** 10-weeks old F344 rats were administered 0.5mg MWCNT-7, -N and SWCNT using intratracheal instillation twice a week over 4 weeks period (8 administrations from day 1 to day 30). Animals were autopsied on the 4th week after treatment for histopathological, immunohistochemical and gene expression analysis. **[Results and conclusion]** The lung weight trended to be increased by all CNTs but there was significant difference in MWCNT-N and SWCNT. Immunohistochemical analysis revealed that recruitment of CD68 positive macrophages in pulmonary alveolus was significantly increased in both MWCNT groups as well as the SWCNT group. Ki67, γ-H2AX, TUNEL positive lung alveolar cells were significantly increased by both MWCNTs, but not altered by SWCNT. TEM analysis indicated that MWCNT-7 and N showed fiber-like shape and were phagocyted by alveolar macrophages in pulmonary alveolus. In contrast, SWCNT was not observed, even though degraded macrophages were frequently shown. These results indicated that pulmonary toxicity of SWCNT may be lower than MWCNT-7 and -N, known as carcinogens to the lung.

P-44＊

Balanitoside as a natural adjuvant to gemcitabine in lung cancer experimental model

○Sara S. Aboueisha[1)], Abeer A. Khamis[2)], Elsayed I. Salim[1)]

[1)] Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)] Biochemistry Division, Chemistry Department. Faculty of Science, Tanta University

[Background] Gemcitabine is utilized as standard malignancy chemotherapy. **[Aim]** Due to the limited use of Gemcitabine for severe side effects, we studied the antitumor impact of balanitoside, a folk medicine, extracted from edible fruits of *Balanites aegyptiaca*, on mice lung carcinogenesis bioassay, either individually or adjuvant with Gemcitabine. **[Materials and Methods]** *Balb c* mice were initiated for lung cancer by urethane/BHT protocol, then treated afterwards with either balanitoside low dose; balanitoside high dose, Gemcitabine, or balanitoside+Gemcitabine in combination, besides a normal control group. **[Results]** Balanitoside when administered alone or in combination with gemcitabine prompted anti-tumor efficacy against lung cancer by reducing tumor incidences (%), multiplicities, and average tumor area sizes. It has decreased the proliferation of tumor cells, induced apoptosis and triggered cell cycle arrest at the G0/G1 level, along with causing a marked reduction in the level of cancer stem cell markers, aldehyde dehydrogenase (ALDH-1) and CD133 (+ve) cell populations. It has also modulated the oxidative stress markers levels in lung tissues. **[Conclusion]** These data demonstrate that balanitoside optimizes the antitumor capability of gemcitabine and could be utilized as a natural adjuvant medication for lung cancer.

P-45＊

肺組織におけるタバコの短期曝露による初期反応バイオマーカーの探索

○西土井 悠作[1)]、鈴木 周五[1)]、魏 民[1,2)]、梯 アンナ[1)]、松江 泰佑[1)]、鰐渕 英機[1)]

[1)]大阪市立大学大学院医学研究科　分子病理学、[2)]大阪市立大学大学院医学研究科　環境リスク評価学

【目的】喫煙により肺がんや慢性閉塞性肺疾患の発症リスクが高まることが知られており、喫煙関連疾患の誘発メカニズムを明らかにすることは治療及び予防のために重要である。タバコ主流煙の短期曝露による肺への影響について炎症関連因子を主体に検証し、その影響の指標となる遺伝子を探索するため、タバコ煙の短期鼻部暴露試験を行った。【材料及び方法】10 週齢の C57 BL/6 雄マウスに、タバコ煙（JT ピース ; ニコチン 2.3 mg、タール 28 mg）を 1 時間 /5 回 / 週、2 週または 4 週間の鼻部吸入曝露を行った。対照群として清浄空気を同条件下で暴露した。最終曝露 24 時間後に肺を摘出し、気管支洗浄液（BAL）を採取し細胞分画測定を実施した。また、右肺を用いて病理組織学的検討を、左肺を用いて遺伝子発現解析を行った。【結果】BAL における細胞分画測定において、曝露群では好中球を主体に増加し、4 週間曝露ではすべての炎症細胞が有意に増加した。病理組織学的に、肺胞腔の破壊や拡張は認められなかったが、曝露群では血管周囲を主体に炎症細胞集蔟像が増加し、4 週間曝露においては有意に増加した。マイクロアレイ解析の結果、曝露群は 2 週間曝露から炎症関連因子遺伝子の変動が認められ、2 週間および 4 週間いずれも発現変化の強い炎症関連因子遺伝子として CCL17、LCN2 及び Retnla が選出された。【結論】炎症関連因子遺伝子として選出した CCL17、LCN2 及び Rentla は、ヒト喫煙者やタバコ関連疾患（COPD、肺腺癌）にも関わることが報告されており、タバコ煙の短期鼻部吸入曝露評価の指標となる遺伝子候補となりうる。

P-46

有機粉じん吸入によるラット肺病変の病理組織学的特徴

○梅田 ゆみ

（独）労働者健康安全機構　日本バイオアッセイ研究センター

【背景 / 目的】架橋型アクリル酸系水溶性高分子化合物（以下ポリマー）の高濃度粉じんを吸引した労働者 5 名が肺線維症、肺気腫、気胸等を発症した事案が厚生労働省労働基準局より 2017 年 4 月に公表され、その後、労災認定された。しかし当時、本ポリマーの吸入性粉じんによる呼吸器への有害性は認知されておらず、病態の発生機序等が不明であった。そこで我々は病態の把握等を目的に全身吸入ばく露等による当該ポリマーの動物実験を実施した。【材料と方法】F344 ラットを用いてポリマーを単回 (0-100 mg/m^3, 1-3 day) 及び反復全身吸入ばく露させ (0-40 mg/m^3, 1 or 5 day/week, 10 or 13 weeks)、初回ばく露後最大 26 週間までの肺組織等を採集し病理組織学的に詳細に解析した。【結果と考察】単回ばく露では、好中球浸潤を伴った肺胞虚脱と牽引性の肺胞管過拡張がびまん性に認められた。反復ばく露では、ばく露終了直後に肺胞領域を主体として多巣性病巣が観察され、これらの病巣は肺胞腔の炎症、肺胞マクロファージの崩壊・集簇と肺胞上皮の腫大・増生から構成されていた。多巣性病変は回復期間に伴い正常肺胞へ回復を示したが、一部では炎症の主座が気腔内から肺胞間質へと移行し、肺胞壁の線維性肥厚を伴う胞隔炎へと進展した。また、肺門周囲の肺胞腔にはリポ蛋白様物質の蓄積（肺胞蛋白症様変化）が特異的に観察されたが、回復する傾向が認められた。以上の結果より、有機粉じんである当該ポリマーの吸入ばく露はラットに肺胞病変の誘発が認められた。本発表では、演者がこれまで経験した無機粉じんの吸入ばく露によるラット肺病変と比較し、本試験で観察された有機粉じん肺病変の特徴について議論したい。

P-47

マウス肺化学発がんモデルを用いた抗腫瘍効果の予測 － 免疫チェックポイント阻害剤と化学療法剤併用での検討

○萩原 顕昭、沼野 琢旬、土井 悠子、今井 則夫、原 智美、宮田 裕人、米良 幸典

（株）DIMS 医科学研究所

【背景及び目的】5 週間で細気管支肺胞腺腫が形成される化学発がんモデルを用い、抗腫瘍効果を確認する目的で免疫チェックポイント阻害剤（抗 PD-1 抗体）を単剤投与した先行試験では、群間有意差は認められなかったが一部個体に増殖抑制効果が示された。そこで、本検討ではヒトで有効性が認められる化学療法剤との併用投与による抗腫瘍効果について検討した。
【方法】ENU(*N*-nitroso-*N*-ethylurea) と BHT（Butylhydroxytoluene）の投与により 5 週間で肺腺腫が形成された雌 Tg-rasH2 マウス 16 例を 2 群に分けた。その後、対照群として IgG2a isotype control を 200 μg/mouse（週 2 回）、併用投与群として抗 PD-1 抗体 200 μg/mouse（週 2 回）及びゲムシタビン 10 mg/kg（週 1 回）を 4 週間、腹腔内投与後に剖検を行った。摘出した全動物の肺の各葉から一定部位を切り出し、常法に従って病理組織標本を作製後、画像解析にて肺と腫瘍の相対面積により抗腫瘍効果を評価した。
【結果】剖検まで両群とも一般状態に変化はなく、体重にも差はみられなかった。肺腫瘍相対面積（mm^2/cm^2）は、対照群で 6.308 に対し、併用投与群では 3.542 であり統計学的に有意な腫瘍増殖抑制効果が認められた（$p<0.05$）。
【結論】マウス肺化学発がんモデルは、自己組織由来の腫瘍のため本来の腫瘍微小環境が保たれていること、自己免疫系も保たれていること、また、中皮腫における併用療法の有効性を示したヒトでの報告に類似していたことから、免疫チェックポイント阻害剤等の免疫系を介した作用機序をもつ薬剤の解析や効果予測に有用な試験系であることが示唆された。

P-48＊

糖尿病モデル動物を用いた ACE2 発現による COVID-19 重症化モデルとしての検討

○畑中 悠里[1)]、美谷島 克宏[1,6)]、宇野 絹子[2)]、当摩 茉莉花[6)]、グエン ハンニユン[1)]、煙山 紀子[1)]、渡辺 寿久[3)]、伊藤 秀樹[3)]、篠原 雅巳[4)]、笹瀬 智彦[5)]、太田 毅[5)]、中江 大[1,6)]

[1)]東京農業大学・応生・食品安全健康学科、[2)]東京農業大学・院・食品栄養学専攻、[3)]日本クレア株式会社 富士生育場
[4)]日本クレア株式会社 業務推進部、[5)]京都大学・院・農学研究科 応用生物学専攻 生体機能学分野
[6)]東京農業大学大学院　応用生物科学研究科　食品安全健康学専攻

［背景と目的］現在世界的に蔓延している新型コロナウイルス（SARS-COV-2）は、肥満や糖尿病などを有する感染者においては重症化しやすいとされている。レニン・アンジオテンシン系（RAS）に関わる酵素 ACE2 は SARS-CoV-2 の機能的受容体であり、ACE2 を介してウイルスが細胞内に侵入することが知られている。本研究では肥満 2 型糖尿病モデルである SDT fatty ラット並びに非肥満 2 型糖尿病モデルである SDT ラットを用いて肺における ACE2、TMPRSS2 の発現を正常動物である SD ラットと比較した。［材料及び方法］20~30 週齢の雄性 SDT fatty ラットと、対照として SD ラットを使用した。餌は基礎食（CRF-1, BD）又は Quick Fat（QF）食に 2%コレステロールを添加したもの（Western diet: WD）を給餌した。解剖時に BALF を採取し、肺についての病理組織学的解析及び遺伝子発現解析を行った。これに加え基礎食 (CE-2) を与えた 24 週齢の雄性 SDT ラットも用いて検討した。［結果及び考察］SD 並びに SDT fatty ラットにおいて肺における ACE2 及び TNF- αの遺伝子発現は増加した。これは SDT ラットにおいても同様の増加傾向を示した。さらに、SDT ラットでは QF 給餌により両遺伝子発現がさらに上昇した。病理組織学的に、SDT fatty ラットの肺では BD と比較し WD において炎症性細胞浸潤と気管支上皮における ACE2 陽性細胞の増加が認められ、ACE2 陽性細胞に一致して TMPRSS2 の発現も認められた。以上より、両モデル動物は新型コロナウイルス感染症の重症化リスクの評価においても有用な動物モデルとなり得る可能性が示唆された。

P-49＊

Bee pollen and its encapsulated nanoproduct loaded with folic acid as antitumor agents against lung cancer cells

○Eman A. Eltonoby[1)], Magdy E. Mahfouz[2)], Nemany A. N. Hanafy[3)], Ezar H. Hamed[1)], Elsayed I Salim[1)]

[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Zoology Department, Faculty of Science, Kafrelsheikh University
[3)]Nanomedicine Division, Institute of Nanoscience and Nanotechnology, Kafrelsheikh University

[Background] Bee pollen (Bp) is an important emerging food product owing to its high concentration of nutrients and bioactive compounds. It comprises at least 200 biologically active substances. Natural products constitute an enormous source for screening potential therapeutic candidates to reverse drug resistance lung cancer, especially non-small cell lung cancer (NSCLC), the leading malignancy worldwide. **[Aim]** This current study evaluates the antitumor efficacy of bee pollen against lung cancer *in vitro.* The study investigates the functional role of alcoholic Bp extract alone and the encapsulation of Bp extract with bovine serum albumin loaded with folic acid targeted to lung cancer. **[Materials and Methods]** Nano encapsulated Bp was fabricated and confirmed by using UV-visible spectrometry, Fourier Transform Infrared (FTIR), Zeta potential, TEM, X-ray differaction. **[Results]** The results of HPLC analysis of Bp encapsulation revealed the presence of different substances such as gallic acid, syringic acid, ferulic acid, naringenin, taxifolin and catechin. The results of MTT assay by using A549 cell lines represented the efficiency of encapsulation of the Bp extract over the pure extract, also results were comparable when administered adjuvant with avastin®, a chemotherapeutic drug against lung cancer. **[Conclusion]** Thus, Bp could be considered a good choice for lung cancer adjuvant therapy.

P-50＊

アクリルアミド反復暴露によるマウス肺由来オルガノイドの形態変化の解析

○田邉 健斗[1)]、平田 暁大[1)]、入澤 祐太[1,2)]、今井 俊夫[3)]、酒井 洋樹[1)]

[1)]岐阜大学　応用生物科学部　共同獣医学科 獣医病理学研究室、[2)]あすか製薬株式会社　薬物動態・安全性研究部　安全性研究課
[3)]国立がん研究センター　研究所　がんモデル開発部門

【背景・目的】オルガノイドは生体組織由来の 3 次元培養組織であり、通常の培養細胞より生体に近い実験系として幅広く応用されており、化学物質の毒性評価への応用も期待されている。近年、化学発がん物質を in vitro で反復暴露したオルガノイドをヌードマウスの皮下に移植すると腫瘍性結節を形成することが報告されている。本研究では、マウスに肺腫瘍を誘発するアクリルアミド（AA）の反復暴露によるマウス肺オルガノイドの形態変化を解析した。【材料と方法】BALB/c 背景の Trp53 ヘテロノックアウトおよび野生型マウスの肺由来オルガノイドを用いた。酵素処理によりオルガノイドを細胞単位に分離し、マトリゲル上で AA（0、0.28 m M、1.4 m M）と S9mix を付加した培養液で 24 時間培養した。その後、AA を含む培養液を除去し、マトリゲルを重層し、通常の培養液を加えて、細胞からオルガノイドを再構築した。合計 3 回 AA の暴露を行い、その都度、再構築されたオルガノイドの形態を位相差観察および組織学的解析により評価した。【結果・考察】いずれの遺伝子型のオルガノイドを用いた解析でも、AA 暴露後の細胞から再構築された肺オルガノイドは、AA 濃度依存性にサイズが小さくなり、さらに、通常は単層構造であるオルガノイドの壁に全周性あるいは局所性に多層化が観察された。以上から、化学発がん物質暴露によりオルガノイドに形態変化が生じることが明らかになった。現在、AA 暴露を繰り返すことによって、これらの形態変化が増強されるか解析している。近年、3R の原則に基づく動物実験の適正化が強く求められており、オルガノイドを用いた化学物質の評価系は動物実験代代替法として期待される。マウスでの造腫瘍性評価に依らず、オルガノイド自体の解析によって化学物質の発がん性を評価できれば、その意義は大きい。

P-51＊

食餌性鉄過剰モデルラットの出血傾向に関わるビタミンＫの影響

○稲井 洋平、井澤 武史、藤原 奨、田中 美有、桑村 充

大阪府立大学　獣医病理学教室

【背景】生体の鉄過剰は肝臓などに酸化ストレス性細胞傷害を誘発し得ることが知られているが、血液凝固系への影響には不明点が多い。今回、食餌性鉄過剰モデルラットにおいて予期せぬ出血傾向が発生したため、そのメカニズム解析を行なった。【材料･方法】６週齢雄の F344 ラットに正常食（Fe 0.02%、ビタミン K 500 μg/kg; Cont 群）もしくは鉄過剰食（Fe 0.8% あるいは 1%、ビタミン K 182 μg/kg; Fe 群）を 4 から 26 週間給餌し、病理学的検査と、一部で血液学検査、生化学検査、凝固系検査を実施した。また、ビタミン K を 750 μg/kg 添加した正常食（Fe 0.02%; Cont+VitK 群）と鉄過剰食（Fe 0.8% あるいは 1%; Fe+VitK 群）を 4 週間給餌し、同様の解析を行った。【結果・考察】0.8% Fe 群の 5/55 個体（9%）、1% Fe 群の 3/27 個体（11%）において、全身性出血が認められた。1% Fe 群では、PT および APTT の延長、ビタミン K 依存性凝固因子 II および VII の活性減弱が認められたが、凝固因子 VIII の活性および末梢血血小板数に変化は認められなかった。また、血清 ALT および AST の増加や肝臓の組織学的異常は認められなかった。これまでの発表者らの経験上、正常食、鉄欠乏食および 0.5% Fe 鉄過剰食（0.8% あるいは 1% Fe 鉄過剰食と背景飼料が同じ）を用いた給餌実験では、出血は認められていない。本研究で使用した鉄過剰食は、米国国立栄養研究所の推奨ビタミン K 含有量（834 μg/kg）よりも飼料中ビタミン K 濃度が低いことから、給餌されたラットは潜在的なビタミン K 不足を起こしており、さらに鉄過剰の誘発によって凝固異常に対する感受性が増加した可能性が疑われた。現在、ビタミン K 添加食の給餌実験を実施しており、0.8% Fe+VitK 群の 31 個体、1% Fe+VitK 群の 13 個体において投与 2~4 週時点までに出血は認められず、凝固系検査を進めている。

P-52＊

ラットを用いた一般毒性試験におけるマイクロサンプリングの毒性評価項目への影響

○栃谷 智秋、佐々木 靖弘、西村 直恵、藤井 雄太、祝迫 隆行、梅屋 直久、橋本 雅世、稲田 拓、千原 和弘、宮脇 出

大日本住友製薬（株） 前臨床研究ユニット

【背景・目的】近年、ラットを用いた一般毒性試験でのトキシコキネティクス評価用の採血には、動物愛護の観点からサテライト群を設けずに、マイクロサンプリングを用いる例が増えている。一方、特に血液毒性を有する化合物の評価では、血液学的検査項目、造血器系の器官・組織等への影響にも留意する必要がある。そこで今回、血液毒性物質を用いてラット 2 週間反復経口投与試験を実施し、マイクロサンプリングによる毒性評価項目への影響を評価した。
【材料と方法】6 週齢の SD 系雌性ラットに媒体（0.5 % メチルセルロース水溶液）、メチレンブルー 300 mg/kg/ 日、アザチオプリン 12 及び 24 mg/kg/ 日を 2 週間反復経口投与した。また、各投与群は非採血群及びマイクロサンプリングによる採血群に分け、採血群では 50 μL/ 時点の血液を投与 1 及び 13 日に各 7 時点（投与後 30 分、1、2、4、6、8 及び 24 時間）、頚静脈から採取した。評価項目は、一般状態、体重、摂餌量、摂水量、尿検査、血液学的検査、血液生化学的検査、剖検、器官重量及び病理組織学的検査とした。
【結果】非採血のメチレンブルー群では、赤血球数やヘマトクリットの低値、総ビリルビンの高値、脾臓における髄外造血の増加などがみられた。非採血のアザチオプリン群では白血球数の低値、骨髄における造血細胞の減少などがみられた。メチレンブルー、アザチオプリン投与の影響は、採血群においても同様に認められ、各投与群の非採血・採血群間で明らかな差は認められなかった。
【結論】血液毒性を有する化合物のラット一般毒性試験においても、マイクロサンプリングによる毒性評価項目への影響は小さいと考えられた。

P-53

Toxicity assessment of a recombinant humanized antibody-drug Conjugate (rhADC) in *cynomolgus* monkeys

○Xueyan Pu, Lu Peng

Pathology Department, Jiangsu Tripod Preclinical Research Labortory Co., LTD

[Background] Antibody-drug conjugates (ADCs) are a new type of anticancer therapeutics, which guides highly cytotoxic small molecules directly to cancer cells via specific antibody. RhADC is a new recombinant humanized antibody-drug Conjugate targeting CD33 for acute myelocytic leukemia therapy.
[Aim] To evaluate the toxicity of a rhADC in *Cynomolgus* Monkeys.
[Materials and Methods] Forty *Cynomolgus* Monkeys were randomly divided into vehicle control, 5, 10, and 15 mg/kg rhADC-treated groups with 5 males and 5 females each group. Vehicle and rhADC were intravenously injected into forelimb 6 times with once per week, followed by 6-week recovery.
[Results] There were mild to severe lymphocytopenia in thymic cortex of all rhADC-treated monkeys after 6-time rhADC administration. Additionally, all rhADC-treated monkeys showed minimal to mild atypical mitotic figure in liver, spleen, and hematopoietic cells of sternum. Biochemically, ALT, AST, and ALP were remarkably elevated in 15 mg/kg rhADC-treated monkeys.
[Conclusion] To our knowledge, it is the first report that in *Cynomolgus* Monkey rhADC induced atypical mitotic figure in spleen and hematopoietic cells of sternum. Though these rhADC-induced toxic effects were reversible in monkeys, it should pay attention to potential adverse effects in clinical trial and application because immune suppression is a commonly clinical feature in cancer patients, and the exact differences exist between monkey and human.

P-54＊

下肢 DES 評価モデルとしての糖尿病・高コレステロール血症ブタモデルの有用性検討

○佐藤 晶子、岩崎 泰造、小路 由佳、菊地 亮介、市村 夏穂、佐藤 秀樹

テルモ株式会社

【背景・目的】薬剤溶出型ステント (DES) はステント留置後にみられる新生内膜の増生を薬剤により抑制し、ステント再狭窄の発生率を軽減させることが知られている。冠動脈用 DES の有効性評価には健常ブタが多用されるが、下肢用 DES では健常ブタの下肢血管は反応性が低く、臨床の病態に近い動物モデルは未だ確立されていない。我々は下肢用 DES の有効性を評価するための動物モデルとして、糖尿病 (DM) 高コレステロール血症 (HC) ブタを作製し、造影検査ならびに病理検査によって本モデルの有用性について検証した。【方法】健常ブタに STZ を投与し DM を発症させ、高脂肪飼料の給餌によって HC を発症させた。給餌開始 1 か月後、両下肢血管に DES およびベアメタルステント (BMS) を留置した。留置後、1 か月ごとに造影によるフォローアップ (FU) を実施した。ステント留置血管の病理評価は、留置後 1 か月後および 3 か月後に HE、E-HE、MT 染色を用いて実施した。また各種臓器の病理検査も行った。【結果・考察】1 か月 FU の時点では BMS 留置血管では臨床と同様に新生内膜の増生が観察されたが、DES 留置血管ではほとんど観察されなかった。この傾向は 3 か月 FU まで継続した。また 1 か月 FU の病理検査では新生内膜の増生以外に顕著な差は認められなかったものの、3 か月 FU では DES 留置血管において Acellular、fibrin deposition、cellular infiltration など治癒遅延を示唆する変化が認められた。これらの変化は DES の臨床でも課題として報告されており、本モデルが臨床における課題も再現できていることを示唆するものと考えられた。【結論】DMHC ブタモデルを作成し、病理評価により DES 評価モデルとしての有用性を評価した結果、DES 評価モデルとしての有用性が示唆された。

P-55

植物芭蕉 (*Musa basjoo*) 抽出物のヒト大腸がん細胞株に対する増殖抑制効果および細胞周期制御分子発現への作用

○松本 晴年、Sultana Nahida、深町 勝巳、酒々井 眞澄

名古屋市立大学大学院　医学研究科　神経毒性学分野

Musa basjoo (MB) は同種に分類される 50 種類の植物のひとつであり、その生物活性は未知の部分が多い。本研究ではヒト大腸がん細胞株に対する増殖抑制効果、細胞周期制御分子発現に対する影響、移植腫瘍縮小効果を調べた。乾燥した葉身・葉柄を材料にアセトンあるいはメタノールを溶媒として有効成分を抽出し検体とした。コロニーアッセイにて各抽出物は HT29 および HCT116 株の増殖を抑制し、その効果はアセトン抽出物がメタノール抽出物に比べて高かった。薄層クロマトグラフ分析では、共役二重結合を含む芳香族、ヒドロキシ基を持つ抗酸化化合物の存在が示唆された。フローサイトメトリー解析では subG1 期は誘発されず、G1 期の増加を認めた。タンパク発現について、cyclinD1、cyclinE、cdk2 および cdk4 が減少、$p21^{CIP1}$、$p27^{KIP1}$ および p53 が増加、PARP および cleaved PARP は変化なしの所見であった。マウス実験では移植腫瘍縮小傾向を認めた。実験期間中の有意な体重減少を認めず、主要臓器において組織学的な毒性影響は見られなかった。実験結果より、MB の葉身・葉柄から得られた抽出物にはヒト大腸がん細胞株の増殖を抑制する化合物が含まれ、これは細胞周期制御分子の発現に影響することが示された。

P-56＊

Riceberry bran oil ameliorates carcinogens-induced liver and colon carcinogenesis through the mechanism of cell apoptosis, anti-inflammation, and gut microbiota

○Warunyoo Phannasorn[1)], Aroonrat Pharaphirom[1)], Parameth Thiennimitr[2)], Rawiwan Wongpoomchai[1)]

[1)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)] Department of Microbiology, Faculty of Medicine, Chiang Mai University

[Background] Riceberry bran oil (RBBO) containing high amounts of phytonutrients and phytochemicals exhibited anti-proliferation activity in various cancer cells. However, it lacks of anti-carcinogenicity in animal model. **[Aim]** This study aimed to investigate the effect of RBBO on carcinogens-induced liver and colon carcinogenesis. **[Materials and Methods]** Male rats were fed with 100 mg equivalent to γ -oryzanol/kg of RBBO, 5 days a week for 10 weeks and injected with diethylnitrosamine and 1,2-dimethylhydrazine to initiate liver and colon carcinogenesis, respectively. **[Results]** The administration of RBBO could inhibit the number of preneoplastic lesion including glutathione *S*-transferase placenta form positive foci in liver and aberrant crypt foci in colon of carcinogens-treated rats. These lesions could suppress by RBBO through hepatocytes and colonocytes apoptosis evaluating by TUNEL assay. Moreover, RBBO ameliorated the expression of pro-inflammatory genes including TNF-α, IL-6 and IL-1β in liver and colon of carcinogens-treated rats. Interestingly, the fecal short-chain fatty acids produced by gut microbiota were significantly increased in RBBO administration in carcinogens-induced group. RBBO administration could improve the population of Firmicutes and Bacteroidetes to the normal levels. **[Conclusion]** These findings suggested the novel mechanism of RBBO that promoted the chemopreventive properties.

P-57＊

Vanillic acid attenuates rat hepatocarcinogenesis induced by diethylnitrosamine and 1,2-dimethylhidrazine

○Charatda Punvittayagul[1)], Arpamas Chariyakornkul[2)], Kanokwan Jarukamjorn[3)], Rawiwan Wongpoomchai[2)]

[1)] Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University
[2)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[3)] Research Group for Pharmaceutical Activities of Natural Products using Pharmaceutical Biotechnology, Faculty of Pharmaceutical Sciences, Khon Kaen University

[Background] Vanillic acid (VA) is commonly phenolic acid found in several plants, especially rice. Numerous biological activities of VA have been reported. **[Aim]** Cancer chemopreventive potential of VA in diethylnitrosamine (DEN)- and 1,2-dimethylhydrazine (DMH)-induced liver and colon carcinogenesis in rats was investigated. **[Materials and Methods]** The 0.75 and 75 mg/kg bw of VA were treated rats before and after carcinogens injection. Blood was collected for liver function test. Preneoplastic lesions, hepatic glutathione S-transferase placental form (GST-P) positive foci and colonic aberrant crypt foci (ACF), were examined. Likewise, mechanistic studies involved immunohistochemistry and gene expression were evaluated. **[Results]** VA at the dosage of 75 mg/kg bw presented hepatoprotective effect on carcinogens-induced rats. It diminished the number and areas of GST-P positive foci, while did not influence on ACF. VA shown antiproliferative effect as evidenced by decreased proliferating cell nuclear antigen and cyclin D1 expression. Moreover, it induced apoptosis in VA-treated rat via induction of apoptosis, upregulation of caspase-3 and Bad as well as downregulation of Bcl-2. The detoxification system was markedly increased by enhancing the expression of GSTA-5 and Nrf-2 genes. **[Conclusion]** VA possessed hepatoprotective potency against DEN- and DMH-induced carcinogenesis through reduction of cell proliferation, induction of apoptosis and modulation of detoxification system.

P-58

唾液分泌機能が低下したアロキサン誘発１型糖尿病ラットでは、耳下腺における腺房細胞の異常のみならず筋上皮細胞の肥大が出現する

○兒玉 安史[1)]、寺山 由依[2)]、松浦 哲郎[2)]、松田 美和[3)]、尾崎 清和[2)]

[1)]広島国際大学　薬学部　病態薬理学研究室、[2)]摂南大学　薬学部　病理学研究室
[3)]広島国際大学　保健医療学部　医療技術学科

【背景・目的】糖尿病患者では唾液量が減少し、肥大した耳下腺の腺房細胞では脂肪が蓄積する。アロキサン (AL) およびストレプトゾトシン誘発１型糖尿病ラットの耳下腺でも同様の変化が誘発され、その病理発生について腺房細胞を中心とした研究が行われている。唾液分泌には、腺房細胞のみならず、筋上皮細胞も重要な役割を担っていることから、今回、両細胞と唾液分泌障害の関連性について病理組織学的に解析した。【方法】7 週齢の雌 F344 ラットに AL を投与し糖尿病を誘発させた AL 群を未処置の C 群と比較解析した。AL 投与後 0, 7, 13, 26 週時にピロカルピン刺激による唾液分泌量を測定し、投与後 26 週に剖検後、唾液腺に対する組織学的および免疫組織化学的解析を行った。【結果】AL 群の唾液分泌量は C 群と比べ、AL 投与後 7 週以降、著しく低下した。AL 群の耳下腺相対重量は、C 群と比べ有意に増加した。組織学的に、AL 群の全例の耳下腺腺房細胞に脂肪蓄積および核の大小不同が認められ、大型核は頻繁に Ki67 陽性を示した。C 群の耳下腺の筋上皮細胞では p63 陽性の核が散見され、CK14 および平滑筋アクチン (SMA) 陽性の細胞質がごく僅かに観察される程度であった。一方、AL 群の筋上皮細胞では、p63 陽性の大型核が頻繁にみられ、CK14 および SMA 陽性の細胞質面積は C 群と比べ、著しくかつ有意に増加し、さらに Ki67 陽性細胞も軽度であるが、C 群よりも増加していた。【結論】AL 誘発１型糖尿病ラットの唾液分泌機能障害には、耳下腺における腺房細胞の異常に加え、筋上皮細胞の肥大が関連していることが明らかであり、筋上皮細胞は腺房細胞の障害に対し代償性に肥大した可能性もあるのではないかと考えられた。

P-59＊

Palmitoyl piperidineopiperidine induces selective anticancer activity against human colon carcinoma cell lines

○Sultana Nahida、深町 勝巳、松本 晴年、酒々井 眞澄

名古屋市立大学大学院　医学研究科　神経毒性学分野

We have invented a novel compound, palmitoyl piperidinopiperidine (PPI; Japan Patent no. 5597427), to investigate its selective anticancer activity on colon carcinogenesis. PPI inhibited the growth of the several types of human colon carcinoma cell lines. PPI also exhibited the selective property of growth inhibition. In silico docking analysis demonstrated that PPI binds to the SH2 domain of a transcription factor STAT3 with higher affinity than other conventional inhibitors, and inhibited the transcriptional activity in carcinoma cells. In the chromatin fraction of cells, PPI decreased the expression levels of pSTAT3/STAT3 but increased those of pSTAT3/STAT3 in the cytosolic fraction, suggesting the inhibition of translocation of these molecules. Moreover, PPI altered the expression levels of cell cycle and apoptosis related molecules. PPI exhibited significant dose-dependent inhibition of the angiogenesis of the chick chorioallantoic membrane. In a mouse xenograft model, PPI inhibited the growth of implanted carcinoma cells. Transcriptional inhibition of STAT3 by PPI may be one possible mechanism, where the functional molecules related to apoptosis, angiogenesis and cell cycle progression are affected, and eventually contributed to the growth inhibition.

P-60

ラット非アルコール性脂肪肝炎に対する紫米抽出物の化学予防効果

○内木 綾、加藤 寛之、小村 理行、高橋 智

名古屋市立大学　大学院医学研究科　実験病態病理学

【背景】非アルコール性脂肪肝炎 (non-alcoholic steatohepatitis：NASH) は、近年の食生活変化に伴い発生率が増加している。NASH における炎症や線維化は、肝硬変や肝癌へ進展する危険性が指摘されている。我々はこれまでにアントシアニンを豊富に含む紫米（*Oryza sativa* L. *indica*）抽出物が、前立腺癌化学予防効果を持つことを明らかにしてきた。本研究では、NASH および肝発癌に対する紫米抽出物ヘキサン不溶性画分（HIF）の化学予防効果を検討した。【目的・方法】7 週齢雄 Cx32 ドミナントネガティブトランスジェニック (Tg) ラットを対照食群、高脂肪食（HFD）群、HFD+1%HIF 群の 3 群に分け、5 週目からは dimethylnitrosamine 腹腔内投与 (1 回 /2 週間) を開始した。17 週間後に解剖を行い、肝の組織学的解析と NASH 関連炎症性サイトカイン mRNA およびタンパク質の発現解析を行った。【結果】HFD 群では、肝における脂肪沈着、小葉の炎症、風船状腫大などの NASH の組織学的変化や架橋を伴う線維化が対照群と比較して有意に認められ、HIF 投与によりこれらは有意に抑制された。また、HFD 群では炎症性サイトカイン mRNA (*Tnfα*, *Il1β* , *Il18*, *Ifnγ*, *Il6*, *Tgfβ*, *Timp1*, *Timp2*, *Col1a1*) の高発現や NF-κB および JNK シグナルに属するタンパク質の活性化を認め、HIF によって有意に抑制された。また肝前癌病変 GST-P 陽性病巣の数および面積が HIF 投与により減少する傾向にあった。【結論】紫米抽出物は NF-κB および JNK シグナルの抑制により NASH の進展に対して抑制的に働くことが明らかとなり、新規予防法への応用の可能性が示唆された。

P-61＊

有機ヒ素化合物 DPAA のマウス経胎盤曝露による次世代に対する発がん影響及びその機序の検討

○藤岡 正喜[1)]、魏 民[2)]、鈴木 周五[1)]、梯 アンナ[1)]、大石 裕司[1)]、山口 貴嗣[1)]、鰐渕 英機[1)]

[1)]大阪市立大学大学院　医学研究科　分子病理学、[2)]大阪市立大学大学院　医学研究科　環境リスク評価学

【背景】これまでに我々は有機ヒ素化合物 Dimethylarsinic acid のマウス経胎盤ばく露によって雄性 F1 マウス肺および肝臓にがんを生じることを明らかにし、さらに肺発がんについてはヒストン修飾異常の関与を明らかにしている。【目的】本研究は、同じ有機ヒ素化合物であるジフェニルアルシン酸（DPAA）の経胎盤ばく露による発がん性及びその機序を明らかにすることを目的として、DPAA 経胎盤ばく露がん原性試験を行った。【材料と方法】妊娠期の雌 CD1 マウスに DPAA を 0、6.25、12.5 および 25 ppm の用量で飲水投与し、経胎盤ばく露により作製した雄仔マウス 481 匹を 84 週齢まで無処置で経過観察を開始した。また、メカニズム解析としてがん原性試験と同様に妊娠期に DPAA の飲水投与により得られた 6 週齢雄性 F1 マウスを用いた。【結果】全臓器の病理組織学的解析の結果、DPAA 25 ppm 群で対照群と比較して肝腫瘍発生頻度の有意な増加が認められた。一方で、DPAA は肝臓以外の臓器に対しては発がん性を示さないことを確認した。さらに DPAA 経胎盤ばく露による肝発がん機序について検討した結果、DPAA 25ppm 群の 6 週齢雄仔マウス肝臓において、細胞増殖の有意な亢進が認められた。また、マイクロアレイ解析により、対照群と比較して 2 倍以上発現が変動した遺伝子を 168 個確認し、そのうちの 23 遺伝子が肝発がんに関与することを Ingenuity pathway analysis により見出した。加えて、投与群においてゲノムワイドな DNA 低メチル化状態が認められた。【結論】DPAA の経胎盤ばく露による雄仔マウスにおける肝発がん性を明らかにした。さらに、マウスにおける DPAA 経胎盤ばく露による肝発がん機序には F1 マウスの幼若期から肝細胞増殖能の亢進および DNA メチル化異常の関与が示唆された。

P-62

1,4- ジオキサンの *in vivo* 変異原性及び発がん性の定量解析

○魏 民[1,2)]、鈴木 周五[2)]、藤岡 正喜[2)]、梯 アンナ[2)]、鰐渕 英機[2)]

[1)]大阪市立大学大学院医学研究科　環境リスク評価学、[2)]大阪市立大学大学院医学研究科　分子病理学

【目的】1,4-dioxane は合成化学工業において溶媒として広く用いられており、一般的な浄水処理では除去できず、水道水や食物にも存在し、ヒトへの健康被害が危惧される。げっ歯類において肝発がん性を有するため、ヒトへの発がん性が懸念されているが、その発がん機序は不明である。本研究では、1,4-dioxane の変異原性に着目し、発がん機序の解明と定量的な発がんリスク評価を行った。【方法】遺伝子突然変異を検出する Transgenic 動物 gpt delta ラットに、種々の用量で 1,4-dioxane を 16 週間飲水投与し、肝臓における変異原性を検索した。また、肝臓の遺伝子発現解析および前がん病変を指標とした発がん性評価を行った。さらに、変異原性及び発がん性の用量反応関係について、Benchmark Dose(BMD) 法を用いて Point of Departure(PoD) を検討した。【結果】肝臓における遺伝子変異頻度及び前がん病変の発生は、2-20ppm までは対照群と変化なく、200 ppm 以上で増加傾向を、5000 ppm で有意な増加を示した。その際に誘発された変異の特徴は A：T bp の塩基置換であった。また、5000 ppm で DNA 損傷修復遺伝子の誘導が認められた。さらに、1,4-dioxane の変異原性及び肝発がん性には無作用量が存在することと、変異原性の PoD は肝発がん性のそれよりよりも低いことが明らかになった。【結論】1,4-dioxane は変異原陽性物質で、遺伝毒性的発がん機序を介して発がん性を示すことが初めて明らかとなった。1,4-dioxane の変異原性及び肝発がん性には実際的な閾値が存在することが示された。BMD 法を用いることで低用量域における発がんリスクを適切に評価できることが考えられた。

P-63

ラット早期肝癌発生に対する Bear Bile Powder の予防治療作用

○金 美蘭[1,2]、董 鋭[2]、洪 澤宣[2]、賈 貴楊[2]

[1]中國　西南大学　実験動物センター、[2]中國　西南大学　動物医学院　獣医病理研究室

【背景】今まで、我々は天然薬 Bear Bi\le Powder(BBP) が肝癌形成早期や後期に対して弱いながらも抑制作用を有していることを報告した。【目的】本実験では低用量 BBP 前処理のラット肝癌発生に対する予防治療効果を探索した。【方法】6 週齢の雄 SD ラット 45 匹を 3 群 (1 群：対処群、2 群：DEN+ NMOR、3 群：DEN+NMOR+BBP) に分け、実験開始から 15 週まで第 3 群に 10 mg/kg BBP を経口投与し、第 13 週目に全群のラットに 200 mg/kg diethylnitrosamine (DEN) でイニシエーション処置を行った。そして、第 16 週から実験終了まで第 2 と 3 群に 80 ppm N-nitrosomorpholine (NMOR) を引水投与した。実験終了後に生存率 , 体重、肝臓と肺重量測定 , 病理組織学検査 , 肝臓における Ki67、GST-P、Caspase3 及び Caspase9 免疫染色や遺伝子発現解析を行った。【結果】その結果、第 3 群のみ 100% 生存率であった。体重、肝臓と肺重量において第 3 群と第 2 群の間には有意な差はなかった。病理組織検査結果 , 第 3 群の変異肝細胞巣、肝腺腫の発生率は第 2 群に比べ有意な差はなかったが、肝癌の発生率は減少傾向を示した。第 3 群の Ki67 陽性細胞率及び GST-P 陽性細胞巣の数と面積は第 2 群に比べ有意な減少または減少傾向を見せた。さらに、第 3 群の Caspase3 及び Caspase9 の mRNA 発現率や蛋白レベルも有意な増加または増加傾向を示した。また、DNA 修復に関連する JWA 遺伝子発現レベルも第 3 群において有意に増加した。【結論】BBP の前処理は DNA 修復、細胞増殖抑制、アポトーシスの促進を通してラット肝癌の発生に対して一定の抑制効果を発揮している。

P-64＊

肝発がん物質フランの葉特異的毒性発現

○相馬 明玲[1]、日比 大介[2,3]、高須 伸二[3]、石井 雄二[3]、梅村 隆志[1,3]

[1]ヤマザキ動物看護大学　動物看護学研究科　動物看護学専攻修士課程、[2]小野薬品工業（株）、[3]国立医薬品食品衛生研究所

【背景】フランは食品香料のフラン誘導体の基本骨格であり、ラットの肝臓に肝細胞腫瘍や肝内胆管腫瘍を誘発する。しかし、in vivo 変異原性試験で陰性を示すなど、その発がん機序は不明である。一方、尾状葉における肝腫瘍の発生頻度が他の葉と比較して高く、胆管線維症の発生も尾状葉で高い。今回、フランの発がん機序解明を目的に、この葉特異性に着目し、各葉における病理学的変化について検証した。【材料と方法】雄 7 週齢の F344 系 gpt delta ラット各群 5 匹にフランを 8 mg/kg 体重 / 日の用量で 1 日 1 回、週 5 日の頻度で 8 週間強制経口投与した。対照群には溶媒のコーン油を同様に投与した。投与終了後、肝臓を摘出し、病理組織学的検索、GST-P 陽性巣の定量解析ならびにフラン投与により特異的に発現する SOX9 陽性肝細胞の単位面積当たりの個数を尾状葉、中間葉、外側左葉、外側右葉ごとに検索した。【結果】投与群では、Oval 細胞の増生、肝細胞のアポトーシス、被膜下への炎症細胞浸潤が観察されたが、それらの発現頻度に葉特異性は認められなかった。しかし、胆管線維症が投与群の 1 例で尾状葉に観察された。GST-P 陽性巣の出現に葉特異性は認められなかった。投与群の SOX9 陽性肝細胞の単位面積当たりの数は対照群に比して約 10 倍、投与群の尾状葉では他の葉に比して、約 2 倍の高値となった。【考察】フランを 8 週間投与したラット肝尾状葉において、肝内胆管腫瘍の前がん病変である胆管線維症が観察された。また、胆管上皮への分化を制御する転写因子の SOX9 発現肝細胞が尾状葉において多数観察された。以上より、SOX9 陽性肝細胞の生物学的意義の探索がフラン発がん機序解明に重要であることが示唆された。

P-65＊

細胞質内封入体が示す methyl carbamate の染色体異常と肝発がんへの関与

○瀧本 憲史[1,2]、石井 雄二[1]、満元 達也[1,3]、並木 萌香[1]、高須 伸二[1]、能美 健彦[1]、渋谷 淳[2]、小川 久美子[1]

[1]国立医薬品食品衛生研究所　病理部、[2]東京農工大学大学院　獣医病理学研究室、[3]ヤマザキ動物看護大学　動物看護学科

【目的】飲料の低温殺菌剤 dimethyl dicarbonate の反応生成物 methyl carbamate（MC）は、強力なラット肝発がん物質である。MC の発がん機序は不明であるが、ラット肝細胞に特徴的な細胞質内封入体を誘導することが知られる。最近我々は、MC の構造類似物質である acetamide 投与ラットで同様の細胞質内封入体を認め、肝発がん機序への染色体異常の関与を見出した。本研究では MC の肝発がんにおける染色体異常の関与を明らかにするため、gpt delta ラットを用いた in vivo における包括的な遺伝毒性評価と、肝臓に生じた封入体について分子病理学的解析を実施した。【方法】雄性 6 週齢の F344 系 gpt delta ラットに MC を 100、200 又は 400 mg/kg 体重で 4 週間強制経口投与し、肝臓における病理組織学的及び免疫組織化学的検索、gpt 及び Spi- assay による変異原性評価、骨髄及び肝臓小核試験による染色体異常の評価を実施した。【結果】400 mg/kg で肝細胞の好塩基性細胞質内封入体、カリオメガリー及び異常分裂を伴う核分裂像の増加などの変化が見られた。肝臓小核試験では 200 mg/kg 以上で大型小核を、400 mg/kg で小型小核を有する肝細胞が有意に増加した。一方で、骨髄小核試験は陰性であった。封入体は核酸成分を有し、DNA 損傷を示唆する変化に加え、核膜関連タンパクの消失や発現異常が見られた。【考察】骨髄小核試験の陰性結果に対し、肝臓では小核保有肝細胞の増加と染色体断片を伴う異常分裂像が認められ、MC が肝細胞特異的に染色体異常を誘発することが示唆された。また、大型小核と一致する封入体は acetamide 誘発の封入体と同様の特徴を示し、MC の肝発がんに小核を起点とした染色体再構成が寄与する可能性が考えられた。今後、肝臓における in vivo 変異原性の検索を実施し、それらの結果についても併せて報告する。

P-66＊

Aristolochic acid I promotes clonal expansion but did not induce hepatocellular carcinoma in adult rats

○Lu Henglei、Tan Rongrong、Xiu Xiaoyu、Zhu Huaisen

Centre for Drug Safety Evaluation and Research (CDSER), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences (CAS)

[Objective] To investigate the association between Aristolochic acid I (AAI) exposure and HCC in adult rats using a sensitive rat liver bioassay with several cofactors. **[Methods]** Conducted a medium-term (8-week) study to investigate whether AAI had any tumor initiating or promoting activity. Then a long-term (52-week) study was conducted to determine whether AAI can directly induce HCC. Formation of glutathione S-transferase placental form positive (GST-P+) foci, accumulation of AA-DNA adducts and histopathology diagnosis was used as the evaluation index. **[Results]** oral administration of single dose of AAI (20, 50 or 100 mg/kg) in combination with partial hepatectomy (PH) to stimulate liver proliferation did not induce typical GST-P+ foci in liver. In the 8-week study, only high dose of AAI (10 mg/kg/day, 5 days a week for 6 weeks) in combination with PH significantly increased the number and area of GST-P+ foci initiated by diethylnitrosamine (DEN) in liver. Similarly, only high dose of AAI (10 mg/kg/day, 5 days a week for 52 weeks) in combination with PH significantly increased the number and area of hepatic GST-P+ foci in the 52-week study. No any nodules or HCC were observed in liver of any AAI-treated groups. Besides, AAI-DNA adducts accumulated liver with a time- and dose-dependent manner. **[Conclusion]** AAI promotes clonal expansion only in the high dose group but did not induce any nodules or HCC in liver of adult rats till their deaths.

P-67＊

マウスにおける食餌性非アルコール性脂肪肝炎（NASH）病態の進展過程における Sox9 の役割

○中根 冴[1)]、煙山 紀子[2)]、阿部 有加里[3)]、渡邉 颯人[1)]、結城 恵美[4)]、美谷島 克宏[1,2,3)]、梅村 隆志[5,6)]、中江 大[1,2,3)]

[1)]東京農業大学大学院　応用生物科学研究科　食品安全健康学専攻、[2)]東京農業大学　応用生物学部　食品安全健康学科
[3)]東京農業大学大学院　農学研究科　食品安全健康学専攻、[4)]アドバンテック株式会社病理委託事業部
[5)]国立医薬品食品衛生研究所　病理部、[6)]ヤマザキ動物看護大学　動物看護学部　動物看護学科

【背景・目的】種々の細胞や臓器の発生に重要な転写因子として報告されている SRY-box9(Sox9) 遺伝子は、胆管上皮細胞に発現し、また、肝障害の進展に関与していると報告されているが、非アルコール性脂肪肝炎 (NASH) の進行への関与に関する報告がほとんどない。本研究は、Sox9 の発現が NASH の進展にどのように関与しているかを明らかにすることを目的とし、NASH 動物モデルにおける発現の経時的変化を解析した。【方法】実験は、6 週齢の C57/BL6J 系雄性マウスに基礎食またはコリン欠乏メチオニン低減高脂肪アミノ酸食（CDAA-HF、脂質 45 kcal%、メチオニン 0.1%）を 2・13・26・52・63 週間投与した群から肝臓を採取し、Sox9 の発現について解析を行なった。【結果】2 週間 CDAA-HF 投与群では、脂肪化が著明で、軽度の線維化および胆管上皮以外での Sox9 の発現を認めた。13 週間投与群では、線維化の進行と、その周囲に Sox9 の顕著かつびまん性の発現を認め、α -SMA と Sox9 の二重染色において部分的に一致ないし近傍での発現を認めた。26 週間以上投与群に発生した腫瘤内の肝細胞には Sox9 の発現が認められ、52・63 週間投与群でみられた肝細胞腺腫または肝細胞癌においては Sox9 の陽性細胞巣と陰性領域が確認された。また、52・63 週間投与群でみられた胆管線維症においては、Sox9 の高発現が認められた。【結論】Sox9 は、線維化周辺部位において顕著に発現していたことから、NASH の線維化に関与していることが示唆された。また、腫瘤内の肝細胞において発現が認められたことから、Sox9 の発現が NASH 合併肝発がんにも関与している可能性が示された。

P-68＊

Tumor promoting effect of iron (III)-tannic acid nanoparticles in diethylnitrosamine-induced hepatocarcinogenesis in rats

○Chi Be Hlaing[1)], Arpamas Chariyakornkul[1)], Chalermchai Pilapong[2)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Center of Excellence for Molecular Imaging (CEMI), Department of Radiologic Technology, Faculty of Associated Medical Sciences, Chiang Mai University

[Background] Metal-polyphenol nanoparticles gain attention in cancer nanotheranostics in recent years. Ferric-tannic acid nanoparticles (Fe-TA NPs) presented antiproliferative effect via enhanced autophagic cell death and MRI signal in the liver cancer cells. Our previous study suggested it was not genotoxic using Ames test and liver micronucleus test. **[Aim]** This study aimed to investigate the effect of Fe-TA NPs on DEN-induced hepatocarcinogenesis in rats. **[Materials and Methods]** DEN was intraperitoneally injected to male Wistar rats at 100 mg/kg bw once a week for 3 weeks, followed by partial hepatectomy. Then, 0.55, 1.75 and 17.5 mg/kg bw of Fe-TA NPs were injected intraperitoneally once a week for 10 weeks. Immunohistochemical studies of glutathione *S*-transferase placental form (GST-P) positive foci as the endpoint preneoplastic marker, proliferating cell nuclear antigen (PCNA) positive cells and TUNEL assay for apoptotic cells were performed in liver tissues collected 24 hours after last injection. **[Results]** Fe-TA NPs did not induce hepatic preneoplastic lesion in rats but 1.75 mg/kg bw of Fe-TA NPs enhanced both number and area of GST-P positive foci together with increased number of PCNA-positive cells in GST-P positive foci, and decreased apoptotic cells, compared to DEN alone group. It indicated Fe-TA NPs promoted DEN-induced hepatocarcinogenesis. **[Conclusion]** The non-genotoxic Fe-TA NPs would act as non-genotoxic carcinogen and exhibited tumor promoting action.

P-69＊

ラットにおけるジンクマルトール誘発膵臓病変の病理学的解析

○藤原 咲春、諸木 孝泰、人見 将也、佐藤 亮、寺山 由依、吉川 剛

大塚製薬株式会社 徳島研究所 前臨床研究センター 安全性研究部

【目的】亜鉛の投与により膵炎が誘発されることは報告があるが，文献によってその形態学的な記載は様々である。今回，亜鉛錯体化合物であるジンクマルトールのラットにおける 4 週間反復経口投与で誘発された膵臓病変について，病理組織学的解析を実施した。【材料・方法】6 週齢，雄の SD ラットにジンクマルトールを 1000 mg/kg/day の用量で 4 週間経口投与した。解剖して得られた膵臓の標本について，HE 染色，マッソントリクローム染色及び免疫組織化学染色を施し，病理組織学的解析を行い，病変部について透過型電子顕微鏡で観察を行った。【結果】ジンクマルトール投与群では，びまん性の腺房萎縮，間質の線維化及び軽微な単核細胞の浸潤が見られた。残存する腺房の周囲では SOX9 を発現する導管様構造が増生していた。増生した線維化領域は豊富な膠原線維と vimentin 陽性の紡錘形細胞から成り，α -SMA 及び desmin 陽性の筋線維芽細胞が散見されたが，膵星細胞マーカーである GFAP 陽性の細胞は僅かであった。間質に浸潤する細胞の多くは Iba-1 陽性であった。電子顕微鏡による観察では，萎縮した腺房は Zymogen 顆粒を殆ど持たない腺房細胞と導管上皮細胞から構成される小さな腺管構造として認められた。【考察】本病変は腺房の萎縮が顕著であったことから，腺房の傷害を主体とし，二次的にマクロファージの浸潤及び線維化が起こったと考えられた。膵臓では膵星細胞から分化した筋線維芽細胞が線維化を促進するとされるが，今回の検討では膵星細胞の増生は示されなかった。げっ歯類における亜鉛イオン化合物の投与で急性膵炎や腺房壊死が報告されているが，今回は分葉核球の浸潤や腺房壊死が乏しく，既報の亜鉛誘発の膵炎とは異なる形態学的特徴が得られた。

P-70

gpt delta ラットを用いた 3-acetyl-2,5-dimethylfuran の一般毒性・遺伝毒性・発がん性包括的毒性評価

○高須 伸二、石井 雄二、並木 萌香、中村 賢志、能美 健彦、小川 久美子

国立医薬品食品衛生研究所　病理部

【背景】3-Acetyl-2,5-dimethylfuran（ADF）はフラン骨格を有する香料化合物である。本物質は定量的構造活性相関（QSAR）を用いた遺伝毒性スクリーニングにおいて Ames 変異原性が示唆され、Ames 試験で陽性を示すことが確認された。しかし、ADF の毒性情報は乏しく、*in vivo* における遺伝毒性や発がん性に関する情報はこれまでにない。そこで、本研究では ADF の一般毒性、変異原性及び発がん性を評価するため、*gpt* delta ラットを用いた包括的毒性試験を実施した。【材料と方法】雄性 6 週齢の F344 系 *gpt* delta ラットに ADF を 0、30 または 300 mg/kg の用量で 13 週間強制経口投与し、一般毒性評価を実施した。肝臓では重量増加とともに病理組織学的変化及び細胞増殖の亢進がみられたことから、変異原性及び発がん評価の対象を肝臓として、*gpt* assay 及び前がん病変マーカーである GST-P 陽性細胞巣の免疫組織化学的検索を実施した。【結果】一般毒性評価では、300 mg/kg 投与群において体重増加抑制がみられ、30 mg/kg 以上の投与群において、トリグリセリド、総コレステロール、リン脂質の低下が認められた。病理組織学的検索の結果、300 mg/kg 投与群では小葉中心性肝細胞肥大および鼻腔嗅上皮の壊死、呼吸上皮化生が認められた。肝臓の *gpt* 変異体頻度は 300 mg/kg 投与群で有意な高値を示し、同群では GST-P 陽性細胞巣の数及び面積が有意に増加した。【結論】一般毒性評価の結果、ADF はラットに対して毒性影響を有することが示唆された。また、肝臓では前がん病変マーカーの増加に加えて、*gpt* 変異体頻度の有意な上昇が認められたことから、ADF は遺伝毒性ラット肝発がん物質である可能性が示された。

P-71

ジフェニルアルシン酸の C57BL6/J マウスにおける慢性毒性試験及び発がん性試験

○山口 貴嗣[1)]、魏 民[2)]、藤岡 正喜[1)]、鈴木 周五[1)]、大石 裕司[1)]、鰐渕 英機[1)]

[1)]大阪市立大学大学院　医学研究科　分子病理学、[2)]大阪市立大学大学院　医学研究科　環境リスク評価学

【背景】第二次世界大戦後の不法投棄のため、日本の一部の地方の地下水や土壌には、有機ヒ素であり、神経毒性を有するジフェニルアルシン酸（以下、DPAA）が存在する。 本研究の目的は、マウスにおける DPAA の慢性毒性及び発がん性を評価することである。【方法】雌雄の C57BL6/J マウスに 0, 6.25, 12.5, 及び 25ppm の濃度の DPAA を 52 週間（慢性毒性試験）及び 78 週間（発がん性試験）飲水投与した。評価項目は両試験とも体重、摂餌量、摂水量、臓器重量及び病理組織学的検査とし、さらに慢性毒性試験では、血液生化学検査及び雌の 0 及び 25ppm の DPAA 群の肝臓におけるプロテオミクス解析を実施した。【結果】慢性毒性試験：雌雄の各コントロール群と比較して、雄では 25ppm の DPAA 群で肝臓の相対重量の有意な増加、雌では 25ppm の DPAA 群で肝臓の絶対重量の有意な増加が認められた。さらに、肝臓において、雌の 25ppm の DPAA 群では、胆管炎及び胆管上皮過形成の発生数の有意な増加が認められた。またプロテオミクス解析では、雌の 25ppm の DPAA 群で Phase I 代謝酵素である CYP2E1 タンパクの過剰発現が認められた。発がん性試験：6.25、12.5 及び 25ppm の濃度の DPAA を投与した雌雄の C57BL6/J マウスでは、どの臓器及び組織においても腫瘍発生率の有意な増加は認められなかった。【結論】これらの結果より、DPAA は C57BL6/J マウスにおいて、肝内胆管上皮及び肝細胞に対して毒性を示し、CYP2E1 が DPAA の代謝及び毒性に関与すること、さらに本試験条件下において、DPAA の無毒性量は雄で 12.5ppm、雌で 6.25ppm であると考えられた。また発がん性試験では、DPAA は発がん性を有しないと考えられた。

P-72＊

28-day repeated inhalation toxicity study of 1,2-dichlorobenzene in Fischer 344 rats

○Hee-Seon Park, Hye-Yeon Choi, Yong-Soon Kim, Mi-Ju Lee

Pathology Department, Inhalation Toxicity Research Center, Chemical Research Bureau, Occupational Safety and Health Research Institute
Korea Occupational Safety and Health Agency

[Background] 1,2-Dichlorobenzene is widely used around the world as solvent for various substances and degreasing agent for metals, leather, and paper. It has aroused concern since inhalation of mist or vapor may result in damage to several organs including lung, liver and kidneys. **[Aim]** The quantitative and available data is limited to make toxicity profile of 1,2-dichlorobenzene. Therefore, we performed 28-day repeated inhalation toxicity using F344 rats. **[Materials and Methods]** Each sex of animals was randomly divided to four groups consisting of five rats. 1,2 dichlorobenzene was exposed in whole body chamber at concentration of 0, 50, 150 and 450 ppm 6 hours per day, five times per week for 28 days and followed by organ weight measurement, hematology, serum biochemistry, and histopathologic examination. **[Results]** Body weight was decreased in rats exposed to 1,2-dichlorobenzene. APTT and PT were elongated in rats exposed to 1,2-dichlorobenzene. Total protein, albumin, and ALT concentration were increased in rats exposed to 1,2-dichlorobenzene. Absolute and relative liver weights were increased in rats exposed to 150 and 450 ppm 1,2-dichlorobenzene. Histopathologically, karyomegaly and vacuolation in the liver were noted in rats exposed to 1,2-dichlorobenzene. **[Conclusion]** Taken together, these results suggest that liver was the major target organ of 1,2-dichlorobenzene.

P-73

四塩化炭素（CCl4）皮下注射によるラット非アルコール性脂肪肝モデルの病理特徴とバイオマーカーの研究

○金 毅[1)]、李 静[2)]、呂 愛貞[2)]、李 明[2)]、金 志虎[2,3)]

[1)]深セン市薬品検験研究院、[2)]広東東陽光薬業株式会社、[3)]深セン金質科技株式会社

【背景】四塩化炭素（CCl4）皮下注射によるラット非アルコール性脂肪肝モデルの病理特徴が腹腔内注射、或いは内服による肝臓病変と顕著に異なることを発見した。【目的】CCl4 皮下注射によるラット非アルコール性脂肪肝モデルの病理特徴とバイオマーカーを探索する。【材料と方法】雄ラットを用いて、コントロールグループとモデルグループ、予防投与グループ、治療グループに分けられ、後者の二組は漢方薬の通絡却濁方を投与した。９週にて動物実験を終え、光学顕微鏡でラットの肝臓組織を観察し、ラットの血漿を HPLC-QTOF/MS にて代謝分析を行った。【結果】CCl4 皮下注射によるラット非アルコール性脂肪肝モデルの肝臓病変が脂肪変性が顕著に認められ、他のルートで CCl4 投与されたモデルと違った。リノール酸エステルとリン脂質コリ PC(0:0/18:0) が各グループの間で顕著に違った（P<0.05）。【結論】リノール酸エステルとリン脂質コリ PC(0:0/18:0) が CCl4 に誘導された NAFLD ラットモデルのバイオマーカーの可能性が提示された。漢方薬の通絡却濁方が NAFLD ラットモデルの脂肪変性した肝細胞に効果が見られた。

P-74

Establishment of mouse orthotopic transplantation tumor models of human hepatoma and comparison of their characteristics

○Jun Yin[1)]、Du Mu[3)]、Dingsha Lijing[1)]、Huiming Zhang[2)]、Ruiping She[2)]、Conglin Zuo[2)]

[1)]北京昭衍新薬研究中心有限公司、[2)]中国農業大学動物医学院、[3)]昭衍（蘇州）新薬研究中心有限公司

[Objective] Three human hepatoma cell lines were injected into livers of four mice with different immune function defects to establish orthotopic xenograft models of human hepatoma for comparison. **[Methods]** Human HepG2, HUH-7, and QGY-7703 cell suspensions were injected in BALB/c nude, NOD SCID, NOG and NPG mice liver. Survival time, mortality, liver weight, B-mode ultrasound, and histology were used to analyze and compare the characteristics of liver cancer models in the mice. **[Results]** All experimental animals showed tumor nodule formation in livers. All animals injected with a HepG2 cell suspension into livers died at about 20 days. The survival time of NOG and NPG mice was significantly shorter than that of BALB/c and NOD SCID mice. Experimental groups with injected HUH-7 and QGY-7703 cell suspensions into livers were autopsied at day 92 and 104. The liver volumes of NOG and NPG model mice were increased significantly and formed large tumor masses, whereas BALB/c nude and NOD SCID mice showed only small tumor nodules in livers. The weights of NOG and NPG mouse livers were significantly higher than those of BALB/c nude and NOD SCID mouse livers. **[Conclusion]** Compared with BALB/c nude and NOD SCID mice, hepatoma cells grew more rapidly in the liver of NOG and NPG mice, and the survival time was short, the liver volume was large, and the weight was increased.

P-75＊

ヒト化マウスを用いた薬物性肝障害モデル作出の試み

○藤原 奨、井澤 武史、田中 美有、桑村 充

大阪府立大学　獣医病理

【背景・目的】PXB マウスは肝臓の 70% 以上がヒト由来肝細胞で置換され，ヒト肝臓と同様の薬物代謝酵素を発現する．PXB マウスはヒトの薬物動態予測に有用であることが報告される一方で，肝毒性の感受性に関する報告は少ない．本研究では PXB マウスに肝毒性物質であるアセトアミノフェン（APAP），四塩化炭素（CCl_4），アリルアルコール（AA）を投与し，誘発される肝病変を解析した．【材料・方法】18 から 19 週齢の PXB 雄マウスに CCl_4（0.75, 1.25, 2.00 ml/kg），AA（35, 50, 70 mg/kg），APAP（500 mg/kg）あるいは生理食塩水を単回ないし 3 日間連続腹腔内投与した．最終投与後 18 ないし 24 時間で採材し，血液生化学検査と病理組織学的検査を行った．肝小葉の zone 特異的マーカーの免疫染色を行い，移植ヒト肝細胞領域における metabolic zonation を評価した．【結果】CCl_4 モデルでは，1.25 ml/kg の単回および 3 回投与個体にて ALT の上昇がみられ，単回投与個体では残存するマウス肝細胞に凝固壊死が認められた．ヒト肝細胞領域には壊死はみられなかった．AA および APAP モデルでは，肝逸脱酵素値の上昇と肝細胞の壊死は観察されなかった．PXB マウスのヒト肝細胞領域では，Zone 1 に ASS1，Zone 3-2 に CYP2E1，Zone 3 に glutamine synthetase が発現しており，ヒト肝組織と同様の metabolic zonation の形成が認められた．alcohol dehydrogenase 1（ADH1）の発現は小葉全体に認められた．【結論・考察】げっ歯類の肝毒性容量を超える投与量設定にもかかわらず，PXB マウスのヒト肝細胞領域では明らかな肝障害が認められず，肝毒性感受性が低い可能性が示された．その機序として，代謝酵素活性の変化，解毒経路の活性化，抗ストレス応答の活性化などが考えられ，現在さらなる解析を進めている．

P-76

NAFLD モデルラットにおける糖尿病誘発の影響

○井澤 武史、水口 恵理、山手 丈至、桑村 充

大阪府大　獣医病理

【背景・目的】非アルコール性脂肪性肝疾患（NAFLD）の肝障害や線維化の進展に糖尿病が関わることが報告されているが，詳細なメカニズムは不明である。本研究では，Western diet（WD）誘発 NAFLD モデルに糖尿病を負荷することで，肝病変への影響を調べた。【材料・方法】1）Zucker+WD モデル：6 週齢の雄 ZDF-*Lepr*^{fa} /CrlCrlj ラットに正常食（Zucker+ND; 脂質 4%）または WD（脂質 21%・果糖 34% 含有食＋糖水）を 13 週間投与し，その病態を解析した。2）STZ+WD モデル：6 週齢の雄 F344/DuCrlCrlj ラットに WD を 20 週間給餌した。実験開始 6 週目に低容量ストレプトゾトシン（STZ; 20 mg/kg）を 3 日間連続腹腔内投与し，糖尿病を誘発した。【結果】1）Zucker+ND 群と比べて，Zucker+WD 群では血中総コレステロールが増加，中性脂肪が減少した。肝病変は個体差が大きいものの，Zucker+WD 群で Zone 1 からびまん性に肝細胞の小滴性脂肪化が強くみられ，ALT，AST の上昇を伴っていた。Zucker+ND 群の 1 個体でも，肝酵素上昇を伴う小滴性脂肪化がみられた。2）高血糖を発症した STZ+WD 群では，WD 単独群と比べて，血中脂質（特に中性脂肪）の上昇，インスリンの低下がみられ，Zone 3 を中心とした大滴性脂肪化の増加が認められたが，肝酵素の上昇はみられず，肝臓の炎症は軽微であった。【結論】Zucker+WD モデルではコレステロール代謝異常に基づく小滴性脂肪化が促進され，肝障害を伴っていることから，実験期間を延長することで，線維化の誘発が期待される。STZ+WD モデルでは，高トリグリセリド血症に基づく大滴性脂肪化が促進されるものの，脂肪性肝炎を誘発するには酸化ストレスや炎症をさらに誘導する必要があると考えられた。

P-77＊

ラットにおける非アルコール性脂肪性肝炎（NASH）病態の肝線維化への CD44 の関与

○宇野 絹子[1)]、美谷島 克宏[2,3)]、当摩 茉莉花[3)]、煙山 紀子[2)]、中江 大[2,3)]

[1)]東京農大院 農学研究科 食品栄養学専攻、[2)]東京農大　食品安全健康学科
[3)]東京農大院　応用生物科学研究科　食品安全健康学専攻

【目的】近年、メタボリックシンドローム患者数の増大に伴い、非アルコール性脂肪性肝炎（NASH）の患者数が世界的に増加している。NASH は、肝細胞の脂肪化や炎症、及び肝線維化を特徴とする肝疾患であり、肝硬変や肝がんへ進行するリスクを有するため、根治的な治療法の確立が求められる。CD44 は、NASH における肝炎症を中心とした病態の制御において主要な因子と考えられている。本研究では、コリン欠乏メチオニン低減アミノ酸食（CDAA 食）誘発性の NASH 様病態について肝線維化における CD44 の寄与を解析した。【方法】雄性 6 週齢の Fischer 344（F344）ラットに、CDAA 食を 2, 4, 13 または 26 週間給餌した。給餌期間中は一般状態の観察と体重測定を行った。解剖時は、採血後に肝臓を摘出し、一部をホルマリン固定、残りを凍結した。血液は血液生化学的検査に用い、肝臓は病理組織学的解析及び遺伝子発現解析に用いた。【結果および考察】CDAA 食給餌によって早期から肝障害パラメーターの上昇や、炎症関連遺伝子発現の上昇、病理組織学的に肝細胞脂肪化が見られ、NAFLD/NASH 病態を呈し、13 週間給餌以降では、明らかな肝線維化を示した。CD44 は、肝中遺伝子発現解析及び病理組織学的解析において、経時的な発現上昇を示した。CD44 の発現は、これまで報告されてきた炎症性細胞のみならず、一部の胆管上皮細胞においても観察された。肝線維化は、CD44 陽性胆管上皮細胞の増加に伴って増強し、CD44 の主要なリガンドとされているヒアルロン酸は CD44 陽性胆管周囲性に観察され、肝線維化への寄与が考えられた。以上の結果から、CD44 は肝炎症のみならず、肝線維化においても重要な因子である可能性が示唆された。

P-78＊

hL-FABP tg マウスを用いた L-FABP の早期 NAFLD バイオマーカーとしての有用性に関する検討

○当摩 茉莉花[1)]、美谷島 克宏[1,2)]、大畑 敬一[3)]、宇野 絹子[4)]、堀内 彩花[2)]、煙山 紀子[2)]、中江 大[1,2)]

[1)]東京農業大学大学院　応用生物科学研究科　食品安全健康学専攻、[2)]東京農業大学 応用生物科学部 食品安全健康学科
[3)]シミックホールディングス株式会社　L-FABP 事業部　研究開発グループ、[4)]東京農業大学大学院 農学研究科 食品栄養学専攻

【背景及び目的】非アルコール性脂肪性肝疾患 (NAFLD) の発症・進展に至る機序は未だ明らかではなく、根治的な治療法も確立されていない。NASH の早期段階にあたる NAFLD の診断において、より早期からのバイオマーカーが重要視され、L-FABP は既に NASH のバイオマーカーとしてその有用性が報告されているが、早期 NAFLD のマーカーとしての知見は少ない。食餌誘発性 NASH 様病変の動物モデルであるコリン欠乏メチオニン低減アミノ酸食 (CDAA) 及び高脂肪食 (HFD) で誘発された早期段階の肝病変に対して、血中 L-FABP の NAFLD のバイオマーカーとしての可能性を検討した。【材料及び方法】16 週齢の雄性 hL-FABP tg マウスに、CDAA 食または HFD をそれぞれ 1, 3 及び 7 日間給餌後、解剖し、肝臓の病理組織学的観察、血液生化学的検査、ELISA による hL-FABP 濃度測定を行った。対照として通常食 7 日間給餌群を設定した。【結果】病理組織学的観察にて、CDAA の 1 日目では、肝小葉全域においてびまん性に小型の脂肪滴の沈着が認められ、その後小葉全域における大型の脂肪滴沈着像へと経時的に推移した。HFD の 1 日目では、小葉辺縁性の軽度の肝細胞の脂肪化が認められ、経時的に脂肪化の領域が小葉辺縁より広まり、脂肪滴が顕著となった。血中 hL-FABP 濃度は、CDAA 及び HFD の 1 日間給餌に於いて最も濃度が高く、その後 3 乃至 7 日間給餌では緩やかに減弱した。血液生化学的検査の結果、血中 hL-FABP 濃度は、血中 ALT 活性と正の相関を示した。【考察】CDAA 食と HFD では給餌の早期段階において病理組織像に差異が生じたが、血中 L-FABP 濃度は何れのモデルにおいても 1 日目から増加する事が明らかとなった。血中 L-FABP 濃度は血中 AST 及び ALT 活性の上昇に比較し、より早期の段階で検出された事から、NAFLD の早期バイオマーカーとしても有用である可能性が示された。

P-79＊

2 型糖尿病動物モデルの病態におけるグルカゴンの関与

○万代 康平[1)]、美谷島 克宏[1,2,3)]、渡邉 果奈[1)]、石塚 佳菜[1)]、宇野 絹子[4)]、煙山 紀子[2)]、篠原 雅美[5)]、笹瀬 智彦[5)]、渡辺 寿久[6)]、伊藤 秀樹[6)]、篠原 雅巳[7)]、太田 毅[5,8)]、中江 大[1,2,4)]

[1)]東京農業大学　応用生物科学部　食品安全健康学専攻、[2)]東京農業大学　応用生物科学部　食品安全健康学科
[3)]東京農業大学　農学研究科　食品安全健康学専攻、[4)]東京農業大学大学院　農学研究科　食品栄養学専攻
[5)]日本クレア株式会社　東京 AD 部、[6)]日本クレア株式会社　富士生育所、[7)]日本クレア株式会社　業務推進部
[8)]京都大学大学院　農学研究科　応用生物科学専攻　生体機能学分野

【背景・目的】近年、２型糖尿病が健康問題となっている。糖尿病患者においては、インスリンの作用不足のみならず、グルカゴンの異常分泌が報告され、糖尿病患者における病態悪化との関連が疑われている。そこで、肥満 2 型糖尿病モデル動物におけるグルカゴン及びその関連臓器についての解析を行い、糖尿病病態への影響を検討する。
【材料・方法】5 週齢の雄性 SDT fatty ラット (SDTf) と SD ラット (SD) に CE-2（BD: 基礎食）及び Quick Fat (QF: 高脂肪高ショ糖食) を SD に 21 週間、SDTf に 23 週間自由給餌させた。飼育期間終了後に採血し、諸臓器の採取後各種解析を行った。
【結果】体重は SD に対し、SDTf で低い値を示し、両系統とも QF による体重増加傾向を示した。血液生化学検査では、AST と ALT は SD に対し SDTf で高い値を示し、血糖値も同様の結果を示した。インスリン濃度は、SDTf 群で低い値を示し、TG 及び TC においては、いずれの系統も QF による高い値を示した。病理組織学的解析では、SDTf において、膵島の不整や萎縮が観察された。また SD に対し SDTf で膵島中のインスリン陽性細胞面積の減少、グルカゴン陽性細胞面積の増加も見られた。肝臓の遺伝子発現解析では、SDTf 群でグルカゴンにより発現が亢進する PGC-1 αと糖新生関連遺伝子の発現上昇が見られ、解糖系遺伝子の発現低下が見られた。いずれの系統でも肝臓において QF 食による FGF21 の発現上昇が見られた。また、褐色脂肪細胞においては、SDTf 群で、UCP1 とその関連遺伝子の発現低下が見られた。
【結論】2 型糖尿病においては、インスリン抵抗性のみならず、グルカゴンの作用増強による糖新生の亢進が、糖尿病病態の悪化に関連している可能性が示された。

P-80

膵癌モデルラットを用いた膵癌の血清診断マーカ LRG-1 の同定

○深町 勝巳[1)]、Sultana Nahida[1)]、松本 晴年[1)]、津田 洋幸[2)]、酒々井 眞澄[1)]

[1)]名古屋市立大学大学院医学研究科、[2)]名古屋市立大学

膵がんは 5 年生存率が 10% 以下で、罹患率と死亡率がほぼ同じの難治がんである。膵癌の克服には早期診断、早期治療が重要である。しかし、これまでに臨床で用いられてきた膵がんの腫瘍マーカーは早期診断には有用ではないため、膵がんの新たな診断マーカーを同定する多くの試みがなされている。我々は、これまでに遺伝子改変ラットを作製し、ラット膵がんモデルを確立した。Cre/loxP システムを用いた活性型 RAS コンディショナルトランスジェニックラットの膵管内に Cre リコンビナーゼ発現アデノウイルスを注入することにより活性型 RAS を膵臓に発現させるとヒトに極めて類似した間質の豊富な膵管がんを発生させることが可能である。本研究において、我々はラット膵がんモデルにおいて正常膵に比較し膵がんで高発現している Leucine-rich α 2-glycoprotein-1 (LRG-1) を同定した。血清 LRG-1 の濃度は膵がんが発生したラットにおいてコントロールラットと比較し有意に高かった。膵炎での影響を検討するため慢性膵炎のモデルである雄 WBN/Kob ラットにおける血清 LRG-1 濃度を測定したが、慢性膵炎による血清中の LRG-1 濃度の変化はなかった。以上より、LRG-1 は膵がんの血清診断マーカーとして有用であることが示された。また、本ラット膵がんモデルは、ヒト膵がんに応用できるバイオマーカー候補の同定に有用な系であると考えられる。

P-81＊

肝毒性評価モデルとしての肝スライス培養法

○加藤 由隆、高橋 尚史、藤原 千夏、宮崎 新也、伊藤 強、小山 彩、志賀 敦史、大塚 亮一、武田 眞記夫、原田 孝則

（一財）残留農薬研究所

【背景・目的】肝スライス培養法は生体内細胞環境の再現性が高く、病理組織学的検査が可能、3Rs における削減および代替に寄与できるなどの利点を有し、新規 *in vitro* 技術研究が進んでいる現在においてもその利用価値は高い。本研究では肝スライス培養を用いた肝毒性評価法の確立を目的として、[1] 代表的な肝毒性物質を用いた評価、[2] CAR-siRNA を用いた評価を実施し、その有用性について検討した。
【材料・方法】Krumdieck slicer を使用して、厚さ 200-250 μ m のラット肝スライス切片を作製した。これを [1] Phenobarbital (PB) (100 μ M), Acetaminophen (APAP) (2.5mM), Lipopolysaccharide (LPS) (100 μ g/mL) をそれぞれ添加、もしくは [2] CAR-siRNA および PB を添加し、95% O_2/5% CO_2、37℃の条件下で最大 72 時間培養した。それぞれについて培養液と組織を経時的に採材し、分子病理学的に解析した。
【結果】[1] PB 群では肝細胞肥大は観察されなかったものの、*Cyp2b1* 発現量は顕著に増加した。APAP 群では balloon cell 様の水腫変性がみられ、周囲には PCNA 陽性細胞が多数観察された。LPS 群では AST、ALT、LDH の有意な増加および肝細胞壊死が観察されるとともに、oval cell の増生もみられた。[2] PB 群と比較して CAR-siRNA + PB 群では、*Car* 発現量が約 70% knock down され、*Cyp2b1* 発現量も約 5% に抑制された。また抗 CYP2B1 抗体を用いた免疫染色では、PB 群において CYP2B1 の小葉中心性の局在が確認され、CAR-siRNA + PB 群では陽性率の減弱がみられた。
【結論】肝スライス培養法を用いた肝毒性評価モデルは、生体における反応を精度よく再現すると共に、初代培養をはじめとする従来の *in vitro* 試験系では検出が難しい組織学的変化を捉えることができる、有用な試験系であることが確認された。

P-82＊

Deep learning-based Image analysis algorithm for classification and quantification of multiple histopathological lesions of the rat liver

○島嵜 大志[1)]、牟田 恭孝[1)]、山田 直人[1)]、安井 雄三[1)]、Deshpande Ameya[2)]、Hajra Anindya[2)]、Thomas Tijo[2)]、正田 俊之[1)]

[1)]日本たばこ産業株式会社　医薬総合研究所　横浜リサーチセンター、[2)]AiraMatrix

【背景と目的】AI を用いた画像解析アルゴリズムを用いて，ラット肝臓における複数の病理組織学的所見を学習させ，異常部位の検出及び定量化を試み、得られた結果について精度を評価した。【材料と方法】8 週齢の雄性 SD ラットの肝臓における典型的な病理組織学的所見群（空胞化，単細胞壊死，肝細胞肥大など）の WSI をトレーニングセットとして 92 枚，テストセットとして 59 枚を用いアルゴリズムの学習及び検証を行った。フィードバックされた結果の確認及び再学習を繰り返し、アルゴリズムの精度を深化させた。最終的に 255 枚の肝臓の WSI 標本を解析し，WSI 標本ごとに異常部位の検出及び定量化を試みた。また標本ごとに得られた各所見の定量値に対して社内パソロジスト達が診断した病理組織学的グレード情報を付与し，定量値から「所見なし / あり」を識別できるように閾値を算出した。【結果】本アルゴリズムによる上記所見の検出精度は良好であった。また定量分析の結果及び閾値から導き出される診断の判別結果は，パソロジスト達が診断した病理組織学的診断と相関していた。【結論】本アルゴリズムは，ラットの病理組織画像の識別に特化しており，最大の特徴は 1 枚の WSI 上の，様々な異常部位を検出し，かつこれら異常部位の組織形態から予測される毒性所見名を提示し，かつ，その異常部位を定量化することができることである。所見によって検出精度に差は認められるものの，毒性試験への実装にあたり概ね許容範囲の精度と考えられた。毒性所見の検出及び定量化機能は，パソロジストの病理評価における補助的機能として，主に非 GLP の早期毒性試験の毒性病理学的検査の一次スクリーニングに有用であると考えられた。今後は他の臓器についても開発を進めていく予定である。

P-83

Quantification of hepatic fibrosis in Sprague-Dawley rats using deep learning instance segmentation focused on H&E staining whole slide level

○Ji-Hee Hwang[1)], Hyun-Ji Kim[1,2)], Heejin Park[1)], Byoung-Seok Lee[1)], Hwa-Young Son[2)], Yong-Bum Kim[3)], Sang-Yeop Jun[4)], Jong-Hyun Park[4)], Jaeku Lee[4)], Jae-Woo Cho[1)]

[1)] Toxicologic Pathology Research Group, Toxicology Mechanism Research Divison, Department of Advanced Toxicology Research, Korea Institute of Toxicology
[2)] College of Veterinary Medicine, Chungnam National University
[3)] Department of Advanced Toxicology Research, Korea Institute of Toxicology
[4)] Research & Development team, LAC Inc

[Background] The exponential development in artificial intelligence since the advent of deep learning has affected clinical and non-clinical studies attempting the application of the technology to pathological diagnosis.
[Aim] We applied 'Mask R-CNN', one of the image segmentation algorithms, to test whether the deep learning technique can be applied to detect the toxicologic pathology lesion, hepatic fibrosis.
[Materials and Methods] Hepatic fibrosis in SD rats was induced by NDMA, and H&E stained Whole slide image(WSI)s were used for data preparation. Total 2,011 cropped images were collected from 51 WSIs, and hepatic fibrosis was annotated using VGG 2.0.1.0. Training and detection of hepatic fibrosis via Mask R-CNN were performed by Tensorflow 2.1.0, powered by an NVIDIA 2080 Ti GPU. The trained model validation at the WSI level was conducted by comparing the model predictions in 18 WSIs at 20X and 10X magnifications with ground truth annotations and board-certified pathologists.
[Results] 95% of model accuracy was observed from the test process using tile images. The validation at the WSI level showed a high correlation between ground truth annotation and model prediction (R2 = 0.9660). Furthermore, the predictions at 20X showed a good correlation with the average fibrosis rank by pathologists (R2 = 0.8887).
[Conclusion] We confirmed the possibility of quantification and automatic diagnosis of hepatic fibrosis of SD rats in H&E stained WSIs using a deep learning algorithm.

P-84＊

膵癌における DPYD 発現の寄与と発現抑制機序の検討

○加藤 寛之、内木 綾、小村 理行、高橋 智

名古屋市立大学　大学院医学研究科　実験病態病理学

【背景】我々は以前の本学会にてフラボノイドの一種である Luteolin(Lut) が BOP 誘導のハムスター膵発癌を抑制し、その機序として dipyrimidine dehydrogenase (DPYD) の抑制が寄与する事を発表した。DPYD は 5-FU の分解酵素として知られているが、その発現自体の膵癌への寄与は不明である。本研究では、DPYD の発現による膵癌細胞における 5-FU の感受性の違いや癌の進展への寄与、DPYD の制御機構および DPYD 抑制に重要な Lut の化学構造について検討した。【方法】低 DPYD 発現膵癌細胞株 (AsPC1, 8988T) に DPYD を強制発現させ、両細胞の増殖能、5-FU の感受性を検討した。また、DPYD 強制発現 AsPC1 をヌードマウスに皮下移植し、腫瘍生着率と腫瘍体積を調べた。DPYD の制御に関しては、miRNA のマイクロアレイ解析と DPYD に結合しうる miRNA を検討した。また、Lut に類似した化学構造を有する他のフラボノイドを含む 19 種類の物質について、DPYD 発現の抑制効果を検討した。【結果】DPYD 導入細胞の増殖能は有意に高く、低濃度の 5-FU において細胞増殖抑制効果が有意に低下していた。皮下移植腫瘍は現在実験進行中であるが、AsPC1-DPYD の腫瘍体積は AsPC1-LacZ より大きい傾向がみられた。マイクロアレイ解析により、Lut 投与によって上昇する miRNA は 164 個みられ、そのうち DPYD に結合しうる miRNA として miR-494-3p が抽出された。Lut 投与により miR-494 発現が上昇することを確認した。Lut 骨格については、flavone 骨格の 3', 5' 位の水酸基が維持された２物質で DPYD 抑制作用が見られた。【結語】膵癌細胞における DPYD 発現は増殖能を上昇させるとともに 5-FU に対する感受性を低下させ、その制御機構として miR-494 の関与が示唆された。また、DPYD の抑制には少なくとも flavone 骨格の 3', 5' 位の水酸基が維持される事が重要であることが判明した。

P-85

職業性膀胱がん関連芳香族アミンの膀胱尿路上皮への影響及び尿中代謝物との関係

○鈴木 周五、魏 民、藤岡 正喜、梯 アンナ、鰐渕 英機

大阪市大　院医　分子病理学

【目的】芳香族アミンによる職業性膀胱癌は社会的な問題の一つであり、最近でも o-toluidine(OTD) 等の芳香族アミンを取り扱う従事者から膀胱癌が発生しており、今後も類似の芳香族アミン類による膀胱がん発生の危惧がある。我々は福井県の化学工場で曝露を認めた種々の芳香族アミンを用いて、その膀胱尿路上皮への影響とともに尿中代謝物に着目し影響の相関を検討した。【材料と方法】6 週齢雄 F344 ラットに 0.6% anilinium chloride (ANL)、0.3％ p-toluidine hydrochloride (PT)、1.5% acetoaceto-o-toluidide (AAOT) および 0.6% OTD を混餌投与した。投与第 4 週目に新鮮尿を採取し、液体クロマトグラフ質量分析計（LC-MS/MS）により尿中の芳香族アミンおよびその代謝物を測定した。4 週間後に屠殺・剖検し膀胱を採取、病理組織検討、免疫組織化学染色および TUNEL 染色を行った。【結果】AAOT および OTD 投与群では膀胱に単純過形成病変が有意に増加し、Ki67 陽性率の有意な上昇を認めた。一方、ANL および PT 投与群では対照群と比較し、いずれも差が見られなかった。TUNEL 陽性率についてはいずれの群でも差が見られなかった。AAOT および OTD 投与群において、尿中に最も多く存在する物質は OTD であり、その代謝物も存在した。一方、ANL および PT 投与群では、それぞれの投与物質および代謝物が確認され、OTD はほとんど認められなかった。【結論】AAOT および OTD 群において、ラット膀胱発がん性に関与する尿中化学物質は OTD およびその代謝物である可能性を示した。

P-86

オルト - トルイジンおよびオルト - アニシジン代謝物の 28 日間反復経口投与によるラット膀胱への影響

○豊田 武士[1)]、小林 琢磨[2)]、三好 規之[2)]、松下 幸平[1)]、赤根 弘敏[1)]、森川 朋美[1)]、小川 久美子[1)]

[1)]国立医薬品食品衛生研究所　病理部、[2)]静岡県立大学　生化学研究室

【背景と目的】染料・顔料の製造原料に用いられるオルト - トルイジン（*o*-Tol）およびオルト - アニシジン（*o*-Ans）は、膀胱発がん性を有する芳香族アミンとして知られるが、発がん機序に関与する代謝物の詳細はいまだ明らかではない。本研究では、共同研究者らによって新たな尿中代謝物として報告された *o*-Tol・*o*-Ans それぞれの head-to-tail 二量体（MMBD および MxMxBD）について、短期反復経口投与によるラット膀胱への影響を、病理組織学的・免疫組織化学的手法により解析した。

【方法】6 週齢の雄 F344 ラット（各群 5 匹）に、MMBD, MxMxBD, *o*-Tol, *o*-Ans を 100 mg/kg/day の用量で 28 日間強制経口投与（溶媒：コーン油）した。投与量は各二量体を合成可能な最大量に合わせて設定した。比較のための高用量群として、400 mg/kg *o*-Tol および 600 mg/kg/day *o*-Ans 群を併せて設置した。膀胱における病理組織学的検索およびγ -H2AX・膀胱幹細胞マーカー（KRT14, ALDH1A1, CD44）の免疫染色を実施した。

【結果】病理組織学的検索の結果、*o*-Tol・*o*-Ans 高用量群では過形成等の膀胱病変が誘発されたが、低用量群および MMBD・MxMxBD 群では 100 mg/kg *o*-Tol 群における単核細胞浸潤以外に明らかな病変はみられなかった。*o*-Tol・*o*-Ans 高用量群では膀胱尿路上皮におけるγ -H2AX 形成の有意な増加が認められたが、MMBD・MxMxBD 群では対照群と同じレベルに留まった。一方、膀胱幹細胞マーカーの免疫染色では、*o*-Tol・*o*-Ans 投与群に観察された ALDH1A1 発現増加が、MMBD・MxMxBD 群においても認められた。

【考察】MMBD・MxMxBD は膀胱粘膜に ALDH1A1 発現を誘導し、それぞれ *o*-Tol・*o*-Ans の膀胱発がん過程に関与している可能性が示唆された。同二量体の経口投与によって膀胱病変およびγ -H2AX 形成増加を誘導するには、より高い用量が必要と考えられた。

P-87＊

The potential effect of thymoquinone and *Nigella sativa* crude oil extract on experimental urinary bladder cancer model

○Areeg M. Khalifa, Elsayed I. Salim

Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University

[Background] *Nigella sativa* oil and its main constitute Thymoquinone are both known for being effective on a broad spectrum of the biological pathways in living organisms. **[Aim]** The present study aimed to investigate the effect of both *Nigella sativa* and Thymoquinone on the urothelial lesions induced by *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) in male Wistar rats. **[Materials and Methods]** A six-week-old male Wistar rats were divided into four groups: The 1st group received no treatment as -ve control, the 2nd was treated with 0.05% BBN and 5% Sodium ascorbate as +ve control. The 3rd was treated the same as the 2nd group then was post treated with 200 mg/kg/b.wt. *Nigella sativa* by inter-gastric luminal gavage (i.g.) respectively until the end. The 4th also was the same as the 2nd group but was post treated with 10 mg/kg/b.wt. Thymoquinone by inter-peritoneal (i.p.) also until the end after 32 weeks. **[Results]** *Nigella sativa* and Thymoquinone treatments inhibited the incidence and multiplicities of bladder tumours. The immunohistochemical proliferating cell nuclear antigen labeling index (PCNA LI %) was significantly inhibited in bladder tissues and tumours by both treatments. While, Nigella sativa treatment has caused *p53* gene down regulation as compared with control. Furthermore, the results of blood biochemical analysis revealed that *Nigella sativa* ameliorate lipid, liver and kidney functions. **[Conclusion]** In conclusion, *Nigella sativa* has a sufficient therapeutic effect against bladder carcinogenesis through their free radical scavenging, inhibition of cellular proliferation and modulation of anticancer genetic pathways.

P-88＊

アシクロビル結晶誘発性腎症に関連した心血管病変の解析

○杉山 淳一、田中 英樹、吉田 翔太、蟹江 尚平、別枝 和彦

大鵬薬品工業株式会社　安全性研究所

【背景】結晶誘発性腎症（CN）は，尿難溶性薬剤が主に遠位尿細管で析出し，尿排出停滞と腎臓間質障害を引き起こす病態であり，抗ウイルス薬の静脈内過剰投与等によって惹起される．今回アシクロビル投与ラットにおいて，CN 病変に加えて，これまで報告のない心血管系に病変が認められたため，その病態について病理学的に検討した．
実験 1：【材料・方法】6 週齢 SD ラットにアシクロビル 250 mg/kg を 1 日 1 回，10 mL/kg の容量で，分速 1 mL にて静脈内投与したところ，投与 3 日目に 1 例死亡発見されたため，剖検に供した．また，残る動物も切迫剖検した．【結果】肉眼的な腎臓の褪色・腫大，組織学的な腎髄質間質の炎症と尿細管の拡張・変性がみられ，遠位尿細管及び集合管腔内には偏光顕微鏡下で偏光性を有する微細顆粒状物質の貯留を認めた．骨及び上皮小体に組織学的変化は認められなかった．死亡例では心血管に高度な石灰沈着が認められた．
実験 2：【材料・方法】CN による急激な鉱質バランスの変動が動物の死因となったと考え，実験 1 と同様の投与条件にてアシクロビルを単回又は 3 日間反復静脈内投与し，経日的な血液化学的パラメータの推移を解析した．投与開始 3 日後に剖検に供し，各種検査を実施した．【結果】組織学的に CN 病変が認められたのに加え，血中クレアチニン，尿素窒素及びリンが初回投与翌日に顕著に上昇し，その後回復傾向に転じた．一方で血中カルシウムは低下していた．血中リンが特に高値だった個体には心血管断面の不整化と血管周囲炎がみられた．
【結論】今回認められた心血管病変は，高リン血症に付随した異所性石灰化であり，腎機能障害の早期段階から誘発されることが示唆された．

P-89

薬剤性腎障害の慢性化を予測するバイオマーカーとしての CD44 の有用性の検証

○松下 幸平、豊田 武士、赤根 弘敏、森川 朋美、小川 久美子

国立医薬品食品衛生研究所　病理部

【背景】急性腎障害（AKI）が生じた後、尿細管の再生機構が破綻した場合には不可逆的な慢性腎臓病（CKD）へ移行する。我々はこれまで、種々の腎障害モデルラットにおいて再生機構の破綻した尿細管には CD44 が発現することを見出した。本研究ではシスプラチン誘発 AKI to CKD モデルラットを用い、CD44 を指標とした薬剤性腎障害（DIKI）の慢性化を予測する体液診断の可能性について検証した。
【方法】6 週齢雄性 SD ラットに 0、2 及び 6 mg/kg のシスプラチンを単回腹腔内投与し、対照群は 28 日後、シスプラチン投与群は 1、3、5、7、10、14 及び 28 日後に剖検した。各時点の腎臓を病理組織学的に解析し、5、7 及び 28 日における血清中 CD44 濃度を ELISA 法により測定した。
【結果】2 及び 6 mg/kg 群ともに 1 から 5 日にかけて尿細管の変性 / 壊死が認められ、2 mg/kg 群では 5 から 28 日にかけて尿細管再生により組織が修復された。一方、6 mg/kg 群では 5 日から拡張した尿細管が多く観察され、10 日以降には間質の線維化がみられた。線維化病変内では拡張尿細管に加えて萎縮した尿細管も観察された。CD44 の免疫染色では、6 mg/kg 群の 5 日以降にみられた拡張 / 萎縮尿細管に明らかな発現を認めた。血清中 CD44 濃度は観察した全ての時点において 6 mg/kg 群で有意に増加しており、腎臓における CD44 陽性尿細管の数と強い正の相関を示した（ρ =0.884）。
【考察】再生機構の破綻した拡張 / 萎縮尿細管には CD44 が発現することが示され、CD44 陽性尿細管の増加に伴い血清中 CD44 濃度も上昇すると考えられた。6 mg/kg 群では線維化に先立って血清中 CD44 濃度が上昇していたことから、CD44 は DIKI の慢性化を早期に予測することのできるバイオマーカーとなる可能性が示唆された。集会ではマイクロアレイおよびパスウェイ解析による CD44 の機能解析の結果も併せて報告する。

P-90＊

高ショ糖 / 高脂肪食給餌が肥満 2 型糖尿病モデル SDT fatty ラットの腎臓に及ぼす影響について

○渡邉 果奈[1)]、美谷島 克宏[1,2)]、万代 康平[1)]、関口 敬大[2)]、宇野 絹子[3)]、煙山 紀子[2)]、笹瀬 智彦[6)]、渡辺 寿久[4)]、伊藤 秀樹[4)]、篠原 雅巳[5)]、中江 大[1,2)]、太田 毅[6)]

[1)]東京農大院　応用生物科学研究科　食品安全健康学専攻、[2)]東京農大、食品安全健康学科
[3)]東京農大院　農学研究科　食品栄養学専攻、[4)]日本クレア株式会社　富士生育場、[5)]日本クレア株式会社　業務推進部
[6)]京都大学院　農学研究科　応用生物科学専攻　生体機構学分野

【背景】糖尿病の三大合併症の糖尿病性腎臓病は患者数が最も多く、病態が進行すると人工透析を必要とし、QOL の低下が予測される。糖尿病モデル動物を使用した病態解析や要因解析は、糖尿病性腎症の治療や早期予防の観点から重要な役割を担っている。【目的】本研究では、肥満２型糖尿病モデルである SDT fatty ラットに高ショ糖 / 高脂肪食（Quick Fat: QF）を与えることにより腎臓に及ぼす影響を評価することで、新たな糖尿病性腎臓病（DKD）モデルとしての可能性を探索した。【材料と方法】4 週齢の雄性 SDT fatty ラットに標準食 CE-2 及び QF（いずれも日本クレア（株））を自由摂取させた。飼育は 27 週齢までとし、体重・摂餌量・血糖値を測定し、飼育期間終了後には剖検及び臓器重量測定を行い、血液並びに腎臓を採取した。採取材料を用いて血液生化学検査、腎臓の病理組織学的観察及び遺伝子発現解析を実施した。上記の病態群に対し、対照群として同様に雄性 SD ラットを飼育した群も設定した。【結果】腎臓の病理組織学的観察において、病態群の CE-2 群では、糸球体の大型化・メサンギウム増生・萎縮、尿細管の尿円柱形成、炎症性細胞浸潤が軽度に認められ、尿細管の拡張、再生、Armani-Ebstein 病変が中程度に認められた。QF 群では、これらの病変の程度が増し、特に尿細管の拡張と尿円柱形成が重度に認められた。さらに、QF 群では一部の尿細管に脂肪滴の沈着も認められた。また、ED-1 の免疫組織化学染色において、尿細管間質における陽性細胞は、病態群の CE-2 群と比較し QF 群で増加傾向を示した。【結論】以上の結果より、QF 給餌は SDT fatty ラットの腎病態を悪化させ、新たな DKD モデルとしての可能性が示された。

P-91＊

DIC 発症モデルにおける尿中 L-FABP の COVID19 重症化の早期バイオマーカーとして検証

○グエン ハン・ニユン[1)]、美谷島　克宏[1,2)]、大畑 敬一[3)]、河口 友香[1)]、畑中 悠里[1)]、堀内 彩花[1)]、宇野 絹子[4)]、当麻 茉莉花[2)]、新井 かりん[1)]、上地 哲平[1)]、煙山 紀子[1)]、中江 大[1,2)]

[1)]東京農業大学・応生・食品安全健康学科、[2)]東京農業大学、[3)]東京農業大学大学院・応用生物科学研究科・食品安全健康学専攻
[4)]シミックホールディングス株式会社　L-FABP 事業部 研究開発グループ、[5)]東京農業大学大学院・農学研究科・食品栄養学専攻

【背景と目的】新型コロナウイルス感染症による重症化患者の増加は医療従事者の負担増加に関連し、その重症化リスクを早期段階から予見できる有用なバイオマーカーの確立が求められる。尿中 L-FABP は新型コロナウイルス感染症患者の早期重症化予測マーカーとして、その有用性が国内外の臨床試験から報告されている。我々はヒト重症化症例において顕著にみられる血栓誘発病態に着目し、ヒト型 L-FABP 遺伝子導入マウスを用いた播種性血管内凝固症候群 (DIC) モデルにおける尿中 L-FABP 濃度の推移と腎臓の病理組織学的変化との関連を検討した。【材料と方法】12-13 週間雄性 C57BL/6-hL-FABPTg マウスに LPS とヒストンをそれぞれ腹腔内もしくは静脈内投与し、一定時間経過までの蓄積尿を用いて L-FABP 濃度を測定し、腎臓の病理組織学的解析を実施した。さらに新型コロナウイルス感染症の重症化リスクを高めるとされる肥満や糖尿病に着目し、予め高脂肪食摂餌や STZ 投与により重症化リスクの増大を模倣した基礎疾患群も設定し評価した。【結果と考察】LPS 投与及びヒストン投与において溶媒群と比べ尿中 L-FABP 濃度は有意に高値を示した。病理組織学的観察ではヒストン投与により腎臓では尿円柱の増加が認められた。基礎疾患群では、ヒストン投与により誘発される尿中 L-FABP 濃度が溶媒群と比較しさらに高値を示した。以上より、尿中 L-FABP 濃度は、hL-FABP Tg マウスを用いた血栓誘発モデルにおいて顕著に増加することが明らかとなり、本実験系は COVID-19 重症化病態に特徴的な血栓誘発病態に対する新たな治療薬の開発や食品による予防効果を見出すための研究にも応用可能であると考えられた。

P-92＊

Karnovsky 固定液のアンチセンス核酸投与時にみられる空胞化アーチファクト防止に対する有用性検討

○仁科 嘉修、西川 智美、樫村 茜、水川 真緒、坂入 鉄也

田辺三菱製薬（株） 安全性研究所

【背景・目的】アンチセンスオリゴヌクレオチド（ASO）を投与した個体の腎臓では、近位尿細管に好塩基性顆粒と空胞が認められることが広く知られている。また、空胞化に関して、標本作製時に ASO の流出が生じることによる二次的なアーチファクトである可能性が高いと報告されている。しかし、この事象について詳細を検討した報告はない。我々は、空胞が二次的なアーチファクトであることを示すため、ASO 投与個体の腎臓を Karnovsky 固定液、4% パラホルムアルデヒド溶液（PFA）および 10% 中性緩衝ホルマリン液（NBF）で固定し、組織学的に比較検討した。【材料と方法】LNA 修飾した ASO（50 mg/kg）を 4 週齢の雌 SD ラットに計 4 回間歇的に 1 または 2 週間反復静脈内投与し、摘出した同側腎臓をそれぞれ Karnovsky 固定液、PFA および NBF の各固定液にて浸漬固定し、病理組織学的検査を実施した。【結果】NBF 固定した腎臓では、近位尿細管において空胞および好塩基性顆粒が観察された。免疫組織化学染色では、空胞化上皮の大部分は KIM-1 に対して陰性であった。一方、Karnovsky 固定液で固定した腎臓では、近位尿細管に好塩基性顆粒が認められたが空胞は認められなかった。また、PFA 固定した腎臓では、NBF 固定と同様に近位尿細管に空胞および好塩基性顆粒が観察された。【結論】NBF 固定を用いた場合、標本作製時のアーチファクトにより空胞化が過大評価される可能性が示唆された。Karnovsky 固定液が、アンチセンス核酸の毒性評価において、腎毒性とアーチファクトによる空胞の鑑別に有用である可能性が示された。

P-93

Pathological study for chronic progressive nephropathy in rats

○Beibei Wang、Du Mu、Yanan he、Jun Yin、Wenyu Wu、Rui Zhang、Sucai Zhang、Huiming Zhang

北京昭衍新薬研究中心有限公司

[Background and Aim] To observe the incidence and characteristics of chronic progressive nephropathy (CPN) in rats in 104 weeks of continuous feeding, and to accumulate valuable data for the study of rats CPN. **[Materials and Methods]** 4 weeks of age 60 imported SD rats, 120 domestic SD rats and 120 domestic Wistar rats were given feeding import food and domestic food. In the same feeding conditions, the animals were taken for euthanasia after feeding for 104 weeks. Kidney was collected for conventional slide and staining. The incidence and pathological lesion were analyzed in different strains, different gender and different food feeding for CPN. **[Results]** The total incidence of CPN is 31.87%, of which male rat is 48.54% and female rat is 15.12%. The CPN incidence in Wistar rats is higher than that of SD rats. The CPN incidence in domestic food feeding rats is higher than that of imported food feeding rats; Glomerular basement membrane and mesangial hyperplasia with segmental sclerosis are first mover lesions of CPN, nevertheless degeneration and regeneration of renal tubular epithelium with renal interstitial fibrosis are secondary changes. **[Conclusion]** There is a higher incidence of CPN in rat, and there are differences for gender and fodder in incidence. The change in Glomerulus came first, which leading to secondary tubule change.

P-94

Halo AI を用いた抗糸球体基底膜腎炎モデルマウスの糸球体硬化の検出

○村井 厚子[1)]、松尾 沙織里[1)]、宇佐美 晶子[2)]、羽田 奈津子[2)]、金森 正和[2)]、山崎 雅輝[1)]、大西 慎一[1)]、加藤 淳彦[1)]

[1)]中外製薬株式会社　TR 本部　安全性研究部、[2)]中外製薬株式会社　研究本部　創薬薬理研究部

【背景と目的】抗糸球体基底膜（GBM）腎炎モデルマウス（抗 GBM マウス）は、GBM に対する抗体を投与することで、糸球体硬化や半月体病変を起こす。Halo AI は、AI を搭載した画像解析装置で、病理画像の学習と画像解析ができる。今回、Halo AI を用いて、抗 GBM マウスの糸球体硬化病変を検出した。【材料と方法】7 週齢の雌の C57BL/6JJcl マウスに、Sheep IgG を皮下投与した 5 日後から抗 GBM 抗体を含む Nephrotoxic serum（NTS）を 3 日間静脈内投与した。NTS を最初に投与してから 14 日後に剖検して腎臓を採材し、PAM 及び PAS 染色標本を作製、鏡検した。画像解析には、Halo AI の Classifier（DenseNet AI V2（Plugin））を使用した。複数例の硬化糸球体、非硬化糸球体をアノテーションして学習させ、糸球体分類モデルを作成した。その後、全例を解析した。【結果】鏡検で抗 GBM マウスに糸球体硬化が認められ、PAM 染色標本で平均して 18.5％の糸球体に糸球体硬化が認められた。Halo AI では、分節性も含めて糸球体硬化が適切に検出され、20.4% で糸球体硬化が認められた。鏡検下と Halo AI の結果には強い相関が認められた。一方、PAS 染色標本は Halo AI では 8.9% と少なく検出された。その他、PAM 染色で 2 個の糸球体が 1 個と認識される場合がみられた。【考察】PAM 染色標本を Halo AI で解析すると、適切に糸球体硬化が検出できることが明らかとなった。一方、染色によって検出のしやすさに差がある可能性が示唆された。糸球体の認識の改善方法については、当日紹介したい。

P-95

ラットモデルを用いたキトサンオリゴ糖の乳癌抑制効果の検証

○吉岡 正浩[1)]、茶谷 桃花[2)]、又間 梨央[3)]、三好 真由[3)]、木下 勇一[4)]、岡本 芳晴[5)]、義澤 克彦[2,3)]

[1)]甲子園大学　栄養学部　栄養学科、[2)]武庫川女子大学大学院　生活環境学研究科
[3)]武庫川女子大学　食物栄養科学部　食創造科学科、[4)]和歌山県立医科大学附属病院、[5)]鳥取大学　農学部　共同獣医学科

【背景】キトサンオリゴ糖（COS）は様々な生理活性を有する機能性食品であり、数種のがんを抑制することが報告されていた。我々は MNU 誘発乳癌ラットモデルを用いた動物実験を行い、COS の経口投与により乳癌が抑制されることを明らかにし、2021 年に報告している。しかし、その抑制機序は未解明である。
【目的】乳癌を予防する新たな機能性食品や乳癌に対する新しい治療法の開発の知見を得るべく、COS による乳癌抑制メカニズムを明らかにすることを本研究の目的とし、動物実験と細胞実験を行った。
【材料と方法】動物実験：6 週齢の雌 SD 系ラットを購入し、Control 群、COS 単独群、MNU 単独群、MNU+COS 投与群の 4 群を設定した。MNU 単独群、MNU+COS 投与群は 7 週齢時に MNU（50 mg/kg）を単回腹腔内投与することで乳癌を誘発した。11 週齢時から COS 水の経口投与を行い（1% を 3 週間、2% を 2 週間、4% を 2 週間）、18 週齢時（MNU 投与 11 週間後）に解剖を実施し、鼠径部乳腺と腫瘍を摘出し、病理組織学的評価を行った。細胞実験：ヒト乳癌細胞株 MCF-7 を 1×10^3 cells/well になるように 96 穴プレートに播種し、24 時間前培養した。その後、COS を各濃度で含有する培地に置換し、120 時間培養した。120 時間後、細胞生存率を算出し、COS による乳癌細胞に対する増殖抑制効果を検証した。
【結果】MNU による乳癌誘発前から COS を投与していた前回の実験結果と異なり、MNU 投与後に COS を投与した今回の実験では、COS の投与による乳癌抑制効果は見られなかった。また、細胞実験においても COS による乳癌細胞の増殖抑制は見られなかった。
【結論】COS による乳癌抑制作用は、腫瘍細胞の増殖抑制や細胞死の誘導によるものではなく、発癌発生初期段階、すなわちイニシエーション期に COS が作用することで乳癌発生が抑制されると推察される。

P-96＊

RNA シーケンス解析を利用した放射線誘発ラット乳がんにおける融合遺伝子の同定

○渡辺 光[1,2)]、臺野 和広[1)]、石川 敦子[1)]、今岡 達彦[1,2)]、西村 まゆみ[1)]、高畠 賢[1,2)]、井上 一雅[2)]、福士 政広[3)]、柿沼 志津子[1)]

[1)]量研　放医研　放射線影響、[2)]東京都立大院　人間健康科学　放射線、[3)]つくば国際大　診療放射線

【目的】乳腺は放射線による発がん感受性が最も高い臓器の 1 つであるが、放射線による発がんの原因となる遺伝子異常についてはまだよく分かっていない。放射線は染色体再配列を起こすことが知られる。融合遺伝子の多くは、染色体転座や逆位といった染色体再配列によって生成される。そこで本研究では、放射線によって誘発されたラットの乳がん検体を用いて、RNA シーケンス解析により融合遺伝子を同定することを目的とした。
【方法】本研究では、7 週齢時にγ線（4 Gy）を照射した雌ラット（Sprague-Dawley 系統）に発生した乳がん 6 検体から抽出した Total RNA を用いて RNA シーケンシングを行い、取得したデータを用いて STAR-Fusion ソフトウェアにより融合遺伝子を検出した。続いて、RT-PCR やサンガーシーケンシング法を用いて、乳がんにおける融合遺伝子の発現の確認を行った。
【結果】検出された候補融合遺伝子の配列情報から、融合蛋白質を生成し、かつ、がん化に機能すると予測される融合遺伝子を抽出した結果、3 検体でそれぞれ 1 種類の候補融合遺伝子が抽出された。3 候補の融合遺伝子は、これらが検出された個体の正常乳腺組織では検出されなかった。さらに、γ線照射群に生じた乳がん 3 検体を追加し、合計 9 検体について同様の解析を行ったところ、融合遺伝子の 1 つは 9 検体中 2 検体においてその発現が確認された。また、これら融合遺伝子は、非照射群に発生した乳がん（9 検体）では検出されなかった。現在、免疫組織化学染色により、融合遺伝子の下流で働くと予想されるシグナル経路の活性化を調査している。
【結論】ラット乳がんにおいて、放射線によって誘発される融合遺伝子の存在が示唆された。

P-97

テストステロンのラット胎盤発生に対する影響

○古川 賢[1)]、辻 菜穂[1)]、林 清吾[1)]、黒田 雄介[1)]、木村 真之[1)]、早川 知里[1)]、竹内 和也[1)]、杉山 晶彦[2)]

[1)]日産化学株式会社　生物科学研究所、[2)]岡山理科大学　獣医学部

【目的】テストステロンのラット胎盤発生に対する影響を経時的に検索した。【材料及び方法】妊娠 Wistar Hannover ラット 24 匹を供試した。テストステロンプロピオン酸塩をオリーブオイルで懸濁し、0 及び 5mg/animal の用量にて妊娠 14 ～ 18 日に皮下投与した。妊娠 15、17 及び 21 日に胎児 / 胎盤を摘出し、重量想定した。胎盤はホルマリン固定後、病理組織検査を実施した。【結果】テストステロン投与群（TP 群）では母動物は臨床症状を示さなかったものの、妊娠 19 日以降、体重は減少した。胎児死亡率の上昇は認められなかったが、胎児重量、胎盤重量及び胎児 / 胎盤重量比の減少並びに子宮内胎児発育遅延（IUGR）率の上昇が、妊娠 21 日でのみ認められ、肉眼的に小胎盤を呈していた。また、妊娠 21 日の雌性胎児では肛門性器間距離は伸長していた。胎盤の病理組織学的検査において妊娠 15 及び 17 日では、異常は認められなかった。一方、妊娠 21 日では、TP 群で迷路層において栄養膜中隔は栄養膜細胞の増加を伴って肥厚し、母体血管洞は狭窄していた。これら変化により、迷路層は十分な母体血液を含有することができず、菲薄化していた。妊娠 21 日における TP 群の胎盤重量並びに迷路層の厚さ、組織学的形態及び栄養膜中隔の細胞密度は、妊娠 17 日の対照群及び TP 群とほぼ同程度であった。一方、基底層及び間膜腺では試験期間を通して著変は認められなかった。【結論】テストステロンによって誘発された小胎盤は、GD17 以降、迷路層において栄養膜中隔が菲薄化せず、母体血管洞が拡張しなかったことにより誘発されたことが明らかとなった。これにより、妊娠 17 日以降、急速に発育する胎児に対して十分な母体血液が胎盤に流入することができず、IUGR 率が上昇したものと推察した。

P-98＊

AI 画像解析プラットフォーム IBM® Visual Insights を用いたラット性周期自動分類モデルの構築

○大西 慎一[1)]、江上 陸[2)]、長島 慶宜[2)]、中村 祐哉[2)]、西原 香織[1)]、松尾 沙織里[1)]、村井 厚子[1)]、林 修次[1)]、山崎 雅輝[1)]、 水野 英明[2)]、加藤 淳彦[1)]

[1)]中外製薬株式会社 トランスレーショナルリサーチ本部、[2)]中外製薬株式会社 研究本部

【背景と目的】毒性試験では被験物質の生殖器への影響を確認するために、雌性生殖器（卵巣、子宮、膣）の性周期を組織像から発情休止期、発情前期、発情期、発情後期に分類して評価する必要がある。病理評価の効率化を目的として、ラットの子宮と膣の性周期を Whole slide image（WSI）を用いて AI により自動分類することができるかを検討した。【材料と方法】5 人の毒性病理学専門家が子宮と膣の性周期を分類し、4 人以上の判定が一致した例を抽出した。抽出例の WSI を 2000 × 2000 ピクセル以下に圧縮し、教師データ（子宮：47 例、膣：41 例）と検証データ（子宮：20 例、膣：15 例）に分割した。AI 画像解析プラットフォームである IBM® Visual Insights を用いて、教師データの子宮、膣の各性周期の画像を学習させ、それらを自動検出する object detection モデルを作成した。さらに検証データでモデルの正答率を検証した。【結果】モデルの正確性は、子宮で 90%、膣で 62%であった。【結論】IBM® Visual insights を用いたラットの子宮の性周期自動分検出モデルは正答率が高く、有用であると考えられた。一方で、膣の検出モデルは十分な正答率が得られなかった。正答率の差は子宮と膣の分類に寄与する観察倍率の違いが影響している可能性が考えられ、大きな WSI 画像を小さな画像に分割（パッチ分割）して解析する必要が考えられた。

P-99＊

ACTH-induced stress in weaned sows impairs LH receptor expression steroidogenesis capacity in the ovary

○Zhu Huaisen[1,2)]、Tan Rongrong[1)]、Xiu Xiaoyu[1)]、Lu Henglei[1)]

[1)] AnLing Biomed (ShenZhen) Co., Ltd
[2)] Centre for Drug Safety Evaluation and Research (CDSER), Shanghai Institute of MateriaMedica (SIMM), Chinese Academy of Sciences (CAS)

[Background] Endocrine disruption, which is closely related to the persistent follicles, is possibly one of the results of stress. Since luteinizing hormone receptor (LHR) in ovarian follicular wall and concentrations of steroid hormone in follicular fluid are related to the development of persistent follicles, this study is designed to evaluate the effect of administered adrenocorticotrophic hormone (ACTH) to weaned pigs on their ovarian steroidogenesis capacity and LHR expression. **[Aim]** To explore the effects of changes in ovarian LHR and steroidogenesis capacity on ovarian ovulation during stress. **[Materials and Methods]** Ten multiparous sows were weaned and randomly divided into two groups (n = 5 each). Sows received 1 IU/kg ACTH or saline every 8 h from days 3-9 after jugular vein intubation. Blood samples were collected throughout the experiment, and ovaries were collected after slaughter on day 10. **[Results]** The plasma cortisol concentration was significantly elevated after ACTH injection. The E2 and ASD concentrations in FF were significantly lower in the ACTH group. The LHR, 3β -HSD, P450arom, and P450c17 mRNA levels were significantly reduced in the ACTH group. Immunohistochemical staining showed significant differences in the distribution of 3β -HSD, P450c17, LHR, and P450arom between the two groups. **[Conclusions]** These findings indicated that ACTH significantly diminished the LHR expression and steroidogenesis capacity of the ovaries of weaned sows.

P-100

マウス正常組織由来オルガノイドを用いる新たな DMBA 誘発性乳腺発がん機序の解明

○今井 俊夫[1,2)]、石ケ守 里加子[1)]、中西 るり[1)]、町田 雪乃[3)]、成瀬 美衣[1)]

[1)]国立がん研究センター　研究所　動物実験施設、[2)]国立がん研究センター　研究所　がんモデル開発部門
[3)]日本獣医生命科学大学　獣医病理学研究室

【背景】BALB/c-*Trp53* ヘテロノックアウト雌マウスに 7,12-dimethylbenz[*a*]anthracene（DMBA）を 1 回（50 mg/kg 体重）経口投与することで、高頻度に *Hras* 変異があり、病理組織学的に二相性を呈する特徴的な乳がんが誘発される。一方、同系マウスの乳腺組織由来オルガノイドに *in vitro* で 3 回 DMBA（0.6 μ M）に暴露させた後ヌードマウス皮下に接種することで、造腫瘍性を示すことを報告した。【目的】*In vitro* で化学物質に暴露させた後ヌードマウス皮下に接種するオルガノイド発がんモデルで誘発される病変について、従来のマウス化学発がんモデルと病理組織学的および変異遺伝子の特性が類似しているか異なるかを明らかにするため、両者の比較解析を行った。【材料と方法】両病変の病理組織学的、免疫組織学的解析、ならびにオルガノイド由来の腫瘍について全エクソーム解析を行った。【結果】オルガノイド発がんモデルで誘発された腺がんにはサイトケラチン（CK）18 陽性の腺房細胞とα平滑筋アクチン陽性の筋上皮細胞に由来するがん細胞が混在し、ヌードマウス皮下にて継代することで CK14 陽性の扁平上皮がんに変化し、マウス発がんモデルと異なる特性を示した。また、オルガノイド由来腺がんに *Hras* 変異はなく、*Tgfbr2* など他の遺伝子変異が発がんに関与している可能性が示された。【結論】DMBA 誘発性オルガノイド由来の腫瘍は、マウスモデルとは異なる遺伝子変異に起因すると考えられる特異的な形質を示した。今後、オルガノイド発がんモデルを用いて幅広い化学物質による影響解析を進めることで、従来の動物モデルとは異なる発がん機序を可視化できる可能性がある。

P-101＊

Assessment of the molecular and physiological role of micro RNA in chemically-induced mammary gland carcinoma in rats

○Fatma A. Elmalah[1)], Mona M. Hegazi[1)], Doha M Beltagy[2)], Elsayed I. Salim[1)]

[1)] Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)] Biochemistry Department, Faculty of Science, Damanhour University

[Background] Breast cancer is the leading cause of death among all cancers types in women. Recent advances in expression biology have shifted in identifying and developing specific and sensitive biomarkers, such as micro RNAs (*miRNAs*) for cancer diagnosis and prognosis. **[Aim]** We attempted to provide a comprehensive profile of key *miRNAs* involved in experimental breast cancer to establish a more reliable non-invasive clinical biomarkers for early detection. **[Materials and Methods]** In this experiment, three groups of female Sprague-Dawley rats were administered either 0.09% saline, Methylnitrosourea (MNU) or MNU+Doxorubicin to evaluate the expression role of *miR-21*, *miR-155*, *miR-195*, *miR-122* and *miR-17-3p* in mammary tumors and after treatment with Doxorubicin. **[Results]** The results showed that *miR-21, miR-155* and *miR*-195 were up-regulated in breast cancer, while *miR-122* and *miR-17-3p* were downregulated. This expression was modified by Doxorubicin. Other investigations such as blood biochemistry, histopathology, immunohistochemistry and antioxidant enzymes activities were demonstrated to correlate with the changes occurred. **[Conclusions]** The study explained that *miR-21*, *miR-155*, *miR-195*, *miR-122* and *miR-17-3p* expressions differed in the normal mammary tissue, mammary gland tumors and after treatment with chemotherapy, this encourages the promising use of *miRNAs* as new prognostic biomarkers for breast cancer.

P-102＊

Promoting effect of sunset yellow at low doses on *N*-methyl *N*-nitrosourea-induced rat mammary gland carcinogenesis

○Malak I. Elbassuny[1)], Magdy E. Mahfouz[2)], Elsayed I. Salim[1)]

[1)] Zoology Department, Research Lab. for Molecular Carcinogenesis. Faculty of Science, Tanta University
[2)] Zoology Department, Faculty of Science, Kafrelsheikh University

[Background] Sunset Yellow (Yellow 6: SY (E110)) a food coloring linked to health risks in animal models. **[Aim]** We investigated the role of SY during chemically-induced mammary carcinogenesis in rats. **[Materials and Methods]** *N*-methyl *N*-nitrosourea (MNU) was injected into female rats then they were divided into 3 groups. Group 1 were set on high fat diet after MNU. Group 2 were administered SY at 161.4 mg\kg\day, Group 3 were given lower dose of SY (80.7 mg\kg\day) after MNU. The SY doses were chosen below the human acceptable daily intake (ADI) of the WHO/FAO guidelines. Group 4 were control. Groups 5 and 6 were administered SY at the same doses as groups 2 and 3 respectively but without MNU. **[Results]** After 22 weeks, SY in both doses significantly increased tumor incidences, multiplicities, volumes, and average tumor burden, as well as it decreased tumor latency as compared with positive control. Estrogen and progesterone hormones levels significantly increased in SY-treated groups, also oxidative stress parameters especially MDA as well as ERα, PR and PCNA immunohistochemical indexes were elevated in groups treated with SY vs. control. *ERα* and *EGFR* mRNA expression was upregulated in SY-treated groups vs. control. **[Conclusions]** SY significantly promoted incidence and multiplicities of mammary tumors in rats, therefore may have strong potency for breast cancer development in humans.

P-103

The histopathologic changes in lungs of mice and cynomolgus monkeys administrated intravenously with human umbilical cord-derived mesenchymal stem cells

○Yanjun Cui, Xu Zhu, Yi Zhou, Xuezhou Cai, Yichao Tian, Li Zhou

Hubei Topgene Biotechnology Co. Ltd Wuhan Branch

[Objective] Effects of human umbilical cord-derived mesenchymal stem cells (HUC-MSCs) were evaluated in single and repeated dose toxicity studies using mice and Cynomolgus monkeys (macaca fascicularis).
[Materials and Methods] KM mice (40 mice for the single dose toxicity study) and Cynomolgus monkeys (four monkeys for the single dose study, eighteen monkeys for the two-week repeated-dose toxicity study), were intravenously administrated with HUC-MSCs.
[Results] In the single dose studies, six mice (30%) were dead and thrombosis was found , and thrombosis comminated with inflammation in the was observed in one monkey(25%) in the vessel of lung. In the repeated-dose of toxicity studies, alveolar septum thickened that may be caused by the HUC-MSCs infilled were observed in two monkeys (33%) of low dose group and three animals (50%) of high dose group. Additionally, thrombosis and inflammatory nodular formation in and around pulmonary vessel was found in one animal (17%) of high dose group.
[Conclusions] Treatment-related pathological changes in pulmonary vessel were found in both mice and monkeys. Special attention should be paid for thrombosis induced by HUC-MSCs in further non-clinical and clinical studies.

P-104

Histopathological investigation of islets in SD rat by subcutaneous injection with a repeat dose new hypoglycemic compound

○Du Mu、Qi Wei、Guo Jin、Zhang Rui、Guo Hui、Liu Xiangjiang、Wang Beibei、He Yanan、Yin Jun、
廣内 康彦

昭衍（蘇州）新薬研究中心有限公司

[Background and Aim] There are many drugs for the type 2 diabetes included insulin, linsulin analogs and GLP-1 receptor agonists, but there is not report on the effect of islet in SD rat. This report describes the lesion of islets in SD rat with a repeat dose new hypoglycemic compound. **[Materials and Methods]** 6-9 weeks SD rat were administrated new hypoglycemic compound 4 weeks by subcutaneous injection at 60, 120 and 180 nmol/kg respectively. The rats were euthanized after 4 weeks on Day 29 and 4-week recovery on Day 57. The blood was collected for clinical chemistry. The pancreas was weighted and fixed in 10% neutral buffered formalin for HE staining, immunohistochemistry was performed with Insulin and Glucagon. **[Results]** There was no difference in the pancreas weight in all dose group. Dose dependent blood glucose decreased was observed in all dose groups. The HE and IHC staining showed that the islets of each dose group on Day 29 were small in size, A cells increased, A cells mitosis and B cell atrophy. After a 4-week recovery on Day 57, minimal A cell increased was observed in high dose group, but the severity and incidence was significant lower, other findings were recovery. **[Conlusion]** Because the blood glucose decreased caused by the test article, A cell increased, A cell mitosis and B cell atrophy were considered to be a secondary pathological changes caused by a pharmacological effects rather than adverse lesion.

P-105＊

ラットにおける化学物質誘発抗甲状腺作用検出における病理組織学的及び免疫組織化学的手法と血中ホルモン値との比較

○赤根 弘敏[1)]、豊田 武士[1)]、松下 幸平[1)]、森川 朋美[1)]、小坂 忠司[2)]、田島 均[2)]、青山 博昭[2)]、小川 久美子[1)]

[1)]国立医薬品食品衛生研究所　病理部、[2)]一般財団法人残留農薬研究所　毒性部

【背景】げっ歯類を用いた反復投与毒性試験における甲状腺ホルモン値測定は、甲状腺機能抑制物質の検出に有用であるが、採血時の条件による変動や血液量の制限等の問題が指摘されている。本研究では、化学物質の抗甲状腺作用を短期間で効率的に評価可能な指標の特定を目指し、病理組織学的・免疫組織化学的手法と血中ホルモン値測定との比較検討を実施した。【方法】6 週齢の雌雄 SD ラット（5 匹 / 群）に、抗甲状腺物質である propylthiouracil（PTU）及び methimazole（MMI）をそれぞれ 0.03、0.1、0.3、1、3 mg/kg 及び 0.3、1、3、10 mg/kg の用量で 28 日間強制経口投与した。臓器重量測定、病理組織学的検索、T4・TSH の免疫組織化学的検索を実施し、甲状腺ホルモン値の変動と比較した。【結果】血清 T3・T4 の有意な減少は概ね PTU 1 mg/kg 以上及び MMI 3 mg/kg 以上投与群で認められ、雄でより顕著であった。甲状腺重量の増加が雌雄の同投与群で観察され、下垂体重量の増加は雄でのみ認められた。病理組織学的検索では、甲状腺濾胞上皮細胞の肥大 / 過形成が雌 PTU 0.03 mg/kg 群を除く両物質の全用量で、下垂体前葉細胞の肥大 / 空胞化が雄の両物質の全用量、雌の PTU 1、3 mg/kg、MMI 3、10 mg/kg 群で観察された。免疫組織化学的検索では、甲状腺 T4 の染色性低下が、上述の組織学的変化を示した全ての群で用量依存的に認められた。また、下垂体前葉の TSH 陽性面積率は用量依存的に増加し、雌雄ともに血清 T4 値減少を示した群で有意差が認められた。【考察】甲状腺重量及び下垂体 TSH 陽性面積率の有意な変動は血清 T4 減少に随伴して認められ、抗甲状腺物質の検出に利用可能と考えられた。また、甲状腺の病理所見及び T4 発現低下は、甲状腺ホルモン値の有意な減少を伴わない低用量から認められ、より鋭敏な指標となる可能性が示唆された。

P-106

両生類変態試験 (AMA) の陽性対象物質処理区でみとめられた甲状腺の病理組織学的変化

○永池 美香、山本 格、馬場 雄大、池田 瑛人、岡田 亜季子、本郷 直子、乾 公正

石原産業（株）　中央研究所　安全科学研究室

【背景・目的】AMA(OECD テストガイドライン 231) は環境生物に対する内分泌かく乱作用（ED）を評価する試験のひとつであり、欧州当局は農薬登録の際、甲状腺機能を介した ED 作用を検出するアッセイ系としてしばしば求めるようになった。両生類ではオタマジャクシからカエルに変態する際、甲状腺ホルモンが後脚の発育を促進する。本発表では、陽性対照物質の過塩素酸ナトリウム (Sodium Iodide Symporter 阻害剤) を処理したアフリカツメガエル（*Xenopus laevis*）の in-life 測定データおよび甲状腺の病理組織を提示する。【材料と方法】テストガイドライン 231 に準拠し、0.5 m g/L の濃度の試験水にてアフリカツメガエルのオタマジャクシに発生ステージ 51 (17 日齢) から 21 日間流水暴露した。トリカインにて安楽殺後、湿重量、鼻排泄口長（SVL）、後脚長（HLL）を計測した。固定後のオタマジャクシの頭部を冠状断で切り出して常法に従いパラフィン包埋し、甲状腺の連続切片を作成した。また、同化合物を飲水に 1% の濃度で混入し、90 日間 ICR 系マウスに反復経口投与して、甲状腺の病理組織標本を作製した。【結果】対照区と比較し検体処理区のオタマジャクシでは、生存率、湿重量や SVL に影響はない一方、HLL は有意に短縮した。病理組織検査では左右の甲状腺が互いに接するほど顕著な肥大が認められ、甲状腺濾胞上皮細胞は肥大し、細胞分裂像の増加、びまん性過形成を呈していた。一方、濾胞腔内のコロイドは減少していた。同物質を 90 日間飲水投与したマウスでは、オタマジャクシの組織変化をさらに重篤化した甲状腺濾胞上皮細胞肥大および過形成が認められ、コロイドはほぼ消失していた。

P-107＊

脳底部に観察された神経節起源と考えられる腫瘍性塊

○Qi Wei、Du Mu、Guo Jin、Guo Hui、Zhang Rui、Liu Xiangjiang、廣内 康彦、Li Zheng

昭衍（蘇州）新薬研究中心有限公司

目的 SD ラットの 脳底部に水腫状の 0.4cm の塊を観察した。末梢神経節に発生したと考えられる腫瘍性病変を経験したので、その病理組織学的特徴について報告する。方法 26 週間の反復投与試験の対照群に供した SD ラット（雄）を解剖し、脳底部に観察された水腫状塊を採取した。10％中性緩衝ホルマリン液で固定後、パラフィン切片を作成、HE 染色および各種抗体を用いて免疫染色を施し病理組織学的検査を行った。結果神経節を構成する細胞は大型の神経細胞、外套細胞（satellite cell）および髄鞘を構成する神経鞘細胞（シュワン細胞）である。本症例の組織学的観察では大型神経細胞の増殖は見られない。クロマチンに富む細胞質に乏しい卵円形細胞の増生が顕著で、さらに一部に嚢胞形成が見られた。円形で淡い染色性の核の混在も観察された。ほとんどの有髄神経の髄鞘は膨化、変性を伴っていた。免疫組織化学的染色の結果、髄鞘は S100 で陽性、さらには卵円形細胞の細胞質の一部が陽性であった。円形で淡い染色性の細胞は形態的特徴から外套細胞と考えられた。考察免疫染色結果、卵円形細胞は密に増生し、さらに嚢胞形成しいることから三叉神経節に発生した良性神経鞘腫（アントニー B) と判断した。

P-108

A spontaneous benign meningioma in an ICR mouse

○Hu Yiwen、Kong Qingxi、Lv Ai

Pharmaron Inc.

[Background] A spontaneous meningioma is rare in the brain of ICR (Crj: CD-1) mouse. To the best of our knowledge, this might be the first report concerning the spontaneous benign meningioma in a strain ICR mouse in China. **[Aim]** To introduce the feature of a spontaneous benign meningioma of fibroblastic type occurring in an aged ICR mouse. **[Materials and Methods]** The brain sample was from a 77-wk-old found dead ICR (Crj: CD-1) mouse in a 78-wk carcinogenicity study. Study animals were purchased from Jihui Laboratory Animal Technology in Shanghai. Grossly, meningeal thickening was observed in the brain at necropsy. After collection, brain tissues were trimmed, dehydrated, cleared, infiltrated with paraffin, embedded, sectioned into 5μm thick sections, mounted onto glass slides, and stained with hematoxylin and eosin stain. **[Results]** Microscopically, the normal surface of the brain was covered by multifocal masses of delicate spindle-shaped cells with pale eosinophilic cytoplasm, and small elongated hyperchromatic nuclei. The cells formed loosely interwoven bundles and exhibited myxomatous areas. **[Conclusion]** For the tumor appeared well demarcated and was characterized by rare mitotic figures and expansive growth compressing the adjacent brain, but without any invasion of the underlying brain parenchyma, the tumor was diagnosed as a benign meningioma of fibroblastic type.

P-109＊

強膜に軟骨化生がみられた Kbs:JW ウサギの 1 例

○山田 康太郎、山際 慶典、政次 美紀、原ノ園 祐、倉田 昌明

千寿製薬株式会社　研究開発本部　総合研究所

【緒言】強膜の骨化生は高齢 F344 ラットで高頻度に認められ、軟骨化生も稀に発生するとされているが、ウサギでは報告がない。今回、若齢日本白色種ウサギの強膜に自然発生と考えられる軟骨化生を認めたので報告する。【材料と方法】症例は 14 週齢の雄性 Kbs:JW ウサギで、心血管系影響評価のため剖検前日にイソプロテレノール（IP）を 20% 濃度で単回点眼投与されていた。投与日及び投与翌日の一般状態観察、投与翌日の前眼部観察並びに剖検で異常は認めなかった。IP 投与眼の病理組織学的検査で強膜に軟骨様組織がみられた。当該眼球のパラフィンブロックから新たに病理組織標本を作製し、アルシアンブルー染色及び vimentin の免疫組織化学染色を施した。【結果】ヘマトキシリン・エオジン染色では、硝子軟骨様の組織が眼球後極の強膜線維間に巣状に認められ、小腔を有する淡明な好塩基性均質の軟骨様基質及び小腔内の楕円形又は多角形の軟骨様細胞で構成されていた。アルシアンブルー染色では、軟骨様基質は均一な青色を呈した。免疫組織化学染色では軟骨様細胞は vimentin 陽性であった。【考察】以上の組織学的特徴から、本症例はウサギの強膜軟骨化生と診断した。強膜の軟骨様組織は眼球後極に限局し、薬物が曝露された部位である角膜や隣接する強膜には異常を認めなかった。また、IP の全身投与による強膜の軟骨化生はこれまで報告されていない。したがって、投与に関連した変化ではないと考えられた。軟骨は強膜と同様神経堤由来組織であり、ヒト強膜由来培養細胞が軟骨形成能を有するとの報告もあることから、発生異常による自然発生性変化と考えられた。ウサギにおける強膜軟骨化生の報告例はなく、本例はウサギの背景病変として有用な知見と考えられた。

P-110＊

ビーグル犬にみられた肺の低形成の 1 例

○等々力 舞、増田 湊介、吉見 直、古屋 真、森 重之

全薬工業株式会社　創薬研究部　安全性研究室

【背景】今回、予備検討用のビーグル犬において非常に稀な病態である肺の低形成を経験したため発表する。【症例】雌ビーグル犬（28 ヵ月齢）の 1 例で、投薬の影響で一般状態の悪化や体重減少が見られたが、呼吸状態や呼吸数に異常はなかった。剖検において右肺前葉に限局性の白色斑が 2 ヵ所見られ、最大で 25 × 10 mm であった。その他、肉眼的異常は認められなかった。肺、肝臓、腎臓、脾臓および胸骨・骨髄を 10% 中性緩衝ホルマリンで固定後，常法に従い HE 染色を施し組織学的検査を行った。肺についてはマッソントリクローム（MTC）染色も実施した。【結果】右肺前葉の限局性白色斑の領域では、組織学的に発育形成不全を呈していた。肺胞は小さく数も乏しく虚脱しており、隔壁は厚く 2 型細胞と考えられる立方状上皮細胞に内張されていた。気管支周囲には顕著な線維化がみられ（MTC 染色：青染）、終末細気管支様の未熟な管状構造が散在していた。一部では限局性の炎症細胞浸潤が認められた。その他の肺葉は正常で低形成は認められず、その他の器官・組織にも肺低形成に起因した特記すべき変化は認められなかった。【まとめ】肺の低形成は肺の発育形成不全で、終末細気管支、肺胞の形成不全と 2 型細胞の顕在化が組織学的特徴である。肺の圧迫、羊水過小および呼吸運動の減少等の理由で肺の発達が途中で抑えられることにより起こるとされている。本症例では気管支周囲に肺胞が存在せず肺実質の形成不全が認められた。また形成不全の肺実質には終末細気管支様の未熟な管状構造が存在し、肺の発生過程である仮腺期の形態に類似していた。これらの特徴から肺の低形成と診断した。現在、更なる詳細観察のため、免疫染色および電子顕微鏡観察を実施中である。

P-111＊

ICR マウスの心冠状動脈の血管炎

○安野 恭平[1)]、今岡 尚子[1)]、大澤 徹也[1)]、岡戸 恵子[2)]、甲斐 清徳[1)]、土屋 由美[1)]

[1)]第一三共（株）、安全性研究所、[2)]第一三共 RD ノバーレ（株）、トランスレーショナル研究部

Crlj:CD1(ICR) マウスを用いた毒性試験の病理組織学的検査では、心冠状動脈の炎症がみられることがある。本研究では、無処置又は媒体のみを投与した若齢の ICR マウスの心冠状動脈の炎症について、組織学的検査及び超微形態学的検査により背景情報を収集した。その結果、6 ～ 8 週齢の ICR マウス 144 例のうち 10 例（7.0%）で冠状動脈に血管炎がみられた。病変は右心室壁に多く認められ、ときに右心房壁あるいは左心室壁にも存在した。血管炎は組織学的に、軽度なものでは血管平滑筋細胞の肥大及び血管周囲へのマクロファージの浸潤として認められ、病変が顕著な個体では更に血管平滑筋細胞の単細胞壊死、中膜の出血、血管壁のフィブリノイド壊死、及び／又はリンパ球の浸潤を伴っていた。病変部位の超微形態学的検査では、内弾性板の断裂及びその直下における変性・壊死した血管平滑筋筋細胞が観察された。
以上より、本病変では内弾性板の断裂及び血管平滑筋細胞の変性・壊死により、血漿成分の漏出や中膜の出血に至り、血管炎の進行及び血管周囲への炎症細胞の浸潤が誘導されていることが示唆された。ICR マウスでは、右心室を好発部位として石灰化が稀にみられる。初期の病変は心筋線維の壊死と同部位における限局性の石灰沈着であり、その病因は異所性石灰化と考えられている。本病変では血管壁を含め、心臓のどの部位においても石灰沈着がみられなかったことから、若齢の ICR にみられる心冠状動脈の炎症は ICR マウスの心臓の石灰化とは別の病態である可能性がある。

P-112＊

若齢 SD ラットにおける自然発生性のリンパ管腫の一例

○石川 玲奈、後藤 彩、関 由妃、中島 康太、太田 恵津子

エーザイ（株） メディスン開発センター　BA 機能ユニット　グローバル安全性研究部

若齢ラットの頸部および胸腔内にみられた病変について，免疫組織化学染色を含めて詳細な検討を行ったので報告する。【材料と方法】本症例は，ある化合物の毒性試験に用いた 9 週齢の Crl:CD(SD) ラット，雄の一例である。剖検時に，頸部皮下に直径 7mm 大の軟性赤色腫瘤および胸腺近傍結合組織の浮腫を認めた。組織採材後，10% 中性緩衝ホルマリンで固定，パラフィン包埋し，連続切片を作製し以下の染色を実施した［HE 染色，マッソントリクローム染色，免疫染色（CD31，LYVE-1，Cytokeratin（CK）AE1/AE3，Ki-67，α -SMA）］。【結果】肉眼的に認められた腫瘤及び結合織浮腫では，いずれの部位でも組織学的に扁平な細胞からなる叢状管腔構造の形成が認められた。周囲の正常組織への圧排性はなく，細胞の異型性や分裂像は認められなかった。一部には弁状の構造物を伴っており，頸部皮下の切片において頸部リンパ節との連続が認められた。免疫組織化学染色では，管腔を内張りする細胞は LYVE-1，CD31 陽性，CK AE1/AE3，Ki67 陰性であったため，α -SMA 陽性の平滑筋に裏打ちされたリンパ管内皮と考えられた。【結論】リンパ管内皮に内張りされた管腔の形成およびリンパ節との連続性を有する点，若齢かつ組織学的特徴から腫瘍性病変とは考え難い点から，リンパ管奇形（リンパ管腫）と診断した。ヒトにおけるリンパ管腫も臨床的病態に腫瘍とは異なる挙動が知られており，近年の ISSVA（国際血管奇形研究学会）分類においてはリンパ管奇形に含められている。本症例は，ヒトにおけるリンパ管腫と組織学的特徴，発生部位・年齢も類似しており，ヒトと同様に若齢のラットに発生した稀な奇形性病変であったと推測された。

P-113

Gastric carcinoid tumors in rats with parietal cell atrophy in a long-term carcinogenicity study

○Shirai Norimitsu、Choudhary Shambhunath、Houle Christopher

Pfizer Inc. Drug Safety R&D, Pathology

Gastric carcinoids are very rare as spontaneous tumors in rats, but can be induced through a feedback loop via increases in the plasma gastrin levels following administration of agents that block gastric acid for prolonged periods. We aim to present microscopic data from a long-term carcinogenicity study of a small molecule antagonist against the cannabinoid-1 receptor in which carcinoids and parietal cell atrophy coincided, focusing on a causal link. Test article was administered to 60 rats/sex/group once daily by oral gavage at low, mid or high dose for 2 years. Two separate groups of rats received vehicle only and served as controls. Microscopic examination was performed on H&E sections of stomach from all animals. Sevier-Munger silver stain for neuroendocrine tissues was used to aid diagnosis. Carcinoid and neuroendocrine cell hyperplasia occurred in 2/60 females and 1/60 females, respectively, only at the high dose. Parietal cell atrophy was increased in incidence at the high dose (11/60 males, 22/60 females) compared to controls (2/120 males only). Carcinoids exhibited expansive growth obliterating normal mucosal architecture and infiltrating into the submucosa. Tumor consisted of densely packed nests of round to polygonal cells delineated by fine fibrovascular stroma. Sevier-Munger staining revealed argyrophil granules in cell cytoplasm. Carcinoids are rare in control rats, and in this case, were likely secondary to test article-related parietal cell atrophy.

P-114

SD ラットにみられた胸腔内に充満する巨大食道憩室の 1 例

○藤島 純子、山下 弘貴、笹木 祐司、小林 欣滋、前田 博

（株）新日本科学　安全性研究所

【背景と目的】消化管憩室は消化管壁の一部が外側に拡張し嚢状を形成した病変であり，小腸及び大腸に好発するが，食道においても発生することが知られている．今回，無処置ラットにおいて胸腔内に充満する巨大食道憩室が認められたため，病理組織学的に精査した．
【材料と方法】症例（Crl:CD(SD) ラット，雌，11 週齢）は無処置の予備飼育動物で，飼育期間中の一般状態に異常はみられなかった．剖検時に灰白色充実性の胸腔内腫瘤（35x25x20 mm）がみられ，右肺，大動脈及び食道を巻き込み胸壁及び横隔膜と癒着していたが，胸腔内に液性貯留や食渣等の異物はみられなかった．採取された腫瘤及び胸腔内器官は常法に従って 10% 中性緩衝ホルマリン液で固定し，HE 染色を施した．また，特殊染色及び免疫組織化学染色も実施した．
【結果】腫瘤は膠原線維，一部で粘膜筋板を欠く扁平上皮で内張りされ，内腔に食渣と考えられる異物及び膿を容れていた．腫瘤周辺には食道，大動脈，気管及び肺が認められ，それらと腫瘤の境界は明瞭であったが，食道外層の結合組織は腫瘤を形成する結合組織に連続し，結合組織内にはデスミン陽性を示す横紋を持つ細胞がみられた．
【結論】食道外層と腫瘤の結合組織に連続性がみられ，扁平上皮の内張りが一部でみられたこと，膠原線維内に食道筋層の骨格筋の残存の可能性があること，内腔に食渣を含むことから，本症例は食道憩室と考えられた．憩室には発育異常などによる先天性変化と物理的刺激や炎症性病変の二次変化などによる後天性変化がある．本症例では粘膜及び筋層が不完全ではあるが，個体には投与等の処置歴がなく，11 週齢の若齢個体であることから，先天的に存在した病変部に食渣等が貯留して巨大憩室が形成された可能性が示唆された．

P-115＊

ラット空腸に認められた嚢胞状結節性病変の 1 例

○馬場 雄大、池田 瑛人、岡田 亜季子、本郷 直子、乾 公正、永池 美香

石原産業株式会社　中央研究所　安全科学研究室　安全性グループ

【目的】加齢ラットの空腸腸間膜側に、小腸粘膜で裏打ちされた嚢胞状結節性病変を認めたので報告する。
【材料と方法】本症例は発がん性試験の対照群に供された BrlHan:WIST@Jcl(GALAS) ラット雌動物で、111 週齢時に計画殺された。剖検時、膵臓と隣接する空腸の腸間膜側に直径約 6 mm の乳白色嚢胞状結節が認められた。
【結果】HE 染色において、結節は隣接する空腸に似た組織像を呈する嚢胞様組織で、内腔側より小腸粘膜、平滑筋層、漿膜より構成されていた。平滑筋層は薄く走行は著しく乱れ、隣接部位では空腸と共有されていた。検索した範囲では粘膜筋板や神経細胞叢は認められなかった。嚢胞の粘膜は、丈の高い絨毛が分岐し過形成を呈する領域と、平坦となって絨毛を欠く領域が混在した。粘膜は刷子縁を有する吸収上皮細胞と杯細胞で裏打ちされており、平坦な部位の吸収上皮細胞には顕著な空胞化が認められた。粘膜固有層には骨化生が認められた。嚢胞腔内は好塩基性顆粒物や好酸性絮状物で充満していた。
【考察】小腸の嚢胞状結節性病変としては、メッケル憩室あるいはその他の憩室、重複腸管、腫瘍が挙げられる。本症例の肉眼的な発生部位および組織学的検査結果を踏まえて病理発生を考察したい。

P-116

Study on pathomorphological changes of liver in Beagle dog with spontaneous hepatocirrhosis

○Hu Jian-ting、Qiu Bo、Ying Yong

New Drug Evaluation Center of Shandong Academy of Pharmaceutical Sciences

[Background] During repeated toxicity tests, one dog in the control group developed severe liver cirrhosis. **[Aim]** To study the liver pathomorphological and serum biochemical Changes in Beagle dog with spontaneous hepatocirrhosis and establish the background information of experimental animals for GLP. **[Materials and Methods]** The ALT, AST, TP, ALB, ALP, TBIL, TC, TG and GGT were detected by automatic biochemical analyzer, compared the differences of above index between blank control and diseased animal. The histopathological feature of liver was described with optical microscope. **[Results]** Compared with blank control, the ALT, AST, ALP, TBIL and GGT of diseased animal were increased significantly, and the ALB decreased significant. Compared with normal, the liver cells were nodular regeneration and arranged irregularly and False leaflets formation. The false leaflets were packaged with collagen fiber. **[Conclusion]** It is suggested that spontaneous lesions should be monitored so as to provide experimental animals histopathological background information for drug safety evaluation.

P-117＊

腎臓に観察された腎間葉系腫瘍と考えられる一例

○Guo Jin、Du Mu、Qi Wei、Zhang Rui、Guo Hui、Liu Xiangjiang、廣内 康彦

昭衍（蘇州）新薬研究中心有限公司

【目的】SDrat を用いた 26 週間の安全性試験において、雌の腎臓に結節が観察された。尿管由来の腫瘍および腎芽腫は少数例報告されている。今回、自然発生性に腎間葉系腫瘍を認めたので、病理組織学的特徴を報告する。【方法】本症例は 23 週時に死亡後に発見し、剖検時に腎臓に結節が観察された。採取した腎臓組織は 10％中性緩衝ホルマリン液で固定後、パラフィン切片を作成し、HE 染色、特殊染色および各種抗体を用いた免疫染色を施し病理組織学的検査を行った。【結果】観察された結節は、腎臓の皮質から発生したと考えられ、浸潤性の発育様式はない。境界が明瞭な圧排性のやや円形の結節で、平滑筋繊維および膠原線維成分の混在した渦巻状の配列が特徴的であった。これらの細胞に細胞分裂は見られなかった。結節内部には好中球が散在背に浸潤していた。さらに細胞密度の高い腺様構造が散在性に介在していた。また、核は円形、細胞質は好酸性並びに泡沫状が特徴の細胞が敷石状に観察された。【結論】糸球体様の構造がないことから腎芽腫は否定できた。また腎尿細管由来の腫瘍形態も見られなかった。以上のことから平滑筋および膠原線維を主とする腎間葉系腫瘍と考えた。敷石状に観察された細胞の起源は不明であった。

P-118＊

卵巣の絨毛癌により死亡した 9 週齢の雌性 CBA/J マウスの一例

○小林 俊夫、大嶋 浩、山本 季美花、森岡 久子、堀内 雅史、坪倉 靖祐、宮田 克己、寶珠山 五月

（一財）化学物質評価研究機構

【背景】マウスの卵巣における絨毛癌の発生頻度は非常に低く、National Toxicology Program のデータでは、B6C3F1 マウス 41,102 例のうち 7 例（29 ～ 94 週齢）でのみ報告されている。近年、若齢（8 週齢）の ICR マウスにおいても絨毛癌が報告されているが、CBA/J マウスではこれまでに報告がない。今回、9 週齢の雌性 CBA/J マウスにおいて、卵巣の絨毛癌に遭遇したため報告する。【症例】皮膚感作性試験の媒体対照群に供した 1 例であり、1 日 1 回、媒体を耳介へ塗布していたところ、塗布 3 日目に死亡発見された。剖検後、病変を含む主要臓器について病理組織学的に検索した。【結果】生存期間中の一般状態に異常は認められず、死亡発見時の体重についても塗布 1 日目（死亡 2 日前）と比較して変動はなかった。剖検では、腹腔内出血（約 0.6 mL）、並びに左側卵巣の暗赤色化及び腫大がみられた。組織学的には、卵巣の大部分を血液嚢胞が占め、辺縁の実質では壊死性変化のほか、巨大な異型核と細胞質内に赤血球を含む巨細胞、並びに細胞性栄養膜細胞に類似したやや大型の腫瘍細胞がみられた。【考察】特徴的な病理組織像から、本症例は卵巣の絨毛癌と診断した。本症例は CBA/J マウスにおける卵巣絨毛癌の最初の報告であり、9 週齢で致死的影響を及ぼした極めて珍しい症例である。集会では主要臓器の検索結果及び特殊染色結果を含めて報告する。

P-119＊

Malignant tumour of ovary in a young Rhesus monkey - Case Report

○Wang Haoan[1)]、He Yang[1)]、Chen Ke[1)]、Qiu Shuang[1)]、Yang Kaixuan[2)]、Cen Xiaobo[1,3)]、Hu Chunyan[1)]

[1)] Westchina-Frontier Pharma Tech Co., Ltd (WCFP)
[2)] West China Second University Hospital, Sichuan University
[3)] National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, and Collaborative Innovation Center for Biotherapy

[Background] Right ovarian mass with nodules in the lung were found in a 3.5-year old female Rhesus monkey in control group of a toxicity study during the necropsy. **[Aim]** To determine the histopathological classification of the ovarian tumor and investigate the relationship between the ovarian tumor and nodules noted in the lung. **[Materials and Methods]** Tumor tissues were embedded in paraffin, 4-μm slides were stained with hematoxylin and eosin, and immunohistochemistry labeling for CK18, CK-p, P27, α -inhibin, HPL, SALL4, Ki67, and CD117 were also performed. **[Results]** Microscopically, the tumors of the ovary mainly composed of three components. In most parts of the tumor, neoplastic cytotrophoblasts and syncytiotrophoblasts were arranged around blood vessels; some parts existed vesicular or cystic structure containing a large amount of mucus, hyaline droplets were found in the cytoplasm of the lining tumor cells; in addition, small foci of embryonal carcinoma component were present. Tumor cells were positive for CK18, CK-p, P27, α -inhibin, HPL, Ki67 and SALL4, but negative for CD117. For the lung, the tumor contained cytotrophoblasts and syncytiotrophoblasts as well as vesicular or cystic structure, and the tumor cells in the lung were positive for CK18, Ki67 and SALL4. **[Conclusion]** Malignant mixed germ cell tumor originated from the ovary was diagnosed based on the histologic and immunohistochemical features, and partial components of the tumor were metastases to the lung.

P-120

A case of spontaneous pituitary gland adenocarcinoma in a nineteen-week-old female Sprague-Dawley rat

○Duyeol Kim, Jong-Il Shin, Hyun Kyung Song, Byung-Woo Lee, Hyun-Woo Kim, Han Kyul Lee, Sun-Hee Park

Biotoxtech Co

Pituitary gland tumors have been known as one of the most common tumors occurring in aging rats, with arising from pars distalis, but they are rare in young rats.

[Aim]

We describe an adenocarcinoma from the pituitary gland and the cancer within hypothalamus in a young female SD rat.

[Materials and Methods]

The masses in the pituitary gland and hypothalamus of 19-week-old female SD rat were prepared for histopathology. In addition, the masses were analyzed by staining with antibodies against cytokeratin (CK), vimentin, S-100b, ED-1, RM-4 and GFAP, and stained with PAS.

[Results]

At necropsy, white nodule is located in the pituitary gland and the mass pressed the hypothalamus. The mass is characterized by abundant eosinophilic matrix and severe invasion to the hypothalamus. Small islands composed of neoplastic cells are scattered in the abundant matrix. Round to oval tumor cells showed high N/C and two-three mitotic figures (hpf). In the hypothalamus, it is also observed that the tumor cells cluster is located within meninges and hypothalamus, and the histological characteristics are similar to those in the pituitary gland.

On IHC and histochemical staining, the cells stained positive for only CK antibody in the cytoplasm and the matrix was positive for PAS staining.

[Conclusion]

Taken together, the pituitary tumor was diagnosed as adenocarcinoma derived from basophil and the tumor in the hypothalamus was the result of invasion of the pituitary tumor.

P-121＊

ヒトの clear cell sarcoma に類似する雌 SD ラットの足蹠部自然発生腫瘍

○斎藤 翼、岡野 拡、青木 萌子、神谷 有美子、藤原 史織、橋口 収、山口 裕子

（株）ボゾリサーチセンター

【背景】ヒト腫瘍の病理分類では clear cell sarcoma は分化未定腫瘍（tumor of uncertain differentiation）と分類されている。しかし一部の研究では軟部組織、特に下肢の腱や腱膜から発生し、メラノーマ関連抗原が検出されることから、神経堤細胞に由来する”melanoma of soft parts”と報告されている。今回 SD ラットの後肢・足蹠部に形態学的にヒトの clear cell sarcoma に類似する腫瘍が認められたので、その組織学的特徴を報告する。
【材料と方法】本症例はがん原性試験のための背景データ収集に用いられた雌の 1 例であり、85 週齢時に瀕死例として剖検に供された。剖検後、組織は 10% 中性緩衝ホルマリン液で固定し、当該組織を K-CX で脱灰後、HE 染色及び各種免疫染色、特殊染色に供した。
【結果】剖検時、当該病変は肉眼的に左足蹠部の腫脹として観察された。組織検査の結果、足蹠部皮下組織から中足骨にかけて、淡明な細胞が足底腱膜から一部連続する様に塊状に増殖していた。腫瘍細胞は、細線維状構造によって胞巣状、小柱状に隔てられており、微細なクロマチンを有する小型円形核、淡明豊富で一部好酸性微細顆粒状を呈する細胞質を有していた。有糸分裂像はほとんど認められなかった。同細胞は PAS 反応陰性であり、免疫組織化学染色では S100 陽性、vimentin 一部陽性、desmin 陰性、α -SMA 陰性、Iba-1 陰性であった。脱灰標本であるため Ki-67 及び PNL2 は適切な染色性が得られなかった。その他、本症例には瀕死原因である下垂体腫瘍や種々の自然発生性の加齢性病変が認められたが、足蹠部の病変に関連すると考えられる所見は認められなかった。
【まとめ】本症例は形態学的にヒトの clear cell sarcoma に類似する自然発生腫瘍であった。ラットにおいて同様な報告はなされておらず、本症例は非常に稀な腫瘍と考えられる。

Joint Meeting of JSTP and AUTP 2022

The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology

The 1st Meeting of the Asian Union of Toxicologic Pathology

Table of Contents

Joint Meeting of JSTP and AUTP 2022

The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology
The 1st Meeting of the Asian Union of Toxicologic Pathology

1. Date　January 26 (Wed) - 28 (Fri), 2022

2. Theme　Create the Future of Toxicologic Pathology: Technology & Creativity

3. Venue　Kobe International Conference Center
6-9-1, Minatojima-nakamachi, Chuo-ku, Kobe-shi, Hyogo, 650-0046, Japan
TEL: +81-78-302-5200

4. President　Hideki Wanibuchi, M.D., Ph.D.
(Osaka City University Graduate School of Medicine)

5. Program Committee

Chair	Satoru Takahashi	(Nagoya City University Graduate School of Medical Sciences)
Committee	Kumiko Ogawa	(National Institute of Health Sciences)
	Etsuko Ohta	(Eisai Co., Ltd.)
	Atsuhiko Kato	(Chugai Pharmaceutical Co., Ltd.)
	Mitsuru Kuwamura	(Osaka Prefecture University)
	Kinji Kobayashi	(Shin Nippon Biomedical Laboratories, Ltd.)
	Akihito Shimoi	(Ina Research Inc.)
	Dai Nakae	(Tokyo University of Agriculture)
	Shim-mo Hayashi	(National Institute of Health Sciences)
	Izumi Matsumoto	(Sumitomo Dainippon Pharma Co., Ltd.)
	Yuko Yamaguchi	(BoZo Research Center Inc.)
	Katsuhiko Yoshizawa	(Mukogawa Women's University)

6. Office　[Congress Secretariat]
The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology
1-4-3 Asahi-machi, Abeno-ku, Osaka-City, Osaka, Japan
Tel: +81-6-6645-3736　Fax: +81-6-6646-3093
E-mail: jstp38@med.osaka-cu.ac.jp
[Management Secretariat]
C/O Proactive, Inc.
3F Sannomiya Century Bldg, 83 Kyomachi Chuo-ku, Kobe 650-0034, Japan
Tel: +81-78-332-2505　Email: jstp38@pac.ne.jp

7. Homepage　https://www.pac-mice.jp/jstp38/

Greetings

It is my great pleasure to invite you to attend the 38th Annual Meeting of the Japanese Society of Toxicologic Pathology (JSTP) that will be held on January 27th and 28th, 2022, in a Hybrid format that can be attended both at the Kobe International Conference Center (Kobe City, Hyogo Prefecture, Japan) and online. We are also planning an international joint meeting with the 1st Meeting of the Asian Union of Toxicologic Pathology (AUTP) at the same time. In addition, the 34th Annual JSTP Slide Conference, the Commentary Session of the JSTP Diplomat Examination, and the 1st JSTP-CPA-STP (Chinese Pharmaceutical Association-Society of Toxicologic Pathology) Joint Education Seminar is scheduled to be held on January 26th, 2022. We invite you to attend these events and will provide opportunities for both domestic and international participation.

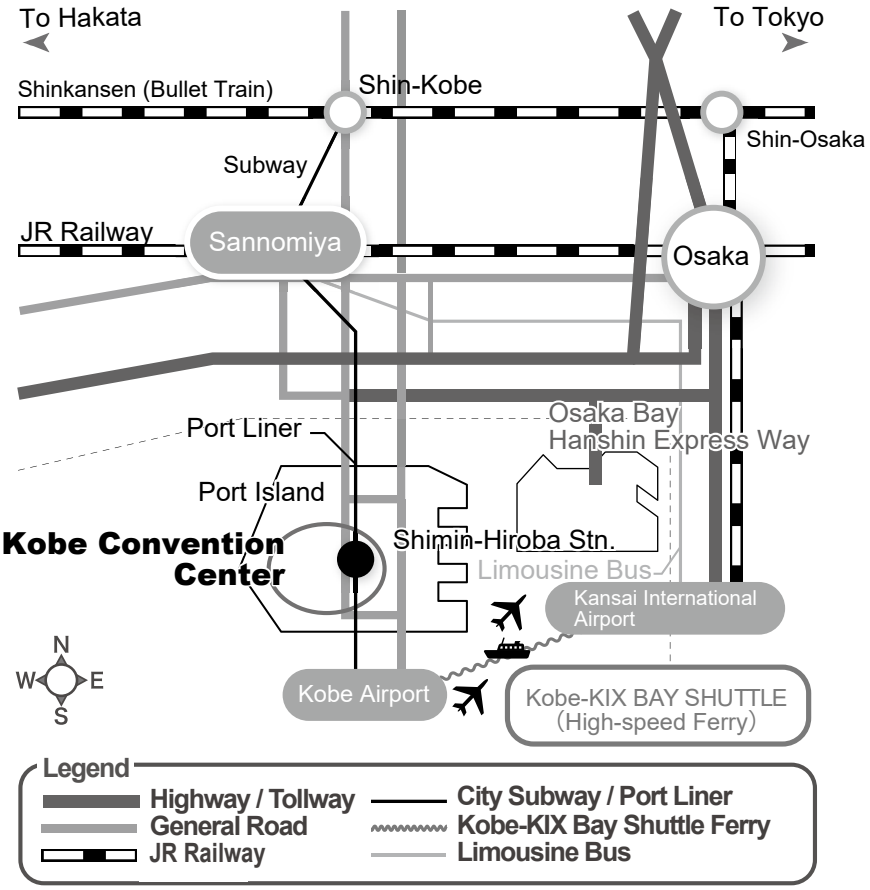
The theme of the JSTP meeting is "Create the Future of Toxicologic Pathology: Technology & Creativity". The aim of the JSTP is to improve human and animal health using an interdisciplinary scientific approach based on pathology and toxicology. It has become increasing important to develop not only novel toxicological models, which have played an important role in the development of small-molecule drugs, but also new methodologies for elucidation of the toxicological mode of action, such as digital pathology, imaging analysis, and artificial intelligence (AI)-based diagnosis. Under the theme of "Creating the Future of Toxicologic Pathology", we will invite experts in image digitization, AI-based pathologic diagnosis, and novel visualization technologies as symposium speakers. We will also invite experts in the fields of genome editing of experimental animals and cancer microenvironment to share up-to-date knowledge in these fields.

During the annual meeting, I also would like to hold the 1st Meeting of AUTP with toxicological pathologists from Japan, China, Korean, India, Thai, Egypt, EU, and United States of America. I hope we can take this opportunity to expand international cooperation and establish partnerships with Asian toxicologic pathology societies.

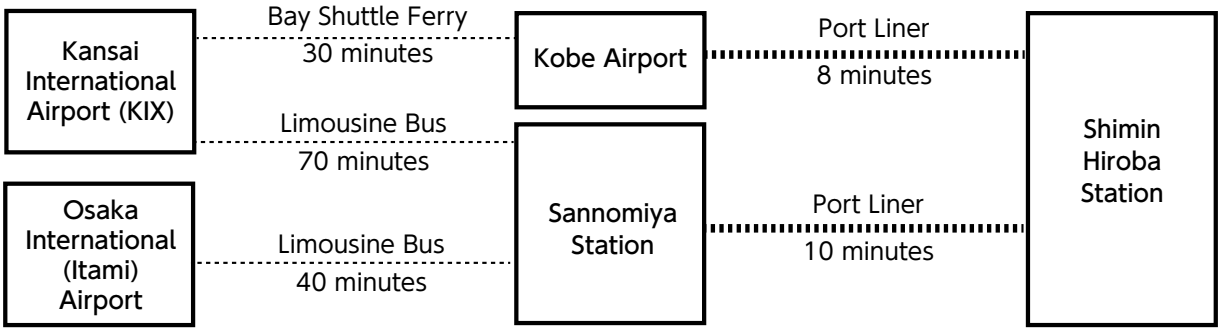
At the JSTP Annual meeting and the other scheduled events, we hope that a large number of participants will come together, present their achievements, interact and exchange opinions, and thereby advance future visions under the theme "Create the Future of Toxicologic Pathology: Technology & Creativity". I am eagerly looking forward to your active participation in the events we have planned in lovely Kobe City and online!

Hideki Wanibuchi, M.D. Ph.D.
President
The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology
The 1st Meeting of Asian Union of Toxicologic Pathology
(Osaka City University Graduate School of Medicine)

Access

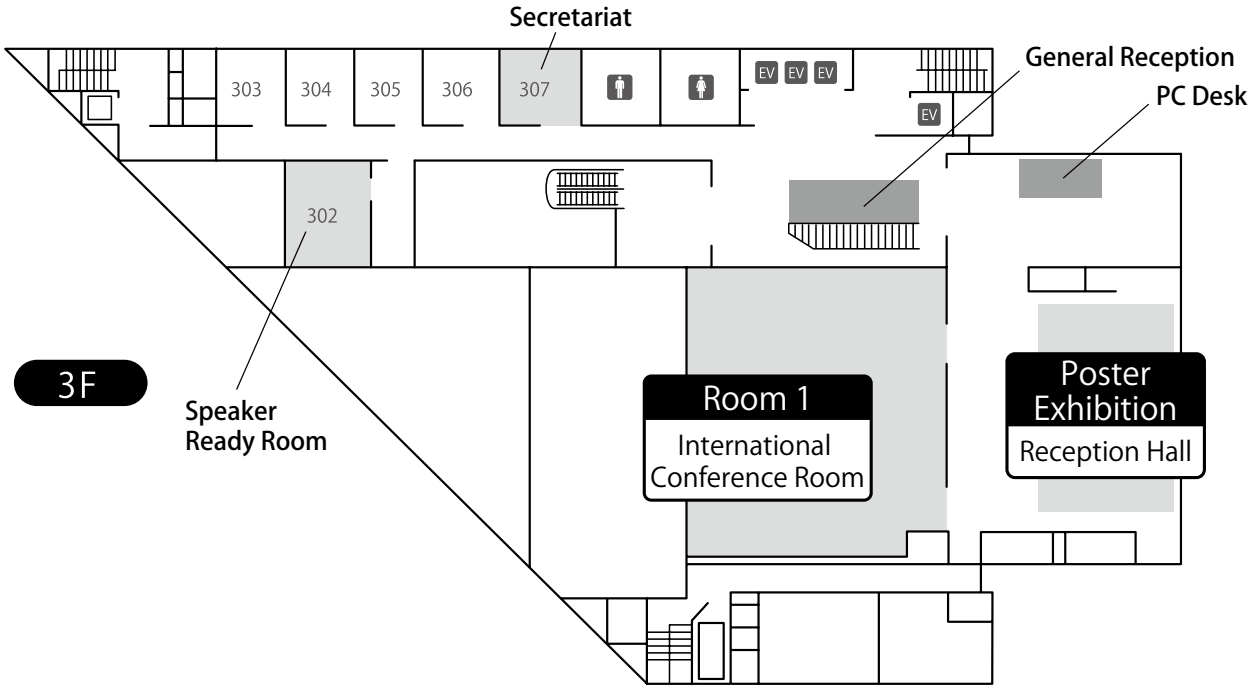


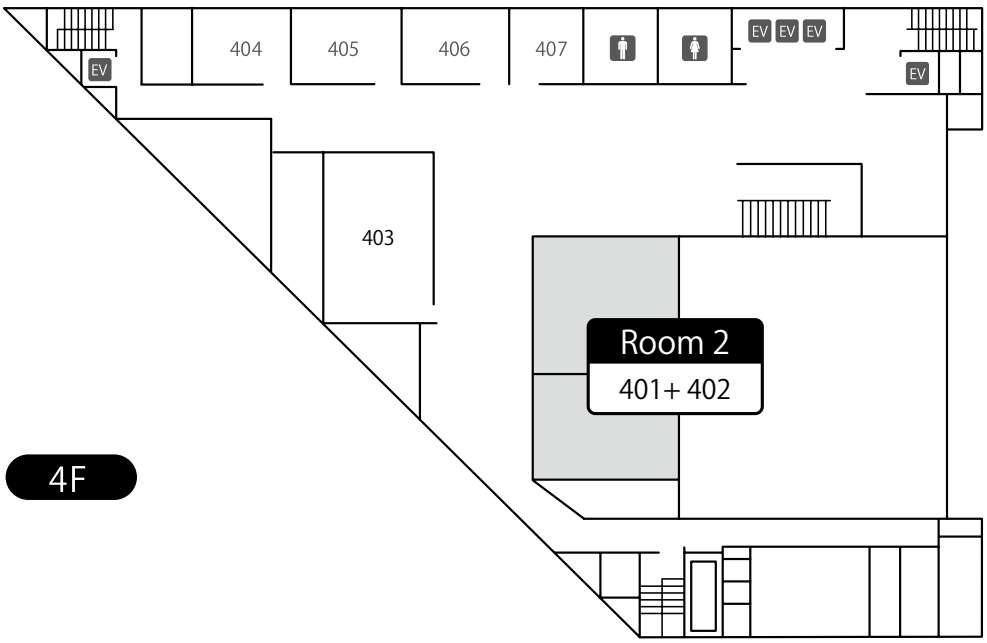
■By airplane



■By Shinkansen

Floor Plan


Secretariat
General Reception
PC Desk
303
304
305
306
307
EV EV EV
EV
302
3F
Speaker
Ready Room
Room 1
International
Conference Room
Poster
Exhibition
Reception Hall


404
405
406
407
EV EV EV
EV
EV
403
Room 2
401+ 402
4F

Information for Participants

The Joint Meeting of JSTP and AUTP 2022 will be held as a "Hybrid" meeting IATP Lecture and 1st JSTP-CPA-STP Joint Education Seminar to prevent spread of COVID-19 - both in-person and an online meeting using a Web conference system. All the designated sessions (Special Lecture, Symposium, Panel discussion, Workshop, IATP Lecture and 1st JSTP-CPA-STP) will be streamed "live" online. All Poster presentations will be published on our website and available on-demand. We appreciate your understanding and look forward to your participation.

Sessions	Format
Special Lecture Symposium Panel Discussion Young Researchers Workshop IATP Maronpot Guest Lecture	On-site & Live Streaming
1st JSTP-CPA-STP Joint Education Seminar	Live Streaming
Poster Presentations※	On-demand (January 20 (Thu)～February 13 (Sun) 23:59)

※ Candidates of Young Researcher Poster Award and Case Report Award will be placed onsite at the Exhibition area during the meeting.

● For Participants

1. Pre-registration is required for participation.
2. Special Lecture, Symposium, Panel Discussion, Workshop, IATP lecture, and 1st JSTP-CPA-STP Joint Education Seminar* will be streamed live using a Web conference system.
   *Please note that the 1st JSTP-CPA-STP Joint Education Seminar is presented in Chinese. A PDF version of the presentation slides (in English) will be available to seminar attendees after the seminar.
3. If you have any questions or comments on the above presentations, please post them in the Q&A system. Please note that it is up to the chairs to select questions or comments.
4. Poster presentations will not be streamed live and be available for participants to view on-demand until February 13 (Sun) at 23:59. You can submit your questions to the Q&A system.
5. All materials on the meeting site are not for download, and the recording or screenshots are prohibited.
6. If you have any inquiries, please contact the 38th JSTP Secretariat by e-mail (jstp38@pac.ne.jp).

● General Assembly and Board of Councilors

Internathional Conference Room & Live Streaming.
Date and Time: Jan. 28 (Fri) 2022, 15:35–17:05
Agenda: Performance and annual review in 2021
Budget and planning for annual performance in 2022
Recommendation of meritorious members
Election of board members and councilors
Election of president for 2024 annual meeting

● For Presenters

COI Disclosure

Please disclose COI (Conflict of Interest) to your best knowledge. Corporate employees are also required to disclose COI to show that they have COI with other corporations, in case they have one. Oral Presenters are required to show COI on the second slide (after the first title slide). Presenters for PDF Poster Presentation are required to disclose COI at the end of their presentations.

Sample 1

COI Disclosure Information

Taro Dokusei

In connection with this presentation, there is

no COI to be disclosed with any companies.

本演題に関連して開示すべき利益相反はありません。

Sample 2

COI Disclosure Information

Hanako Dokusei

In connection with the presentation, we

disclose COI with following companies.

本演題に関連して開示すべき利益相反は以下の通りです。

Executive / Advisory Position:	(○○Company)
Funded research / Collaborative research:	(○○Company)
Lecture Honorariums, etc.:	(○○Company)

Oral Presentations

You may choose one of the following presentation methods.

1） In-person at the Kobe International Conference Center
2） Deliver a presentation online (Live) using Zoom.
3） Submit a pre-recorded video and participate in the online Q&A Discussion (Live) using Zoom. You may prepare your presentation video (MP4 Format) by using PowerPoint (16:9) with audio or by recording with Zoom App.

Poster Presentations

1. The poster presentations will be conducted by displaying PDF data on our website and available on-demand until Sunday, February 13, 23:59.
2. The presenters will receive questions or comments on the Web conference system. Please reply to them by Sunday, February 13, 23:59.
   ※ There is no "live" streaming session.
   ※ The annual meeting president's award will be selected among the first authors of the poster presentation under the age of 40.

● Luncheon・Evening・Morning Seminars (On-site & Live Streaming)

Day 1, January 27, Thursday

Luncheon Seminar 1

Time and Place: 12:00 - 13:00　Room 1 (International Conference Room)
Title: AI Decision Support Tool Development in Toxicologic Pathology
Speaker: Esther Crouch（Veterinary Pathologist, Global Digital Pathology, Charles River）
Chairperson: Masamichi Kaminishi（Chares River）
Co-Sponser: Charles River

Luncheon Seminar 2

Time and Place: 12:00 - 13:00　Room 2 (401+402)
Title: Evaluation of the Regenerative Potential of Cytokines and Biomaterials in Periodontal Tissue Regeneration in Laboratory Animals
Speaker: Yoshinori Shirakata（Department of Periodontology, Field of Oral and Maxillofacial Rehabilitation, Graduate School of Medical and Dental Sciences, Kagoshima University）
Chairperson: Kinji Kobayashi（Department of Pathology, Drug Safety Research Laboratories, Shin Nippon Biomedical Laboratories）
Co-Sponser: Shin Nippon Biomedical Laboratories, Ltd.

Evening Seminar

Time and Place: 18:35 - 19:35　Room 1 (International Conference Room)
Title: Application of Quanticell to Clinical specimens
Speaker: Koji Tsuta（Department of Pathology,Kansai Medical University)

Title: Introducing a Quanticell immunohistochemistry service that is highly sensitive, semi-quantitative and spatial assay of target molecules.
Speaker: Kemji Nishikawa（Pharma Business Development & Sales Division,KONICA MINOLTA REALM, INC.)

Co-Sponser: KONICA MINOLTA REALM, INC.

Day 2, January 28, Friday

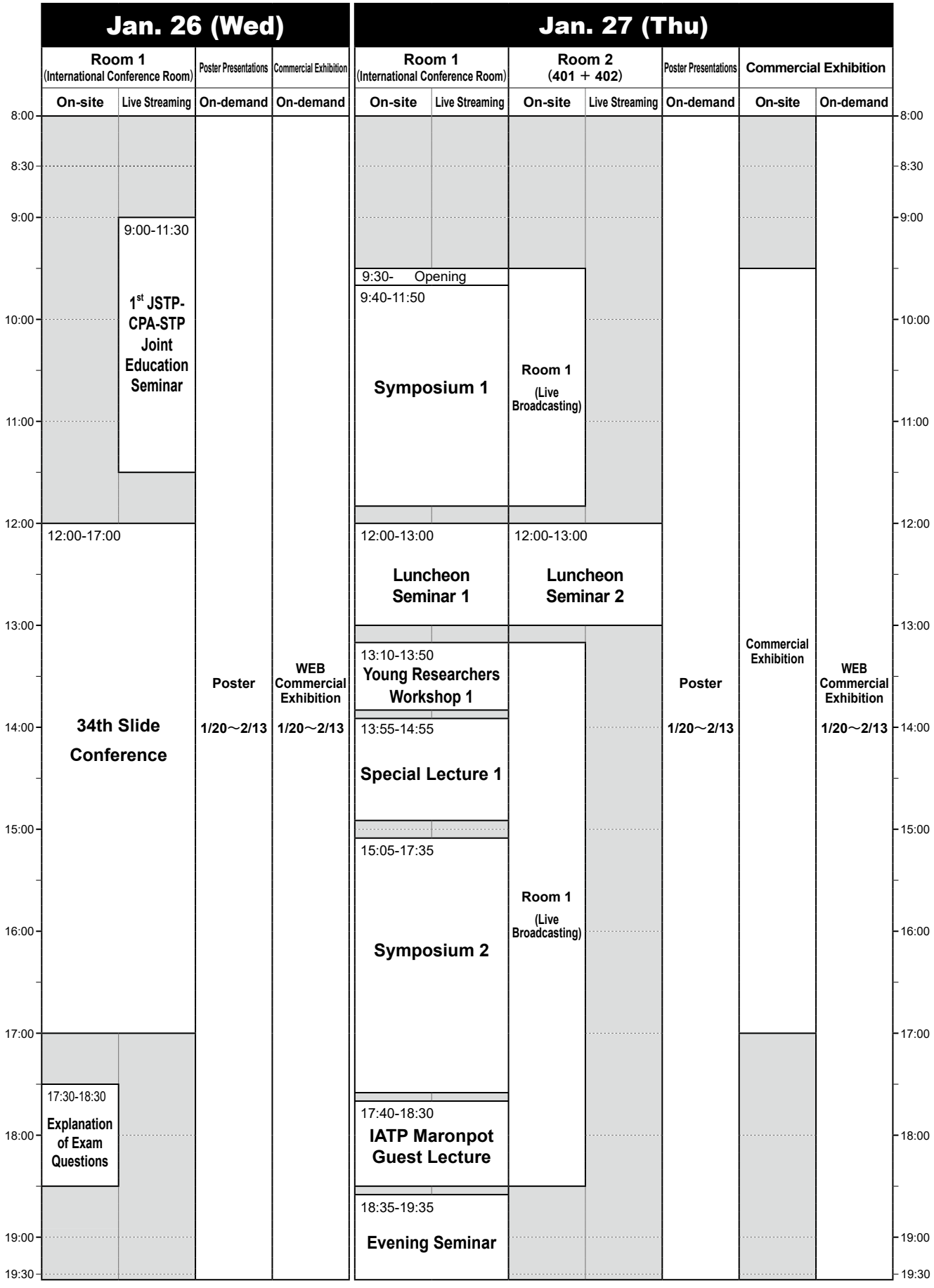
Morning Seminar

Time and Place: 8:00 - 8:40　Room 2 (401+402)
Title: Microscopic Observations for Infectious Disease Models (Tentative)
Speaker: Carson Sakamoto（Anatomic Pathologist, Southern Research）
Chairperson: Toshihide Hayashi（Ina Research Inc.）
Co-Sponser: Ina Research Inc.

Luncheon Seminar 3

Time and Place: 12:00 - 13:00　Room 1 (International Conference Room)
Title: Spatially map and quantify the whole transcriptome in the tissue context with Visium Spatial solutions
Speaker: Yosuke Amagai（Science & Technology Advisor　10x Genomics）
Chairperson: Ken Osaki（Regional Marketing Manager, North Asia Pacific　10x Genomics）
Co-Sponser: Scrum Inc./10x Genomics

Timetable


Jan. 26 (Wed)
Jan. 27 (Thu)
Room 1 (International Conference Room)
Poster Presentations
Commercial Exhibition
Room 2 (401 + 402)
On-site
Live Streaming
On-demand
8:00
8:30
9:00
10:00
11:00
12:00
13:00
14:00
15:00
16:00
17:00
18:00
19:00
19:30
9:00-11:30
1st JSTP-CPA-STP Joint Education Seminar
9:30- Opening
9:40-11:50
Symposium 1
Room 1 (Live Broadcasting)
12:00-17:00
34th Slide Conference
12:00-13:00
Luncheon Seminar 1
Luncheon Seminar 2
13:10-13:50
Young Researchers Workshop 1
13:55-14:55
Special Lecture 1
15:05-17:35
Symposium 2
17:30-18:30
Explanation of Exam Questions
17:40-18:30
IATP Maronpot Guest Lecture
18:35-19:35
Evening Seminar
Poster
1/20～2/13
WEB Commercial Exhibition
1/20～2/13
Commercial Exhibition

Timetable

Jan. 28 (Fri)

Room 1 (International Conference Room)		Room 2 (401 + 402)		Poster Presentations	Commercial Exhibition	
On-site	Live Streaming	On-site	Live Streaming	On-demand	On-site	On-demand
		8:00-8:40 Morning Seminar		Poster 1/20～2/13		WEB Commercial Exhibition 1/20 ～ 2/13
9:00-9:50 Special Lecture 2		Room 1 (Live Broadcasting)			Commercial Exhibition	
9:55-11:55 Symposium 3						
12:00-13:00 Luncheon Seminar 3						
13:10-13:50 Young Researchers Workshop 2		Room 1 (Live Broadcasting)				
13:55 ～ 15:25 Panel Discussion						
15:35 ～ 17:05 General Assembly and Board of Councilors Closing						

Program

Special Lecture 1

Day 1, January 27, Thursday 13:55 - 14:55 Room 1（International Conference Room）

Chair: Hideki Wanibuchi (Osaka City University Graduate School of Medicine)

SL-1 Development of novel therapies for diseases associated with intestinal dysbiosis

○Satoshi Uematsu[1,2)]

[1)] Department of Immunology and Genomics, Osaka City University Graduate School of Medicine
[2)] Division of Metagenome Medicine, Human Genome Center, The Institute of Medical Science, The University of Tokyo

Special Lecture 2

Day 2, January 28, Friday 9:00 - 9:50 Room 1（International Conference Room）

Chair: Satoru Takahashi (Nagoya City University Graduate School of Medical Sciences)

SL-2 Contribution of toxicologic pathology to occupational health

○Shoji Fukushima[1,2)]

[1)] Japan Bioassay Research Center (JBRC), Japan Organization of Occupational Health and Safety
[2)] Association for Promotion of Research on Risk Assessment

Symposium 1 Toxicologic pathology and beyond ～ In-depth analysis of pathological specimens utilizing visualization technology ～

Day 1, January 27, Thursday 9:40 - 11:50 Room 1（International Conference Room）

Chair: Kumiko Ogawa (National Institute of Health Sciences)
Kinji Kobayashi (Shin Nippon Biomedical Laboratories, Ltd.)

S1-1 Visualization of chemicals and its metabolites in tissue sections using desorption electrospray ionization mass spectrometry imaging

○Yuji Ishii

Divsion of Pathology, National Institute of Health Sciences

S1-2 Quantitation of cancer histopathology by AI

○Shumpei Ishikawa

Department of Preventive Medicine, Graduate School of Medicine, The University of Tokyo

S1-3 Basics of OCT (optical coherence tomography) examination and the relationship between OCT images and histopathological images

○Tomoaki Araki

Shin Nippon Biomedical Laboratories, Ltd. Drug Safety Research Laboratories.

S1-4 Digital pathology and artificial intelligence in the AI hospital project

○Manabu Takamatsu

Division of Pathology, Cancer Institute of Japanese Foundation for Cancer Research

Symposium 2 Internationalization of Board Certification System for Diplomate of JSTP

Day 1, January 27, Thursday 15:05 - 17:35 Room 1（International Conference Room）

Chair: Dai Nakae (Tokyo University Of Agriculture)
Katsuhiko Yoshizawa (Mukogawa Women's University)

S2-1 The current status and future plans for the globalization of JSTP's certification system for toxicologic pathology

○Katsuhiko Yoshizawa[1,2)]

[1)] Department of Innovative Food Sciences, School of Sciences and Nutrition, Mukogawa Women's University
[2)] Board Certification Committee of JSTP

S2-2 Establishment of accreditation procedures in toxicologic pathology for trainees

○Kevin Keane

International Academy of Toxicologic Pathology (IATP)

S2-3 Regulators' perspective

○Yukie Saegusa

Pharmaceuticals and Medical Devices Agency

S2-4 Current situation in Europe

○Yoshimasa Okazaki

AnaPath Services GmbH

S2-5 Current status and future prospects of pharmaco-toxicologic pathology in China

○Jin Ren

Chinese Pharmaceutical Association-Society of Toxicologic Pathology

S2-6 Korean society of toxicologic pathology and board certification

○Jin Seok Kang

Korean Society of Toxicologic Pathology

S2-7 Overview of society of toxicologic pathology India (STPI) and Indian board of toxicologic pathology (IBTP)

○Venkatesha Udupa[1)], SK Vijayasarathi[2)], Narendra Deshmukh[3)], Shekar Chelur[4)], Kamala Kanan[2)], Jomy Jose[5)], PC Prabu[6)], GJ Nataraju[7)], Geeta Nirody[8)], Madhav Marathe[9)]

[1)] Vice President & Head Toxicology, Glenmark Pharmaceuticals Ltd
[2)] Expert Pathologist, Eurofins Advinus Limited
[3)] Co-Founder and Director, Intox Pvt Ltd
[4)] Director, Preclinical Safety Evaluation, Aurigene Discovery Technologies Ltd, Bengaluru, India; 2Head Pathology, Eurofins Advinus Limited
[5)] Head of the Department, Pathology, Sai Lifesciences
[6)] Assistant Professor, Department of Pathology, Veterinary College & Research Institute
[7)] Head Pathology, Bioneeds India Private Ltd
[8)] Consultant Pathologist
[9)] Vice President Toxicology, Sun Pharma Advanced Research Company Ltd

Symposium 3 Toxicologic pathology and beyond
～ Create a new era of toxicologic pathology with cutting-edge technologies ～

Day 2, January 28, Friday 9:55 - 11:55 Room 1（International Conference Room）

Chair: Etsuko Ohta (Eisai Co., Ltd.)
Mitsuru Kuwamura (Osaka Prefecture University)

S3-1 Application of genome editing technology in medical research

○Tomoji Mashimo

University of Tokyo, Institute of Medical Science

S3-2 Mutual interaction between tumor cells and microenvironment shapes morphogenesis of tumor tissues

○Kiyotaka Nakano[1)], Masaki Yamazaki[1)], Shigeto Kawai[1)], Etsuko Fujii[1)], Hiroyuki Aburatani[2)], Masami Suzuki[3)]

[1)]Chugai Pharmaceutical co., ltd., [2)]Research Center for Advanced Science and Technology, The University of Tokyo
[3)]Central Institute for Experimental Animals

S3-3 Establishment of a dual organ carcinogenicity model in rats for application in cancer chemopreventive studies on natural product and functional food

○Rawiwan Wongpoomchai[1,2)], Charatda Punvittayagul[3)], Sirinya Taya[2)], Arpamas Chariyakornkul[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University
[3)]Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University

S3-4 Recent insights into mechanisms driving NAFLD/NASH-associated hepatocarcinogenesis

○Anna Kakehashi, Hideki Wanibuchi

Dept. Mol. Pathology, Osaka City University, Grad. Sch. Med.

Panel Discussion

Day 2, January 28, Friday 13:55 - 15:25 Room 1（International Conference Room）

Chair: Atsuhiko Kato (Chugai Pharmaceutical Co., Ltd.)
Akihito Shimoi (Ina Research)

PD Workstyle of toxicologic pathologist in the post-corona era – Practice and challenges on remote histopathologic evaluation and remote peer review

Panelist : Kinji Kobayashi (Shin Nippon Biomedical Laboratories, Ltd.)
Izumi Matsumoto (Sumitomo Dainippon Pharma Co. Ltd.)
Hisashi Anayama (Drug Safety Research & Evaluation, Takeda Pharmaceutical Company Limited)
Etsuko Ohta (Global Drug Safety, Eisai Co., Ltd.)
Hiroko Kokoshima (LSIM Safety Institute Corporation)
Hijiri Iwata (Laboratory of Toxicologic Pathology, LunaPath LLC)
Yuko Yamagachi (BoZo Research Center Inc.)
Observer : Kenji Nakano (Pharmaceuticals and Medical Devices Agency)

Young Researchers Workshop 1

Day 1, January 27, Thursday 13:10 - 13:50 Room 1（International Conference Room）

Chair: Aya Naiki-Ito (Nagoya City University)
Shugo Suzuki (Osaka City University)

W-1＊ Carbonic anhydrase inhibitor acetazolamide inhibited invasion of urinary bladder cancers via suppression of Wnt/beta-catenin signaling pathway

○Taisuke Matsue[1,2)], Min Gi[3)], Masayuki Shiota[4)], Shugo Suzuki[1)], Masaki Fujioka[1)], Anna Kakehashi[1)], Junji Uchida[2)], Hideki Wanibuchi[1)]

[1)]Department of molecular pathology, Osaka City University Graduate School of Medicine
[2)]Department of urology, Osaka City University Graduate School of Medicine
[3)]Department of Environmental Risk Assessment, Osaka City University Graduate School of Medicine
[4)]Department of molecular mechanisms of biological regulation, Osaka City University Graduate School of Medicine

W-2＊ Immunohistochemical analysis of cynomolgus monkey endometrial estrogen and progesterone receptors throughout the menstrual cycle

○Yuumi Awazuhara, Hiroko Kokoshima, Yuki Tomonari, Natsumi Shimoyama, Yutaka Nakahara, Yumi Wako, Junko Sato, Takuya Doi

LSIM Safety Institute Corporation Pathology Department Kashima Laboratories

W-3＊ Site-specific genotoxicity of rubiadin indicated by its localization and histopathological changes in rat kidney

○Tatsuya Mitsumoto[1,2)], Yuji Ishii[1)], Norifumi Takimoto[1,3)], Moeka Namiki[1)], Shinji Takasu[1)], Takehiko Nohmi[1)], Kumiko Ogawa[1)]

[1)]Division of pathology, National Institute of Health Science
[2)]Faculty of Animal Health Technology, Yamazaki University of Animal Health Technology
[3)]Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology

W-4＊ Involvement of interleukin-21 receptor (IL-21R) in NASH induced in mice by a choline-deficient, methionine-lowered, L-amino acid, high fat diet (CDAA-HF-T(-))

○Noriko Kemuriyama[1)], Hayato Watanabe[2)], Sae Nakane[2)], Aya Kirigakubo[1)], Kasumi Sasaki[1)], Daiki Tanaka[1)], Masaru Kise[1)], Hina Mandokoro[2)], Kinuko Uno[3)], Katsuhiro Miyajima[1,2)], Dai Nakae[1,2)]

[1)]Dept. Nutr. Sci. Food Safety, Facul. Biosci., Tokyo Univ. Agricul.
[2)]Dept. Nutr. Sci. Food Safety, Grad. Sch. Agricul., Tokyo Univ. Agricul.
[3)]Dept. Food Nutr. Sci., Grad. Sch. Agricul., Tokyo Univ. Agricul.

Young Researchers Workshop 2

Day 2, January 28, Friday 13:10 - 13:50 Room 1（International Conference Room）

Chair: Takeshi Toyoda (National Institute of Health Sciences)
Toshinori Yoshida (Tokyo University of Agriculture and Technology)

W-5＊ Introduction of the novel pulmonary disease originating from cases of industrial accidents caused by inhalation of organic dust

○Shotaro Yamano[1)], Tomoki Takeda[1)], Kenji Takanobu[1)], Hideki Senoh[1)], Shigeki Koda[2)], Kenzo Okamoto[3)], Takumi Kishimoto[4)], Yumi Umeda[1)]

[1)]Japan Bioassay Research Center, Japan Organization of Occupational Health and Safety
[2)]National Institute for Occupational Safety and Health, Japan Organization of Occupational Health and Safety
[3)]Department of Pathology, Hokkaido Chuo Rosai Hospital, Japan Organization of Occupational Health and Safety
[4)]Director of Research and Training Center for Asbestos-Related Diseases, Japan Organization of Occupational Health and Safety

W-6＊ Short term pulmonary toxicity study of carbon nano-horns (CNH) and carbon nano-brushes (CNB) using intra tracheal method

◯Saleh Dina[1,2,3)], Ahmed Omnia[1,2,4)], Alexander David[1)], Alexander William[1)], Gunasekaran Sivagami[1,2)], Takamasa Numano[1)], Hiroshi Takase[5)], Makoto Ohnishi[6)], Satoru Takahashi[2)], Masako Yudasaka[7)], Ryota Yuge[8)], Hiroyuki Tsuda[1)]

[1)] Nanotoxicology Lab project, Nagoya City University
[2)] Departement of Experimental pathology and tumor biology, Graduate school of medicine, Nagoya city university
[3)] Department of Forensic medicine and clinical toxicology, Faculty of medicine, Assuit university
[4)] Department of Forensic medicine and clinical toxicology, Faculty of medicine, Aswan university
[5)] Core laboratory, Graduate school of Medicine, Nagoya City University
[6)] Japan Industrial Safety and Health Association, Japan Bioassay Research Center
[7)] National Institute of Advanced Industrial Science and Technology
[8)] System Platform Research Laboratories, NEC Corporation

W-7＊ Generation of cerebral organoids from human embryonic stem cells

◯Ke Chen[1)], Shuang Qiu[1)], Haoan Wang[1)], Qingxi Kong[2)], Qian Bu[1,3)], Qian Liu[1)], Xiaobo Cen[1,4)], Chunyan Hu[1)]

[1)] Westchina-Frontier Pharma Tech Co., Ltd (WCFP), [2)] Pharmaron
[3)] Healthy Food Evaluation Research Center, Department of Food Science and Technology, College of Light Industry, Textile and Food Engineering, Sichuan University
[4)] National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, and Collaborative Innovation Center for Biotherapy

W-8＊ Detection of drug-induced arteritis in rats using *ex vivo/in vivo* MRI

◯Yuta Fujii[1,2)], Yuka Yoshino[1,2)], Kazuhiro Chihara[1)], Aya Nakae[2,3)], Junichiro Enmi[2,3)], Yoshichika Yoshioka[2,3)], Izuru Miyawaki[1)]

[1)] Preclinical Research Unit, Sumitomo Dainippon Pharma Co., Ltd
[2)] Graduate school of Frontier Biosciences, Osaka University
[3)] Center for Information and Neural Networks (CiNet), National Institute of Information and Communications Technology (NICT) and Osaka University

IATP Maronpot Guest Lecture

Day 1, January 27, Thursday 17:40 - 18:30 Room 1（International Conference Room）

Chair: Shimmo Hayashi (National Institute of Health Sciences)

IATP Digital pathology and tissue image analysis - how did we start and where are we now

◯Aleksandra Zuraw

Charles River Laboratories

1st JSTP-CPA-STP Joint Education Seminar

January 26, Wednesday 9:00 - 11:30 **Live Streaming**

Understanding, detection, and diagnosis of background and induced lesions in toxicity and carcinogenicity studies

Chair：Jin Ren (Shanghai Institute of Material Medica, Chinese Academy of Science)
Min Gi (Osaka City University Graduate School of Medicine)

ES-1 Chemically induced nonproliferative and proliferative lesions in rat and mouse urinary bladder

Min Gi

Osaka City University Graduate School of Medicine

ES-2 Nonproliferative and proliferative lesions observed in the short-term carcinogenicity studies in rasH2 mice

Hemei Wang

Jiangsu ChemPartner

ES-3 Proliferative lesions of the rodent endocrine system

Toko Ohira

Shanghai InnoStar Bio-tech Co., Ltd.

ES-4 Spermatogenesis and testicular staging in rats

Chunyan Hu

WestChina-Frontier PharmaTech

ES-5 Preclinical toxicologic pathology evaluation of cellular therapy products

Jianjun Lyu

Shanghai InnoStar Bio-tech Co., Ltd.

※ An asterisk on a poster number indicates that its first author is younger than 40 years old.

Poster Presentation

On-demand (January 20 (Thu) ～ February 13 (Sun)

P-01＊ Search for developmental neurotoxicity markers focusing on disruption of methylation regulation of hippocampal neurotransmission-related genes in rats

○Yasunori Takahashi[1,2], Ryota Ojiro[1,2], Risako Yamashita[1], Shimizu Saori[1], Natsuno Maeda[1], Hiromu Okano[1,2], Kazumi Takashima[1,2], Qian Tang[1,2], Shunsuke Ozawa[1,2], Toshinori Yoshida[1,2], Makoto Shibutani[1,2]

[1] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[2] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology

P-02＊ Effects of acrylamide on olfactory bulb-subventricular zone neurogenesis in rats

○Bunichiro Ogawa[1,2], Yutaka Nakanishi[1], Masaki Wakamatsu[1], Yasunori Takahashi[2,3], Makoto Shibutani[2,3]

[1] Drug Safety, Taisho Pharmaceutical Co., Ltd.
[2] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[3] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology

P-03＊ Histopathologcial evaluation in SD rat model of optic nerve injury

○Liu Xiangjiang, Du Mu, Qi Wei, Guo Jin, Zhang Rui , Guo Hui, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc.

P-04 Superimposition of mild hypertension on diabetic peripheral neuropathy dose not affect small unmyelinated sensory nerves in the skin in rats with alloxan-induced type 1 diabetes

○Kiyokazu Ozaki, Tetsuro Matsuura

Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University

P-05 Neuroprotective effect of alpha-glycosyl isoquercitrin against developmental neural deficits caused by immune activation induced by nucleic acid treatment of pregnant rats

○Kazumi Takashima[1,2], Hiromu Okano[1,2], Qian Tang[1,2], Yasunori Takahashi[1,2], Ryota Ojiro[1,2], Syunsuke Ozawa[1,2], Mihoko Koyanagi[3], Toshinori Yoshida[1,2], Makoto Shibutani[1,2]

[1] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[2] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology
[3] San-Ei Gen F.F.I., Inc.

P-06＊ Role of CCDC85C, a causative protein for hydrocephalus, and intermediate filament proteins (IFs) during lateral ventricle development in rat brain

○Hasan Md. Mehedi, Shizuka Konishi, Miyuu Tanaka, Takeshi Izawa, Jyoji Yamate, Mitsuru Kuwamura

Laboratory of Veterinary Pathology, Osaka Prefecture University

P-07＊ Involvement of a mutation in *Hcn1* gene in tremor behavior of the VF myelin mutant rat

○Miyuu Tanaka[1,2], Seika Isogai[1], Sakiko Kojima[1], Takeshi Izawa[1], Takashi Kuramoto[2,3], Mitsuru Kuwamura[1]

[1] Veterinary Pathology, Osaka Prefecture University
[2] Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University
[3] Department of Animal Science, Faculty of Agriculture, Tokyo University of Agriculture

P-08 Evaluation of motor neurons in the spinal cord of mice

○Masaharu Tanaka, Yasuko Ogawa, Kengo Homma, Aki Soejima

Mitsubishi Tanabe Pharma Corporation

P-09＊ Search for developmental neurotoxicity markers focusing on disruption of methylation regulation of neurite development and synaptic plasticity-related genes in rat hippocampus

○Ryota Ojiro[1,2], Yasunori Takahashi[1,2], Risako Yamashita[1], Saori Shimizu[1], Natsuno Maeda[1], Hiromu Okano[1,2], Kazumi Takashima[1,2], Qian Tang[1,2], Syunsuke Ozawa[1,2], Toshinori Yoshida[1,2], Makoto Sibutani[1,2]

[1] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[2] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology

P-10＊ Detailed investigation of the relationship between artifacts in rat eyes and fixation times in Davidson's fixative and modified Davidson's fixative

○Minto Nakagawa, Saori Matsuo, Shuji Hayashi, Atsuhiko Kato

Translational Research Division, Chugai Pharmaceutical Co., Ltd.

P-11＊ Examination about profiling and improvement of detection sensitivity of CNS toxicity by staining and biomarker

○Aya Goto[1], Rena Ishikawa[1], Kota Nakajima[1], Yuki Seki[1], Kenji Nakano[2], Etsuko Ohta[1]

[1] Global Drug Safety, BA Core Function Unit, Medicine Development Center, Eisai Co., Ltd.
[2] Drug Safety & Animal Care Technology Unit, Tsukuba R&D Supporting Division, Sunplanet Co., Ltd.

P-12＊ The application for 3D analysis of paraffin section

○Naoki Iwashita[1,2], Aisa Ozawa[3], Motoharu Sakaue[3]

[1] Bioalchemis, [2] Laboratory of Veterinary Pharmacology, School of Veterinary Medicine, Azabu University
[3] Laboratory of Anatomy II, School of Veterinary Medicine, Azabu University

P-13＊ Neuroprotective effect of α-glycosyl isoquercitrin on oligodendrocyte toxicity by fetal or neonatal lipopolysaccharide exposure in rats

○Hiromu Okano[1], Kazumi Takashima[1,2], Yasunori Takahashi[1,2], Ryota Ojiro[1,2], Qian Tang[1,2], Shunsuke Ozawa[1,2], Mihoko Koyanagi[3], Toshinori Yoshida[1,2], Makoto Shibutani[1,2]

[1] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[2] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology

P-14＊ Historical data for the histopathology on the spinal cord in juvenile Crl:CD(SD) rats

○Hiroaki Sato[1], Jun Watanabe[1], Hirofumi Hatakeyama[1], Tetsuro Kurotaki[1], Haruko Koizumi[1], Tetsuya Kajimura[1], Shin-ichi Sato[1], Hijiri Iwata[2]

[1] Ina Research Inc., [2] LunaPath LLC

P-15＊ Histopathological time course changes of retinal phototoxicity in rats induced by 8-Methoxypsoralen

○Yuka Yoshino, Keigo Ikeda, Sayaka Moriwaki, Kumiyo Okada, Tomoaki Tochitani, Yuta Fujii, Mami Kochi, Izumi Matsumoto, Hiroshi Inada, Kazuhiro Chihara, Izuru Miyawaki

Preclinical Research Unit, Dainippon Sumitomo Pharma Co., Ltd.

P-16＊ Laser induced acute ocular hypertensive damage in cynomolgus monkey

○Guo Hui, Du Mu, Qi Wei, Guo Jin, Zhang Rui, Liu Xiangjiang, Guo Hongnian, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc.

P-17 Immune responses in premetastatic niche of sentinel lymph nodes during metastasis in a mouse mammary cancer model

○Masa-Aki Shibata[1], Atsushi Takeshita[2], Chinatsu Shiraoka[1], Yoshinobu Hirose[2], Yoichi Kondo[1]

[1] Department of Anatomy and Cell Biology, Osaka Medical and Pharmaceutical University
[2] Department of Pathology, Osaka Medical and Pharmaceutical University

P-18＊ A case of epithelioid cell granulomas observed in burkitt lymphoma transplanted mice

○Zhang Rui, Du Mu, Qi Wei, Guo Jin, Guo Hui, Liu Xiangjiang, Li Zheng, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc.

P-19＊ Examination for constructing a new in vivo antitumor evaluation model for immune checkpoint inhibitors

○Keisuke Hotta, Teruaki Hagiwara, Taiki Sugiyama, Mayumi Kawabe, Hiroto Miyata, Yukinori Mera

DIMS Institute of Medical Science, Inc.

P-20＊ Early diagnostic and prognostic role of micro RNAs during 2-amino-3-methylimidazo[4,5-*f*] quinoline- induced liver and colon carcinogenicity in rat

○Elham M. Yousef[1)], Mona M. Hegazi[1)], Doha M. Beltagy [2)], Elsayed I. Salim[1)]

[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Department, Faculty of Science, Damanhour University

P-21＊ The extract of *houttuynia cordata hunb*. Fermented leaf inhibits carcinogenesis via modulates xenobiotic-metabolizing enzymes and cell proliferation

○Chonikarn Singai[1)], Sirinya Taya[2)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University

P-22＊ Cancer chemopreventive effect of hesperidin and mixed extract of sesame and orange seed on diethylnitrosamine -induced hepatocarcinogenesis in rats

○Napaporn Khuanphram[1)], Sirinya Taya[2)], Prachya Kongtawelert[1)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University

P-23＊ Protective effect of color rice bran protein and hydrolysates on carcinogens induced early stage of liver and colon carcinogenesis in rats

○Aroonrat Pharapirom, Arpamas Chariyakornkul, Warunyoo Phannasorn, Kwanchanok Parseatsook, Rawiwan Wongpoomchai

Department of Biochemistry, Faculty of Medicine, Chiang Mai University

P-24＊ Chemopreventive effects of cooked glutinous purple rice on the early stages of rat hepatocarcinogenesis

○Huina Guo, Arpamas Chariyakornkul, Warunyoo Phannasorn, Rawiwan Wongpoomchai

Department of Biochemistry, Faculty of Medicine, Chiang Mai University

P-25＊ Chronic toxicity of calcium disodium EDTA on pregnant rats and fetuses

○Mona E. El-Maghawry, Fouad A. Abou-Zaid, Sabry A. El-Naggar, Elsayed I. Salim

Zoology Department, Faculty of Science, Tanta University

P-26＊ 8-Hydroxydeoxyguanosine levels and histopathological evaluation during placental transfer of zinc oxide nanoparticles in pregnant rats

○Naira M. Al-Fiky, Fouad A. Abou-Zaid, Khalid Y. Abdul-Halim, Elsayed I. Salim

Zoology Department, Faculty of Science, Tanta University

P-27＊ Tissue distribution, placental transfer and excretion of silver nanoparticles in pregnant rats after a single oral dose

○Ahmed S. Abdel-Latif[2)], Khaled Y. Abdel-Halim[2)], Elsayed I. Salim[1)]

[1)]Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Mammalian & Aquatic Toxicology department, Central Agricultural Pesticides Laboratory (CAPL)

P-28 28-day repeated oral dose toxicity of nanosized titanium (IV) oxide in F344 rats

○Jun-ichi Akagi, Yasuko Mizuta, Hirotoshi Akane, Takeshi Toyoda, Kumiko Ogawa

Div. Pathol., Natl. Inst. Health Sci.

P-29＊ Safety assessment of red yeast (*sporidiobolus pararoseus*) powder: acute and subchronic toxicity studies in wistar rats

○Sirinya Taya[1)], Charatda Punvittayagul[2)], Thanongsak Chaiyaso[3)], Rawiwan Wongpoomchai[1,4)]

[1)]Functional Food Research Unit, Science and Technology Research Institute
[2)]Research Affairs, Faculty of Veterinary Medicine, [3)]Division of Biotechnology, Faculty of Agro-Industry
[4)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University

P-30＊ Acute and subchronic toxicity of isomaltooligosaccharide and its effect on gut microbiota

○Arpamas Chariyakornkul[1)], Charatda Punvittayagul[2)], Sirinya Taya[3)], Atigan Thongtharb[4)], Santad Wichienchot[5)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University
[3)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University
[4)]Department of Companion Animal, Faculty of Veterinary Medicine, Chiang Mai University
[5)]Center of Excellence in Functional Foods and Gastronomy, Faculty of Agro-Industry, Prince of Songkla University

P-31 Pathological changes of spontaneous tumors in Sprague-Dawley and Wistar rats

○Yanan He, Du Mu, Beibei Wang, Jun Yin, Wenyu Wu, Zhang Rui, Sucai Zhang, Huiming Zhang

JOINN LABORATORIES (Beijing) Inc.

P-32＊ Search for the primary site of amyloid deposition in transmissible AA amyloidosis

○Susumu Iwaide, Tomoaki Murakami

Cooperative division of Veterinary Medicine, Tokyo University of Agriculture and Technology

P-33 Differences of acute toxicity between polyvinylpyrrolidone coated silver nanospheres and silver nanoplates intraperitoneally administrated in mice.

○Yasuko Mizuta, Cho Young-Man , Jun-ichi Akagi, Tetsuya Ide, Kumiko Ogawa

Division of Pathology, National Institute of Health Sciences

P-34＊ Incidence and types of spontaneous tumors in young Sprague-Dawley rats in 4-week toxicity studies

○Hou Minbo, Jianjun Lyu, Yan Jianyan, Cui Tiantian, Qian Zhuang, Wang Xijie, Toko Ohira

Shanghai Innostar Bio-tech Co., Ltd (Innostar)

P-35 Differentially expressed genes induced by metformin and *d*-limonene as potential effective anticancer agents for HepG2 and MCF-7 cells

○Elsayed I. Salim[1)], Mona M. Alabasy[1)], Doha M. Beltagy[2)], Zihu Guo[3)], Mohamed Shahen[1)]

[1)]Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Department, Faculty of Science, Damanhour University
[3)]College of Life Science, Center of Bioinformatics, Northwest A & F University

P-36 New biomarkers of drug-induced liver and heart injury in preclinical studies

○Zhou Fei, Zhao Xixing, Zhou Tiansheng

WuXi AppTec (Suzhou) Co., Ltd.

P-37＊ Usefulness of TUNEL method for the identification of LNA-modified antisense oligonucleotide

○Hikaru Mitori, Satoru Kajikawa, Miwa Takahashi, Mihoko Ono

Astellas Pharma Inc. Drug Safety Research Labs

P-38 Introduction for the establishment of reference database of clinical pathology in SD rats and Beagle dogs

○Kong Qingxi[1)], Meilan Jin[2)], Qiu Shuang[3)], Chen Ke[3)], Qiao Junwen[4)]

[1)] Pharmaron, [2)] Laboratory Animal Center, Southwest University
[3)] WestChina-Frontier Pharma Tech Co., Ltd, [4)] Insilico Medicine

P-39 INHAND: International harmonization of nomenclature and diagnostic criteria for lesions - An Update - 2022

◯Shim-mo Hayashi[1)], CM Keenan[2)], Bradley A[3)], Goodman DG[4)], Takanori Harada[5)], Herbert R[6)], Hijiri Iwata[7)], Jacobsen M[8)], Kellner R[9)], Mahler B[6)], Meseck E[10)], Nolte T[11)], S Rittinghausen[9)], Vahle J[12)], Katsuhiko Yoshizawa[13)]

[1)]National Institute of Health Sciences, [2)]CM Keenan ToxPath Consulting, [3)]Charles River, [4)]Independent Consultant
[5)]The Institute of Environmental Toxicology, [6)]National Institute of Environmental Health Sciences, [7)]LunaPath LLC
[8)]Astra Zeneca, [9)]Fraunhofer ITEM, [10)]Novartis, [11)]Boehringer Ingelheim, [12)]Eli Lily, [13)]Mukogawa Womens University

P-40 Challenges and measures for SEND dataset creation of histopathological findings when the dataset is created by multiple organizations

◯Takeshi Iidaka[1,6)], Akihiro Ishimoto[1,6)], Shin-ichi Horikawa[2,6)], Konomi Iino[2,6)], Shin-ichi Sato[2,6)], Dai Nakae[3,6)], Hijiri Iwata[4,6)], Takayuki Anzai[5,6)]

[1)]NISSEI BILIS Co., Ltd., [2)]Ina Research Inc., [3)]Tokyo University of Agriculture, [4)]LunaPath Co., Ltd
[5)]Showa University School of Medicine, [6)]G-SEND

P-41＊ Comparative anatomy and histology of lacrimal gland in rat, rabbit, dog and monkey

◯Qiu Shuang[1)], Chen Ke[1)], Hu Chunyan[1)], Wang Haoan[1)], Kong Qingxi[2)]

[1)]WestChina-Frontier PharmaTech, [2)]Pharmaron

P-42 The benefits of SEND-compatible glossaries in histopathology

◯Hirofumi Hatakeyama[1)], Shin-ichi Horikawa[1)], Konomi Iino[1)], Shin-ichi Sato[1)], Takayuki Anzai[2,3)], Hijiri Iwata[4)]

[1)]Ina Research Inc., [2)]Showa University School of Medicine, [3)]PDS Pathology Data Systems
[4)]Laboratory of Toxicologic Pathology, LunaPath LLC.

P-43＊ Evaluation of lung carcinogenicity of single-walled carbon nanotube (SWCNT) compared with MWCNT-7 and MWCNT-N

◯Sheema Asraful Nahar[1)], Aya Naiki-Ito[1)], Hiroyuki Kato[1)], Masayuki Komura[1)], Hiroyuki Tsuda[2)], Satoru Takahashi[1)]

[1)]Department of Experimental Pathology and Tumor Biology, Nagoya City University Graduate School of Medical Sciences
[2)]Nanotoxicology Project, Nagoya City University

P-44＊ Balanitoside as a natural adjuvant to gemcitabine in lung cancer experimental model

◯Sara S. Aboueisha[1)], Abeer A. Khamis[2)], Elsayed I. Salim[1)]

[1)]Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Division, Chemistry Department. Faculty of Science, Tanta University

P-45＊ Early response biomarkers of inhalation exposure to cigarette smoke in the mouse lung

◯Yusaku Nishidoi[1)], Shugo Suzuki[1)], Min Gi[1,2)], Anna Kakehashi[1)], Taisuke Matsue[1)], Hideki Wanibuchi[1)]

[1)]Department of Molecular Pathology, Osaka City University Graduate School of Medicine
[2)]Department of Environmental Risk Assessment, Osaka City University Graduate School of Medicine

P-46 Histopathological characteristics of pulmonary disease by inhalation of organic dust in rat

◯Yumi Umeda

Japan Bioassay Research Center, Japan Organization of Occupational Health and Safety

P-47 Anti-tumor efficacy prediction from the mouse lung chemical carcinogenesis model: Validation with combined ICIs and chemotherapy drugs

◯Teruaki Hagiwara, Takamasa Numano, Yuko Doi, Norio Imai, Tomomi Hara, Hiroto Miyata, Yukinori Mera

DIMS Institute of Medical Science, Inc.

P-48＊ Analysis of ACE2 expression in type2 diabetic rats; SDT and SDT fatty Rats

○Yuri Hatanaka[1)], Katsuhiro Miyajima[1,6)], Kinuko Uno[2)], Marika Tohma[6)], Nguyen Hanh Nhung[1)], Noriko Kemuriyama[1)], Toshihisa Watanabe[3)], Hideki Ito[3)], Masami Shinohara[4)], Tomohiko Sasase[5)], Takeshi Ohta[5)], Dai Nakae[1,6)]

[1)] Department of Nutritional Science and Food Safety, Faculty of Applied Bioscience, Undergraduate School of Tokyo University of Agriculture
[2)] Department of Food and Nutritional Science, Faculty of Applied Bioscience, Graduate School of Tokyo University of Agriculture
[3)] CLEA Japan, Inc. Fuji Breeding Facility, [4)] CLEA Japan Inc. Business Promotion Dept
[5)] Laboratory of Animal Physiology and Functional Anatomy, Graduate School of Agriculture, Kyoto University
[6)] Department of Nutritional Science and Food Safety, Graduate School of Applied Bioscience, Tokyo University of Agriculture

P-49＊ Bee pollen and its encapsulated nanoproduct loaded with folic acid as antitumor agents against lung cancer cells

○Eman A. Eltonoby[1)], Magdy E. Mahfouz[2)], Nemany A. N. Hanafy[3)], Ezar H. Hamed[1)], Elsayed I Salim[1)]

[1)] Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)] Zoology Department, Faculty of Science, Kafrelsheikh University
[3)] Nanomedicine Division, Institute of Nanoscience and Nanotechnology, Kafrelsheikh University

P-50＊ Morphological changes of murine normal lung-derived organoids after repeated in vitro exposures to acrylamide

○Kento Tanabe[1)], Akihiro Hirata[1)], Yuta Irisawa[1,2)], Toshio Imai[3)], Hiroki Sakai[1)]

[1)] Laboratory of Veterinary Pathology, Gifu University, [2)] ASKA Pharmaceutical Co., Ltd
[3)] Department of Cancer Model Development, National Cancer Center Research Institute

P-51＊ Influence of vitamin K on bleeding tendency in rats fed high-iron diets

○Yohei Inai, Takeshi Izawa, Sho Fujiwara, Miyuu Tanaka, Mitsuru Kuwamura

Laboratory of Veterinary Pathology, Osaka Prefecture University

P-52＊ Effect of microsampling on toxicity endpoints in a general toxicity study using rats

○Tomoaki Tochitani, Yasuhiro Sasaki, Naoe Nishimura, Yuta Fujii, Takayuki Iwaisako, Naohisa Umeya, Masayo Hashimoto, Hiroshi Inada, Kazuhiro Chihara, Izuru Miyawaki

Preclinical Research Unit. Sumitomo Dainippon Pharma Co., Ltd

P-53 Toxicity assessment of a recombinant humanized antibody-Drug Conjugate (rhADC) in *cynomolgus* monkeys

○Xueyan Pu, Lu Peng

Pathology Department, Jiangsu Tripod Preclinical Research Labortory Co., LTD

P-54＊ Evaluation of diabetes and hypercholesterolemia swine as a model for peripheral DES

○Akiko Sato, Taizou Iwasaki, Yuka Shouji, Ryosuke Kikuchi, Natsuho Ichimura, Hideki Sato

TERUMO CORPORATION

P-55 The dried leaf extract of *Musa basjoo* induces growth inhibition and changes in protein expression level of cell cycle control molecules in human colon carcinoma cell lines

○Harutoshi Matsumoto, Nahida Sultana, Katsumi Fukamachi, Masumi Suzui

Department of Neuro Toxicology, Graduate School of Medical Sciences and Medical School, Nagoya City University

P-56＊ Riceberry bran oil ameliorates carcinogens-induced liver and colon carcinogenesis through the mechanism of cell apoptosis, anti-inflammation, and gut microbiota

○Warunyoo Phannasorn[1)], Aroonrat Pharaphirom[1)], Parameth Thiennimitr[2)], Rawiwan Wongpoomchai[1)]

[1)] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)] Department of Microbiology, Faculty of Medicine, Chiang Mai University

P-57＊ Vanillic acid attenuates rat hepatocarcinogenesis induced by diethylnitrodamine and 1,2-dimethylhydrazine

○Charatda Punvittayagul[1)], Arpamas Chariyakornkul[2)], Kanokwan Jarukamjorn[3)], Rawiwan Wongpoomchai[2)]

[1)]Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University
[2)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[3)]Research Group for Pharmaceutical Activities of Natural Products using Pharmaceutical Biotechnology, Faculty of Pharmaceutical Sciences, Khon Kaen University

P-58 Myoepithelial cell hypertrophy along with acinar cell abnormality in the parotid gland is associated with salivary gland dysfunction in the AL-induced diabetic rats.

○Yasushi Kodama[1)], Yui Terayama[2)], Tetsuro Matsuura[2)], Miwa Matsuda[3)], Kiyokazu Ozaki[2)]

[1)]Laboratory of Pharmacology and Pathophysiology, Faculty of Pharmaceutical Sciences, Hiroshima International University
[2)]Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University
[3)]Department of Medical Science and Technology, Faculty of Health Sciences, Hiroshima International University

P-59＊ Palmitoyl piperidineopiperidine induces selective anticancer activity against human colon carcinoma cell lines

○Sultana Nahida, Katsumi Fukamachi, Harutoshi Matsumoto, Masumi Suzui

Department of Neuro Toxicology, Nagoya City University Graduate School of Medical Sciences

P-60 Chemopreventive effect of purple rice extract on rat non-alcoholic steatohepatitis and hepatocarcinogenesis

○Aya Naiki-Ito, Hiroyuki Kato, Masayuki Komura, Satoru Takahashi

Department of Experimental Pathology and Tumor Biology, Nagoya City University Graduate School of Medical Sciences

P-61＊ Carcinogenicity induced by prenatal exposure to diphenylarsinic acid in CD1 mice

○Masaki Fujioka[1)], Min Gi[2)], Shugo Suzuki[1)], Anna Kakehashi[1)], Yuji Oishi[1)], Takashi Yamaguchi[1)], Hideki Wanibuchi[1)]

[1)]Department of molecular pathology, Osaka city university graduate school of medicine
[2)]Department of environmental risk assessment, Osaka city university graduate school of medicine

P-62 Quantitative Analysis of *in vivo* mutagenicity and carcinogenicity of 1,4-dioxane in rats

○Min Gi[1,2)], Shugo Suzuki[2)], Masaki Fujioka[2)], Anna Kakehashi[2)], Hideki Wanibuchi[2)]

[1)]Department of Environmental Risk Assessment, Osaka City University Graduate School of Medicine
[2)]Department of Molecular Pathology, Osaka City University Graduate School of Medicine

P-63 Preventive and therapeutic effects of bear bile powder on the development of hepatocarcinoma in SD rats

○Jin Meilan[1,2)], Rui Dong[2)], Hong Zexuan[2)], Jia Guiyang[2)]

[1)]China Southwest university Laboratory animal center
[2)]Laboratory of Veterinary Pathology, College of Veterinary medicine, Southwest University

P-64＊ Lobe-specific toxicological changes in the liver of rats given a hepatocarcinogen, furan

○Meili Soma[1)], Daisuke Hibi[2,3)], Shinji Takasu[3)], Yuji Ishii[3)], Takashi Umemura[1,3)]

[1)]Graduate School of Animal Health Technology, Yamazaki University of Animal Health Technology
[2)]Ono Pharmaceutical Co. Ltd., [3)]Division of Pathology, National Institute of Health Science

P-65＊ Formation of cytoplasmic inclusion bodies exhibiting the involvement of chromosome aberrations in hepatocarcinogenesis of methyl carbamate

○Norifumi Takimoto[1,2)], Yuji Ishii[1)], Tatsuya Mitsumoto[1,3)], Moeka Namiki[1)], Shinji Takasu[1)], Takehiko Nohmi[1)], Makoto Shibutani[2)], Kumiko Ogawa[1)]

[1)]Division of Pathology, National Institute of Health Sciences
[2)]Laboratory of Veterinary Medicine, Tokyo University of Agriculture and Technology
[3)]Faculty of Animal Health Technology, Yamazaki University of Animal Health Technology

P-66＊ Aristolochic acid I promotes clonal expansion but did not induce hepatocellular carcinoma in adult rats

○Lu Henglei, Tan Rongrong, Xiu Xiaoyu, Zhu Huaisen

Centre for Drug Safety Evaluation and Research (CDSER), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences (CAS)

P-67＊ Role of Sox9 in the pathogenesis of dietarily induced nonalcoholic steatohepatitis (NASH) in mice

○Sae Nakane[1)], Noriko Kemuriyama[2)], Akari Abe[3)], Hayato Watanabe[1)], Megumi Yuki[4)], Katsuhiro Miyajima[1,2,3)], Takashi Umamura[5,6)], Dai Nakae[1,2,3)]

[1)] 1Dept. Nutr. Sci. Food Safety, Grad. Appl. Bioscience, Tokyo Univ. Agricul.
[2)] Department of Nutritional Science and Food Safety, Faculty of Applied Bioscience, Tokyo University of Agriculture
[3)] Department of Nutritional Science and Food Safety, Graduate School of Agriculture, Tokyo University of Agriculture
[4)] Advantec Co.,Ltd. Pathology Department, [5)] Division of Pathology, National Institute of Health Science
[6)] Faculty of Animal Health Technology, Yamazaki University of Animal Health Technology

P-68＊ Tumor promoting effect of iron (III) - tannic acid nanoparticles in diethylnitrosamine - induced hepatocarcinogenesis in rats

○Chi Be Hlaing[1)], Arpamas Chariyakornkul[1)], Chalermchai Pilapong[2)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Center of Excellence for Molecular Imaging (CEMI), Department of Radiologic Technology, Faculty of Associated Medical Sciences, Chiang Mai University

P-69＊ Pathological analysis of pancreatic lesions induced by Zinc Maltol in rat

○Sakura Fujiwara, Takayasu Moroki, Masaya Hitomi, Makoto Satou, Yui Terayama, Tsuyoshi Yoshikawa

Otsuka Pharmaceutical Co., Ltd. Tokushima Research Institute, Nonclinical Research Center, Department of Drug Safety Research

P-70 Comprehensive evaluation of general toxicity, genotoxicity, and carcinogenicity of 3-acetyl-2,5-dimethylfuran using *gpt* delta rats

○Shinji Takasu, Yuji Ishii, Moeka Namiki, Kenji Nakamura, Takehiko Nohmi, Kumiko Ogawa

Division of Pathology, National Institute of Health Sciences

P-71 Chronic toxicity and carcinogenicity study of diphenylarsinic acid in C57BL/6J mice

○Takashi Yamaguchi[1)], Min Gi[2)], Masaki Fujioka[1)], Shugo Suzuki[1)], Yuji Oishi[1)], Hideki Wanibuchi[1)]

[1)] Department of Molecular Pathology, Osaka City University Graduate School of Medicine
[2)] Department of Environmental Risk Assessment, Osaka City University Graduate School of Medicine

P-72＊ 28-day repeated inhalation toxicity study of 1,2-dichlorobenzene in fischer 344 rats

○Hee-Seon Park, Hye-Yeon Choi, Yong-Soon Kim, Mi-Ju Lee

Pathology Department, Inhalation Toxicity Research Center, Chemical Research Bureau, Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency

P-73 Study on the pathological features and biomarkers of CCl4 induced non-alcoholic fatty liver disease in rat

○Jin Yi[1)], Jing Li[2)], Lv Aizhen[2)], Li Ming[2)], Jin Zhihu[2,3)]

[1)] Shenzhen Institute for Drug Control, [2)] Sunshine Lake Pharma Co., Ltd, [3)] Shenzhen Jinzhi Techmology Co., Ltd

P-74 Establishment of mouse orthotopic transplantation tumor models of human hepatoma and comparison of their characteristics

○Jun Yin[1)], Du Mu[3)],Dingsha Lijing[1)], Huiming Zhang[2)], Ruiping She[2)], Conglin Zuo[2)]

[1)] JOINN LABORATORIES (Beijing) Inc., [2)] China Agricultural University College of Veterinary Medicine
[3)] JOINN LABORATORIES (Suzhou) Inc.

P-75＊ Attempt to make a drug-induced liver injury model using humanized mouse

○Sho Fujiwara, Takeshi Izawa, Miyuu Tanaka, Mitsuru Kuwamura

Laboratory of Veterinary Pathology Osaka Prefecture University

P-76 Influence of diabetes induction on rat NAFLD model

○Takeshi Izawa, Eri Mizuguchi, Jyoji Yamate, Mitsuru Kuwamura

Laboratory of Veterinary Pathology, Osaka Prefecture University

P-77＊ Participation of CD44 in hepatic fibrosis of non-alcoholic steatohepatitis in rats

○Kinuko Uno[1)], Katsuhiro Miyajima[2,3)], Marika Toma[3)], Noriko Kemuriyama[2)], Dai Nakae[2,3)]

[1)]Dept. Food and Nutri. Sci., Fac. Agricul., Graduate School of Tokyo Univ. Agricul
[2)]Dept.Nutri. Sci. Food Safety, Fac. Applied Bioscience, Undergraduate School of Tokyo Univ. of Agricul
[3)]Dept. Nutri. Sci. Food Safety, Fac. Applied Bioscience, Graduate School of Tokyo Univ. Agricul

P-78＊ Investigation of the usefulness of liver-type fatty acid binding protein (L-FABP) as a biomarker for early stage of nonalcoholic fatty liver disease (NAFLD)

○Marika Tohma[1)], Katsuhiro Miyajima[1,2)], Keiichi Ohata[3)], Kinuko Uno[4)], Ayaka Horiuchi[2)], Noriko Kemuriyama[2)], Dai Nakae[1,2)]

[1)]Department of Nutritional Science and Food Safety, Graduate School of Applied Biosciences, Tokyo University of Agriculture
[2)]Department of Nutritional Science and Food Safety, Faculty of Applied Biosciences, Tokyo University of Agriculture
[3)]L-FABP Business Department, CMIC Holdings Co., Ltd
[4)]Department of Food and Nutrition Science, Graduate School of Agriculture, Tokyo University of Agriculture

P-79＊ Involvement of glucagon in pathophysiology of type 2 diabetic animal model

○Kouhei Mandai[1)], Katsuhiro Miyajima[1,2,3)], Kana Watanabe[1)], Kana Isizuka[1)], Kinuko Uno[4)], Noriko Kemuriyama[2)], Masami Shinohara[5)], Tomohiko Sasase[5)], Toshihisa Watanabe[6)], Hideki Ito[6)], Masami Shinohara[7)], Takeshi Ohta[5,8)], Dai Nakae[1,2,4)]

[1)]Department of Nutritional Science and Food Safety, Faculty of Applied Bioscience, Graduate School of Tokyo University of Agriculture
[2)]Department of Nutritional Science and Food Safety, Faculty of Applied Bioscience, Tokyo University of Agriculture
[3)]Department of Nutritional Science and Food Safety, Graduate School of Agriculture, Tokyo University of Agriculture
[4)]Department of Food and Nutrition Science, Graduate School of Agriculture, Tokyo University
[5)]Tokyo Animal & Diet Dept. CLEA Japan, Inc., [6)]CLEA Japan, Inc. Fuji Breeding Facility
[7)]CLEA Japan Inc. Business Promotion Dept
[8)]Laboratory of Animal Physiology and Functional Anatomy, Graduate School of Agriculture, Kyoto University

P-80 LRG-1 is a promising blood marker for pancreas cancer

○Katsumi Fukamachi[1)], Nahida Sultana[1)], Harutoshi Matsumoto[1)], Hiroyuki Tsuda[2)], Masumi Suzui[1)]

[1)]Nagoya City University Graduate School of Medical Sciences, [2)]Nagoya City University

P-81＊ Precision-cut liver slice (PCLS) as a model for evaluation of hepatotoxicity

○Yoshitaka Katoh, Naofumi Takahashi, Chinatsu Fujiwara, Shinya Miyazaki, Tsuyoshi Ito, Aya Koyama, Atsushi Shiga, Ryoichi Ohtsuka, Makio Takeda, Takanori Harada

The Institute of Environmental Toxicology

P-82＊ Deep learning-based Image analysis algorithm for classification and quantification of multiple histopathological lesions of the rat liver

○Taishi Shimazaki[1)], Kyotaka Muta[1)], Naohito Yamada[1)], Yuzo Yasui[1)], Deshpande Ameya[2)], Hajra Anindya[2)], Thomas Tijo[2)], Toshiyuki Shoda[1)]

[1)]Yokohama Research Center, Central Pharmaceutical Research Institute, Japan T obacco Inc., [2)]AIRA Matrix Private Limited

P-83 Quantification of hepatic fibrosis in Sprague-Dawley rats using deep learning instance segmentation focused on H&E staining whole slide level

○Ji-Hee Hwang[1)], Hyun-Ji Kim[1,2)], Heejin Park[1)], Byoung-Seok Lee[1)], Hwa-Young Son[2)], Yong-Bum Kim[3)], Sang-Yeop Jun[4)], Jong-Hyun Park[4)], Jaeku Lee[4)], Jae-Woo Cho[1)]

[1)]Toxicologic Pathology Research Group, Toxicology Mechanism Research Divison, Department of Advanced Toxicology Research, Korea Institute of Toxicology
[2)]College of Veterinary Medicine, Chungnam National University
[3)]Department of Advanced Toxicology Research, Korea Institute of Toxicology
[4)]Research & Development team, LAC Inc

P-84＊ Role of DPYD expression in pancreatic cancer and the mechanism of its suppression

○Hiroyuki Kato, Aya Naiki-Ito, Masayuki Komura, Satoru Takahashi

Department of Experimental Pathology and Tumor Biology Nagoya City University Graduate School of Medical Sciences

P-85 Relationship between urinary bladder carcinogenicity and urinary metabolites of occupational urinary bladder cancer-related aromatic amines

○Shugo Suzuki, Min Gi, Masaki Fujioka, Anna Kakehashi, Hideki Wanibuchi

Dept. Mol. Pathol., Osaka City Univ. Grad. Sch. Med.

P-86 Effects of repeated oral administration of *o*-toluidine and *o*-anisidine metabolites on the rat urinary bladder

○Takeshi Toyoda[1)], Takuma Kobayashi[2)], Noriyuki Miyoshi[2)], Kohei Matsushita[1)], Hirotoshi Akane[1)], Tomomi Morikawa[1)], Kumiko Ogawa[1)]

[1)] Division of Pathology, National Institute of Health Sciences, [2)] Laboratory of Biochemistry, University of Shizuoka

P-87＊ The potential effect of thymoquinone and *Nigella sativa* crude oil extract on experimental urinary bladder cancer model

○Areeg M. Khalifa, Elsayed I. Salim

Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University

P-88＊ Analysis of cardiovascular lesions associated with acyclovir crystal-induced nephropathy

○Junichi Sugiyama, Hideki Tanaka, Shota Yoshida, Shohei Kanie, Kazuhiko Besshi

Toxicology Laboratory, Taiho Pharmaceutical Co., Ltd.

P-89 Potential of CD44 as a biomarker capable of predicting chronicity of drug-induced kidney injury

○Kohei Matsushita, Takeshi Toyoda, Hirotoshi Akane, Tomomi Morikawa, Kumiko Ogawa

Division of Pathology, National Institute of Health Sciences

P-90＊ Effect of high sucrose/high fat diet on the kidneys in obese type 2 diabetes model SDT fatty rats

○Kana Watanabe[1)], Katsuhiro Miyajima[1,2)], Kouhei Mandai[1)], Keita Sekiguti[2)], Kinuko Uno[3)], Noriko Kemuriyama[2)], Tomohiko Sasase[6)], Toshihisa Watanabe[4)], Hideki Ito[4)], Masami Shinohara[5)], Dai Nakae[1,2)], Takeshi Ohta[6)]

[1)]Dept. Nutri. Sci. Food Safety, Fac. Applied Bioscience, Graduate School of Tokyo Univ. Agricul
[2)]Dept.Nutri. Sci. Food Safety, Fac. Applied Bioscience, Undergraduate School of Tokyo Univ. of Agricul
[3)]Dept. Food and Nutri. Sci., Fac. Agricul., Graduate School of Tokyo Univ. Agricul
[4)]CLEA Japan, Inc. Fuji Breeding Facility, [5)]CLEA Japan Inc. Business Promotion Dept
[6)]Laboratory of Animal Physiology and Functional Anatomy, Graduate School of Agriculture, Kyoto University

P-91＊ Application of urinary liver-type fatty acid-binding protein (L-FABP) on the mice DIC (disseminated intravascular coagulation) models in COVID-19 study

○Nguyen Hanh Nhung[1)], Katsuhiro Miyajima[1,2)], Keiichi Ohata[3)], Yuka Kawaguchi[1)], Yuri Hatanaka[1)], Ayaka Horiuchi[1)], Kinuko Uno[4)], Marika Tohma[2)], Karin Arai[1)], Teppei Uechi[1)], Noriko Kemuriyama[1)], Dai Nakae[1,2)]

[1)]Dept.Nutri. Sci. Food Safety, Fac. Applied Bioscience, Undergraduate School of Tokyo Univ. of Agricul
[2)]Dept.Nutri. Sci. Food Safety, Fac. Applied Bioscience, Undergraduate School of Tokyo Univ. of Agricul
[3)]Dept. Nutri. Sci. Food Safety, Fac. Applied Bioscience, Graduate School of Tokyo Univ. Agricul
[4)]L-FABP Business Department, CMIC Holdings Co., Ltd.
[5)]Dept. Food and Nutri. Sci., Fac. Agricul., Graduate School of Tokyo Univ. Agricul

P-92＊ Karnovsky's fixative prevents artifacts appearing as vacuolation derived from tissue processing in kidneys treated with antisense oligonucleotide

○Hironobu Nishina, Satomi Nishikawa, Akane Kashimura, Mao Mizukawa, Tetsuya Sakairi

Safety Research Laboratories, Mitsubishi Tanabe Pharma Corporation

P-93 Pathological study for chronic progressive nephropathy in rats

○Beibei Wang, Du Mu, Yanan He, Jun Yin, Wenyu Wu, Zhang Rui, Sucai Zhang, Huiming Zhang

JOINN LABORATORIES (Beijing) Inc.

P-94 Detection of glomerulosclerosis using Halo AI in a mouse model of anti-glomerular basement membrane glomerulonephritis

○Atsuko Murai[1)], Saori Matsuo[1)], Shoko Usami[2)], Natsuko Hada[2)], Masakazu Kanamori[2)], Masaki Yamazaki[1)], Shinichi Onishi[1)], Atsuhiko Kato[1)]

[1)]Translational Research Division, Non-clinical Safety Assessment Dept., Chugai Pharmaceutical Co., Ltd
[2)]Research Division, Discovery Pharmacology Dept., Chugai Pharmaceutical Co., Ltd

P-95 Anticarcinogenic effect of chitosan oligosaccharide supplementation on breast cancer in a rat model.

○Masahiro Yoshioka[1)], Momoka Chatani[2)], Rio Matama[3)], Mayu Miyoshi[3)], Yuichi Kinoshita[4)], Yoshiharu Okamoto[5)], Katsuhiko Yoshizawa[2,3)]

[1)]Department of Nutrition, School of Nutritional Science, Koshien University
[2)]Graduate School of Human Environmental Sciences, Mukogawa Women's University
[3)]Department of Innovative Food Sciences, School of Food Sciences and Nutrition, Mukogawa Women's University
[4)]Wakayama Medical University Hospital, [5)]Joint Department of Veterinary Medicine, Faculty of Agriculture, Tottori University

P-96＊ Identification of fusion genes in radiation-induced rat mammary carcinomas using RNA sequencing

○Hikaru Watanabe[1,2)], Kazuhiro Daino[1)], Atsuko Ishikawa[1)], Tatsuhiko Imaoka[1,2)], Mayumi Nishimura[1)], Masaru Takabatake[1,2)], Kazumasa Inoue[2)], Masahiro Fukushi[3)], Shizuko Kakinuma[1)]

[1)]Dept. Radiat. Effects Res., NIRS, QST, [2)]Dept. Radiol. Sci., Grad. Sch. Human Health Sci., Tokyo Metropolitan Univ.
[3)]Dept. Radiol. Tech., Tsukuba International Univ.

P-97 Effects of testosterone on rat placental development

○Satoshi Furukawa[1)], Naho Tsuji[1)], Sego Hayashi[1)], Yusuke Kuroda[1)], Masayuki Kimura[1)], Chisato Hayakawa[1)], Kazuya Takeuchi[1)], Akihiko Sugiyama[2)]

[1)]Biological Research Laboratories, Nissan Chemical Corporation
[2)]Faculty of Veterinary Medicine, Okayama University of Science

P-98＊ Development of an automated rat estrus cycle classification model using an AI image analysis platform

○Shinichi Onishi[1)], Riku Egami[2)], Yoshinobu Nagashima[2)], Yuya Nakamura[2)], Kaori Nishihara[1)], Saori Matsuo[1)], Atsuko Murai[1)], Shuji Hayashi[1)], Masaki Yamazaki[1)], Mizuno Hideaki[2)], Atsuhiko Kato[1)]

[1)]Translational Research Division, Chugai Pharmaceutical Company, [2)]Research Division, Chugai Pharmaceutical Company

P-99＊ ACTH-induced stress in weaned sows impairs LH receptor expression steroidogenesis capacity in the ovary

○Zhu Huaisen[1,2)], Tan Rongrong[1)], Xiu Xiaoyu[1)], Lu Henglei[1)]

[1)] AnLing Biomed (ShenZhen) Co., Ltd
[2)] Centre for Drug Safety Evaluation and Research (CDSER), Shanghai Institute of MateriaMedica (SIMM), Chinese Academy of Sciences (CAS)

P-100 An exploration of novel carcinogenic mechanisms by DMBA treatment in mouse normal mammary tissue-derived organoids

○Toshio Imai[1,2)], Rikako Ishigamori[1)], Ruri Nakanishi[1)], Yukino Machida[3)], Mie Naruse[1)]

[1)] Central Animal Division, National Cancer Center Research Institute
[2)] Department of Cancer Model Development, National Cancer Center Research Institute
[3)] Laboratory of Veterinary Pathology, Nippon Veterinary and Life Science University

P-101＊ Assessment of the molecular and physiological role of micro RNA in chemically-induced mammary gland carcinoma in rats

○Fatma A. Elmalah[1)], Mona M. Hegazi[1)], Doha M Beltagy[2)], Elsayed I. Salim[1)]

[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Department, Faculty of Science, Damanhour University

P-102＊ Promoting effect of sunset yellow at low doses on *N*-methyl *N*-nitrosourea-induced rat mammary gland carcinogenesis

○Malak I. Elbassuny[1)], Magdy E. Mahfouz[2)], Elsayed I. Salim[1)]

[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis. Faculty of Science, Tanta University
[2)]Zoology Department, Faculty of Science, Kafrelsheikh University

P-103 The histopathologic changes in lungs of mice and cynomolgus monkeys administrated intravenously with human umbilical cord-derived mesenchymal stem cells

○Yanjun Cui, Xu Zhu, Yi Zhou, Xuezhou Cai, Yichao Tian, Li Zhou

Hubei Topgene Biotechnology Co. Ltd Wuhan Branch

P-104 Histopathological investigation of islets in SD rat by subcutaneous injection with a repeat dose new hypoglycemic compound

○Du Mu, Qi Wei, Guo Jin, Zhang Rui, Guo Hui, Liu Xiangjiang, Wang Beibei, He Yanan, Yin Jun, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc.

P-105＊ Comparison of histopathological and immunohistochemical methods with blood hormone levels in detection of chemical-induced antithyroid effect in rats

○Hirotoshi Akane[1)], Takeshi Toyoda[1)], Kohei Matsushita[1)], Tomomi Morikawa[1)], Tadashi Kosaka[2)], Hitoshi Tajima[2)], Hiroaki Aoyama[2)], Kumiko Ogawa[1)]

[1)] Division of Pathology, National Institute of Health Sciences, [2)] Toxicology Division, Institute of Environmental Toxicology

P-106 Histopathological changes in the thyroid of tadpole in the positive control group of the Amphibian Metamorphosis Assay (AMA).

○Mika Nagaike, Itaru Yamamoto, Yuta Baba, Eito Ikeda, Akiko Okada, Naoko Hongo, Kosei Inui

Ishihara Sangyo Kaisha, LTD., Central Research Institute, Safety Science Research Laboratory

P-107＊ Neoplastic mass of ganglionic origin seen at the base of the brain

○Qi Wei, Du Mu, Guo Jin, Guo Hui, Zhang Rui, Liu Xiangjiang, Yasuhiko Hirouchi, Li Zheng

JOINN LABORATORIES (Suzhou) Inc.

P-108 A spontaneous benign meningioma in an ICR mouse

○Hu Yiwen, Kong Qingxi, Lv Ai

Pharmaron Inc.

P-109＊ A case of cartilaginous metaplasia in the sclera of a Kbs:JW rabbit

○Kotaro Yamada, Yoshinori Yamagiwa, Miki Masatsugu, Yu Haranosono, Masaaki Kurata
Central Research Laboratories, Research & Development Division, Senju Pharmaceutical Co., Ltd

P-110＊ Pulmonary hypoplasia in a Beagle dog

○Mai Todoroki, Sousuke Masuda, Hisashi Yoshimi, Makoto Furuya, Shigeyuki Mori
Department of Drug Discovery R&D Center., Zenyaku Kogyo Co., Ltd

P-111＊ Inflammation of the cardiac coronary artery in ICR mice

○Kyohei Yasuno[1)], Masako Imaoka[1)], Tetsuya Ohsawa[1)], Keiko Okado[2)], Kiyonori Kai[1)], Yoshimi Tsuchiya[1)]
[1)]Medicinal Safety Research Laboratories, Daiichi Sankyo Co., Ltd
[2)]Department of Translational Research, Daiichi Sankyo RD Novare Co, Ltd

P-112＊ Spontaneous lymphangioma in a young SD rat

○Rena Ishikawa, Aya Goto, Yuki Seki, Kota Nakajima, Etsuko Ohta
Global Drug Safety, BA Core Function Unit, Medicine Development Center, Eisai Co.,Ltd

P-113 Gastric carcinoid tumors in rats with parietal cell atrophy in a long-term carcinogenicity study

○Norimitsu Shirai, Choudhary Shambhunath, Houle Christopher
Pfizer Inc. Drug Safety R&D, Pathology

P-114 A case of giant esophageal diverticula filling the thoracic cavity in a SD rat

○Junko Fujishima, Hiroki Yamashita, Yuji Sasaki, Kinji Kobayashi, Hiroshi Maeda
Drug Safety Research Laboratories, Shin Nippon Biomedical Laboratories, Ltd

P-115＊ Case report: Cystic nodular lesion in the jejunum of a rat.

○Yuta Baba, Eito Ikeda, Akiko Okada, Naoko Hongou, Kosei Inui, Mika Nagaike
Safety Sciences Group, Safety Science Research Laboratory, Central Research Institute, Ishihara Sangyo Kaisha, Ltd

P-116 Study on pathomorphological changes of liver in Beagle dog with spontaneous hepatocirrhosis

○Hu Jian-ting, Qiu Bo, Ying Yong
New Drug Evaluation Center of Shandong Academy of Pharmaceutical Sciences

P-117＊ A case of renal mesenchymal tumor observed on kidney

○Guo Jin, Du Mu, Qi Wei, Zhang Rui, Guo Hui, Liu Xingjian, Yasuhiko Hirouchi
JOINN LABORATORIES (Suzhou) Inc.

P-118＊ A mortal case of 9-week-old CBA/J mouse due to ovarian choriocarcinoma.

○Toshio Kobayashi, Yutaka Oshima, Kimika Yamamoto, Hisako Morioka, Masafumi Horiuchi, Yasuhiro Tsubokura, Katsumi Miyata, Satsuki Hoshuyama
Chemicals Evaluation and Research Institute

P-119＊ Malignant tumour of ovary in a young Rhesus monkey - Case Report

○Wang Haoan[1)], He Yang[1)], Chen Ke[1)], Qiu Shuang[1)], Yang Kaixuan[2)], Cen Xiaobo[1,3)], Hu Chunyan[1)]
[1)]Westchina-Frontier Pharma Tech Co., Ltd (WCFP)
[2)]West China Second University Hospital, Sichuan University
[3)]National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, and Collaborative Innovation Center for Biotherapy

P-120 A case of spontaneous pituitary gland adenocarcinoma in a nineteen-week-old female Sprague-Dawley rat

○Duyeol Kim, Jong-Il Shin, Hyun Kyung Song, Byung-Woo Lee, Hyun-Woo Kim, Han Kyul Lee, Sun-Hee Park
Biotoxtech Co.

P-121＊ Spontaneous tumor resembling human clear cell sarcoma of the planta in a female SD rat

○Tsubasa Saito, Hiromu Okano, Moeko Aoki, Yumiko Kamiya, Shiori Fujiwara, Osamu Hashiguchi, Yuko Yamaguchi

BoZo reserch center Inc.

Abstracts

Special Lecture

Symposium

Panel Discussion

Young Researchers Workshop

IATP Maronpot Guest Lecture

1st JSTP-CPA-STP Joint Education Seminar

SL-1

Development of novel therapies for diseases associated with intestinal dysbiosis

○Satoshi Uematsu[1,2)]

[1)] Department of Immunology and Genomics, Osaka City University Graduate School of Medicine
[2)] Division of Metagenome Medicine, Human Genome Center, The Institute of Medical Science, The University of Tokyo

With the development of next-generation sequencers, the analysis of the intestinal microbiota has changed from the classical culture method to genome analysis. Dysbiosis, an abnormal composition of gut microbiota, has been found in various diseases such as infectious diseases, inflammatory bowel disease, obesity, diabetes, and psychiatric disorders. In dysbiosis, the beneficial effects of the gut microbiota on the host are impaired and homeostasis is disrupted. In addition, in inflammatory bowel disease and diabetes, the existence of symbiotic commensal bacteria (pathobionts) that are directly involved in the onset of disease has also been revealed. As a new way to control diseases, methods to correct dysbiosis or to specifically control or eliminate pathobionts are required. In our laboratory, we are conducting metagenomic analysis by whole genome sequencing. We have constructed a pipeline for ultra-fast metagenomic analysis by using homology search software GHOST-MP driven on a supercomputer, which enables high-speed analysis. In this talk, I will give an overview of the ultra-fast pipeline, and introduce the analysis of intestinal bacteriome and virome using the pipeline. In addition, I will report on the development of mucosal vaccines for the correction of dysbiosis and specific elimination of pathobionts, as well as the establishment of genomic analysis method for phage therapy.

Biography

Satoshi Uematsu

Professor, Department of Immunology and Genomics, Osaka City University Graduate School of Medicine

School Education:
- 1991-1997 Osaka City University, Medical School (M.D. degree, 1997)
- 2000-2004 Graduate School of Medicine, Osaka University (Prof. Shizuo Akira's lab) (Ph.D. degree, 2004)

Employment History:
- 1997-1999 Residency of Medical Doctor, Internal Medicine II at Hospital of Osaka City University Medical School (Prof. Hirotoshi Morii)
- 2003-2004 Research Fellow (DC2) of Japan Society for the Promotion of Science (JSPS)
- 2004-2009 Assistant Professor, Department of Host Defense, Research Institute for Microbial Diseases, Osaka University (Prof. Shizuo Akira's lab)
- 2009-2012 Associate Professor, Laboratory of Host Defense, Immunology Frontier Research Center, Osaka University
- 2012-2020 Project Professor, Division of Innate Immune Regulation, International Research and Development Center for Mucosal Vaccines, Institute of Medical Science, The University of Tokyo
- 2014-2018 Professor, Department of Mucosal Immunology, Graduate School of Medicine and School of Medicine, Chiba University
- 2018-present Professor, Department of Immunology and Genomics, Osaka City University Graduate School of Medicine
- 2020-present Project Professor, Division of Metagenome Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo

Memberships:
- Japanese Society of Immunology. (Board member)

Honors and Prizes:
- 2009 JSI Young Investigator Award

SL-2

Contribution of toxicologic pathology to occupational health

○Shoji Fukushima[1,2)]

[1)] Japan Bioassay Research Center (JBRC), Japan Organization of Occupational Health and Safety
[2)] Association for Promotion of Research on Risk Assessment

In general, the toxicity of chemical substances to humans is evaluated based on toxicity tests using test animals. It is particularly important to determine if genotoxicity is involved in the harmful effects, e.g., carcinogenicity and reproductive toxicity, elicited by the tested chemical. Toxic substances are divided into genotoxic and non-genotoxic substances. The non-genotoxic substances are considered to have threshold exposure levels below which no toxic effects are produced. The substances have S-shaped dose-response curves from which NOAEL and LOAEL values can be obtained. This allows the generation of permissible exposure values that can be applied to occupational health. In contrast, the genotoxic substances are considered to not have threshold levels below which they do not exert harmful effects, and therefore, to lack permissible exposure levels. However, in reality, various situations do need to set permissible exposure values for substances that are considered genotoxic. It is well known that workers exposed to solid substances have respiratory diseases such as lung cancer and mesothelioma. The JBRC has investigated the inhalation carcinogenicity of numerous chemical substances using rats and mice. In this talk, I will focus on the rat pulmonary carcinogenicity of the solid substances, e.g. fibrous multi-walled carbon nanotube and indium tin oxide. I will then discuss using BMD or NOAEL as points of departure to derive occupational health guidance values.

Biography

Shoji Fukushima, MD., Ph.D.

President, Association for Promotion of Research on Risk Assessment
Advisor, Japan Bioassay Research Center, Japan Organization of Occupational Health and Safety
Visiting Professor, Kitasato University School of Medicine

School Education

1961-1967 Nagoya City University Medical School

Employment History

1977-1979 University of Massachusetts, School of Medicine, USA, Research Associate
1980-1990 Nagoya City University Medical School, Department of Pathology, Associate Professor
1990-2006 Osaka City University Medical School, Department of Pathology, Professor
2002-2006 Osaka City University Medical School, Dean
2006-2016 Japan Bioassay Research Center, Director
2016- Association for Promotion of Research on Risk Assessment, President

Honors and Prizes

Minister of Health, Labor and Welfare Achievement Award
Yasuda Memorial Medical Award
Mochizuki Kitashi Memorial Award Achievement Award
Osaka City Medical Association Award
Kenkou Award

Main research

Chemical carcinogenesis
Carcinogenic risk assessment of environmental factors
Toxicologic pathology
Pathology of human bladder cancer

S1-1

Visualization of chemicals and its metabolites in tissue sections using desorption electrospray ionization mass spectrometry imaging

○Yuji Ishii

Divsion of Pathology, National Institute of Health Sciences

Mass spectrometry imaging (MSI) allowed us to visualize the distribution of compounds and biomolecules in tissue sections. MSI is expected to be a new tool in the field of toxicological pathology because it can provide positional and structural information not only on known molecules but also on unknown molecules. Matrix-assisted laser desorption/ionization (MALDI), the current mainstream of MSI, efficiently ionizes proteins and achieves high resolution imaging, but it lacks versatility due to requiring a matrix and skilled techniques for matrix preparation. On the other hand, desorption electrospray ionization (DESI) extracts molecules by spraying electrified droplets onto the surface of a tissue, thus eliminating the need for a matrix and complicated preparation. The analysis can be started by simply drying a frozen section of a ten or more μ m thick on a glass slide and setting it on the stage. In addition, unlike MALDI, DESI is non-destructive because no laser is used. Therefore, sections can also be analyzed with histopathologically by staining after MSI, leading to additional significant advantages in this field. In this presentation, I will introduce the mechanism and properties of DESI-MSI and will describe results of visualizing the distribution of low-molecular chemicals and their metabolites by DESI. Furthermore, the present usefulness and future prospects of this analytical technique will be discussed.

Biography

Yuji Ishii

National Institute of Health Sciences, Biological Safety Research Center, Section Chief of Division of Pathology

School Education:
- 1998-2002 Hoshi University, Department of Analytical Chemistry
- 2002-2004 Master's Course, Department of Analytical Chemistry, Graduate School of Pharmaceutical Sciences, Hoshi University
- 2004-2007 Doctoral Course, Department of Analytical Chemistry, Graduate School of Pharmaceutical Sciences, Hoshi University.

Employment History:
- 2007-2009 Post-doctoral researcher, Division of Pathology, National Institute of Health and Sciences
- 2009-2012 Researcher, Division of Pathology, National Institute of Health and Sciences
- 2012-2017 Senior Researcher, Division of Pathology, National Institute of Health and Sciences
- 2017- Section Chief, Division of Pathology, National Institute of Health and Sciences

Memberships:
- The Japanese Society of Toxicology (Councilor)
- The Japanese Environmental Mutagen and Genome Society (Councilor)

Honors and Prizes:
- JEMS Incentive Award 2019, Pfizer Highly Cited Paper Award 2016, JSTP Excellent Award 2014, JSTP Best Award 2012

Symposium

S1-2

Quantitation of cancer histopathology by AI

○Shumpei Ishikawa

Department of Preventive Medicine, Graduate School of Medicine, The University of Tokyo

The histopathological image used for pathological diagnosis and toxicity evaluation is difficult to express objectively or quantitatively, and it has been impossible to directly compare it with other cases, accumulate a large number of case information, and quantify correlation with other modality data. We found that the deep texture information obtained from the middle layer of the neural network, well express the cancer histopathology and is a method to universally structure the histopathological finding as a numerical vector. The structured histopathology of cancer can be treated, as numerical values, in the same manner as genomics data such as an expression profile and clinical laboratory test data, and can be widely applied to various uses. For example, it is possible to identify rare subtypes by capturing an overview of histopathological diversity, search for histopathologically similar images from many image databases (so-called Contents Based Image Retrieval), and predict mutations of the cancer genome. By structuring the histopathological image, it is expected that histopathology can be transformed to data science like genome science, and can brings high-level evidence to basic and clinical medicine.

Biography

Shumpei Ishikawa

Graduate School of Medicine, Department of Preventive Medicine, the University of Tokyo Professor.

School Education:
- 1994-2000 Faculty of medicine, the Univ. of Tokyo, M.D.
- 2000-2004 Department of Pathology, Graduate School of Medicine, the Univ. of Tokyo, Ph.D.

Employment History:
- 2004-2007 Genome Science Division, Research Institute of Advanced Science and Technology, the Univ. of Tokyo (Project Assistant Professor)
- 2007-2012 Department of Pathology, Graduate School of Medicine, the Univ. of Tokyo (Assistant and Associate Professor)
- 2013-2018 Department of Genomic Pathology, Medical Research Institute, Tokyo Medical and Dental University (Professor)
- 2018- present Department of Preventive Medicine, Graduate School of Medicine, the University of Tokyo (Professor)

Memberships：
- Japanese Cancer Association (Auditor, Councilor)
- The Japanese Society of Pathology (Councilor)

Honors and Prizes:
- 2nd Yamato Science Award
- The 34th The Young Investigator Awards of the Japanese Cancer Association
- The 61th Pathology Research Awards of the Japanese Society of Pathology
- JCA-Mauvernay Award 2021

S1-3

Basics of OCT (optical coherence tomography) examination and the relationship between OCT images and histopathological images

○Tomoaki Araki

Shin Nippon Biomedical Laboratories, Ltd. Drug Safety Research Laboratories

Humans obtain about 80% of their sensory information from vision, and loss of this sense significantly impairs quality of life. Therefore, evaluating the effects on vision is important in safety studies of pharmaceuticals. Since animals cannot tell examiners about visual abnormalities or symptoms and there is a limit to the changes in visual function that can be detected by observations of general condition, comprehensive investigation of the presence of morphological changes in the retina and optic nerve through ophthalmologic and physiologic examinations is important. In recent years, the use of OCT has become widespread in examination of morphological changes in the retina. Since OCT, unlike histopathology, allows for non-invasive capture of images, it is possible to examine the morphology of each layer of the retina in 3D in a live animal, regardless of species. In addition, when an abnormality is found in the fundus, images can be obtained over time, shedding light on the primary lesion and the characteristics of the change, enabling investigation of the mechanism. However, compared with histopathology, background data on OCT examination are sparse. Gathering data on OCT and its relationship with histopathological examination can lead to more accurate evaluation of ocular toxicity. In this lecture, I will introduce our work with retinal OCT examination as part of non-clinical safety studies and discuss the relationship between OCT and histopathological images.

Biography

Tomoaki Araki

Shin Nippon Biomedical Laboratories, Ltd. Drug Safety Research Laboratories.
Unit manager, Ophthalmology Research Unit, Safety Assessment Department 1

School Education:
・1998-2002 Department of Biotechnology, Faculty of Engineering, Fukuyama University

Employment History:
・2002- Shin Nippon Biomedical Laboratories, Ltd. Drug Safety Research Laboratories.
・2013- Shin Nippon Biomedical Laboratories, Ltd. Drug Safety Research Laboratories.
Unit manager, Functional Examinations Group, Laboratory Research Department
・2018- Shin Nippon Biomedical Laboratories, Ltd. Drug Safety Research Laboratories.
Unit manager, Safety Assessment Unit 2, Safety Assessment Department 1
・2020- Shin Nippon Biomedical Laboratories, Ltd. Drug Safety Research Laboratories.
Unit manager, Ophthalmology Research Unit, Safety Assessment Department 1

Memberships:
・The Japanese Society of Comparative and Veterinary Ophthalmology (Secretariat, Councilor)
・The Japanese Society of Toxicology (Member)
・The Japanese Society for Clinical Electrophysiology of Vision (Member)
・The Society of Primate Diseases and Pathology (Secretary)

Certifications:
・Diplomate Japanese College of Fundamental Ophthalmologist
・Japanese Senior Laboratory Animal Technician

S1-4

Digital pathology and artificial intelligence in the AI hospital project

○Manabu Takamatsu

Division of Pathology, Cancer Institute of Japanese Foundation for Cancer Research

In recent years, most of the medical information have been digitized and managed on hospital servers, which enables rapid and efficient medical practice by immediate retrieval of various information from the terminal computers connected to the in-hospital network. Regarding pathology workflow, pathological order information and diagnostic information have been managed as digital data. However, only a small number of facilities digitize slide glasses for pathological diagnosis. There are two major categories of pathologic information: macro- and microscopic images. Pathologists diagnose the cases with these high-dimensional data through lesion recognition and disease classification. It is often difficult to collect appropriate information for morphologic analysis even by well-trained pathologist. Digitizing pathologic information and utilizing artificial intelligence (AI) may solve these issues and lead to optimized, stable, and high-quality medical services.We have participated the AI Hospital Program and digitizing the pathology workflow. For macro photographs, we have developed an AI that detect the sample and its lesion with cutline and estimates the lesion area by comparison with the digitized microscopic images. For microscopic images, pathologists can make diagnoses on computer screens with whole-slide images. In addition, we developed histologic classification AI and annotation tool for teacher data creation for machine learning.

Biography

Manabu Takamatsu

Division of Pathology, Cancer Institute of Japanese Foundation for Cancer Research (JFCR), Scientist

School Education:
- 2002-2008 Medical School, Gifu University
- 2010-2014 Graduate school of medicine, Gifu University

Employment History:
- 2008-2010 Clinical internship
- 2014-2018 Division of Pathology, Cancer Institute, JFCR, Project Scientist
- 2018- Division of Pathology, Cancer Institute, JFCR, Scientist

Memberships:
- The Japanese Society of Pathology
- Japanese Cancer Association

Honors and Prizes:
- 2020 International Academy of Pathology (IAP) Young Investigator Award

Symposium

S2-1

The current status and future plans for the globalization of JSTP's certification system for toxicologic pathology

○Katsuhiko Yoshizawa[1,2)]

[1)] Department of Innovative Food Sciences, School of Sciences and Nutrition, Mukogawa Women's University
[2)] Board Certification Committee of JSTP

The Japanese Society of Toxicologic Pathology (JSTP) aims to promote the advancement and development of toxicologic pathology sciences by sharing the common goals of promoting education, scientific research, and dissemination of information. In 1994 the JSTP developed a toxicologic pathology certification system. The examinee's practical skills in macro- and microscopic pathology are assessed by examinaton of pathology slides and also includes a written examination to test knowledge of toxicological pathology. The recent passing rate is 30 to 50%. As of September 2021, the number of certified diplomates was 371, including 6 foreigners. The microscopic examination consists of 30 microscopic slides of neoplastic and non-neoplastic lesions including many slides with drug-induced lesions. Starting in 2022, the microscopic examination will be carried out using virtual slides. All examination questions are prepared in English for the benefit of foreign candidates.The JSTP relaxed the qualification of candidacy for the certification examination in order to give talented young pathologists and international candidates an early opportunity to qualify for the examination. As part of JSTP's global strategy, JSTP would like to contribute to the development of toxicologic pathology professionals by making the certification available to toxicologic pathologists in each country, especially in the Asian region.

Biography

Katsuhiko Yoshizawa

Professor, Department of Innovative Food Sciences, School of Food Sciences and Nutrition, Mukogawa Women's University

School Education:
- 1984-1987 Tottori University, Faculty of Agriculture, Department of Veterinary Medicine
- 1984-1986 Master's Course, Department of Veterinary Science, Graduate School of Agriculture, Tottori University

Employment History:
- 1989-2009 Astellus Pharamaceutical Co. Ltd., Drug Safety Research Laboratories, Principal Researcher
- 2009-2017 Kansai Medical University, Department of Medicine, Assistant Professor
- 2017- Mukogawa Women's University, School of Food Sciences and Nutrition, Department of Innovative Food Sciences, Professor
- 2018- Osaka City University, School of Medicine, Visiting Professor

Memberships:
- The Japanese Society of Toxicological Pathology (Board member, Councilor)
- The Japanese Society of Toxicology (Councilor)
- Japanese College of Veterinary Pathologists (Board member, Councilor)
- The Japanese Society of Pathology (Councilor)
- Hamamatsu Toxicology Study Forum(Councilor)
- International Academy of Toxicologic Pathology (Fellow)
- Japanese Society of Food Chemistry (Councilor)

Honors and Prizes:
- JTP Achievement Award 2018
- JTP Best-Case-Report-of-the-Year Award 2015
- JTP Incentive Award 2012
- The Kitashi Mochizuki Prize Young Researcher Award 2005

S2-2

Establishment of accreditation procedures in toxicologic pathology for trainees

○Kevin Keane

International Academy of Toxicologic Pathology (IATP)

Toxicologic pathology has evolved and grown over the years from a niche, poorly defined, sub-specialty into a distinct, scientific discipline with a well-developed set of best practice in methods, procedures, and terminology that are expected of its practitioners. The training and experiences required of experts in this field have not been uniformly established within this profession and these are generally gained on ad hoc basis after completion of formal educational programs. The IATP was established to create an accreditation program that is flexible in recognizing the various educational pathways and experiences one might accomplish to become an expert in this field and thus recognized as a Fellow. Recently, the IATP has approved an associate Fellow membership category with the express purpose encouraging young trainees to participate in a formal mentorship program that will guide them through activities that will optimize their acquisition of expertise in toxicologic pathology.

Biography

Kevin Keane, DVM, Ph.D. Fellow IATP

Current full-time position: Senior Director of Pathology, Blueprint Medicines, Cambridge, Massachusetts USA
Current part-time position: Editor-in-Chief, Toxicologic Pathology (official journal of STP, BSTP, & ESTP)
Current part-time position: President, International Academy of Toxicologic Pathology (Term: Jan 2021 – Dec 2022)

Education

- 1986-1990 Bachelor Arts, Cornell University, Ithaca, New York USA
- 1992-1995 Doctor Veterinary Medicine, University of Tennessee, Knoxville, Tennessee, USA
- 1995-1998 Resident in Anatomical Pathology, Colorado State University, Fort Collins, Colorado, USA
- 1995-2001 Ph.D. Pathology, Colorado State University, Fort Collins, Colorado, USA

Professional experience

- 2001- 2002 ICOS Corporation, Bothell, Washington, USA
- 2003- 2010 Schering Plough /Merck, Lafayette, New Jersey, USA
- 2011- 2012 Huntingdon Life Sciences, Princeton, New Jersey, USA
- 2011- 2013 Consultant, Hopewell, New Jersey, USA / Beijing, China
- 2013- 2021 Novo Nordisk, Beijing, China / Copenhagen, Denmark
- 2021- Present Blueprint Medicines, Cambridge, Massachusetts, USA

Memberships

- Society of Toxicologic Pathology
- European Society of Toxicologic Pathology
- International Academy of Toxicologic Pathology
- Boston Area Pharmacology Toxicology Group
- Davis-Thompson Foundation for Comparative Veterinary Pathology

S2-3

Regulators' perspective

○Yukie Saegusa

Pharmaceuticals and Medical Devices Agency

The Japanese Society of Toxicologic Pathology (JSTP) has established a board certification system of diplomate of JSTP (DJSTP) in 1992, in order to certify high qualified toxicologic pathologists, to improve quality of pathology review of toxicity studies conducted in Japan and to contribute to the progress of toxicologic pathology. The certification system will be commemorated for its 30th anniversary in 2020. During this period, 371 pathologists have been certified as the DJSTP (as of April 2021) and they have worked as the experts in various fields such as academic, industrial fields and regulatory bodies. On the other hand, among Asian countries, the regions which have certification systems for toxicological pathologists have been limited, and at present, Japan, having issued JSTP, is the only such country. Toxicological pathologists have contributed a lot to ensure the reliability of pathological data in GLP studies conducted in Japan, and to improve the quality of documentation for regulatory submission. In addition, under the progress of globalization, the role and field of DJSTP are expected to be expanded even more with the development of INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) terminology, the introduction of digital pathology and artificial intelligence. In this presentation, I would like to share my opinions on the future direction of the JSTP's board certification system from regulators 'perspective.

Biography

Yukie Saegusa

Principal Reviewer, Office of New Drug Ⅴ, Pharmaceuticals and Medical Devices Agency

School Education
- 1994 BA, Department of Veterinary Medicine, College of Bioresource Sciences, Nihon University
- 2010 PhD, Pathogenetic Veterinary Science, United Graduate School of Veterinary Sciences, Gifu University

Employment History
- 1994-2005 Drug Safety Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd.
- 2010-present Pharmaceuticals and Medical Devices Agency

Memberships
- The Japanese Society of Toxicological Pathology
- The Japanese Society of Toxicology
- The Japanese College of Veterinary Pathology
- The Japanese Society of Veterinary Science

Certificates
- License of Veterinarian
- Diplomate, Japanese Society of Toxicologic Pathologist
- Diplomate, Japanese College of Veterinary Pathologist
- Diplomate, Japanese Society of Toxicology

Honors and Prizes
- 2009 JSTP Excellent Award

S2-4

Current situation in Europe

○Yoshimasa Okazaki

AnaPath Services GmbH

In Europe, the European Society of Toxicologic Pathology (ESTP) was established in 2002 by a transition of the Gesellschaft fuer Toxikologische Pathologie, in order to adapt to future challenges and form a strong Europe oriented international society in the field of toxicologic pathology. The ESTP is providing various continuing educational programs to all scientists working in the field of toxicologic pathology, however, there is no certification system.In the meantime, the ESTP is actively engaged in the joint program with ESVP (European Society of Veterinary Pathology) and ECVP (European college of Veterinary Pathologists). The ECVP was established in 1995 as a consequence of a growing desire to harmonize postgraduate training and provide certification in veterinary pathology in Europe, and the first ECVP certifying exam was organized in 1999. The number of certified diplomates by exam is 238 as of July 2020. The ECVP Exam comprises five sections: Histopathology, Gross Pathology, General Pathology, Veterinary Pathology (VP), and Comprehensive Pathology including at least one subsection for the toxicological pathology. Recently an item for toxicological pathology was omitted as a part of the VP, due to a fact that only occasional candidates have chosen this field. I'm going to talk about the current status in the certification system for toxicologic pathologists, taking the ECVP exam and a national pathology certification system in Germany as representative examples.

Biography

Yoshimasa Okazaki

Current position: AnaPath Services GmbH; Senior Pathologist

School Education:
- 1983-1987 Miyazaki University, Faculty of Agriculture, Department of Veterinary Medicine
- 1987-1989 Miyazaki University, Graduate School of Agriculture Master's Course
- 1998-2002 Yamaguchi University, The United Graduate School of Veterinary Science, Doctoral Course

Employment History:
- 1989-1994 Dainippon Pharmaceutical Co. Ltd.; Staff Pathologist
- 1994-2003 Mitsubishi Chemical Safety Institute ltd., Kashima Laboratory; Senior Pathologist
- 2003-2010 Fujisawa Pharmaceutical Co. Ltd. (2005-: Astellas Pharma Inc.); Senior Pathologist
- 2010-2011 Harlan Laboratories Ltd.; Staff Pathologist
- 2011-2016 AnaPath GmbH; Staff Pathologist
- 2016-2018 The Institute of Environmental Toxicology; Senior Pathologist / Chief of Pathology Division
- 2019- AnaPath Services GmbH; Senior Pathologist

Memberships:
- The Japanese Society of Toxicological Pathology. (Councilor)
- The Japanese Society of Veterinary Science (Councilor)
- The Japanese College of Veterinary Pathologists (Councilor)

S2-5

Current status and future prospects of pharmaco-toxicologic pathology in China

○Jin Ren

Chinese Pharmaceutical Association-Society of Toxicologic Pathology

Chinese Pharmaceutical Association-Specialty group of Toxicologic Pathology (CPA-STP) was established on 19th March 2015 in Beijing, which is the first STP Committee in China, representing a new milestone in this field. The committee was composed 38 members. The total number of professional staffs in the field has been expanding, from about 200 to over 700, of which more than 70% members are young.

The CPA-STP has held four conferences since its establishment in 2015. Each it had a different theme and 40 overseas or domestic experts have been invited to give lectures. Also 40 online or offline slide-reading symposiums have been conducted in the different areas in China. So far, the participants have reached over 1000. CPA-STP completed the "Terminology of Toxicologic Pathology (First Edition)", which was officially released at the CPA last year. It is of benefit to promote the professionalization, harmonization and standardization.

In Nov. 2019, the CPA-STP invited Prof. Hideki Wanibuchi, the president of JSTP, to attend the 3rd academic symposium in Suzhou China, and to give a lecture. Consensus and preliminary framework of agreements were reached, and it was an important foundation for China-Japan in-depth cooperation in future.

I would like to express my sincere gratitude to Professor Hideki Wanibuchi for his great efforts in advancing the friendly China-Japan cooperation and promoting the development in the field of toxicologic pathology in China.

Biography

Jin Ren, MD. Ph.D.

Current position President of Chinese Pharmaceutical Association-Specialty group of Toxicologic Pathology (CPA-STP)
Director and Test Facility Manager of CDSER, SIMM, CAS, China

Education

- 1977-1982 B.M. China Medical University, China
- 1982-1985 Master's degree, in Medical Pathology, China Medical University, China
- 1986-1991 Doctoral degree, in Medical Pathology, Hokkaido University School of Medicine, Sapporo, Japan

Professional experience

- 1990-1992 Postdoctoral, Roswell Park Memorial Institute, Buffalo, New York, U.S.A
- 1997-2001 Dept. of Neuropathology, School of Medicine, The University of Tokyo, Tokyo City, Japan (JST, CREST Program)
- 2001- present Center for Drug Safety Assessment and Research in SIMM, CAS, China

Memberships

- The Japanese Society of Toxicological Pathology (member)
  The British Royal College of Pathology (FRCPath Fellow)
  The International Academy of Toxicity Pathology (IATP Fellow)

Honors and Prizes

Cancer Research Award of IWAZAWARUI by Japanese Cancer Research Foundation
Second Prize of National Scientific and Technological Progress, China (first listed owner)
First prize in Science and Technology by Chinese Pharmaceutical Association (first listed owner)
Ho Liang Ho Lee Foundation for scientific and Technological Progress Award, Hong Kong

Symposium

S2-6

Korean society of toxicologic pathology and board certification

○Jin Seok Kang

Korean Society of Toxicologic Pathology

Korean Society of Toxicologic Pathology (KSTP) is a professional society of experts in the fields of toxicopathology and related sciences. The KSTP has accomplished remarkable progress over the years, gaining strong reputation since it was established in 2002. The KSTP aims to promote the academic development of toxicopathology and to serve as a platform for its utmost interaction with related societies and organizations, that are actively making contributions to the development of toxicopathology. The KSTP supports research activities that encompass the whole areas of toxicopathology matters including toxicological and carcinogenicity studies. The KSTP also provides a fundamental scientific view and takes an initiative in solving problems related to safety issues and risk assessment of foods, medicines, cosmetics, insecticides, medical devices and so on. The KSTP holds annual conference and educational program. In general, the conference consists of several plenary lectures, symposia and poster presentations focusing on the latest research breakthroughs. And the educational programs function as continuing education for practicing toxicologic pathologists and trainees. Each education program covers a target organ or system. Korean Board of Toxicologic Pathology was founded in 2002 to facilitate the education of toxicologic pathologists and certification exam, that is required to get a diploma of Korean Board of Toxicologic Pathology. The education program is offered in May every year. And the certification examination is given every three years on average, and is composed of two parts, a written test and a practical test of toxicopathology.

Biography

Jin Seok Kang, D.V.M., Ph.D.

Director of Student Affair, Namseoul University
Professor, Department of Biomedical Laboratory Science, Namseoul University
President, Korean Society of Toxicologic Pathology

Education

- 1986-1990 Doctor of Veterinary Medicine, Seoul National University, Republic of Korea
- 1990-1992 Master's degree, Seoul National University, Republic of Korea
- 2002-2006 Doctoral degree, Osaka City University, Japan

Professional experience

- 1990- 1998 Daewoong Pharmaceutical Co. Ltd, Republic of Korea
- 1998- 2008 Korea Food and Drug Administration, Republic of Korea
- 2008- present Namseoul University, Republic of Korea
- 2017- 2018 University of Missouri, USA

Memberships

- The Korean Society of Toxicologic Pathology
- The Japanese Society of Toxicologic Pathology
- The Korean Society of Toxicology
- The Korean Society of Laboratory Animal Science

Honors and Prizes

- Science Good Paper Award from Ministry of Science and Technology of Korea Government, Republic of Korea (2017)
- Good Teacher Award from Ministry of Education of Korea Government, Republic of Korea (2019)

S2-7

Overview of society of toxicologic patology India (STPI) and Indian board of toxicologic pathology (IBTP)

○Venkatesha Udupa[1)], SK Vijayasarathi[2)], Narendra Deshmukh[3)], Shekar Chelur[4)], Kamala Kanan[2)], Jomy Jose[5)], PC Prabu[6)], GJ Nataraju[7)], Geeta Nirody[8)], Madhav Marathe[9)]

[1)]Vice President & Head Toxicology, Glenmark Pharmaceuticals Ltd
[2)]Expert Pathologist, Eurofins Advinus Limited
[3)]Co-Founder and Director, Intox Pvt Ltd
[4)]Director, Preclinical Safety Evaluation, Aurigene Discovery Technologies Ltd, Bengaluru, India; 2Head Pathology, Eurofins Advinus Limited
[5)]Head of the Department, Pathology, Sai Lifesciences
[6)]Assistant Professor, Department of Pathology, Veterinary College & Research Institute
[7)]Head Pathology, Bioneeds India Private Ltd
[8)]Consultant Pathologist
[9)]Vice President Toxicology, Sun Pharma Advanced Research Company Ltd

IBTP is an affiliate of STP-I established in 2011 to encourage the study of Toxicologic Pathology and its allied fields to stimulate the advancement of existing standards in Industry for professional practice to prepare and administer procedures, including testing, for the recognition of such standards by certification for those members of the profession who demonstrates competence deserving recognition as Diplomats of the IBTP (DIBTP). The IBTP consists of members who are primarily a Diplomate of IBTP involved in setting up the eligibility criteria, evaluating applicants, and conducting examinations. IBTP ensures running at least two training programs in a year involving practical slide reading, lecture on various topics, before they appear for examination in line with other International Certifying Boards. IBTP gathers questions from Board members and Resource matter specialists, and has a question bank. IBTP, in association with STPI, has collected thousands of glass slides, CDs, teaching materials to train DIBTP aspirants. IBTP certification examination involves theory, practical (glass slide and image) and objective type questions running over nearly 6 hours. Candidates must pass all the 3 sections to obtain DIBTP. The certification is valid for 5-years, and the status has to be renewed by appearing for a recertification examination. Starting October 2012, the board examination is conducted annually with 43 Diplomates to date and are increasingly recognized in the Indian toxicology industry.

Biography

Venkatesha Udupa MVSc (Path), MSc (Tox, UK), DABT, ERT (UK), DIBTP, DSP, PhD

Dr. Venkatesha Udupa is currently working as Vice President and Head – Toxicology at Glenmark Pharmaceuticals Ltd, Mumbai. In this role, Dr. Udupa supports drug discovery and development for several unprecedented targets by providing scientific input in the design and execution of early discovery and nonclinical toxicology experiments that focus on characterizing the safety of the candidates and/or understanding potential mode of action for toxicity in pre-clinical studies. Prior to joining Glenmark Pharmaceuticals, he worked at Ranbaxy Laboratories Ltd (Gurgaon, India), Maccine Pvt Ltd (Singapore) and Himalaya Drug Company (Bangalore, India) in the area of toxicology and pathology.
Dr. Udupa completed his Masters in Veterinary Pathology and PhD in Biochemistry. He is a recipient of Commonwealth Scholarship for Master's program in Toxicology at University of Surrey, UK. He is a Diplomate of American Board of Toxicology (DABT), Diplomate of Safety Pharmacology (DSP), European Registered Toxicologist (ERT, UK) and Diplomate of Indian Board of Toxicological Pathologists (IBTP) and actively involved in various professional activities of STPI, IBTP, IFSTP, STP, ESTP and SOT. He has 20 international publications in peer reviewed journals and 18 national publications, co-inventor in couple of patents and a coauthor for a book chapter on topics in 'Discovery and Regulatory Toxicology in Pharmaceutical Industry' and 'Regulatory Toxicology in Pharmaceuticals' published in 2021 by Springer Nature.

SK Vijayasarathi, MVSc, PhD, Fellow STP-I, Fellow IATP

Dr SK Vijayasarathi has ~50 years of experience in the field of Veterinary Pathology. Dr Vijayasarathi worked at Veterinary College, University of Agricultural Sciences, Bangalore, India in 1969 and served in various capacities till 2004. During this period, he was involved in teaching and also lead supervisor for 25 Master's and 4 Doctoral students, and advisor for more than 150 graduate students (MVSc/PhD). He was the principal investigator for several federal and private funded research projects. Has visited various veterinary and Medical academic institutions as an external examiner to evaluate Masters and Doctoral thesis and to conduct final examinations. He has over 95 scientific publications to his credit and has presented several research paper/ abstracts at various National and international forums. Dr. Vijayasarathi has received several awards for scientific/professional achievements. He is actively involved in the field of regulatory toxicology for more than 28 years for histopathological evaluation to understand the toxicological potential of pharmaceuticals, agrochemicals and biologics in a variety of animal models. He is the author of nearly 700 safety evaluation GLP study reports, including more than 28 carcinogenicity studies. Further, he has peer reviewed nearly 100 GLP studies.

S3-1

Application of genome editing technology in medical research

○Tomoji Mashimo

University of Tokyo, Institute of Medical Science

Although single-component Class 2 CRISPR systems, such as type II Cas9 or type V Cas12a, are widely used for genome editing in eukaryotic cells, the application of multi-component Class 1 CRISPR has yet to be developed. Recently we demonstrate that type I-E CRISPR, which is composed of Escherichia coli Cascade, Cas3, and programmable pre-crRNA, mediates distinct DNA cleavage activity in human cells. Notably, Cas3, which possesses helicase and nuclease activity, predominantly triggered several thousand base pair deletions upstream of the 5-ARG PAM, without prominent off-target activity. This Cas3-mediated directional and broad DNA degradation can be used to introduce functional gene knockouts and knock-ins. As an example of potential therapeutic applications, we show Cas3-mediated exon-skipping of the DMD gene in patient-iPSCs. We also highlights potential use for Cas3-mediated rapid, low-cost, instrument-free detection method for SARS-CoV2. This Cas3-based assay is comparable with Cas12- and RT-PCR-based assays in its speed and sensitivity, but offers greater specificity for single-base-pair discrimination while negating the need for highly trained operators.

Biography

Tomoji Mashimo

The University of Tokyo, Institute of Medical Science, Laboratory Animal Research Center, Division of Animal Genetics

School Education:

- 1990-1994 Department of Animal Science, Faculty of Agriculture, Kyoto University
- 1995-2000 Department of Environmental Conservation and Development, Graduate School of Human and Environmental Studies, Kyoto University

Employment History:

- 2000–2002 Unité de Génétique des Mammifères, Département d'Immunologie, Pasteur Institute, France
- 2003–2015 Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University
- 2015–2020 Institute of Experimental Animal Sciences, Graduate School of Medicine, Osaka University
- 2019– Laboratory Animal Research Center, Institute of Medical Science, the University of Tokyo

Memberships:

- The Japanese society for Genome Editing, vice-president
- Japanese Association for Laboratory Animal Science (JALAS), executive board
- Disease Model Cooperative Research Association (DMCRA), executive board

S3-2

Mutual interaction between tumor cells and microenvironment shapes morphogenesis of tumor tissues

○Kiyotaka Nakano[1)], Masaki Yamazaki[1)], Shigeto Kawai[1)], Etsuko Fujii[1)], Hiroyuki Aburatani[2)], Masami Suzuki[3)]

[1)] Chugai Pharmaceutical co., ltd., [2)] Research Center for Advanced Science and Technology, The University of Tokyo
[3)] Central Institute for Experimental Animals

Tumor tissues are composed of a variety of cell types including tumor cells, fibroblasts and immune cells. Pathological analysis of clinical samples gives important findings, however it is difficult to understand the function of each cells. Therefore, we examined the effects of tumor environment through pathological analysis of experimental xenograft models and cancer organoids. First, we evaluated subcutaneously engrafted mice model of colon cancer cell line PLR123 and detected small cluster structure including cancer stem cell marker LGR5 positive tumor cells in the invasive front. Single cell RNA sequencing revealed heterogeneity of stromal cells as was observed in clinical tumors. We speculate expansion of tumors initiates from this small cluster. Using cancer organoids, we found that fibroblast enhance the formation of the small cluster. Next, in tumor metastasis model of PLR123, we found difference in tumor morphology depending on the site of metastasis. To analyze the effect of the tumor environment, we used the cancer organoid and found that oxygen pressure or growth factors affects the stemness of cancer cells. Finally, we evaluated the effect of mutant RHOA in gastric cancer in orthotopic model. Expression of mutant RHOA in cancer cells enhanced the invasion of tumor cells that recapitulated clinical scirrhous cancer. In conclusion, combination of experimental pathology and cutting-edge technologies such as organoid accelerate the understanding of tumor environment.

Biography

Kiyotaka Nakano

Chugai Pharmaceutical co., ltd. Pharmaceutical Science Department, Group Manager of Micro PhysioMimic Research Group

School Education:
- 1991-1995 Kyushu University, Faculty of Pharmaceutical Sciences
- 1995-1997 Kyushu University Master's Course, Faculty of Pharmaceutical Sciences
- 2012-2013 Tsukuba University Doctoral Course, Faculty of Life and Environmental Sciences

Employment History:
- 1997- Chugai Pharmaceutical co., ltd. Fuji-gotemba laboratory
- 2021- Chugai Pharmaceutical co., ltd. Pharmaceutical Science Department, Group Manager of Micro PhysioMimic Research Group

Symposium

S3-3

Establishment of a dual organ carcinogenicity model in rats for application in cancer chemopreventive studies on natural product and functional food

○Rawiwan Wongpoomchai[1,2], Charatda Punvittayagul[3], Sirinya Taya[2], Arpamas Chariyakornkul[1]

[1] Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2] Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University
[3] Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University

[Background] The anticarcinogenic properties of natural products and functional food are usually evaluated in a single organ-specific test. [Aim] To reduce the cost and time of analysis, a dual organ carcinogenicity test using diethylnitrosamine (DEN) and 1,2-dimethylhydrazine (DMH) was developed.

[Materials and Methods] Triple intraperitoneal administrations of DEN were made before, during or after double subcutaneous injections of DMH. At the end of the experiment, the preneoplastic hepatic glutathione-S-transferase placental form (GST-P) positive foci and colonic aberrant crypt foci (ACF) were analyzed.

[Results] The combined treatment of these carcinogens increased toxicity to rats. Administration of DMH alone did not induce hepatic GST-P positive foci, while co-treatment with DMH enhanced GST-P positive foci formation. However, DEN did not influence the size or number of colonic ACF. The treatment with DMH alone induced CYP2E1, demonstrating that DMH enhanced DEN metabolism in DEN-and DMH-treated rats. These findings were related to increases in hepatic O6-methylguanine DNA adducts and hepatotoxicity, associated with the induction of cell proliferation and liver cancer development. DEN-induced early stages of rat hepatocarcinogenesis was synergistically promoted by DMH via metabolic enzyme induction leading to enhanced DNA mutation and hepatocarcinogenicity.

[Conclusion] The dual organ carcinogenicity model might be an alternative model for anticarcinogenicity testing.

Biography

Rawiwan Wongpoomchai

Associated Professor, Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Thailand
Head of Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University, Thailand

Employment History:

- 1997- until now: Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Thailand

Commitee Memberships:

- Thai Society of Toxicology (2006~)
- Thai Environmental Mutagen Society (2006~)
- Thai Association for Laboratory Animal Science (2006~)
- The Science Society of Thailand (2007~)
- The Biochemical and Molecular Biology Society of Thailand (2007~)

Honors and Prizes:

2006 Young Scientist Award, The 3rd Regional Meeting of Asian Pacific Organization for Cancer Prevention, January 20-21, 2006, Nagoya, Japan
2010 The Best Award for Thesis Advisor in Health Science, Graduate School of Chiang Mai University
2010 Bo Holmstedt Memorial Foundation Travel Award. The XII International Congress of Toxicology, July 19-23, 2010, Barcelona, Spain
2011 Travel Grant Award. The 70th Annual Meeting of the Japanese Cancer Association, October 3-5, 2011, Nagoya, Japan
2013 Travel Grant Award. The 72nd Annual Meeting of the Japanese Cancer Association, October 3-5, 2013, Kanagawa, Japan
2014 The Best Research Award on Supra Cluster of Agriculture and Food. The 3rd Thailand National Research Universities Summit. July 31-August 1, 2014, Bangkok, Thailand.
2018 The Best Award for Thesis Advisor in Health Science, Graduate School of Chiang Mai University
2019 The 1st Price on the 2019 winner of the Flash Talk Session 2 Competition in The 7th International Conference on Food Factors and The 12th International Conference and Exhibition on Nutraceutials and Functional Food organized by The International Society for Nutraceutials and Functional Food. Dec 1-5, 2019, Kobe Convention Center, Japan.

S3-4

Recent insights into mechanisms driving NAFLD/NASH-associated hepatocarcinogenesis

○Anna Kakehashi, Hideki Wanibuchi

Dept. Mol. Pathology, Osaka City University, Grad. Sch. Med.

Nonalcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) are now very common chronic hepatic conditions predisposing to hepatocellular carcinoma (HCC) development. According to the recent "multiple-parallel-hits hypothesis", NASH could be observed in both obese and non-obese patients and is caused by multiple events such as abnormal metabolism and accumulation of lipids, mitochondrial dysfunction, and oxidative and endoplasmic reticulum stresses. In the last decade, translational research studies have identified novel proteins and signaling pathways that participate not only in the development of hepatic steatosis, but also disease progression to NASH, cirrhosis, and HCC. Nevertheless, the mechanisms of HCC developing from precancerous lesions have not yet been fully elucidated. Meanwhile, research is starting to emerge describing underlying molecular pathways that mediate alterations in lipid and glucose metabolism, which leads to fat accumulation in liver. The role of mTOR signaling in NASH progression to HCC has recently attracted attention. The goals of our research are: 1) To explore the novel genetic and protein contributions to NAFLD/NASH; 2) To investigate how these insights might reveal the sequence of events that cause NASH-associated HCC; 3) To develop the reliable biomarkers of NASH/HCC.

Biography

Anna Kakehashi

Osaka City University Graduate School of Medicine, Department of Molecular Pathology, Lecturer

Education:
- 1989-1993 St-Petersburg State University, Faculty of Biology
- 1993-1995 St-Petersburg State University, Faculty of Biology, Department of Biochemistry, Master course
- 1999-2003 Doctoral Course, Osaka City University Graduate School of Medicine, Department of Pathology

Employment History:
- 2003-2006 Osaka City University Graduate School of Medicine, Department of Molecular Pathology, supported by the grant for young researches from the Ministry of Health, Labor and Welfare of Japan, Research Resident
- 2006-2011 Osaka City University Graduate School of Medicine, Department of Molecular Pathology, Research Associate
- 2011- Osaka City University Graduate School of Medicine, Department of Molecular Pathology, Lecturer

Commetee Memberships:
- Japanese Society of Toxicological Pathology (JSTP) (Councilor)
- Japanese Association for Cancer Research (JACR) (Councilor)
- Japanese Association for Cancer Prevention (JACP) (Councilor)
- Japanese Pathology Association (JPA) (Councilor)

Honors and Prizes:
- The 18th Annual Meeting of JSTP Conference presentation award/President award, 2002
- The 30th Annual Meeting of JSOT, Conference presentation award for young scientists, 2003

Osaka City University Graduate School of Medicine, Dean Award of Excellence, 2018
Osaka City Medical Association Award, 2018

PD

Workstyle of toxicologic pathologist in the post-corona era – Practice and challenges on remote histopathologic evaluation and remote peer review

Panelist : Kinji Kobayashi (Shin Nippon Biomedical Laboratories, Ltd.)
Izumi Matsumoto (Sumitomo Dainippon Pharma Co. Ltd.)
Hisashi Anayama (Drug Safety Research & Evaluation, Takeda Pharmaceutical Company Limited)
Etsuko Ohta (Global Drug Safety, Eisai Co., Ltd.)
Hiroko Kokoshima (LSIM Safety Institute Corporation)
Hijiri Iwata (Laboratory of Toxicologic Pathology, LunaPath LLC)
Yuko Yamagachi (BoZo Research Center Inc.)
Observer : Kenji Nakano (Pharmaceuticals and Medical Devices Agency)

Upon the current pandemic of COVID 19, changes in workstyle have been considered in many industrial sectors. For us toxicologic pathologists working in the post-corona era, we should take this opportunity to shape our own workstyle that would enable us to work in a way that is more stress-free, more efficient, and more integrated for generating pathological data. We will discuss what a workstyle of toxicologic pathologist in this new era should be, and elucidate the obstacles in order to find the way for our own envisioned future.
To this end, top experts of consultant, pharma, and CRO pathologists will gather as a panelist to discuss this topic. The goal of the discussion is to create a shared vision of our future workstyle and a wish list for achieving the vision. We hope the wish list will contribute to future proposals in shaping the workstyle of toxicologic pathologists.

W-1＊

Carbonic anhydrase inhibitor acetazolamide inhibited invasion of urinary bladder cancers via suppression of Wnt/beta-catenin signaling pathway

○Taisuke Matsue[1,2], Min Gi[3], Masayuki Shiota[4], Shugo Suzuki[1], Masaki Fujioka[1], Anna Kakehashi[1], Junji Uchida[2], Hideki Wanibuchi[1]

[1] Department of molecular pathology, Osaka city university graduate school of medicine
[2] Department of urology, Osaka City University Graduate School of Medicine
[3] Department of Environmental Risk Assessment, Osaka City University Graduate School of Medicine
[4] Department of molecular mechanisms of biological regulation, Osaka City University Graduate School of Medicine

[Background] We previously identified carbonic anhydrase 2 (CA2) as a novel cancer-associated protein by proteome analysis of the rat bladder cancer (BC) model. [Aim] We investigated the antitumor effect of the CA2 inhibitor Acetazolamide (Ace) on N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN)-induced BC in mice. Furthermore, we explored the effects and molecular function of CA2 in human BC cell lines. **[Materials and Methods]** Male C57BL/6J mice were treated with 0.05% BBN in drinking water for ten weeks. Subsequently, the mice were treated with vehicle, Ace, cisplatin (Cis), and combination of both drugs for 12 weeks. Bladders were collected after autopsy for histopathological examination. Human BC cell lines T24 and UMUC3 were transfected with the CA2 gene, and migration and invasion assays, gene expression analysis, and expression analysis of EMT-related proteins were performed. **[Results]** Incidences of invasive BC were significantly decreased in Ace group and Ace+Cis combination groups compared with the BBN alone group. Migration and invasion ability in CA2-transfected cells was increased, possibly via induction of the phospholipid kinase PIP5K1B, and thereby induce EMT via activation of the Wnt/beta-catenin signaling pathway. **[Conclusion]** Our results demonstrated the inhibitory effects of Ace on invasion of BCs in mice and suggested that Ace inhibited the EMT by supression of Wnt/beta-catenin signaling pathway activation and EMT.

W-2＊

Immunohistochemical analysis of cynomolgus monkey endometrial estrogen and progesterone receptors throughout the menstrual cycle

○Yuumi Awazuhara, Hiroko Kokoshima, Yuki Tomonari, Natsumi Shimoyama, Yutaka Nakahara, Yumi Wako, Junko Sato, Takuya Doi

LSIM Safety Institute Corporation Pathology Department Kashima Laboratories

Introduction Cyclic changes in sex hormones and endometrium in female cynomolgus monkeys (cyno) are similar to those in humans. In humans, expression of estrogen receptor (ER) and progesterone receptor (PgR) during the menstrual cycle has been reported, but not in cyno. In this study, we examined the receptor expression in the normal uterus of cyno during each phase of the menstrual cycle. **Materials and Methods** Ovaries and uteri of 24 female cyno aged 3 to7 years were examined by HE staining. The uteri were immunohistochemically stained with anti-ER and anti-PgR antibodies. They were histologically classified as follows: 2 in menstrual phase (M), 11 in early to mid growth phase (EG), 2 in late growth phase (LG), 5 in early secretory phase (ES), and 4 in late secretory phase (LS). **Results** ER: Endometrium was first positive in EG, and gradually weakened and became negative in LG. In ES to LS, only the basal layer was positive in many cases. PgR: Endometrium was positive in EG and LG, and mostly negative and only partial weak positive in ES. In LS, only stromal cells were positive. **Conclusion** In humans, ER was expressed in almost all cells in EG to LG and became negative in mid secretory phase (MS), while PgR was expressed in almost all cells in EG to LG, decreased in MS and became negative in LS. We found that the ER of cyno was similar to humans, but PgR was positive even in LS. It suggests that cyno has a unique receptor expression dependent on the menstrual cycle.

W-3＊

Site-specific genotoxicity of rubiadin indicated by its localization and histopathological changes in rat kidney

○Tatsuya Mitsumoto[1,2], Yuji Ishii[1], Norifumi Takimoto[1,3], Moeka Namiki[1], Shinji Takasu[1], Takehiko Nohmi[1], Kumiko Ogawa[1]

[1] Division of pathology, National Institute of Health Science
[2] Faculty of Animal Health Technology, Yamazaki University of Animal Health Technology
[3] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology

[Introduction] We have demonstrated that rubiadin (Rub) is specifically distributed in outer stripe outer medulla (OSOM) in the kidneys of rats treated with madder color for a single dose using DESI-MSI. Although Rub showed positive results in Ames test, *in vivo* mutagenicity in the kidneys of rats is still uncertain. In the present study, we examined distribution of Rub and its metabolites in the kidney of *gpt* delta rats repeatedly administered with Rub along with histopathological changes and mutagenicity, to clarify the relationship between these changes and localization. **[M&M]** Six-week-old male F344 *gpt* delta rats were given 0, 0.01, 0.03 and 0.1% of Rub by feeding for 4 weeks. A part of left kidney was embedded in 4% carboxy methylcellulose and frozen for MSI, and the rest was fixed in 10% formalin for histopathology and γ-H2AX immunohistochemistry. The cortex and medulla of the right kidney were collected separately for reporter gene mutation assay. **[Results]** MSI showed that the deprotonated ions (m/z 253.050 and 333.007) of Rub and its sulfate conjugate were detected in OSOM. In OSOM, karyomegaly was also observed histopathologically in the 0.1% group, and γ-H2AX positive renal tubule cells were increased. **[Conclusion]** MSI revealed that Rub and its metabolite were distributed in OSOM specifically even after repeated dose as same as single dosing. The consistency of these distributions and histopathological changes suggests that Rub induces DNA damage specifically in OSOM.

W-4＊

Involvement of interleukin-21 receptor (IL-21R) in NASH induced in mice by a choline-deficient, methionine-lowered, L-amino acid, high fat diet (CDAA-HF-T(-))

○Noriko Kemuriyama[1], Hayato Watanabe[2], Sae Nakane[2], Aya Kirigakubo[1], Kasumi Sasaki[1], Daiki Tanaka[1], Masaru Kise[1], Hina Mandokoro[2], Kinuko Uno[3], Katsuhiro Miyajima[1,2], Dai Nakae[1,2]

[1] Dept. Nutr. Sci. Food Safety, Facul. Biosci., Tokyo Univ. Agricul., [2] Dept. Nutr. Sci. Food Safety, Grad. Sch. Agricul., Tokyo Univ. Agricul
[3] Dept. Food Nutr. Sci., Grad. Sch. Agricul., Tokyo Univ. Agricul.

[Background and Aim] Our previous studies have suggested that IL-21R is associated with SREBPs, a lipid synthesis transcription factor that is much expressed in the liver. In this study, we analyzed the involvement of IL-21R in the development of nonalcoholic steatohepatitis (NASH) in order to investigate the life-style-related pathophysiological significance of IL-21R in the liver.[Materials and Methods] Six-week-old male C57BL/6J mice, wild-type or IL-21R deficient, were fed a control diet or CDAA HF-T(-) (45% fat by a shortening without trans fat, methionine 0.1%), for 4 weeks.[Results] In the CDAA-HF-T(-) group, blood ALT was increased, and in the liver lipid accumulation and overexpression of IL-21and IL-21R, and inflammatory and fibrotic genes. The IL-21R deficiency enhanced the ALT increase and inhibited the overexpression of fibrotic genes. In the normal diet group, no particular changes were observed. [Conclusion] In the early stage of murine NASH induced by a 4-week CDAA-HF-T(-) administration, hepatic IL-21 and IL-21R gene expression were increased, suggesting that they are involved in the development and progression of NASH. In addition, it is suggested that IL-21R is not involved in CDAA-HF-T(-)-induced hepatic steatosis and inflammation, but may specifically be involved in the progression of hepatic fibrosis.

W-5＊

Introduction of the novel pulmonary disease originating from cases of industrial accidents caused by inhalation of organic dust

○Shotaro Yamano[1)], Tomoki Takeda[1)], Kenji Takanobu[1)], Hideki Senoh[1)], Shigeki Koda[2)], Kenzo Okamoto[3)], Takumi Kishimoto[4)], Yumi Umeda[1)]

[1)] Japan Bioassay Research Center, Japan Organization of Occupational Health and Safety
[2)] National Institute for Occupational Safety and Health, Japan Organization of Occupational Health and Safety
[3)] Department of Pathology, Hokkaido Chuo Rosai Hospital, Japan Organization of Occupational Health and Safety
[4)] Director of Research and Training Center for Asbestos-Related Diseases, Japan Organization of Occupational Health and Safety

[Background/Aim] Recently in Japan, six workers at a chemical plant that manufactures resins developed lung diseases such as fibrosis, interstitial pneumonia, emphysema, and pneumothorax after being involved in loading and packing cross-linked water-soluble acrylic acid polymers (CWAAPs) for packaging. Because it is not well known that CWAAPs are affected to the respiratory organ, this study examined its pathological mechanism. **[Materials and Methods]** F344 rats were administered the CWAAP dissolved in PBS intratracheally or by systemic inhalation (0-40 mg/m3, 1 or 5 days/week, 10 or 13 weeks), and lung tissue and blood were collected up to 26 weeks after the first administration and subjected to biological and histopathological analyses. **[Results and Conclusion]** CWAAP caused alveolar injury in the acute phase, and continuous administration resulted in regenerative changes in the alveolar epithelium with activation of transforming growth factor β signaling. During the recovery period after the last exposure, such alveolar lesions were partially recovered in the chronic phase, but the other remaining lesions developed into alveolitis with fibrous thickening of the alveolar septum. These results indicated that inhalation exposure of the CWAAP induced alveolar damage in rats. In this presentation, we would like to report and discuss the comparative study with inorganic dust and NOAEC to set the allowable concentration.

W-6＊

Short term pulmonary toxicity study of carbon nano-horns (CNH) and carbon nano-brushes (CNB) using intra tracheal method

○Saleh Dina[1,2,3)], Ahmed Omnia[1,2,4)], Alexander David[1)], Alexander William[1)], Gunasekaran Sivagami[1,2)], Takamasa Numano[1)], Hiroshi Takase[5)], Makoto Ohnishi[6)], Satoru Takahashi[2)], Masako Yudasaka[7)], Ryota Yuge[8)], Hiroyuki Tsuda[1)]

[1)] Nanotoxicology Lab project, Nagoya City University
[2)] Departement of Experimental pathology and tumor biology, Graduate school of medicine, Nagoya city university
[3)] Department of Forensic medicine and clinical toxicology, Faculty of medicine, Assuit university
[4)] Department of Forensic medicine and clinical toxicology, Faculty of medicine, Aswan university
[5)] Core laboratory, Graduate school of Medicine, Nagoya City University
[6)] Japan Industrial Safety and Health Association, Japan Bioassay Research Center
[7)] National Institute of Advanced Industrial Science and Technology, [8)] System Platform Research Laboratories, NEC Corporation

Use of carbon nanotubes (CNT) is expanding. Carbon nanohorns (CNH) are graphene-based tubular objects ended by a five-pentagon conical cap, and thousands of these tubular objects assemble into spherical aggregates. Carbon nanobrushes (CNB) are linear assemblies of CNH spherical aggregates. Their unique structures with high surface area make CNH and CNB promising materials for many high technology fields. We have been examining multi-walled carbon nanotubes (MWCNTs) for pulmonary and pleural hazards using intra-tracheal intra-pulmonary spraying (TIPS). Using this method, we examined the pulmonary and pleural toxicity of CNH (0.5 mg/rat and 1 mg/rat) and CNB (0.5 mg/rat and 1 mg/rat) with MWCNT-7 (0.5 mg/rat) as the reference material. Test materials were administrated every other day for 15 days and rats were observed without further treatment until sacrifice at week 6. Results: Histopathological analysis showed alveolar macrophages engulfing all 3 types of CNTs and formation of granulation tissue. Granulation tissue, macrophage count, and alveolar cells and pleural mesothelial cells positive for PCNA (cell proliferation index) were all significantly lower in the CNH and CNB groups compared to the MWCNT-7 group ($p<0.05$). Conclusion: Our results show that inflammatory lesion development is significantly less in CNH and CNB exposed lung tissue compared to MWCNT-7, and thus CNH and CNB are less harmful to the rat lung than MWCNT-7.

W-7＊

Generation of cerebral organoids from human embryonic stem cells

○Ke Chen[1)], Shuang Qiu[1)], Haoan Wang[1)], Qingxi Kong[2)], Qian Bu[1,3)], Qian Liu[1)], Xiaobo Cen[1,4)], Chunyan Hu[1)]

[1)] Westchina-Frontier Pharma Tech Co., Ltd (WCFP), [2)] Pharmaron
[3)] Healthy Food Evaluation Research Center, Department of Food Science and Technology, College of Light Industry, Textile and Food Engineering, Sichuan University
[4)] National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, and Collaborative Innovation Center for Biotherapy

[Background] In traditional neurotoxicity research animal or human nerve cell lines are mostly used as models, both of them can't reflect the complexity of the human brain structure and function. **[Aim]** To provide a better model in vitro for studying cerebral development and neurotoxicity. **[Materials and Methods]** The cerebral organoids were generated from H1 hESC line. A 3D culture system was introduced to generate the hESC-derived cerebral organoids in Matrigel. **[Results]** During the 2D subculture of the hESCs in vitro, chromosome karyotyping, immunofluorescence, trilineage differentiation test and teratoma experiment showed that the hESCs maintained the normal human diploid karyotype with differentiation pluripotency. During the 3D culture process, the immunofluorescence showed that the cerebral organoids not only contained differentiated cell types, also self-assembled into cerebral cortex with complex morphology, including the human VZ-like area, organized horizontal multilayers structure, and synapse network. The multi-electrode arrays also recorded consistent increases in electrical activity in the cerebral organoids, as parametrized by burst frequency and firing rate, which indicated a continually evolving neural network. **[Conclusion]** A 3D culture systerm was successfully developed to generate cerebral organoids model from hESCs. This research provided a novel platform for developmental neurotoxicity studies in vitro.

W-8＊

Detection of drug-induced arteritis in rats using *ex vivo/in vivo* MRI

○Yuta Fujii[1,2)], Yuka Yoshino[1,2)], Kazuhiro Chihara[1)], Aya Nakae[2,3)], Junichiro Enmi[2,3)], Yoshichika Yoshioka[2,3)], Izuru Miyawaki[1)]

[1)] Preclinical Research Unit, Sumitomo Dainippon Pharma Co., Ltd., [2)] Graduate school of Frontier Biosciences, Osaka University
[3)] Center for Information and Neural Networks (CiNet), National Institute of Information and Communications Technology (NICT) and Osaka University

[Background and Aim] Drug-induced arteritis is one of the major issues in drug development, since there are no specific and sensitive biomarkers. MRI has been used for over 30 years in clinical practice. The research use of MRI on rodents had not well progressed due to their size. In recent years, in vivo imaging techniques including ultra high-field MRI in rodents have made progress. In this study, we conducted ex vivo/in vivo MRI in rats at 11.7 T to clarify whether the drug-induced arteritis can be detected by MRI. **[Materials and Methods]** SD rats were administered fenoldopam mesylate (FM), which induces arteritis by vasodilatory action, or Midodrine hydrochloride, which induces arteritis by vasoconstrictor action, subcutaneously for 2 days and subjected to ex vivo and/or in vivo MRI. Histopathological examination was conducted after MRI measurements. **[Results]** The drug induced arteritis was detectable by both ex vivo and in vivo MRI. Perivascular edema in histopathology was recognized as the high signal intensity regions around artery on MRI. In addition, intramural hemorrhage in histopathology was recognized as low signal intensity spots in the arterial wall on MRI in ex vivo. **[Conclusion]** Since it was possible to detect the both drug induced arteritis with different mechanisms of action noninvasively by MRI, it was considered to be a versatile method. It was speculated that high signal intensity regions around artery could be one of the biomarkers in clinical trials.

IATP

Digital pathology and tissue image analysis - how did we start and where are we now

○Aleksandra Zuraw

Charles River Laboratories

The field of digital pathology was born with the development of telepathology in the 1980's of the last century. It originated with the need of remote consultation, evolved over more than 30 years, and now allows us to serve patients and advance science from home during a global pandemic.

The aspects of current digital pathology span from classical telepathology and collaboration tools all the way to artificial intelligence-powered image analysis. Digital pathology is a cutting-edge discipline where pathology, computer science and computer vision meet and scientists collaborate.

To advance the field of digital pathology individuals specializing in each of those disciplines need to understand each other and work together efficiently. This presentation is an overview of the history and evolution of digital pathology as well as a source of background knowledge necessary for a pathologist to navigate and contribute to this rapidly evolving field.

Biography

Aleksandra Zuraw, DVM, Ph.D.

Charles River Laboratories, Veterinary Pathologist II, Digital Pathology

Education

- 2003-2009 Master's degree, Veterinary Medicine, Wroclaw University of Environmental and Live Sciences, Poland
- 2012-2016 Doctoral degree, Veterinary Pathology, Freie Universitaet Berlin, Germany

Professional experience

- 2016-2018 Senior Pathologist, Definiens, Germany
- 2018-present Veterinary Pathologist II, Charles River Laboratories, USA
- 2019-present Founder and Publisher of Digital Pathology Place (www.digitalpathologyplace.com)

Memberships

- Society of Toxicologic Pathology (STP)
- American College of Veterinary Pathologists (ACVP)

Honors and Prizes

- Best Presentation Award at the Second Joint European Congress of the European Society of Veterinary Pathology, European Society of Toxicologic Pathology and the European College of Veterinary Pathologists (2014)

ES

1st JSTP-CPA-STP Joint Education Seminar
Understanding, detection, and diagnosis of background and induced lesions in toxicity and carcinogenicity studies

Chairperson：Jin Ren (Shanghai Institute of Material Medica, Chinese Academy of Science)
Min Gi (Osaka City University Graduate School of Medicine)

The Japanese Society of Toxicologic Pathology (JSTP) and the Chinese Pharmaceutical Association-Society of Toxicologic Pathology (CPA-STP) are proud to offer our first joint education seminar. This seminar brings together toxicopathology specialists from China and Japan to share their expertise in pathological examination. This seminar will cover basic and advanced toxicology topics with the aim of developing the abilities of younger pathologists in understanding, detection, and diagnosis of background and induced lesions in toxicity and carcinogenicity studies. Attendees will gain a solid understanding of induced non-proliferative and proliferative lesions of the rodent urinary bladder; proliferative lesions of the rodent endocrine system; background and non-proliferative and proliferative lesions in rasH2 mice; spermatogenesis and stages of the seminiferous epithelium cycle in rats; and the latest advances in preclinical assessment of cellular therapy products.

ES-1 Chemically induced nonproliferative and proliferative lesions in rat and mouse urinary bladder
Min Gi (Osaka City University Graduate School of Medicine)

ES-2 Nonproliferative and proliferative lesions observed in the short-term carcinogenicity studies in rasH2 mice
Hemei Wang (Jiangsu ChemPartner)

ES-3 Proliferative lesions of the rodent endocrine system
Toko Ohira (Shanghai InnoStar Bio-tech Co., Ltd)

ES-4 Spermatogenesis and testicular staging in rats
Chunyan Hu (WestChina-Frontier PharmaTech)

ES-5 Preclinical toxicologic pathology evaluation of cellular therapy products
Jianjun Lyu (Shanghai InnoStar Bio-tech Co., Ltd)

Poster Presentation

An asterisk on a poster number indicates that its first author is younger than 40 years old.

P-01 ～ P-121

P-01＊

Search for developmental neurotoxicity markers focusing on disruption of methylation regulation of hippocampal neurotransmission-related genes in rats

○Yasunori Takahashi[1,2], Ryota Ojiro[1,2], Risako Yamashita[1], Shimizu Saori[1], Natsuno Maeda[1], Hiromu Okano[1,2], Kazumi Takashima[1,2], Qian Tang[1,2], Shunsuke Ozawa[1,2], Toshinori Yoshida[1,2], Makoto Shibutani[1,2]

[1] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[2] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology

[Background and Objectives] To obtain irreversible markers of developmental neurotoxicity, we recently obtained genes that show hypermethylation and expression downregulation in the dentate gyrus (DG) after developmental exposure to propylthiouracil (PTU), valproic acid (VPA), or glycidol (GLY), all of which irreversibly disrupt hippocampal neurogenesis, in rats. In this study, we focused on neurotransmission and neurogenesis-related genes and analyzed their properties as marker molecules. **[Methods]** Validation analysis in the transcript and promoter methylation levels of candidate genes was performed on postnatal day (PND) 21 and PND 77. Candidate molecules were analyzed in the DG by immunohistochemistry (IHC). **[Results]** Three genes by PTU and 1 gene by GLY were irreversibly downregulated, and their promoter hypermethylation was confirmed. IHC revealed irreversible decrease of neurogranin $(NG)^+$ cells in the granule cell layer by GLY. NG^+ cells were also decreased by PTU at PND 21, and by EtOH at PND 77 after developmental exposure. NG^+ cells also trended to decrease by 28-day EtOH exposure. **[Discussion]** NG is known to be involved in the regulation of synaptic plasticity via calcium signaling pathway. We previously revealed that developmental and/or 28-day exposure to PTU, GLY, and EtOH suppressed synaptic plasticity. Thus, NG may be an effective marker for the suppression of synaptic plasticity due to disruption of methylation regulation.

P-02＊

Effects of acrylamide on olfactory bulb-subventricular zone neurogenesis in rats

○Bunichiro Ogawa[1,2], Yutaka Nakanishi[1], Masaki Wakamatsu[1], Yasunori Takahashi[2,3], Makoto Shibutani[2,3]

[1] Drug Safety, Taisho Pharmaceutical Co., Ltd., [2] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[3] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology

[Background] Acrylamide (ACR) is well known axon terminal toxicant, and we have previously reported that ACR targets granule cell lineage subpopulations active in neurite outgrowth and synaptogenesis in hippocampal neurogenesis after developmental exposure. Olfactory bulb (OB)-subventricular zone (SVZ) is an organ where neurogenesis continues after birth, similar to the hippocampus, but the impact of ACR on this endpoint is not known. The present study investigated the effects of ACR on OB-SVZ neurogenesis. **[Materials and Methods]** Male SD rats were orally administered 0, 5, 10, or 20 mg/kg ACR for 28 days, and immunohistochemistry was performed for neural lineage markers on the OB and SVZ (n=10). qRT-PCR analysis of neurogenesis-related genes was conducted in the granular cell layer of OB in the 0 and 20 mg/kg groups (n=6). **[Results]** PSA-$NCAM^+$ and Doublecortin $(DCX)^+$ cells were decreased in the OB in the 10 and 20 mg/kg groups. No changes were observed for other neural lineage markers (CALB2, NeuN in the OB; GFAP, SOX2, TBR2, PSA-NCAM, DCX in the SVZ). The qRT-PCR revealed downregulation of *Ncam2* and *Bdnf* in the OB. **[Conclusion]** Since the PSA-$NCAM^+$ and DCX^+ cells decreased in the OB but not in the SVZ, the target of ACR was considered to be immature neurons migrated into the OB and rostral migratory stream. In addition, the ACR toxicity mechanism in the OB might be impaired neurite extension and synaptogenesis due to suppressed BDNF support and NCAM2 expression.

P-03＊

Histopathologcial evaluation in SD rat model of optic nerve injury

○Liu Xiangjiang, Du Mu, Qi Wei, Guo Jin, Zhang Rui , Guo Hui, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc.

[Background] The establishment of an animal model of incomplete optic nerve injury is a prerequisite for the study of optic nerve injury. The existing models of optic nerve injury have poor repeatability due to the instability of injury degree. In this study, the model of optic nerve injury was induced by clamping the posterior optic nerve of SD rats, and histopathological evaluation was conducted. **[Materials and Methods]** Anesthetized the SD rats, cut the upper eyelid, separated the rectus muscle, fully exposed the optic nerve, removed the sheath of the optic nerve 1-3 mm behind the eyeballs, and clamped the sheath 2 mm behind the eyeballs with a vessel clip. The optic nerves and eyeballs were examined by HE stain. **[Results]** The main findings were swelling and degeneration of the optic nerve, and the arrangement of the optic nerve was disordered. Since the optic nerve is composed of axons of ganglion cells, the damage of the optic nerve will further affect the ganglion cells, which may eventually cause retinal findings. Disorder of retinal arrangement was seen in the retina, and retinal atrophy was seen in severe cases.

P-04

Superimposition of mild hypertension on diabetic peripheral neuropathy dose not affect small unmyelinated sensory nerves in the skin in rats with alloxan-induced type 1 diabetes

○Kiyokazu Ozaki, Tetsuro Matsuura

Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University

Hypertension is considered to be a risk factor for diabetic peripheral neuropathy (DPN) in humans. We have previously reported that superimposing severe hypertension on hyperglycemia accelerated a reduction in the intraepidermal nerve density (IENFD) of alloxan (AL)-induced diabetic rats. In this study, we tried to clarify the effects of prolonged mild hypertension on DPN in the AL-induced diabetic rats. Ten-week-old male WBN/Kob rats were divided into 3 groups: AL-induced diabetes rats (AL group), AL-induced diabetes rats given a saline (AN group), and intact rats (C group). AL was injected at 10 weeks of age (AL and AN groups), and tap water containing 0.5% saline was given from 13 weeks of age for 36 weeks (AN group). All animals were euthanized at 49 weeks of age. Severe hyperglycemia and glucosuria continued in the AN and AL groups, meanwhile blood and urinary glucose were elevated after 43 weeks of age in the C group. The blood pressure was mildly increased with the same level until 33 weeks of age, however that in the AN group was further increased, and was significantly higher (148 mmHg) at 49 weeks of age compared to the AL and C groups (120 and 100 mmHg). IENFD in the AN group was significantly lower than in the C group, and that in the AL group also showed a tendency to be lower than in the C group, but there was no difference between the AN and AL groups. These findings suggest that superimposing prolonged mil

P-05

Neuroprotective effect of alpha-glycosyl isoquercitrin against developmental neural deficits caused by immune activation induced by nucleic acid treatment of pregnant rats

○Kazumi Takashima[1,2], Hiromu Okano[1,2], Qian Tang[1,2], Yasunori Takahashi[1,2], Ryota Ojiro[1,2], Syunsuke Ozawa[1,2], Mihoko Koyanagi[3], Toshinori Yoshida[1,2], Makoto Shibutani[1,2]

[1] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[2] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology
[3] San-Ei Gen F.F.I., Inc.

[Purpose] This study investigated the effect of α-glycosyl isoquercitrin (AGIQ) as an antioxidant on a rat model of neural deficits in offspring induced by nucleic acid-induced maternal immune activation. **[Method]** Pregnant rats were intravenously injected polyinosinic-polycytidylic acid (poly(I:C)) at 4 mg/kg on gestation day 15. AGIQ was dietarily administered to dams at 0.25% or 0.5% from gestation day 10 to 21st day after delivery, and to pups thereafter. Male offspring were subjected to analysis. **[Results]** On postnatal day (PND) 21, poly(I:C) injection decreased the number of $TBR2^+$ cells and $PCNA^+$ cells in the subgranular zone accompanying decreased hilar $reelin^+$ cell number. AGIQ ameliorated these changes at 0.5% accompanying upregulation of genes related to reelin signaling and Wnt/β-catenin signaling in the dentate gyrus. On PND 77, neurogenesis markers were unaltered with poly(I:C). AGIQ increased FOS^+ granule cell numbers at 0.25% and upregulated the expression of NMDA-type glutamate receptor genes at 0.25% and/or 0.5%. **[Discussion]** Maternal poly(I:C) injection transiently suppressed neurogenesis in male offspring targeting type-2b neural progenitor cells (NPCs) in early postnatal life due to inhibition of cell proliferation and reelin signaling. AGIQ alleviated poly(I:C)-induced disruptive neurogenesis through amplification of NPCs due to increased reelin signaling and Wnt/β-catenin signaling at the weaning stage and increased synaptic plasticity at the adult stage.

P-06 ✻

Role of CCDC85C, a causative protein for hydrocephalus, and intermediate filament proteins (IFs) during lateral ventricle development in rat brain

○Hasan Md. Mehedi, Shizuka Konishi, Miyuu Tanaka, Takeshi Izawa, Jyoji Yamate, Mitsuru Kuwamura

Laboratory of Veterinary Pathology, Osaka Prefecture University

Role of CCDC85C, a causative protein for hydrocephalus, and intermediate filament proteins (IFs) during lateral ventricle development in rat brainHasan MM, Konishi S, Tanaka M, Izawa T, Yamate J, and Kuwamura MLaboratory of Veterinary Pathology, Osaka Prefecture University **[Background & Aim]**Coiled-coil domain containing 85c (Ccdc85c) is a causative gene for hydrocephalus and subcortical heterotopia with frequent brain hemorrhage. A few is known on its role during brain development. Here we investigated the role of CCDC85C and IFs including nestin, vimentin, GFAP, and cytokeratin AE1/AE3 during lateral ventricle development in rats. **[Materials & Methods]** F344 wild type (WT) rats and Ccdc85c KO rats were maintained in our university, brains were collected on embryonic days 13 (E13) to E19 and postnatal days 0 (P0) to P30. Immunohistochemistry and immunoelectron microscopy were done. **[Results]** In WT rats, the expression of nestin and vimentin was decreased in the wall of the lateral ventricle in manner similar to CCDC85C, but GFAP expression started immediately after birth and became stronger with age; and had a strong relation with cytokeratin. But in KO rats, misexpression and ectopic expression of IFs was seen that indicates the ultra-expression of IFs at postnatal stages. **[Conclusion]** Expression of CCDC85C may be related to neurogenesis and ependymal cell differentiation. This CCDC85C model may be useful for evaluating the new pathway of neuronal and cell development.

P-07＊

Involvement of a mutation in *Hcn1* gene in tremor behavior of the VF myelin mutant rat

○Miyuu Tanaka[1,2], Seika Isogai[1], Sakiko Kojima[1], Takeshi Izawa[1], Takashi Kuramoto[2,3], Mitsuru Kuwamura[1]

[1] Veterinary Pathology, Osaka Prefecture University
[2] Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University
[3] Department of Animal Science, Faculty of Agriculture, Tokyo University of Agriculture

[Background and Aim] The vacuole formation (VF) rat, an autosomal recessive myelin mutant, has a nonsense mutation in *Dopey1* and is characterized by generalized tremor, hypomyelination, and periaxonal vacuole formation of the central nervous system (CNS). The VF rat also has a missense mutation in *Hcn1* gene (reported as one of the causative gene of essential tremor) as genetic background. In this study, we investigated the involvement of a mutation in *Hcn1* gene in tremor behavior of the VF rat. **[Materials and Methods]** Rats homozygous for *Dopey1,* and heterozygous or wild type for *Hcn1* were selected from F2 progeny obtained from an intercross between (VF strain × TRMRC substrain). We observed tremor behavior of these rats and conducted morphological analyses (HE stain and semi-thin sections stained by toluidine blue), and compared the result with that of VF homozygous rats. **[Results and Discussions]** The rats homozygous for *Dopey1*, and heterozygous or wild type for *Hcn1* showed slight tremor especially in the caudal body between 4 and 10 weeks of age, but the tremor was significantly weaker than that of VF homozygous rat. Histopathologically, hypomyelination and periaxonal vacuole formation similar to those found in VF homozygous rat were observed in the CNS white matter. These results showed that HCN1 deficiency, genetic background of the VF rat, is also involved in tremor behavior of the VF myelin mutant rat.

P-08

Evaluation of motor neurons in the spinal cord of mice

○Masaharu Tanaka, Yasuko Ogawa, Kengo Homma, Aki Soejima

Mitsubishi Tanabe Pharma Corporation

[Background] Spinal motor neurons (MNs) are often assessed by counting positive cells in the gray matter anterior horn by ChAT immunostaining. However, ChAT-positive cells may be found in areas other than the anterior horn, and some morphologically evident MNs shows negative. **[Aim]** To investigate a method for evaluating spinal cord MNs in mice. **[Materials and Methods]** The lumbar spinal cords of 7 ~ 21-week-old SOD1 Tg and WT mice were used in this study.Exp. 1) Immunostaining for MN markers SMI -32, Neogenin, HB -9, and Islet -1 were performed. Nissl staining was also performed. Positive and negative cells in the anterior horn and expression outside the anterior horn were compared with ChAT staining.Exp. 2) The number of neurons ≥ 25 μm in size in the anterior horn will be counted using HE-stained specimens. **[Results]** Exp. 1) All proteins evaluated showed positive in the anterior horn, but neurons other than the anterior horn also showed positive. Furthermore, all proteins were negative in some MNs. Nissle staining was positive for MNs, but it was difficult to distinguish between healthy and degenerated neurons. Exp. 2) In WT mice, a certain number of healthy neurons were counted throughout the evaluation period. Healthy neurons in Tg mice decreased from 7 weeks of age. MNs including degenerating neurons were decreased in 21-week-old Tg mice. **[Conclusion]** The present result suggests that counting with HE-stained specimens is recommended for the evaluation of spinal MNs.

P-09＊

Search for developmental neurotoxicity markers focusing on disruption of methylation regulation of neurite development and synaptic plasticity-related genes in rat hippocampus

○Ryota Ojiro[1,2], Yasunori Takahashi[1,2], Risako Yamashita[1], Saori Shimizu[1], Natsuno Maeda[1], Hiromu Okano[1,2], Kazumi Takashima[1,2], Qian Tang[1,2], Syunsuke Ozawa[1,2], Toshinori Yoshida[1,2], Makoto Sibutani[1,2]

[1] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[2] Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology

[Background and Objectives] In rats, developmental exposure to propylthiouracil (PTU), valproic acid, or glycidol causes irreversible effects on hippocampal neurogenesis. We obtained genes showing promoter-region hypermethylation and downregulation of gene expression in the dentate gyrus (DG) by developmental exposure to each compound. In this study, we selected PTU, an antithyroid agent to cause developmental hypothyroidism, and searched for marker molecules of irreversible developmental neurotoxicity by focusing on genes related to neurite outgrowth and synaptic plasticity. **[Methods]** Methylation and transcript levels of the candidate genes were verified on postnatal day (PND) 21 and 77. Candidate molecules were analyzed in the DG by immunohistochemistry (IHC). **[Results]** Six genes were irreversibly downregulated by PTU, and three of them showed hypermethylation. IHC showed an irreversible decrease in SCN1B-positive cells in the granule cell layer of DG in rats after developmental PTU exposure. **[Discussion]** SCN1B is expressed as a beta 1 subunit of voltage-gated sodium channels and regulates a variety of neurodevelopmental processes, including neurite outgrowth and synaptic plasticity. In this study, developmental hypothyroidism caused irreversible reduction of SCN1B-expressing cells as well as transcript level with sustained hypermethylation even after maturation, suggesting that SCN1B is a valuable candidate for evaluation of developmental neurotoxicity.

P-10＊

Detailed investigation of the relationship between artifacts in rat eyes and fixation times in Davidson's fixative and modified Davidson's fixative

○Minto Nakagawa, Saori Matsuo, Shuji Hayashi, Atsuhiko Kato

Translational Research Division, Chugai Pharmaceutical Co., Ltd.

[Background and Aim] The Society of Toxicologic Pathology has recommended that eyes should be fixed in Bouin's solution, Davidson's fixative (DF), or modified Davidson's fluid (mDF) for 18 to 48 hours. However, little is known about the detailed effects of fixation times on artifacts in eyes in DF and mDF. Therefore, we investigated the optimal fixation times in DF and mDF for rat eyes and elucidated the relationship between artifacts and fixation times in detail. **[Materials and Methods]** Eyes from 21 normal male Crl:CD(SD) rats at 15 to 16 weeks of age were fixed in DF or mDF for 2 and 5 hours, 1, 2, 3, 5, and 7 days (3 eyes at each time point), then transferred to 10% NBF for 2 days. HE stained specimens were prepared for histological evaluation. **[Results and Conclusion]** The most appropriate fixation time for rat eyes in DF was 1 day, although 2 to 3 day fixation was also acceptable. However, artifacts such as shattering of the lens and vacuolation of the optic nerve occurred in the optimal fixation times in DF. The most optimal fixation time for mDF was 1 day, although 5 hour and 2 day fixation were also tolerable. In the eyes fixed in mDF for 5 hours to 2 days, some artifacts, such as perinuclear clear spaces in the outer retinal nuclear layer and vacuolation of the photoreceptor segments, were alleviated, but others remained, including artifacts that occurred regardless of the fixation times in many ocular tissues.

P-11＊

Examination about profiling and improvement of detection sensitivity of CNS toxicity by staining and biomarker

○Aya Goto[1)], Rena Ishikawa[1)], Kota Nakajima[1)], Yuki Seki[1)], Kenji Nakano[2)], Etsuko Ohta[1)]

[1)] Global Drug Safety, BA Core Function Unit, Medicine Development Center, Eisai Co., Ltd
[2)] Drug Safety & Animal Care Technology Unit, Tsukuba R&D Supporting Division, Sunplanet Co., Ltd

To find appropriate histopathologic examination for CNS toxicity, we conducted an exploratory study of chemicals with different toxicologic targets, and several staining and measuring biomarkers in addition to hematoxylin and eosin (HE).Cuprizone, MK-801, Trimethyl tin, or Acrylamide were administrated to male SD rats by single or repeated doses. Animals with CNS signs were necropsied and brains were collected after perfusing fixative. Tissues were processed for paraffin-embedded section and stained with HE and immunohistochemistry and special staining, including: anti-GFAP, Iba-1, MBP, phosphorylated and non-phosphorylated neurofilament heavy chain, Neurofilament light chain [NfL], Caspase3, Klüver-Barrera staining, LFB-HE, LFB-NfL, and Fruolo-Jade C. At necropsy, GFAP and NfL in the cerebrospinal fluid (CSF) and serum were measured by ELISA.There were changes in the brain in each compound-treated animal. Some staining showed higher detection sensitivity than HE, or others provide less information despite of a common special staining for CNS. Therefore, it is considered possible to suggest appropriate staining for CNS changes by clinical signs and characteristics of HE. We will introduce histologic and IHC characteristics, and associated biomarker changes of each compounds.It was indicated that combination of appropriate staining and biomarker will increase detection sensitivity and clarify the characteristics of CNS toxicity.

P-12＊

The application for 3D analysis of paraffin section

○Naoki Iwashita[1,2)], Aisa Ozawa[3)], Motoharu Sakaue[3)]

[1)] Bioalchemis, [2)] Laboratory of Veterinary Pharmacology, School of Veterinary Medicine, Azabu University
[3)] Laboratory of Anatomy II, School of Veterinary Medicine, Azabu University

[Background] Recently, the need for 3D analysis of organism tissue is increasing with the spread of confocal laser microscope (CLM) and simple SEM. On the other hand, paraffin sections for histopathology have been applied to analyze using the microscopes, however, the ordinal sections are too thin to efficiently get 3D information. Therefore, we developed a simple method making a paraffin section at 100 μm thickness and investigated its application. **[Aim]** The application of the thick paraffin section for 3D analysis. **[Material and Methods]** Normal C57BL/6 mice and Wistar rats were sacrificed under anesthesia. These brains, nasal tissues, cochlea, kidney and lung, were collected and fixed in 10% formalin. Then the organs were embedded in paraffin. Paraffin sections (sequentially, 5 μm and 100 μm thickness) from each block were made using Solution X (paraffin softening solution developed in the present study). HOPX expression in lung was observed by CLM. Lumen side surfaces of 100 μm-thick specimens were observed with low-vacuum-SEM. **[Results]** The expression of HOPX could be observed up to about 30 μm from tissue surface. In the observation of SEM, Cell structures on cavity sides, cilia of nasal cavity epithelium, foot process of podocyte, alveolar epithelium and hair cells of Corti's organ, in continuous to the HE stained specimens, were three-dimensionally observed up to 3000 magnifications. **[Conclusion]** Thick paraffin section is more useful in histopathological 3D analysis.

P-13＊

Neuroprotective effect of α-glycosyl isoquercitrin on oligodendrocyte toxicity by fetal or neonatal lipopolysaccharide exposure in rats

○Hiromu Okano[1)], Kazumi Takashima[1,2)], Yasunori Takahashi[1,2)], Ryota Ojiro[1,2)], Qian Tang[1,2)], Shunsuke Ozawa[1,2)], Mihoko Koyanagi[3)], Toshinori Yoshida[1,2)], Makoto Shibutani[1,2)]

[1)]Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology
[2)]Cooperative Division of Veterinary Sciences, Graduate School of Agriculture, Tokyo University of Agriculture and Technology

[Background and Objectives] Infection impair brain development. This study investigated the oligodendrocyte (OL)-targeting properties by lipopolysaccharide (LPS) and ameliorating effects of α-glycosyl isoquercitrin (AGIQ), an anti-inflammatory agent. **[Methods]** LPS was injected intraperitoneally to pregnant rats in Study 1 or to infants in Study 2. AGIQ was dietary administered to dams and then offspring subsequently. Parameters on inflammation and OL differentiation were immunohistochemically examined in the corpus callosum. **[Results]** In Study 1, LPS unchanged the inflammatory markers, but decreased NG2+ cells and OLIG2+ cells on PND 6. AGIQ recovered them. On PND 21, decrease of $NG2^+$ cells was sustained by LPS, but AGIQ recovered it and increased $KLOTHO^+$ cells. On PND 77, all changes disappeared. In Study 2, LPS increased $Iba1^+$ cells, $CD68^+$ cells, and $GFAP^+$ cells and AGIQ recovered them on PND 6. On PND 21, increases of $Iba1^+$ cells and $CD68^+$ cells were sustained by LPS, but AGIQ recovered them and also increased $CD163^+$ cells. LPS decreased $OLIG2^+$ cells, but AGIQ recovered it and tended to decrease $KLOTHO^+$ cells. On PND 77, LPS increased only $KLOTHO^+$ cells. **[Discussion]** Fetal or neonatal LPS exposure reversibly injured OL differentiation, probably due to LPS-induced transient neuroinflammation to cause decreased KLOTHO, an activator of OL maturation. AGIQ exposure from the fetal stage ameliorated the disruptive OL differentiation by suppressing LPS-induced immune activation.

P-14＊

Historical data for the histopathology on the spinal cord in juvenile Crl:CD(SD) rats

○Hiroaki Sato[1)], Jun Watanabe[1)], Hirofumi Hatakeyama[1)], Tetsuro Kurotaki[1)], Haruko Koizumi[1)], Tetsuya Kajimura[1)], Shin-ichi Sato[1)], Hijiri Iwata[2)]

[1)]Ina Research Inc., [2)]LunaPath LLC

[Purpose] Since organ development progresses rapidly in juvenile animals, understanding of normal tissue at each age is important in toxicity studies. ICH-S11 guideline describes myelination in the spinal cord as one of the considerations in the development of the rat organ system. In this study, histopathological examinations were conducted on the spinal cord in the cervical, thoracic, and lumbar region using juvenile rats. **[Method]** The cervical, thoracic, and lumbar spinal cords with vertebral bones from Crl:CD(SD) rats at 4, 7 and 14 days of age were routinely processed, fixed in formalin, decalcified using the chelating agent EDTA. From these, hematoxylin and eosin (HE) stained specimens were prepared for histological observations. **[Results]** At 4 days of age, symmetrical structure surrounding the central canal was observed in the cervical, thoracic, and lumbar spinal cords, and white and gray matter were distinguished in these spinal cords. In all spinal cords, glial cells were found in the white matter, neurons and glial cells were found in the gray matter and sensory neurons were distributed in the dorsal horn, and motor neurons in the ventral horn. As developed, the white matter became thicker, and the H-shape became clearer and the cell density decreased in the gray matter. In addition, we are going to report the result of the myelin staining of each parts at each age using luxol fast blue.

P-15＊

Histopathological time course changes of retinal phototoxicity in rats induced by 8-Methoxypsoralen

○Yuka Yoshino, Keigo Ikeda, Sayaka Moriwaki, Kumiyo Okada, Tomoaki Tochitani, Yuta Fujii, Mami Kochi, Izumi Matsumoto, Hiroshi Inada, Kazuhiro Chihara, Izuru Miyawaki

Preclinical Research Unit, Dainippon Sumitomo Pharma Co., Ltd

[Background] Degeneration in retina, especially atrophy in outer nuclear layer is reported to be observed in the positive control group in *in vivo* phototoxicity evaluation. However, the other histopathological finding is rarely reported. Here, we conducted phototoxicity evaluation using SD rats dosed with 8-Methoxypsoralen (8-MOP), which is widely used as positive control in *in vivo* phototoxicity evaluation, and evaluated histopathological time course changes in retina.
[Materials and Methods] Six-week-old SD rats were dosed orally with vehicle or 8-MOP (10 mg/kg) once and exposed ultra violet (about 10 J/cm2) at 1 hour post-dosing. Three, 7 or 10 days after exposure, rats were dissected and histopathological evaluation in eye was conducted.
[Results] In the 8-MOP group, thickening and detachment in retina, degeneration/necrosis and spaces between cells in inner nuclear layer and degeneration in layer of rods and cones were observed in 3 days after exposure and atrophy of outer nuclear layer and layer of rods and cones at center of retina were observed in 7 and 10 days after exposure. Degeneration and vacuolation in corneal epithelium, edema and neutropil infiltration in corneal stroma and degeneration in lens fiber were also observed.
[Conclusion] In this evaluation, we found that degeneration in retina was observed before atrophy in outer nuclear layer was observed and not only outer nuclear layer but inner nuclear layer were affected by 8-MOP and ultra violet.

P-16＊

Laser induced acute ocular hypertensive damage in cynomolgus monkey

○Guo Hui, Du Mu, Qi Wei, Guo Jin, Zhang Rui, Liu Xiangjiang, Guo Hongnian, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc

[Background and Aim] Evaluation of optic axon decline and loss is key in non-human primate models of acute glaucoma that are used to define mechanisms of RGC and axonal degeneration, and potential neuroprotection. **[Materials and methods]** Experiment ocular hypertension was induced unilaterally in OD by laser photocoagulation of trabecular meshwork in 4 male cynomolgus monkeys. Intraocular pressure (IOP) measurement and automated optic nerve axon counting was conducted. The retinal ganglion cells (RGC) were ex vivo labeled with fluorescein conjugated RBPMS and counted automatically. The optic nerves were embedded in resin, and stained with toluidine blue. **[Results]** The IOP in the experimental eyes (OD) was significantly elevated (about 1.5-2.5 times over baseline) 2 weeks post model induction. The average RGC density in the experimental eyes (OD) was significantly reduced. Healthy nerves displayed regularly distributed glial cell somata across the entire cross section. The morphological changes of damaged optic nerve characterized by axonal loss/degeneration, nerve gliosis and scarring. **[Conclusion]** Acute ocular hypertensive damage characterized by progressive and subtle decline and loss of axons, which associates with increasing reactivity of glial cells and scarring of nerve areas depleted of axons. Our findings are consistent with studies in diverse experimental models of glaucoma.

P-17

Immune responses in premetastatic niche of sentinel lymph nodes during metastasis in a mouse mammary cancer model

○Masa-Aki Shibata[1)], Atsushi Takeshita[2)], Chinatsu Shiraoka[1)], Yoshinobu Hirose[2)], Yoichi Kondo[1)]

[1)] Department of Anatomy and Cell Biology, Osaka Medical and Pharmaceutical University
[2)] Department of Pathology, Osaka Medical and Pharmaceutical University

[Background] Cancer cells exploit several mechanisms to evade destruction by the immune system, enabling them to proceed through the metastatic cascade. **[Aim]** This experiment was conducted to analyze T cells-mediated immune responses in sentinel lymph nodes (SLNs) at the premetastatic phase. **[Materials and Methods]** The number of T cell-associated immune cells in SLNs was immunohistochemically analyzed in a metastatic BJMC3879Luc2 model of mouse mammary cancer. Furthermore, metastatic expansion was analyzed in athymic mice transplanted with BJMC3879Luc2 cells. **[Results]** $CD8^+$ T cells were significantly decreased in the premetastatic phase as compared with non-transplanted tumor controls, and CD4/CD8 ratio indicated suppression in anti-tumor activity of $CD8^+$ T cells. $FOXP3^+$ cells were significantly increased in the premetastatic phase. Regulatory T cells ($CD4^+$/$FOXP3^+$) and immunosuppressive macrophages ($CD68^+$/$FOXP3^+$) were immunohistochemically seen in the SLNs. In addition, PD-$L1^+$ metastatic cancer cells in the lymphatic sinus of the SLNs were found. In athymic mice transplanted with BJMC3879Luc2 cells, lymph node metastasis was significantly increased as compared with BALB/c mice bearing tumors. **[Conclusions]** In our metastatic mammary cancer model, T cell-mediated immune response was suppressed in SNLs of the premetastatic phase, and the microenvironment may influence metastatic action of the primary cancer.

P-18＊

A case of epithelioid cell granulomas observed in burkitt lymphoma transplanted mice

○Zhang Rui, Du Mu, Qi Wei, Guo Jin, Guo Hui, Liu Xiangjiang, Li Zheng, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc

[Objective]A minority of burkitt lymphoma patients were complicated with epithelioid cell granulomas. Multiple epithelioid granulomas were observed in the spleen of humanized mice (NPG immunodeficient mice) which transplanted butkitt's lymphoma via subcutaneously injection. **[Methods]** Human CD34 stem cells were transplanted into immunodeficient mice, followed transplantation of BL Raji strain into mice by subcutaneous injection. All animals were necropsied after 12 weeks. All of the organs were preserved in formalin, stained with hematoxylin and eosin (H&E) and immunohistochemical(CD68, CD163). Evaluated with histopathology, and biochemical, lymphocyte distribution and cytokines were examined. **[Result]** Epithelioid cell granulomas were observed in spleen, bone marrow, liver and adrenal gland, with incidence of 7/10 animals in spleen. A large number of multinucleated giant cell (Langhans giant cell) form by the epithelioid cells characterized by eosinophilic and foamy cytoplasm with strong positive of HCD68. Schaumann bodies were seen in some epithelioid cells, which react similarly to sarcoidosis. It is also similar to the epithelioid granuloma observed in tuberculosis without caseous necrosis. Immunohistochemical staining results showed that epithelioid granulomas were positive for human CD68 and negative for mouse CD68. **[Conclusion]** Epithelioid granuloma were originated form human histocytes, which were activated by transplanted Burkitt lymphoma via subcutaneous injection.

P-19＊

Examination for constructing a new *in vivo* antitumor evaluation model for immune checkpoint inhibitors

○Keisuke Hotta, Teruaki Hagiwara, Taiki Sugiyama, Mayumi Kawabe, Hiroto Miyata, Yukinori Mera

DIMS Institute of Medical Science, Inc

[Aim] We reported that lung tumors formed in Tg-rasH2 mice from the 5th week of the experiment for evaluating cancer immunotherapy using a 2 step chemical carcinogenesis model in which ENU and BHT were used. In this study, we investigated the reproducibility of lung tumor formation and the expression of PD-L1, an efficacy predictor in immune checkpoint inhibitors, in tumor cells.

[Methods] Twelve 7-week-old female Tg-rasH2 mice were treated with ENU: 120 mg/kg, ip, once, and one week later with BHT: 400 mg/kg, po, once a week for 5 weeks. At the 5th week of the experiment, lungs were removed, and histopathological specimens were prepared, the relative tumor area and number of tumors were quantified, and the PD-L1 expression was measured immunohistochemically.

[Results] Lung tumors were found in all mice, and bronchoalveolar epithelial adenoma were identified. Tumor tended to locate in the lung fields around the pleura or bronchi. The mean number of tumors in the lungs was 5.50 ± 2.07 per mouse. Although the expression of PD-L1 in tumor cells was confirmed, there was a difference in the level of expression among tumors of the same individual.

[Conclusion] The expression of PD-L1 in this model was confirmed at the 5th week of the experiment, suggesting that this model can be used as an in vivo anti-tumor evaluation model that adequately evaluate the efficacy of cancer immunotherapy as well of novel modalities of anti-cancer drugs in a short of time while preserving the immune system.

P-20＊

Early diagnostic and prognostic role of micro RNAs during 2-amino-3-methylimidazo[4,5-*f*]quinoline- induced liver and colon carcinogenicity in rat

○Elham M. Yousef[1)], Mona M. Hegazi[1)], Doha M. Beltagy [2)], Elsayed I. Salim[1)]

[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Department, Faculty of Science, Damanhour University

[Background] Micro RNAs (*miRNAs*) are a new class of small non-protein-coding, regulatory RNAs in animals and plants. **[Aim]** This study evaluates the expression of *miR-21*, *miR-155*, *miR-122*, *miR-195* and *miR-17-3p* during early stages of rat colorectal (CRC) and hepatic-carcinogenesis induced by 2-amino-3-methylimidazo [4,5-*f*] quinoline (IQ), and after treatment with 5-fluorouracil (5-FU) or Thymoquinone (TQ) solely or in combination. **[Materials and Methods]** Two rat experiments: a short term (10 weeks), and a long term (40 weeks) with similar experimental design. Group1 (G1) control. G2 administered with IQ. G3 administered with IQ then treated with 5-FU. G4 were administered with IQ then treated with TQ until end. G5 were administered with IQ then treated with combination of 5-FU + TQ. **[Results]** In short-term, upregulation of oncogenic *miR-21*, *miR-155* and downregulation of *miR-122*, *miR-195* and *miR-17-3P* occurred at early stages of HCC and CRC. Combination therapy significantly modulated *miRNA* expression and antioxidative, cellular proliferation markers levels with a significant correlation ecoefficiency. In long term, 5-FU/TQ combination therapy resulted in a comprehensive modulation of numbers and distribution of preneoplastic lesions of HCC and CRC over than single treatments. **[Conclusions]** The studied *miRNAs* may have a role in prognosis of CRC and HCC. The synergistic interaction between TQ and 5-FU against carcinogenesis could be focused for cancer therapy.

P-21＊

The extract of *houttuynia cordata hunb*. fermented leaf inhibits carcinogenesis via modulates xenobiotic-metabolizing enzymes and cell proliferation

○Chonikarn Singai[1)], Sirinya Taya[2)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University

[Background] *Houttuynia cordata*, a native plant in Thailand, contains high amounts of bioflavonoids which significantly increase during fermentation. **[Aim]** This study aimed to investigate anticarcinogenicity of ethanolic extract of fermented *H. cordata* leaves (EFHC) in *in vitro* and *in vivo* models. **[Materials and Methods]** The mutagenicity and antimutagenicity of EFHC was analyzed using Ames test and rat liver micronucleus test. Moreover, the xenobiotic-metabolizing enzyme activities in murine hepatoma cells were measured. The anti-carcinogenicity of EFHC was further evaluated in rats treated by DEN and DMH injection. **[Results]** The result showed that EFHC exerted the antimutagenicity against aflatoxin B1 and MeIQ-induced mutagenesis. Moreover, EFHC showed mutagenic properties in *S. typhimurium*. However, it did not induce the formation of micronucleated hepatocytes in rats, suggesting non-clastogenicity. EFHC at 500 mg/kg bw significantly decreased phase I and increased phase II xenobiotic-metabolizing enzyme activities. Moreover, EFHC significantly reduced the number of preneoplastic lesion including glutathione *S*-transferase placental form positive foci in liver and aberrant crypt foci in colon of carcinogen-treated rats. Furthermore, EFHC significantly inhibited the expression of proliferating cell nuclear antigen in liver and colon of rats. **[Conclusion]** These findings indicated that EFHC displayed anticarcinogenic properties in both *in vitro* and *in vivo* models.

P-22＊

Cancer chemopreventive effect of hesperidin and mixed extract of sesame and orange seed on diethylnitrosamine -induced hepatocarcinogenesis in rats

○Napaporn Khuanphram[1)], Sirinya Taya[2)], Prachya Kongtawelert[1)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University

[Background] Plant extracts containing abundant phytochemicals and exposed greater chemopreventive effects than its single pure compounds. Hesperidin, mainly occurred in orange seed, and sesamin, a major active ingredient in sesame, possessed potent anti-cancer activities. **[Aim]** This study aimed to evaluate cancer chemopreventive effect of mixed extract of sesame and orange seed (MSO) compared with hesperidin and sesame extract (SE) on early stages of diethylnitrosamine (DEN)-induced hepatocarcinogenesis in rats. **[Materials and Methods]** Rats were intraperitoneal injection by 100 mg/kg bw of DEN for 3 times once a week. They were fed with low dose or high dose of all test compounds after the last injection for 10 weeks. Glutathione *S*-transferase placental form (GST-P) positive foci in the liver were used as the end-point marker of early phases of hepatocarcinogenesis in rats. **[Results]** MSO showed stronger inhibition of number and size of GST-P positive foci than hesperidin in DEN-initiated rats, while SE did not affect. MSO and hesperidin lessened number of cell proliferation and raised cell apoptosis in the livers. Furthermore, MSO, hesperidin and SE suppressed triglyceride content and fatty acid synthase expression in the liver. **[Conclusion]** Sesamin might promote chemopreventive effect of hesperidin in DEN-initiated hepatocarcinogenesis in rats. Their inhibitory mechanisms might involve the modulation of cellular homeostasis and hepatic lipogenesis during carcinogenesis.

P-23＊

Protective effect of color rice bran protein and hydrolysates on carcinogens induced early stage of liver and colon carcinogenesis in rats

○Aroonrat Pharapirom, Arpamas Chariyakornkul, Warunyoo Phannasorn, Kwanchanok Parseatsook, Rawiwan Wongpoomchai

Department of Biochemistry, Faculty of Medicine, Chiang Mai University

[Background] Plant proteins and hydrolysates are a source of bioactive compounds. Protein hydrolysates obtaining from color rice bran presented antioxidant activities and antimutagenicity. Among rice proteins, glutelin is a promising bran protein. **[Aim]** This study aimed to examine cancer chemopreventive effects of color rice bran hydrolysates in rats. **[Materials and Methods]** Glutelin (Glu) and various hydrolysates including glutelin hydrolysate (GH), all protein hydrolysate (AH), and non-glutelin hydrolysate (NGH) at the dose of 500 mg/kg bw were orally administrated for 10 weeks in diethylnitrosamine- and 1,2-dimethylhydrazine-initiated rats. The endpoint markers were hepatic GST-P positive foci and colonic aberrant crypt foci (ACF). Cell proliferation and apoptotic status in liver and colon were analyzed by immunohistochemistry, while inflammatory expression was detected using Real-time PCR. **[Results]** The treatment of Glu and GH reduced the formation of hepatic GST-P positive foci and ACF and decreased number of PCNA positive cells, a cell proliferation marker, in liver and colon tissues of carcinogens-initiated rats. Moreover, GH increased number of apoptotic hepatocytes and colonocytes and reduced some inflammatory gene expression in liver and colon tissues. However, the administration of AGH and NGH did not show any protective effect on carcinogen-induced preneoplastic lesions. **[Conclusion]** GH might be a source of cancer chemopreventive peptides of color rice bran.

P-24＊

Chemopreventive effects of cooked glutinous purple rice on the early stages of rat hepatocarcinogenesis

○Huina Guo, Arpamas Chariyakornkul, Warunyoo Phannasorn, Rawiwan Wongpoomchai

Department of Biochemistry, Faculty of Medicine, Chiang Mai University

[Background] Cooking process can alter chemical composition in plants. Our previous study showed heat could destroy some beneficial phytochemicals in purple glutinous rice but its biological functions using *in vitro* assays have still remained. **[Aim]** Here, we aimed to evaluate chemopreventive effects of methanol extract of purple glutinous rice (MR) and cooked rice (MC) in diethylnitrosamine (DEN)-induced early stages of hepatocarcinogenesis in rats. **[Materials and Methods]** Fifteen-week administration of MR and MC was started before triple DEN injection for 2 weeks. **[Results]** The results showed that MR and MC did not induce hepatic glutathione *S*-transferase placental form (GST-P) positive foci formation in rat hepatocarcinogenesis. MR and MC at 100 and 500 mg/kg bw significantly reduced the number and size of GST-P. There was no difference in inhibitory activity between MR and MC. In addition, MR and MC inhibited number of PCNA positive hepatocytes but enhanced number of apoptotic positive hepatocytes in DEN-initiated rats. MR and MC decreased iNOS gene expression level by RT-PCR analysis. **[Conclusion]** The heat stable anticarcinogens in purple glutinous rice might prevent the early stage of rat hepatocarcinogenesis through suppression of cell proliferation, enhancement of apoptosis, and decreased of NO production.

P-25＊

Chronic toxicity of calcium disodium EDTA on pregnant rats and fetuses

○Mona E. El-Maghawry, Fouad A. Abou-Zaid, Sabry A. El-Naggar, Elsayed I. Salim

Zoology Department, Faculty of Science, Tanta University

[Background] Calcium disodium ethylene diamine tetra acetic acid ($CaNa_2EDTA$) is regarded as one of the most common food additives. **[Aim]** Here we determine the possible effects of CaNa2EDTA on rats and their offspring upon chronic oral administration taking in consideration embryological, histopathological, biochemical and molecular developmental changes. **[Materials and Methods]** Rats were divided into four groups. Group 1: Control males. Group 2: Males administrated with 0.5 g/kg of $CaNa_2EDTA$ for 3 months. Group 3: Control females. Group 4: Females administrated with 0.5 g/kg CaNa2EDTA for 3 months. **[Results]** treated female rats showed a decrease in body weights, pregnancy percentage and number of pups in treated dams. Remarkable changes were recorded in foetus's livers and kidneys as well as histopathological alterations in liver, kidney and ovary of treated female rats. Moreover, mild deformation in skeletal system of fetuses from dams maternally treated with $CaNa_2EDTA$ including delayed ossification of inter-parietal, squamosal, humerus, radio-ulna, femur and tibia-fibula. Significant decrease in Zinc ion concentration in fetuses' tissues from dams maternally treated with $CaNa_2EDTA$. Down expression of peroxisome proliferator-activated receptor alpha and gamma genes (PPAR- α and PPAR-γ) in fetus's tissues. No changes in hematological parameters except increasing platelets count in treated male rats, increasing in W.B.Cs counts in treated female rats. Significant increase in luteinizing hormone level in treated female rats and superoxide dismutase level in treated male and female rats. **[Conclusions]** $CaNa_2EDTA$ is probably has toxic effects during pregnancy and on offspring.

P-26＊

8-Hydroxydeoxyguanosine levels and histopathological evaluation during placental transfer of zinc oxide nanoparticles in pregnant rats

○Naira M. Al-Fiky, Fouad A. Abou-Zaid, Khalid Y. Abdul-Halim, Elsayed I. Salim

Zoology Department, Faculty of Science, Tanta University

[Background] In recent years, ZnO-NPs are frequently used in several areas of technology as well as going interest in drug delivery applications. **[Aim]** The present study assesses the toxic effect of ZnO-NPs in pregnant rats at day 19th of gestation. Samples of target organs (serum, liver, spleen, fetus and placenta) are used for quantitative determination of 8-OHdG levels of genotoxicity. Trace metal accumulation levels were analyzed by (ICP-OS). Moreover, histopathological and TEM investigations were assessed. **[Materials and Methods]** ZnO-NPs were prepared through the hydrolysis and condensation of zinc acetate dihydrate by potassium hydroxide in alcoholic medium at low temperature, they were spherical at size 20 ± 5 nm. At the 19th day of gestation, female rats were intravenously administered by 3.1 and 7.75 mg/kg/b.wt of ZnO-NPs and sacrificed after 1, 6, 12 and 24 hrs. **[Results]** The two doses recorded significant high levels of 8-OHdG in fetuses and placenta as compared with controls. The blood showed highest accumulation level after one hour interval at the first dose while after 12 hours liver and uterus show high metal levels for the same dose. After 6 hours the second dose ZnO-NPs mainly accumulated in uterus. Prominent pathological changes are recorded in mothers and fetuses. **[Conclusions]** ZnO-NPs are toxic with evidence with genotoxicity in pregnant rats and fetuses. Greater attention needs to be paid to the toxic effects of ZnO-NPs and exposure to ZnO should be reduced.

P-27＊

Tissue distribution, placental transfer and excretion of silver nanoparticles in pregnant rats after a single oral dose

○Ahmed S. Abdel-Latif[2)], Khaled Y. Abdel-Halim[2)], Elsayed I. Salim[1)]

[1)]Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Mammalian & Aquatic Toxicology department, Central Agricultural Pesticides Laboratory (CAPL)

[Background] Silver nanoparticles (AgNPs) are used as antimicrobial coatings in medical devices and in many medical applications. **[Aim]** A quantitative assessment of silver nanoparticles in fluids and some organs of pregnant rats as well as their fetal blood was carried out in this study. **[Materials and Methods]** A single oral dose (1 mg kg^{-1}) of AgNPs with a size range (4-20 nm) was administered to pregnant rats on 19th of gestation. Five groups were euthanized after 10 min, 1, 6, 12 and 24 h as well as the control group. Silver (Ag^{+}) content was measured in Inductive Coupled Plasma Optical Emission Spectroscopy (ICP-OES). **[Results]** In maternal blood, AgNPs were found increased time dependently after 12 and 24 h into 0.135 and 0.224 µg ml^{-1}, but it was slightly high in fetal blood (0.32 and 0.31 µg ml^{-1}) after 10 min and 1 h. In other samples, the data indicated that NPs were rapidly absorbed from the dosing site (gastrointestinal tract) as evidenced by the detection of Ag^{+} in the analyzed samples. On the other hand, the percentages of urine excretion levels per applied dose at all the time points were higher in urine (8.25%) than those of the feces (4.77%) after 24 h. **[Conclusions]** These findings indicate the ability of AgNPs to accumulate in pregnant rats and transfer to their fetus imposing adverse outcomes and male formation. In fact, further investigations may be done on nanomaterials before recommending for human practices.

P-28

28-day repeated oral dose toxicity of nanosized titanium (IV) oxide in F344 rats

○Jun-ichi Akagi, Yasuko Mizuta, Hirotoshi Akane, Takeshi Toyoda, Kumiko Ogawa

Div. Pathol., Natl. Inst. Health Sci.

[Background] Since we have found that the toxicity of nanosized silver particles greatly varies depending on the particle size, we examined the toxicological effect of nanosized titanium (IV) oxide (TiO_2) with a very small crystallite size of 6 nm for repeated oral administration.

[Aim] To determine the effect of repeated oral administration of nanosized TiO_2 with a crystallite size of 6 nm in rats for 28 days.

[M & M] Nanosized anatase TiO_2 with a crystallite size of 6 nm (AMT-100, TAYCA Co., Ltd.) suspended in 0.2% disodium hydrogen phosphate (D_{50}=Ca. 200 nm in solution) was gavaged for 28 days to 6-week old male and female F344/DuCrj rats at doses of 0, 10, 100, and 1000 mg/kg bw/day.

[Results] No mortality was observed in all groups during the treatment period, and no toxicologically significant changes were observed in body weight, general condition, hematology, organ weights, and histopathology. Serum biochemistry showed a significant increase in triglyceride (TG) in the 1000 mg/kg bw/day group of females. ICP-MS analysis revealed trace amounts of titanium in the liver of all groups, with the 1000 mg/kg bw/day group of females showing a little (corresponding to 0.41 ppm of the average daily dose in the last week) but statistically significant increase compared with the control group.

[Conclusion] The significant increase in TG in the 1000 mg/kg bw/day group of females was not associated with other toxicological change. The NOAEL in this study was 1000 mg/kg bw/day.

P-29＊

Safety assessment of red yeast (*sporidiobolus pararoseus*) powder: acute and subchronic toxicity studies in wistar rats

○Sirinya Taya[1)], Charatda Punvittayagul[2)], Thanongsak Chaiyaso[3)], Rawiwan Wongpoomchai[1,4)]

[1)]Functional Food Research Unit, Science and Technology Research Institute, [2)]Research Affairs, Faculty of Veterinary Medicine
[3)]Division of Biotechnology, Faculty of Agro-Industry
[4)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University

[Background] Oleaginous red yeasts were enriched in lipids for biodiesel production, antioxidant bioactive compounds such as carotenoids, and ß-glucan. Recently, there are increasing about lipids and carotenoids production using several types of oleaginous red yeast especially *Sporidiobolus pararoseus*. Our previous study reported about its antigenotoxicity using rat liver micronucleus test. However, there was no any studies on its systemic toxicity. **[Aim]** Thus, the scientific data of its safety were performed using acute oral and sub-chronic oral administration in rats. **[Materials and Methods]** RYP was prepared by spray drying. A single dose of 5,000 mg/kg bw of RYP was tested for acute toxicity while the repeated dose 90-day oral toxicity of 200, 600 and 2,000 mg/kg bw was performed. **[Results]** In the acute toxicity study, RYP did not show any signs of toxicity or mortality during the 14-day observation period. In subchronic toxicity test, no mortality or clinical signs of treatment was observed throughout the experimental period. RYP did not change in hematological and biochemical parameters of both sexes. Some histopathological changes in liver and epididymis were observed in high dose of RYP treatment. **[Conclusion]** Based on these results, the values of LD50 and NOAEL of RYP was estimated to be 5,000 and more than or equal to 2,000 mg/kg/day in rats, respectively.

P-30＊

Acute and subchronic toxicity of isomaltooligosaccharide and its effect on gut microbiota

○Arpamas Chariyakornkul[1)], Charatda Punvittayagul[2)], Sirinya Taya[3)], Atigan Thongtharb[4)], Santad Wichienchot[5)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University
[3)]Functional Food Research Unit, Science and Technology Research Institute, Chiang Mai University
[4)]Department of Companion Animal, Faculty of Veterinary Medicine, Chiang Mai University
[5)]Center of Excellence in Functional Foods and Gastronomy, Faculty of Agro-Industry, Prince of Songkla University

[Background] Isomaltooligosaccharide (IMO) is one of prebiotic substances isolated from rice starch. It is considered as a potential prebiotic ingredient for dairy and medical food. **[Aim]** The present study determined acute and subchronic toxicity of IMO from rice starch. Furthermore, the gut microbiota profiles and short chain fatty acids (SCFAs) contents were investigated. **[Materials and Methods]** An orally single dosage of 5,000 mg/kg bw of IMO was given to female Wistar rats in an acute toxicity model. For subchronic toxicity test, the effect of daily oral administration of IMO at the dosages of 200, 600 and 2000 mg/kg bw for 90 days were evaluated. The blood biochemical and hematological parameters as well as histopathology of internal organs, gut microbial community and SCFAs contents were examined. **[Results]** IMO at a single high dose was safe in rat without any toxicity. The 90 days-treated with IMO did not induce mortality. Although, some haematological and biochemical parameters were different from those of control rats, these values also exist in normal range. Abnormal histopathology of various organs was not prominently observed. Moreover, the 600 mg/kg bw of IMO was modulated beneficial and pathogenic gut microbiota. SCFAs in feces of medium dose treated rats, particularly butyric acid was higher than normal rats. **[Conclusion]** IMO from rice starch was safety for acute and subchronic administration. It might be an effective prebiotic for food supplement.

P-31

Pathological changes of spontaneous tumors in Sprague-Dawley and Wistar rats

○Yanan He, Mu Du, Beibei Wang, Jun Yin, Wenyu Wu, Rui Zhang, Sucai Zhang, Huiming Zhang

JOINN LABORATORIES (Beijing) Inc

[Background and Aim] To investigate the spontaneous neoplastic lesions and their incidences in SD and Wistar rats, and to accumulate background data for carcinogenicity studies. **[Materials and Methods]** Total 411 rats (176 SD and 235 Wistar) were used in this study. The rats were housed routinely and euthanized after 104 weeks. Histopathological examination was undertaken for all animals to evaluate the incidences of spontaneous tumors. **[Results]** The total tumor incidence in SD rats was 55.7% (benign 48.9%, malignant 15.9%). The total tumor incidence in Wistar rats was 59.1% (benign 51.5%, malignant 14.5%). The main benign tumors were pituitary adenoma (23.3% in SD, 12.3% in Wistar), breast fibroadenoma (21.4% in SD, 12.9% in Wistar) and breast adenoma (16.9% in SD, 9.5% in Wistar) in females; testis Leydig cell tumor (14.3% in Wistar) in males. The main malignant tumors were breast carcinoma (10.1% in SD, 3.5% in Wistar) and uterine leiomyosarcoma (2.6% in Wistar) in females; squamous cell carcinoma of skin (2.3% in SD, 0.9% in Wistar); subcutaneous fibrosarcoma (1.1% in SD, 2.1% in Wistar). **[Conclusion]** In this study, the incidence of benign tumors is higher than that of malignant rumors. The benign tumors mainly are pituitary adenoma, breast fibroadenoma and breast adenoma in females, and testis Leydig cell tumor. The malignant tumors mainly are breast carcinoma in females and some soft tissue sarcomas.

P-32＊

Search for the primary site of amyloid deposition in transmissible AA amyloidosis

○Susumu Iwaide, Tomoaki Murakami

Cooperative division of Veterinary Medicine, Tokyo University of Agriculture and Technology

[Purpose] It is known that the pathogenesis of AA amyloidosis is promoted by administering mouse AA amyloid to mice. However, the mechanism of the transmission is not accurately understood. Therefore, AA amyloid was administered to mice by various routes and sites, and the distribution of amyloid deposition was evaluated over time. **[Methods]** To 6-week-old ICR mice, 30 μg of mouse AA fibrils was administered a single dose in intrahepatic, intrasplenic, intrarenal, intragastric, intra-Peyer's patch, intravenous, intraperitoneal or subcutaneous way (n = 9 in each group). At the same time, 10 mg of silver nitrate was subcutaneously administered to those mice. Three animals in each group were necropsied after 4, 7, and 14 days, respectively, and after collecting systemic organs, the degree and distribution of amyloid deposition were histopathologically evaluated. **[Results]** In the liver, spleen and intrarenal administration groups, amyloid deposits were more heavily observed after 4 days of administration than other groups, and the pathological condition spread remarkably to other organs over time. **[Discussion]** It was suggested that exposure to high concentrations of AA amyloid is important for the deposition of AA amyloid in local organs. From this study, it is important that when AA amyloid is transferred to other organs, amyloid is amplified in one of the organs and reaches a certain concentration, rather than being distributed in blood at a low concentration.

P-33

Differences of acute toxicity between polyvinylpyrrolidone coated silver nanospheres and silver nanoplates intraperitoneally administrated in mice.

○Yasuko Mizuta, Young-Man Cho, Jun-ichi Akagi, Tetsuya Ide, Kumiko Ogawa

Division of Pathology, National Institute of Health Sciences

[Aim] We have reported that intraperitoneally administrated citrate coated silver nanospheres (AgNSs) in 10 nm diameter showed acute toxicity in mice but not in 60 and 100 nm diameter. This study aimed to investigate the effects of surface modification and shape in various sizes of AgNS or silver nanoplates (AgNPls). **[Method]** 7-week-old female BALB/c mice were intraperitoneally injected, (Exp 1) PVP coated AgNS (0.2 mg/mouse) in 5, 10, 60 or 100 nm diameter, (Exp 2) PVP coated AgNPl in 30, 50 or 100 nm diameter. Then sacrificed 6 h after treatment. **[Result]** (Exp 1) The following results were obtained in the 5 nm group. Reduced activity and body temperature, increased respiration rate at 3 h. Increased BUN, Cre, IP, LDH and T-Bil, and decreased Cl and glucose. Hepatic congestion, increased cellular component in sinusoid, vacuolation of hepatocyte, gallbladder edema and thymic cortex apoptosis were observed. (Exp 2) No abnormalities in the general condition were observed. Cl was increased in the 100 nm group, and T-cho was decreased in the 30 and 100 nm group, and TG was decreased in the 50 nm group. There was no obvious histological finding in the liver, but vasculitis with neutrophil infiltration around the blood vessels of the mesenterium was observed in all treated groups. **[Conclusion]** The toxicity of silver nanoparticles varied with the size and shape. Similar hepatotoxicity seen in the previous study was found in the PVP coated AgNS group, but with the smaller particle.

P-34＊

Incidence and types of spontaneous tumors in young Sprague-Dawley rats in 4-week toxicity studies

○Hou Minbo, Jianjun Lyu, Yan Jianyan, Cui Tiantian, Qian Zhuang, Wang Xijie, Toko Ohira

Shanghai Innostar Bio-tech Co., Ltd (Innostar)

[Background and Objective] Neoplastic lesions are less reported in young Sprague-Dawley rats in short-term toxicity studies. Incidence and types of spontaneous tumors in young Sprague-Dawley rats in 4-week toxicity studies can be extremely helpful to interpret data from short-term toxicity studies. **[Materials and Methods]** Spontaneous neoplastic lesion data from 76 4-week toxicity studies of Innostar in the past 5 years were collected and a total of 5632 rats were examined microscopically. The age of the animals at necropsy ranged from 12 to 20 weeks. All studies were performed according to Good Laboratory Practice. **[Results and Conclusion]** Spontaneous tumors were diagnosed in 9 animals from both control and treated animals in 9 different studies, including 2 cases (2/2816, 0.071%) of renal adenoma in males; 3 cases (3/2816, 0.107%) of nephroblastoma in females; 1 case (1/2816, 0.036%) of renal carcinoma in male and female respectively; and 2 cases (2/2816, 0.071%) of lymphoma in males. In the treated animals, the above-mentioned lesions were also considered spontaneous because of the low incidence and no dose-response relationship. The survey shows the incidence and type of early spontaneous tumors in young Sprague-Dawley rats (≤ 20 weeks) from studies performed in our facility, and can be used as useful background data for diagnosing spontaneous tumors in young Sprague-Dawley rats in short-term toxicity studies in the future.

P-35

Differentially expressed genes induced by metformin and *d*-limonene as potential effective anticancer agents for HepG2 and MCF-7 cells

○Elsayed I. Salim[1)], Mona M. Alabasy[1)], Doha M. Beltagy[2)], Zihu Guo[3)], Mohamed Shahen[1)]

[1)]Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Department, Faculty of Science, Damanhour University
[3)]College of Life Science, Center of Bioinformatics, Northwest A & F University

[Background] Recently, exploring strategies of biological mechanisms of many anticancer agents is progressing. **[Aim]** We evaluated the utility of metformin, a therapy for type II diabetes, and *d*-limonene, from citrus oils, for possible therapeutic potential either solely or in combination against HepG2 and MCF-7 cancer cells. **[Materials and Methods]** A systems-based analysis was applied for drug-target-pathway network using integrated systems pharmacology approach. This illustrates molecular correlations between metformin and *d*-limonene to identify genes associated with both drugs. **[Results]** DNA fragmentation assay clearly showed apoptosis induction after treatment especially with combination therapy vs. normal cells. mRNA expressions of *Bax* and *P53* were significantly up-regulated while *Bcl-2*, *iNOS* and *Cox-2* genes were significantly down-regulated in all treated groups vs. normal cells. The percentages of late apoptotic cells in HepG2 and MCF-7 cell lines were higher in all treatment groups particularly after combination treatment. The combination index (CI) revealed synergistic effect of both drugs on HepG2 cells (CI=0.12) and MCF-7 cells (CI=0.22). **[Conclusions]** Metformin, *d*-limonene and their combination exerted significant anticancer potential on HepG2 and MCF-7 cells, with synergistic potency via apoptosis induction and modulation of gene expression of target genes.

P-36

New biomarkers of drug-induced liver and heart injury in preclinical studies

○Zhou Fei, Zhao Xixing, Zhou Tiansheng

WuXi AppTec (Suzhou) Co., Ltd

Hepatotoxicity and cardiac toxicity are the major causes for the drug discontinuation. Biomarker changes prior to the histopathology, which makes the biomarker as a forerunner in the toxicity. Traditional biomarkers had been used in toxicological studies for decades, while limitations of sensitivity, specificity and accuracy in clinical translation have been noted. For the reasons above, new biomarkers were discovered. During acute and chronic hepatocellular injury, Cytokeratin-18 (CK18, a type-I intermediate filament protein) and ccCK18 (caspase-cleaved CK18) were considered as the sensitive and clinically translational biomarkers of hepatocellular necrosis and apoptosis, and have received the letters of support from the FDA as well as EMA. Natriuretic peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), have been identified as predictors of drug-induced cardiac injury, such as hypertrophy or necrosis of the cardiomyocyte. In this presentation, we give a brief introduction of the new biomarkers of hepatotoxicity and cardiac toxicity. Combining the new biomarkers with the traditional ones, more accurate toxicity could be identified in the preclinical studies.

P-37＊

Usefulness of TUNEL method for the identification of LNA-modified antisense oligonucleotide

○Hikaru Mitori, Satoru Kajikawa, Miwa Takahashi, Mihoko Ono

Astellas Pharma Inc. Drug Safety Research Labs

[Aim] One of the common histopathologic features associated with antisense oligonucleotide (ASO) is cytoplasmic basophilic granules in the kidney or liver. Basophilic granules are considered to reflect accumulation of ASO. Their staining qualities are mainly basophilic, but they vary in amphophilic and even eosinophilic. There is no simple method other than immunohistochemistry with specially prepared antibody to prove that basophilic granules are definitely accumulation of ASO. As the basic structure of LNA-modified ASO is single-stranded DNA, we investigated the usefulness of TUNEL method to identify the accumulation of LNA-modified ASO **[Materials and Methods]** The LNA-modified ASO was conjugated to the 5′ end of the ASO with a biotin. The ASO at 20 μM was exposed to Neuro2a cells for 24 hours. The cells were stained by FITC-labeled TUNEL method and Alexa647-labeled streptavidin. Furthermore, the formalin-fixed paraffin-embedded kidneys with basophilic granules in proximal tubules were stained by TUNEL method in a single intravenous dose study in ICR mice. **[Results]** Neuro2a cells exposed by biotin conjugated ASO was diffusely positive for TUNEL method, and it was consistent with Alexa647-positive area. In addition, basophilic granules in the mouse kidneys were positive for TUNEL method. **[Conclusion]** It was indicated that LNA-modified ASO was detected by TUNEL method and TUNEL method was useful to identify the accumulation of LNA-modified ASO.

P-38

Introduction for the establishment of reference database of clinical pathology in SD rats and Beagle dogs

○Kong Qingxi[1)], Meilan Jin[2)], Qiu Shuang[3)], Chen Ke[3)], Qiao Junwen[4)]

[1)] Pharmaron, [2)] Laboratory Animal Center, Southwest University, [3)] WestChina-Frontier Pharma Tech Co., Ltd
[4)] Insilico Medicine

[**Background]** Clinical pathology for blood (hematology, clinical chemistry and coagulation) is one of more sensitive indicators to predict drug toxicities, and also the alterations of analysis values might reflect some biological and/or toxicological significances, especially frequently indicative of potential target organs in histopathology. However, due to differences of inter-animal and/or test methods, these parameters of clinical pathology might have some considerable differences among labs, therefore it is necessary to establish its own reference database as historic control in a preclinical center. **[Aim]** To introduce how to establish the range of reference values in clinical pathology for SD rats and Beagle dogs in Pharmaron. **[Materials and Methods]** Our recent three-year clinical pathology values of 370 SD rats (190 males and 180 females) from Vital River Laboratory Animal Technology, and 240 Beagle dogs (120 males and 120 females, respectively) from Marshall Biotechnology, were analyzed. The average age of control SD rats and Beagle dogs are 10 to 12 weeks and 7 to 9 months, respectively. **[Results]** Acquired clinical pathology historic data of SD rat are similar to the background database (Bruce D. Car, 2006, The Laboratory Rat) indicating the reference intervals of clinical pathology in Pharmaron were reliable. **[Conclusion]** Reference database of clinical pathology are feasible in Pharmaron.

P-39

INHAND: International harmonization of nomenclature and diagnostic criteria for lesions - An Update - 2022

○Shim-mo Hayashi[1)], CM Keenan[2)], Bradley A[3)], Goodman DG[4)], Takanori Harada[5)], Herbert R[6)], Hijiri Iwata[7)], Jacobsen M[8)], Kellner R[9)], Mahler B[6)], Meseck E[10)], Nolte T[11)], S Rittinghausen[9)], Vahle J[12)], Katsuhiko Yoshizawa[13)]

[1)]National Institute of Health Sciences, [2)]CM Keenan ToxPath Consulting, [3)]Charles River, [4)]Independent Consultant
[5)]The Institute of Environmental Toxicology, [6)]National Institute of Environmental Health Sciences, [7)]LunaPath LLC
[8)]Astra Zeneca, [9)]Fraunhofer ITEM, [10)]Novartis, [11)]Boehringer Ingelheim, [12)]Eli Lily, [13)]Mukogawa Womens University

The INHAND Proposal in has been operational since 2005. A Global Editorial Steering Committee (GESC) helps coordinate overall objectives of the project. Development of harmonized terminology for each rodent organ system or non-rodent species is the responsibility of the Organ Working Groups or Non-rodent Working Groups respectively, drawing upon experts from North America, Europe and Japan.Great progress has been made with 15 rodent organ systems published in Toxicologic Pathology and Journal of Toxicologic Pathology as supplements and on a web site. A comprehensive review of all rodent systems to standardize terminology common to organ systems was completed and terminology updated in goRENI. Recommendations of the Apoptosis/Necrosis Working Group have been published. There are 5 non-rodent working groups. The mini-pig, dog, non-human primate and rabbit have been published in 2021. The manuscript on fish will be available for review in 2021. A new group has been formed to address terminology in non-rodent ocular toxicity studies. INHAND guides offer terminology, diagnostic criteria, differential diagnoses and guidelines for recording lesions in toxicity and carcinogenicity studies. The guides provide representative photo-micrographs of morphologic changes, information regarding pathogenesis, and key references.

P-40

Challenges and measures for SEND dataset creation of histopathological findings when the dataset is created by multiple organizations

○Takeshi Iidaka[1,6)], Akihiro Ishimoto[1,6)], Shin-ichi Horikawa[2,6)], Konomi Iino[2,6)], Shin-ichi Sato[2,6)], Dai Nakae[3,6)], Hijiri Iwata[4,6)], Takayuki Anzai[5,6)]

[1)]NISSEI BILIS Co., Ltd., [2)]Ina Research Inc., [3)]Tokyo University of Agriculture, [4)]LunaPath Co., Ltd
[5)]Showa University School of Medicine, [6)]G-SEND

Since SEND was implemented by the US FDA, SEND datasets have been created by various organizations. It is not uncommon that the SEND data are created by a different company from the test facility, and this is no exception in dataset creation of text data such as histopathological findings with numerical data. During dataset creation, the base pathological process including neoplastic and non-neoplastic findings is mapped to applicable SEND controlled terminology (CT). However, the same finding can be mapped to different CT due to interpretative difference between pathologists/facilities which may also arise when extended terms, which are those not included in CT, are used. Adjusting these differences by the parties concerned is also an important process in order to finalize the SEND dataset, and how to do so efficiently is a challenge for SEND. In view of this situation, the Global SEND Alliance (G-SEND) in which we participate investigated the issues involved in creating a SEND dataset at a different organization for histopathological findings collected in a study entrusted to a CRO, using the SEND data creation scenario of NISSEI BILIS Co., Ltd. and Ina Research Co., Ltd. as a case study. In this presentation, in addition to the basic flow used and problems that need to be addressed in the case study, we report the results of this investigation on how to efficiently create a SEND dataset for histopathological findings while being aware of overall optimization.

P-41＊

Comparative anatomy and histology of lacrimal gland in rat, rabbit, dog and monkey

○Qiu Shuang[1)], Chen Ke[1)], Hu Chunyan[1)], Wang Haoan[1)], Kong Qingxi[2)]

[1)] WestChina-Frontier PharmaTech, [2)] Pharmaron

[Background] The lacrimal gland is an exocrine gland. It plays such an essential role in secreting tear fluid. Therefore, histopathologic evaluation of lacrimal gland should be perform for some drugs with ocular administration or eye toxicity. **[Aim]** In this article, we attempted to describe the general anatomy and morphology features of lacrimal gland in rats, rabbits, dogs and monkeys. **[Materials and Methods]** Ten animals (five per sex) of each species were euthanized. All the lacrimal glands were macroscopically observed, collected and fixed in 10% NBF followed by HE staining and microscopic examination. **[Results]** By gross inspection, there are two pairs of lacrimal glands in the rats and rabbits. They are extraorbital and intraorbital lacrimal glands in rat, which are the counterparts of the orbital superior gland and inferior gland in the rabbits. In dogs and monkeys there is only one main gland, located at the supraorbital of lacrimal fossa.By microscopic examination, the lacrimal gland is organized according to the tubuloalveolar scheme. The predominant cell type comprising lacrimal gland acini is generally thought to be of the serous variety. However, different number of mucous cells are present within some acini as well in rat, rabbit, and monkey. The lacrimal gland in dog is mainly composed of mucous cells. **[Conclusion]** There are some different anatomical and histological characteristics among laboratory animals, such as rats, rabbits, dogs and monkeys.

P-42

The benefits of SEND-compatible glossaries in histopathology

○Hirofumi Hatakeyama[1)], Shin-ichi Horikawa[1)], Konomi Iino[1)], Shin-ichi Sato[1)], Takayuki Anzai[2,3)], Hijiri Iwata[4)]

[1)] Ina Research Inc., [2)] Showa University School of Medicine, [3)] PDS Pathology Data Systems
[4)] Laboratory of Toxicologic Pathology, LunaPath LLC.

In the evaluation of toxicologic pathology, glossaries/master dictionaries and Common Finding Lists are generally created at individual research facilities and are thought to be based on references such as New Toxicologic Histopathology, the INHAND list of published terms, SEND Controlled Terminology (CT) and the goRENI database. When creating glossaries/lists, an important objective should not be forgotten - the creation of nonclinical datasets for electronic submission (SEND datasets) to the FDA. Having said that, terms necessary for toxicity evaluation should be used as appropriate, even if they are not among those listed. Here, we present a case study demonstrating the efficiency of SEND data creation using a Common Finding List. In principle, when creating a SEND dataset for histopathology, basic findings must be selected from the list of CT, and if they are not in the list, a definition of these findings should be explained within the nSDRG (Nonclinical Study Data Reviewer's Guide). Maintenance of a Common Finding List, including clear indication of whether or not a term is CT, is important to facilitate efficient microscopic examinations and to make it possible to register findings in a unified manner among pathologists. Optimization of glossaries/lists is useful, not only for creating a SEND dataset, but also for unifying findings within a facility.

P-43＊

Evaluation of lung carcinogenicity of single-walled carbon nanotube (SWCNT) compared with MWCNT-7 and MWCNT-N

○Sheema Asraful Nahar[1)], Aya Naiki-Ito[1)], Hiroyuki Kato[1)], Masayuki Komura[1)], Hiroyuki Tsuda[2)], Satoru Takahashi[1)]

[1)] Department of Experimental Pathology and Tumor Biology, Nagoya City University Graduate School of Medical Sciences
[2)] Nanotoxicology Project, Nagoya City University

[Background and aims] Though carbon nanotubes (CNTs) have been fundamental for various developments in our current technology, it may cause lung carcinogenicity. For example, MWCNT-7 and MWCNT-N have already proven as carcinogenic for lung and pleura. In this study, we examined the effect of SWCNT on lung toxicities by comparison with those of MWCNT-7 or MWCNT-N. **[Materials and methods]** 10-weeks old F344 rats were administered 0.5mg MWCNT-7, -N and SWCNT using intratracheal instillation twice a week over 4 weeks period (8 administrations from day 1 to day 30). Animals were autopsied on the 4th week after treatment for histopathological, immunohistochemical and gene expression analysis. **[Results and conclusion]** The lung weight trended to be increased by all CNTs but there was significant difference in MWCNT-N and SWCNT. Immunohistochemical analysis revealed that recruitment of CD68 positive macrophages in pulmonary alveolus was significantly increased in both MWCNT groups as well as the SWCNT group. Ki67, γ-H2AX, TUNEL positive lung alveolar cells were significantly increased by both MWCNTs, but not altered by SWCNT. TEM analysis indicated that MWCNT-7 and N showed fiber-like shape and were phagocyted by alveolar macrophages in pulmonary alveolus. In contrast, SWCNT was not observed, even though degraded macrophages were frequently shown. These results indicated that pulmonary toxicity of SWCNT may be lower than MWCNT-7 and -N, known as carcinogens to the lung.

P-44＊

Balanitoside as a natural adjuvant to gemcitabine in lung cancer experimental model

○Sara S. Aboueisha[1)], Abeer A. Khamis[2)], Elsayed I. Salim[1)]

[1)]Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Division, Chemistry Department. Faculty of Science, Tanta University

[Background] Gemcitabine is utilized as standard malignancy chemotherapy. **[Aim]** Due to the limited use of Gemcitabine for severe side effects, we studied the antitumor impact of balanitoside, a folk medicine, extracted from edible fruits of *Balanites aegyptiaca*, on mice lung carcinogenesis bioassay, either individually or adjuvant with Gemcitabine. **[Materials and Methods]** *Balb c* mice were initiated for lung cancer by urethane/BHT protocol, then treated afterwards with either balanitoside low dose; balanitoside high dose, Gemcitabine, or balanitoside+Gemcitabine in combination, besides a normal control group. **[Results]** Balanitoside when administered alone or in combination with gemcitabine prompted anti-tumor efficacy against lung cancer by reducing tumor incidences (%), multiplicities, and average tumor area sizes. It has decreased the proliferation of tumor cells, induced apoptosis and triggered cell cycle arrest at the G0/G1 level, along with causing a marked reduction in the level of cancer stem cell markers, aldehyde dehydrogenase (ALDH-1) and CD133 (+ve) cell populations. It has also modulated the oxidative stress markers levels in lung tissues. **[Conclusion]** These data demonstrate that balanitoside optimizes the antitumor capability of gemcitabine and could be utilized as a natural adjuvant medication for lung cancer.

P-45＊

Early response biomarkers of inhalation exposure to cigarette smoke in the mouse lung

○Yusaku Nishidoi[1)], Shugo Suzuki[1)], Min Gi[1,2)], Anna Kakehashi[1)], Taisuke Matsue[1)], Hideki Wanibuchi[1)]

[1)] Department of Molecular Pathology, Osaka City University Graduate School of Medicine
[2)] Department of Environmental Risk Assessment, Osaka City University Graduate School of Medicine

[Purpose] Cigarette smoking is known to increase the risk of cancers and chronic obstructive pulmonary disease (COPD). In this study, we evaluated the effects of short-term nose-only inhalation exposure to cigarette smoke in mice. **[Materials and Methods]** Male 10-week-old C57BL/6 mice were exposed to clean air (control) or mainstream cigarette smoke for 1 hour/day, 5 days/week, for 2 or 4 weeks. Twenty-four hours after the final exposure, lungs were extracted and bronchial lavage fluid (BALF) was collected. The right lung was used for histopathological examination, and the left lung was used for gene expression analysis. **[Results]** Cigarette smoke exposure increased inflammatory cells, especially neutrophils, in the BALF, increased inflammatory cell infiltrated foci of lungs. Microarray gene expression analysis indicated that smoke exposure induced inflammatory responses, including leukocyte migration and activation of phagocytes and myeloid cells, as early as two weeks after initiation of exposure. Importantly, chemokine(C-C motif) ligand 17 (CCL17), lipocalin 2 (LCN2), and resistin like alpha (Retnla) were upregulated. **[Conclusion]** CCL17, LCN2, and Rentla, have been reported to be involved in human smokers and tobacco-related diseases (COPD, lung adenocarcinoma), and may serve as useful early markers of adverse effects of exposure to cigarette smoke.

P-46

Histopathological characteristics of pulmonary disease by inhalation of organic dust in rat

○Yumi Umeda

Japan Bioassay Research Center, Japan Organization of Occupational Health and Safety

[Background/Aim] Recently in Japan, five workers at a chemical plant that manufactures resins developed lung diseases such as fibrosis, interstitial pneumonia, emphysema, and pneumothorax after being involved in loading and packing cross-linked water-soluble acrylic acid polymers (CWAAPs) for packaging. Because it is not well known that CWAAPs are affected to the respiratory organ, this study examined its histopathological characteristics. **[Materials/Methods]** F344 rats were exposed to single and repeated CWAAP by systemic inhalation (0-40 mg/m^3, 1 or 5 days/week, 10 or 13 weeks), and lung tissues were collected up to 26 weeks after the first exposure to histopathological analyses. **[Results/Conclusion]** Alveolar collapse with neutrophilic inflammation was observed in the lungs in single inhalation exposure. In repeated exposure, multifocal lesions were observed in the alveolar region after the end of exposure, and consisted of inflammation of the alveolar air space, disruption/accumulation of alveolar macrophages, and hypertrophy/proliferation of the alveolar epithelium. These inflammation in the alveoli progressed to alveolitis with fibrous thickening of the alveolar wall at the 26 weeks. Accumulation of lipoproteinous materials was also observed in the alveolar air space and tended to recover after the recovery period. These results indicated that inhalation exposure of polymer, an organic dust, induces alveolar lesion in rat lungs.

P-47

Anti-tumor efficacy prediction from the mouse lung chemical carcinogenesis model: Validation with combined ICIs and chemotherapy drugs

○Teruaki Hagiwara, Takamasa Numano, Yuko Doi, Norio Imai, Tomomi Hara, Hiroto Miyata, Yukinori Mera

DIMS Institute of Medical Science, Inc.

[Aim] I n our previous study, an ICI (anti-PD-1 antibody) was singly treated in the mouse lung chemical carcinogenesis model where bronchoalveolar adenomas were formed at the 5th week of the experiment, and some case showed the tumor growth inhibition. Therefore, in this study, we examined the anti-tumor efficacy prediction of the model in the combined administration of ICIs with chemotherapeutic drugs that are effective in humans.
[Methods] Sixteen female Tg-rasH2 mice developed lung adenomas through 5 weeks treatment of ENU+BHT, were divided into two groups of IgG2a isotype (200 μg/mouse twice a week) control and the combination of anti-PD-1 antibody (200 μg/mouse twice a week) and gemcitabine (10 mg/kg once a week). All the mice were treated intraperitoneally for 4 weeks after the 5th week of the experiment, and necropsied. Histopathological specimens were prepared according to the usual method, and the anti-tumor effect of drugs was evaluated by measuring relative area of tumor to lung using image analysis.
[Results] There was no change in the general condition of both groups until the autopsy at the 9th week of the experiment, and no difference in body weight was observed. The relative area of lung tumor (mm^2/cm^2) was 3.542 in the combination group as compared to 6.308 in the control group, showing statistically significant inhibition of tumor growth ($p<0.05$).
[Conclusion] This model was suggested useful for improving the predictive power of the anti-tumor effect.

P-48＊

Analysis of ACE2 expression in type2 diabetic rats; SDT and SDT fatty Rats

○Yuri Hatanaka[1)], Katsuhiro Miyajima[1,6)], Kinuko Uno[2)], Marika Tohma[6)], Nguyen Hanh Nhung[1)], Noriko Kemuriyama[1)], Toshihisa Watanabe[3)], Hideki Ito[3)], Masami Shinohara[4)], Tomohiko Sasase[5)], Takeshi Ohta[5)], Dai Nakae[1,6)]

[1)] Department of Nutritional Science and Food Safety, Faculty of Applied Bioscience, Undergraduate School of Tokyo University of Agriculture
[2)] Department of Food and Nutritional Science, Faculty of Applied Bioscience, Graduate School of Tokyo University of Agriculture
[3)] CLEA Japan, Inc. Fuji Breeding Facility, [4)] CLEA Japan Inc. Business Promotion Dept
[5)] Laboratory of Animal Physiology and Functional Anatomy, Graduate School of Agriculture, Kyoto University
[6)] Department of Nutritional Science and Food Safety, Graduate School of Applied Bioscience, Tokyo University of Agriculture

COVID-19, which is currently spreading worldwide, is considered to be more severe in infected patients with obesity and diabetes. ACE2, an enzyme involved in the renin-angiotensin system (RAS), is a functional receptor for SARS-CoV-2, and it is known that the virus enters cytoplasm via ACE2. In this study, we examined the expression of ACE2 and TMPRSS2 in the lung in SDT fatty rats, a model of obesity type 2 diabetes, and SDT rats, a model of non-obesity type 2 diabetes.Male SDT fatty rats aged 20 to 30 weeks. The rats were fed a basal diet (CRF-1, BD) or a Quick Fat (QF) diet with 2% cholesterol (Western diet: WD). Lung and BALF was collected at autopsy for histopathological analysis, gene expression analysis and cytokine assay. In addition, 24-week-old male SDT rats fed the BD or QF were used for the study. SD rats were also examined as a control.Gene expression of ACE2 and TNF-alpha in the lung was increased in SDT fatty rats, and the change was also observed in SDT rats. Furthermore, both gene expressions were further increased by QF feeding in SDT rats. Histopathologically, in the lungs of SDT fatty rats, inflammatory cell infiltration and an increase in ACE2-positive cells in the bronchial epithelium were observed in WD compared to BD, and TMPRSS2 expression was also observed with ACE2-positive cells. These results suggest that both diabetic animals were possible to be an animal model of the severe risk with COVID19.

P-49＊

Bee pollen and its encapsulated nanoproduct loaded with folic acid as antitumor agents against lung cancer cells

○Eman A. Eltonoby[1)], Magdy E. Mahfouz[2)], Nemany A. N. Hanafy[3)], Ezar H. Hamed[1)], Elsayed I Salim[1)]

[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Zoology Department, Faculty of Science, Kafrelsheikh University
[3)]Nanomedicine Division, Institute of Nanoscience and Nanotechnology, Kafrelsheikh University

[Background] Bee pollen (Bp) is an important emerging food product owing to its high concentration of nutrients and bioactive compounds. It comprises at least 200 biologically active substances. Natural products constitute an enormous source for screening potential therapeutic candidates to reverse drug resistance lung cancer, especially non-small cell lung cancer (NSCLC), the leading malignancy worldwide. **[Aim]** This current study evaluates the antitumor efficacy of bee pollen against lung cancer *in vitro.* The study investigates the functional role of alcoholic Bp extract alone and the encapsulation of Bp extract with bovine serum albumin loaded with folic acid targeted to lung cancer. **[Materials and Methods]** Nano encapsulated Bp was fabricated and confirmed by using UV-visible spectrometry, Fourier Transform Infrared (FTIR), Zeta potential, TEM, X-ray differaction. **[Results]** The results of HPLC analysis of Bp encapsulation revealed the presence of different substances such as gallic acid, syringic acid, ferulic acid, naringenin, taxifolin and catechin. The results of MTT assay by using A549 cell lines represented the efficiency of encapsulation of the Bp extract over the pure extract, also results were comparable when administered adjuvant with avastin®, a chemotherapeutic drug against lung cancer. **[Conclusion]** Thus, Bp could be considered a good choice for lung cancer adjuvant therapy.

P-50＊

Morphological changes of murine normal lung-derived organoids after repeated in vitro exposures to acrylamide

○Kento Tanabe[1)], Akihiro Hirata[1)], Yuta Irisawa[1,2)], Toshio Imai[3)], Hiroki Sakai[1)]

[1)]Laboratory of Veterinary Pathology, Gifu University, [2)]ASKA Pharmaceutical Co., Ltd
[3)]Department of Cancer Model Development, National Cancer Center Research Institute

[Introduction] It was reported that tumor-like lesions were induced from murine normal tissue-derived organoids after repeated in vitro exposures to chemical carcinogens, followed by subcutaneous injection into nude mouse subcutis, suggesting its potential applicability in carcinogenicity assessment of chemicals. In this study, we investigated whether there are any morphological changes in mouse normal lung-derived organoids in vitro after repeated exposures to acrylamide (AA). **[Materials and Methods]** Organoids derived from lung tissues of Trp53 heterozygous and wild-type mice were dissociated into single cells by enzymatic treatment. The dissociated cells were seeded on Matrigel, and incubated in culture medium containing 0, 0.28, 1.4 mM AA and S9 mix. After 24 hours of start of the AA treatment, AA-containing medium was removed, and the treated cells were covered with an additional Matrigel and overlaid with the medium for culturing of organoids. AA exposures were repeated three times. After each treatment, the morphology and sizes of the reconstructed organoids were analyzed using a phase-contrast microscope over time. **[Results]** Regardless of the genotypes, the AA-treated organoids showed a dose-dependent decrease in size and various degree of multi-layered changes. Further studies using other chemicals are needed, but the present data might suggest that chemical carcinogens would induce detectable morphological changes in vitro in murine normal tissue-derived organoids.

P-51＊

Influence of vitamin K on bleeding tendency in rats fed high-iron diets

○Yohei Inai, Takeshi Izawa, Sho Fujiwara, Miyuu Tanaka, Mitsuru Kuwamura

Laboratory of Veterinary Pathology, Osaka Prefecture University

[Background] Little is known about the influence of iron overload on the blood coagulation system. We encountered an unexpected bleeding tendency in rats fed a high-iron diet and thus investigated the mechanism of hemorrhagic diathesis. **[Materials and Methods]** Six-week-old F344 male rats were fed a standard (0.02% Fe, 500 μg/kg vitamin K; Cont group) or a high-iron diet (0.8% or 1% Fe, 182 μg/kg vitamin K; Fe group) for 4 to 26 weeks and were then sampled for clinicopathological examinations. In addition, rats were also fed a normal diet (0.02% Fe; Cont+VitK group) or high iron diet (0.8% or 1% Fe; Fe+VitK group) containing 750 μg/kg of vitamin K and were analyzed. **[Results and Discussion]** Systemic hemorrhage was observed in 5/55 (9%) and 3/27 (11%) of 0.8% and 1% Fe group, respectively. In 1% Fe group, prolongation of PT and APTT, decreased activity of vitamin K-dependent coagulation factors II and VII were observed. The content of vitamin K in our iron-modified diets were lower than the recommendation by American Institute of Nutrition. Therefore, it is suggested that feeding of our iron-modified diets induces latent vitamin K insufficiency, and that dietary iron overload combined with the vitamin K insufficiency may increase susceptibility to coagulation abnormalities. Consistent with this hypothesis, no hemorrhage has been observed in 31 and 13 rats of 0.8% or 1% Fe+VitK group, respectively, until 2 to 4 weeks after starting feeding.

P-52＊

Effect of microsampling on toxicity endpoints in a general toxicity study using rats

○Tomoaki Tochitani, Yasuhiro Sasaki, Naoe Nishimura, Yuta Fujii, Takayuki Iwaisako, Naohisa Umeya, Masayo Hashimoto, Hiroshi Inada, Kazuhiro Chihara, Izuru Miyawaki

Preclinical Research Unit. Sumitomo Dainippon Pharma Co., Ltd

[Background] Microsampling (MS) has been increasingly used in toxicity studies reducing animal use for toxicokinetics. However, especially for hematotoxic compounds, potential effects on hematological parameters and the hematopoietic system must be considered. Here, we conducted a rat 2-week study of hematotoxic compounds and evaluated effects of MS on toxicity endpoints.

[Materials and Methods] Six-week-old female SD rats were orally dosed with vehicle, methylene blue (300 mg/kg/day), or azathioprine (12 and 24 mg/kg/day) for 2 weeks. Each treatment group was divided into non-blood sampling (non-MS) and blood sampling (MS) groups. In the MS group, 50 μL/time point of blood was collected from the jugular vein at 7 time points each on Days 1 and 13. The test items included clinical signs, body weight, urinalysis, hematology, blood chemistry, necropsy, organ weight and histopathology.

[Results] In the non-MS methylene blue group, there were low red blood cell count and hematocrit, high total bilirubin, and increased extramedullary hematopoiesis in the spleen. In the azathioprine group, there were low white blood cell counts and a decrease in hematopoietic cells in the bone marrow. The effects of methylene blue and azathioprine were also observed in the MS groups, and there was no obvious difference between the non-MS and MS groups.

[Conclusion] Effects of MS on toxicity endpoints were considered to be small in rat toxicity studies of hematotoxic compounds.

P-53

Toxicity assessment of a recombinant humanized antibody-drug Conjugate (rhADC) in *cynomolgus* monkeys

○Xueyan Pu, Lu Peng

Pathology Department, Jiangsu Tripod Preclinical Research Labortory Co., LTD

[Background] Antibody-drug conjugates (ADCs) are a new type of anticancer therapeutics, which guides highly cytotoxic small molecules directly to cancer cells via specific antibody. RhADC is a new recombinant humanized antibody-drug Conjugate targeting CD33 for acute myelocytic leukemia therapy.
[Aim] To evaluate the toxicity of a rhADC in *Cynomolgus* Monkeys.
[Materials and Methods] Forty *Cynomolgus* Monkeys were randomly divided into vehicle control, 5, 10, and 15 mg/kg rhADC-treated groups with 5 males and 5 females each group. Vehicle and rhADC were intravenously injected into forelimb 6 times with once per week, followed by 6-week recovery.
[Results] There were mild to severe lymphocytopenia in thymic cortex of all rhADC-treated monkeys after 6-time rhADC administration. Additionally, all rhADC-treated monkeys showed minimal to mild atypical mitotic figure in liver, spleen, and hematopoietic cells of sternum. Biochemically, ALT, AST, and ALP were remarkably elevated in 15 mg/kg rhADC-treated monkeys.
[Conclusion] To our knowledge, it is the first report that in *Cynomolgus* Monkey rhADC induced atypical mitotic figure in spleen and hematopoietic cells of sternum. Though these rhADC-induced toxic effects were reversible in monkeys, it should pay attention to potential adverse effects in clinical trial and application because immune suppression is a commonly clinical feature in cancer patients, and the exact differences exist between monkey and human.

P-54＊

Evaluation of diabetes and hypercholesterolemia swine as a model for peripheral DES

○Akiko Sato, Taizou Iwasaki, Yuka Shouji, Ryosuke Kikuchi, Natsuho Ichimura, Hideki Sato

TERUMO CORPORATION

[Purpose] Drug-eluting stents (DES) are known to reduce the incidence of stent restenosis by inhibiting neointimal growth. Although healthy pigs are often used to evaluate the efficacy of coronary DES, there is no suitable animal model for peripheral DES that mimics clinical conditions. As an animal model for peripheral DES, we created a diabetes (DM) and hypercholesterolemia (HC) pig model and evaluated to assess the efficacy of this model. **[Method]** Healthy domestic pigs were treated with STZ to develop DM, and a high-fat diet fed to induce HC. 1-month after a high-fat diet fed, DES and bare metal stents (BMS) were implanted in both lower limb artery. Follow-up (FU) angiography was performed every month after stenting. Pathological evaluation was performed at 1- and 3-months FU using HE, E-HE, and MT staining. Various organs were also pathologically evaluated. **[Results]** At 1-month FU, neointimal growth was observed in BMS artery, while it was rarely observed in DES artery. This trend continued up to 3-months FU. Pathological examination at 1-month FU showed no differences other than neointimal growth, but at 3-months FU, delayed drug-induced healing was observed in DES artery, such as acellur, fibrin deposition, and inflammatory cell infiltration. These changes have been reported in clinical, suggesting that this model is able to reproduce the clinical problems. **[Conclusion]** We created a DMHC pig model and evaluated its efficacy as a DES evaluation model by pathological evaluation.

P-55

The dried leaf extract of *Musa basjoo* induces growth inhibition and changes in protein expression level of cell cycle control molecules in human colon carcinoma cell lines

○Harutoshi Matsumoto, Nahida Sultana, Katsumi Fukamachi, Masumi Suzui

Department of Neuro Toxicology, Graduate School of Medical Sciences and Medical School, Nagoya City University

Musa basjoo (MB) is classified as one of the 50 species belonging to the genus *Musa*. Biological activity and mechanism of action of MB have been poorly understood. In the current study, antiproliferative activity of the dried leaf extract of MB, its effect on the expression level of cell cycle control molecules, and suppressing activity in implanted tumor size caused by MB treatment were investigated using human colon carcinoma cell line. Dried leaf of MB was extracted with acetone or methanol. The extract of MB inhibited the growth of HT29 and HCT116 cell lines. The effect of acetone extract was higher than that of methanol extract. Thin layer chromatography analysis suggested that the extract of MB contains aromatic compounds with a certain number of conjugated double bond and/or antioxidant compounds with a hydroxy group. Flow cytometric analysis demonstrated that MB extract caused an increase in G1 but did not induce subG1. The protein expression levels of cyclinD1, cyclinE, cdk2 and cdk4 decreased, and those of $p21^{CIP1}$, $p27^{KIP1}$ and p53 increased. Changes in expression level of PARP/cleaved PARP were not found. There was a tendency of a decrease in tumor size in a mouse xenograft model. Specific toxicities caused by MB treatment were not seen in main organ sites. Taken together, the extract of MB contains active components that exert growth inhibition of human colon carcinoma cell lines and affect expression levels of cell cycle control molecules.

P-56＊

Riceberry bran oil ameliorates carcinogens-induced liver and colon carcinogenesis through the mechanism of cell apoptosis, anti-inflammation, and gut microbiota

○Warunyoo Phannasorn[1)], Aroonrat Pharaphirom[1)], Parameth Thiennimitr[2)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Department of Microbiology, Faculty of Medicine, Chiang Mai University

[Background] Riceberry bran oil (RBBO) containing high amounts of phytonutrients and phytochemicals exhibited anti-proliferation activity in various cancer cells. However, it lacks of anti-carcinogenicity in animal model. **[Aim]** This study aimed to investigate the effect of RBBO on carcinogens-induced liver and colon carcinogenesis. **[Materials and Methods]** Male rats were fed with 100 mg equivalent to γ-oryzanol/kg of RBBO, 5 days a week for 10 weeks and injected with diethylnitrosamine and 1,2-dimethylhydrazine to initiate liver and colon carcinogenesis, respectively. **[Results]** The administration of RBBO could inhibit the number of preneoplastic lesion including glutathione *S*-transferase placenta form positive foci in liver and aberrant crypt foci in colon of carcinogens-treated rats. These lesions could suppress by RBBO through hepatocytes and colonocytes apoptosis evaluating by TUNEL assay. Moreover, RBBO ameliorated the expression of pro-inflammatory genes including TNF-α, IL-6 and IL-1β in liver and colon of carcinogens-treated rats. Interestingly, the fecal short-chain fatty acids produced by gut microbiota were significantly increased in RBBO administration in carcinogens-induced group. RBBO administration could improve the population of Firmicutes and Bacteroidetes to the normal levels. **[Conclusion]** These findings suggested the novel mechanism of RBBO that promoted the chemopreventive properties.

P-57＊

Vanillic acid attenuates rat hepatocarcinogenesis induced by diethylnitrodamine and 1,2-dimethylhydrazine

○Charatda Punvittayagul[1)], Arpamas Chariyakornkul[2)], Kanokwan Jarukamjorn[3)], Rawiwan Wongpoomchai[2)]

[1)]Research Affairs, Faculty of Veterinary Medicine, Chiang Mai University
[2)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[3)]Research Group for Pharmaceutical Activities of Natural Products using Pharmaceutical Biotechnology, Faculty of Pharmaceutical Sciences, Khon Kaen University

[Background] Vanillic acid (VA) is commonly phenolic acid found in several plants, especially rice. Numerous biological activities of VA have been reported. **[Aim]** Cancer chemopreventive potential of VA in diethylnitrosamine (DEN)- and 1,2-dimethylhydrazine (DMH)-induced liver and colon carcinogenesis in rats was investigated. **[Materials and Methods]** The 0.75 and 75 mg/kg bw of VA were treated rats before and after carcinogens injection. Blood was collected for liver function test. Preneoplastic lesions, hepatic glutathione S-transferase placental form (GST-P) positive foci and colonic aberrant crypt foci (ACF), were examined. Likewise, mechanistic studies involved immunohistochemistry and gene expression were evaluated. **[Results]** VA at the dosage of 75 mg/kg bw presented hepatoprotective effect on carcinogens-induced rats. It diminished the number and areas of GST-P positive foci, while did not influence on ACF. VA shown antiproliferative effect as evidenced by decreased proliferating cell nuclear antigen and cyclin D1 expression. Moreover, it induced apoptosis in VA-treated rat via induction of apoptosis, upregulation of caspase-3 and Bad as well as downregulation of Bcl-2. The detoxification system was markedly increased by enhancing the expression of GSTA-5 and Nrf-2 genes. **[Conclusion]** VA possessed hepatoprotective potency against DEN- and DMH-induced carcinogenesis through reduction of cell proliferation, induction of apoptosis and modulation of detoxification system.

P-58

Myoepithelial cell hypertrophy along with acinar cell abnormality in the parotid gland is associated with salivary gland dysfunction in the AL-induced diabetic rats.

○Yasushi Kodama[1)], Yui Terayama[2)], Tetsuro Matsuura[2)], Miwa Matsuda[3)], Kiyokazu Ozaki[2)]

[1)]Laboratory of Pharmacology and Pathophysiology, Faculty of Pharmaceutical Sciences, Hiroshima International University
[2)]Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University
[3)]Department of Medical Science and Technology, Faculty of Health Sciences, Hiroshima International University

Hyposalivation reportedly occurs in diabetic patients and animals, and many pathological studies have focused mainly on salivary acinar cells. Meanwhile, myoepithelial cells are known to play an important role in salivation. To clarify the relationship between both salivary gland cells and hyposalivation, we performed histopathological and functional analyses on salivary glands in diabetic F344 rats 26 weeks after Alloxan (AL) treatment (AL group) in comparison with nondiabetic rats (C group). Pilocarpine-induced salivary secretion significantly decreased in the AL group, and the relative weight of the parotid gland was significantly increased compared to the C group. Histopathologically, the acinar cells showed lipid accumulation and anisokaryosis in the AL group, and large nuclei were frequently Ki67 positive. The myoepithelial cells with p63-positive nuclei were scattered in the C group, and the scant cytoplasm was positive for CK14 and SMA. By contrast, in the AL group, p63-positive large nuclei were frequently observed, and CK14- and SMA-positive cytoplasmic area were significantly increased compared to the C group. In addition, Ki67-positive myoepithelial cells were also slightly increased compared to the C group. Myoepithelial cell hypertrophy along with acinar cell abnormality in the parotid gland is associated with salivary gland dysfunction in the AL-induced diabetic rats. Myoepithelial cell hypertrophy may be a compensatory response to acinar cell damages.

P-59＊

Palmitoyl piperidineopiperidine induces selective anticancer activity against human colon carcinoma cell lines

○Sultana Nahida, Katsumi Fukamachi, Harutoshi Matsumoto, Masumi Suzui

Department of Neuro Toxicology, Nagoya City University Graduate School of Medical Sciences

We have invented a novel compound, palmitoyl piperidinopiperidine (PPI; Japan Patent no. 5597427), to investigate its selective anticancer activity on colon carcinogenesis. PPI inhibited the growth of the several types of human colon carcinoma cell lines. PPI also exhibited the selective property of growth inhibition. In silico docking analysis demonstrated that PPI binds to the SH2 domain of a transcription factor STAT3 with higher affinity than other conventional inhibitors, and inhibited the transcriptional activity in carcinoma cells. In the chromatin fraction of cells, PPI decreased the expression levels of pSTAT3/STAT3 but increased those of pSTAT3/STAT3 in the cytosolic fraction, suggesting the inhibition of translocation of these molecules. Moreover, PPI altered the expression levels of cell cycle and apoptosis related molecules. PPI exhibited significant dose-dependent inhibition of the angiogenesis of the chick chorioallantoic membrane. In a mouse xenograft model, PPI inhibited the growth of implanted carcinoma cells. Transcriptional inhibition of STAT3 by PPI may be one possible mechanism, where the functional molecules related to apoptosis, angiogenesis and cell cycle progression are affected, and eventually contributed to the growth inhibition.

P-60

Chemopreventive effect of purple rice extract on rat non-alcoholic steatohepatitis and hepatocarcinogenesis

○Aya Naiki-Ito, Hiroyuki Kato, Masayuki Komura, Satoru Takahashi

Department of Experimental Pathology and Tumor Biology, Nagoya City Universi ty Graduate School of Medical Sciences

[Background] Non-alcoholic steatohepatitis (NASH) recognizes a risk factor of cirrhosis and hepatocellular carcinoma. We have previously reported that anthocyanin-rich extract from purple rice (*Oryza sativa* L. *indica*) has suppressive effects on prostate carcinogenesis. In the present study, we investigated the chemopreventive effect of the hexane insoluble fraction (HIF) of purple rice extract on NASH and its-related hepatocarcinogenesis. **[Aim and Methods]** 7 week-old male Tg rats fed a control diet, a high-fat diet (HFD) or HFD with 1%HIF, and intraperitoneal administration of dimethylnitrosamine was started at week 5. After 17 weeks, rats were sacrificed for the histological analysis and the expression analysis of NASH-related inflammatory cytokines and proteins in the liver. **[Results]** Histological findings of NASH such as fat deposition, inflammation, ballooning injury, and bridging fibrosis were observed in the HFD group as compared to the control group, and were significantly suppressed by HIF. As corresponding to the histological changes, mRNA expression of inflammatory cytokines (*Tnfα*, *Il1β*, *Il18*, *Ifnγ*, *Il6*, *Tgfβ*, *Timp1*, *Timp2*, *Col1a1*) and activation of NF-κB and JNK signaling were observed in the HFD group, and significantly inhibited by HIF. The number and area of hepatic precancerous GST-P positive foci tended to be decreased by HIF. **[Conclusion]** Intake of purple rice as a dietary supplement may suppress the progression of NASH through inactivation of NF-κB or JNK.

P-61 *

Carcinogenicity induced by prenatal exposure to diphenylarsinic acid in CD1 mice

○Masaki Fujioka[1)], Min Gi[2)], Shugo Suzuki[1)], Anna Kakehashi[1)], Yuji Oishi[1)], Takashi Yamaguchi[1)], Hideki Wanibuchi[1)]

[1)] Department of molecular pathology, Osaka city university graduate school of medicine
[2)] Department of environmental risk assessment, Osaka city university graduate school of medicine

[Aim] The purpose of this study is to clarify the carcinogenicity and mechanism of the carcinogenesis by prenatal exposure of diphenylarsinic acid (DPAA) in neonatal male mice. **[Materials and Methods]** The animals were 80 male and female 10-week-old CD-1 mice, which were administered DPAA at doses of 0, 6.25, 12.5, and 25 ppm in drinking water for 10 days from the 8th to the 18th day of pregnancy.DPAA was administered to female CD-1 mice at doses of 0, 6.25, 12.5, and 25 ppm for 10 days from 8 to 18 days of gestation, and male newborn mice prepared. The offspring were sacrificed at 84 weeks of age. A complete necropsy was performed on all moribund animals, animals found dead, and mice at the terminal sacrifice. **[Results]** Histopathological analysis showed a significant increase in the liver tumor incidence in the 25 ppm DPAA group compared to the control group. Microarray analysis using 6-week-old offsprings revealed that 168 genes were upregulated by DPAA transplacental exposure, and 23 of these genes were involved in liver carcinogenesis. In addition, genome-wide DNA hypomethylation was observed in the treatment group. **[Conclusion]** The above results revealed that liver tumors were caused by prenatal exposure to DPAA in mice. Furthermore, the mechanism of hepatocarcinogenesis induced by transplacental exposure to DPAA in mice was suggested to involve increased hepatocyte proliferative potential and abnormal DNA methylation in F1 mice from a young age.

P-62

Quantitative Analysis of *in vivo* mutagenicity and carcinogenicity of 1,4-dioxane in rats

○Min Gi[1,2)], Shugo Suzuki[2)], Masaki Fujioka[2)], Anna Kakehashi[2)], Hideki Wanibuchi[2)]

[1)] Department of Environmental Risk Assessment, Osaka City University Graduate School of Medicine
[2)] Department of Molecular Pathology, Osaka City University Graduate School of Medicine

[Background] 1,4-Dioxane is a widely used synthetic industrial chemical and its contamination of drinking water and food is a potential health concern. It induces liver tumors when administered in the drinking water to rats and mice. **[Aim]** To determine the in vivo mutagenicity and the mode of action (MOA) of the hepatocarcinogenicity of 1,4-dioxane. **[Methods]** gpt delta transgenic F344 rats were administered 1,4-dioxane at various doses in the drinking water for 16 weeks. **[Results]** The overall mutation frequency (MF) and A:T to G:C transitions and A:T to T:A transversions in the gpt transgene were significantly increased by administration of 5000 ppm 1,4-dioxane. A:T to T:A transversions were also significantly increased by administration of 1000 ppm 1,4-dioxane. Furthermore, the DNA repair enzyme MGMT was significantly induced at 5000 ppm 1,4-dioxane, implying that extensive genetic damage exceeded the repair capacity of the cells in the liver and consequently led to liver carcinogenesis. **[Conclusion]** These findings demonstrate that 1,4-dioxane is a genotoxic hepatocarcinogen and induces hepatocarcinogenesis through a mutagenic MOA in rats. Because our data indicate that 1,4-dioxane is a genotoxic carcinogen, we also estimated the point of departure of the mutagenicity and carcinogenicity of 1,4-dioxane using the no-observed effect level approach and the Benchmark dose approach to characterize its dose-response relationship at low doses.

P-63

Preventive and therapeutic effects of bear bile powder on the development of hepatocarcinoma in SD rats

○Jin Meilan[1,2], Rui Dong[2], Hong Zexuan[2], Jia Guiyang[2]

[1] China Southwest university Laboratory animal center
[2] Laboratory of Veterinary Pathology, College of Veterinary medicine, Southwest University

In this experiment, to investigate the preventive and therapeutic effects of low-dose BBP pretreatment on the development of hepatocarcinoma in SD rats, the animals were divide into the three groups and all animals of the BBP-treated group were subjected oral administrations of 10 mg/kg BBP for 15 weeks. All animals of the BBP-treated and the DEN+NMOR groups were received an intraperitoneal (i.p.) injection of DEN at a dose of 200 mg/kg body weight at the 13th week. And, the animals of two groups were given drinking water containing 80 ppm NMOR from the 16th week to the 25th week. As a result, in the body and organ weights, it was no significantly difference between the BBP-treated group and the DEN+NMOR group. A decreased tendency in the incidence of hepatocarcinoma was observed in the BBP-treated group. In addition, the Ki67 positive ratio, the umber and area of GST-P positive foci in the BBP-treated group showed a significant decrease or decreasing tendency compared with the DEN+NMOR group. Also, the mRNA expression levels and protein levels of Caspase 3 and 9 in the BBP-treated group showed a significant increase or increasing tendency. On other, the expression level of JWA gene related to DNA repair was also significantly increased in the BBP-treated group. These results may suggest that pretreatment of BBP exerts a certain inhibitory effect on the development of hepatocarcinoma through DNA repair, cell proliferation inhibition and promotion of apoptosis.

P-64 *

Lobe-specific toxicological changes in the liver of rats given a hepatocarcinogen, furan

○Meili Soma[1], Daisuke Hibi[2,3], Shinji Takasu[3], Yuji Ishii[3], Takashi Umemura[1,3]

[1] Graduate School of Animal Health Technology, Yamazaki University of Animal Health Technology
[2] Ono Pharmaceutical Co. Ltd., [3] Division of Pathology, National Institute of Health Science

[Introduction] Furan is the basic skeleton of furan derivatives used as food flavoring agents and induced hepatocellular and intrahepatic biliary tumors in rats. However, the carcinogenic mechanisms remain unknown. Their tumors as well as cholangiofibrosis occurred at the caudate lobe with higher incidences compared with other lobes. In the present study, some toxicological effects induced by furan treatment were examined at each lobe. **[Materials and methods]** 7-week-old male F344 gpt delta rats were given 8 mg/kg/day (5days/week) furan by gavage. Control animals were given a corn oil at the same volume. Histopathological examination, quantitative analysis of GST-P foci and measurement of number of SOX9-positive hepatocytes were performed at caudate, median, left lateral or right lateral lobes. **[Results]** Oval cell proliferation, hepatocyte apoptosis, and subcapsular infiltration of inflammatory cells were observed in the treatment group, but there were no lobe-specificity in their incidences as well as in the appearance of GST-P foci. One cholangiofibrosis was observed at the caudate lobe in the treatment group. Number of SOX9-positive hepatocytes in the treatment group was 10 times higher than that in the control group and there were 2 times between the number at the caudate lobe and at other lobes. **[Discussion]** The present data suggested that the biological significance of SOX9-positive hepatocyte may be a key factor to clarify furan-induced hepatocarcinogenesis.

P-65＊

Formation of cytoplasmic inclusion bodies exhibiting the involvement of chromosome aberrations in hepatocarcinogenesis of methyl carbamate

○Norifumi Takimoto[1,2], Yuji Ishii[1], Tatsuya Mitsumoto[1,3], Moeka Namiki[1], Shinji Takasu[1], Takehiko Nohmi[1], Makoto Shibutani[2], Kumiko Ogawa[1]

[1] Division of Pathology, National Institute of Health Sciences
[2] Laboratory of Veterinary Medicine, Tokyo University of Agriculture and Technology
[3] Faculty of Animal Health Technology, Yamazaki University of Animal Health Technology

[Aim] Methyl carbamate (MC), a reaction product of dimethyl dicarbonate, is a potent hepatocarcinogen in rats. Although the mechanism of MC carcinogenicity remains unclear, it has been reported that MC induced characteristic cytoplasmic inclusion bodies (CIs) in rat hepatocytes. Recently, we found similar CIs in rats treated with acetamide (AA), and suggested the contribution of chromosomal aberrations to AA hepatocarcinogenesis. In this study, we examined the involvement of chromosomal aberrations in MC hepatocarcinogenesis. **[Methods]** Livers of male 6-week-old F344 gpt delta rats orally gavaged with 100, 200, or 400 mg/kg body weight MC for 4 weeks were examined histopathologically. Reporter gene mutation assays in the liver, micronucleus tests in the bone marrow and liver were also performed. **[Results]** Histopathologically, CIs, karyomegaly and increased mitotic figures with atypia of hepatocytes were observed at 400 mg/kg. Although bone marrow micronucleus test showed negative results, large micronuclei were increased in the livers from 200 mg/kg and above. The CIs showed DNA damage and loss or abnormal expression of nuclear membrane-associated proteins. **[Discussion]** Increases in micronuclei and atypical mitotic figures suggested that MC induces chromosomal aberrations in the liver. The CIs displayed similar characteristics to those observed in AA, suggesting that chromosomal rearrangement through micronuclei formation may contribute to hepatocarcinogenesis in MC.

P-66＊

Aristolochic acid I promotes clonal expansion but did not induce hepatocellular carcinoma in adult rats

○Lu Henglei, Tan Rongrong, Xiu Xiaoyu, Zhu Huaisen

Centre for Drug Safety Evaluation and Research (CDSER), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences (CAS)

[Objective] To investigate the association between Aristolochic acid I (AAI) exposure and HCC in adult rats using a sensitive rat liver bioassay with several cofactors. **[Methods]** Conducted a medium-term (8-week) study to investigate whether AAI had any tumor initiating or promoting activity. Then a long-term (52-week) study was conducted to determine whether AAI can directly induce HCC. Formation of glutathione S-transferase placental form positive (GST-P+) foci, accumulation of AA-DNA adducts and histopathology diagnosis was used as the evaluation index. **[Results]** oral administration of single dose of AAI (20, 50 or 100 mg/kg) in combination with partial hepatectomy (PH) to stimulate liver proliferation did not induce typical GST-P+ foci in liver. In the 8-week study, only high dose of AAI (10 mg/kg/day, 5 days a week for 6 weeks) in combination with PH significantly increased the number and area of GST-P+ foci initiated by diethylnitrosamine (DEN) in liver. Similarly, only high dose of AAI (10 mg/kg/day, 5 days a week for 52 weeks) in combination with PH significantly increased the number and area of hepatic GST-P+ foci in the 52-week study. No any nodules or HCC were observed in liver of any AAI-treated groups. Besides, AAI-DNA adducts accumulated liver with a time- and dose-dependent manner. **[Conclusion]** AAI promotes clonal expansion only in the high dose group but did not induce any nodules or HCC in liver of adult rats till their deaths.

P-67 *

Role of Sox9 in the pathogenesis of dietarily induced nonalcoholic steatohepatitis (NASH) in mice

○Sae Nakane[1)], Noriko Kemuriyama[2)], Akari Abe[3)], Hayato Watanabe[1)], Megumi Yuki[4)], Katsuhiro Miyajima[1,2,3)], Takashi Umamura[5,6)], Dai Nakae[1,2,3)]

[1)] 1Dept. Nutr. Sci. Food Safety, Grad. Appl. Bioscience, Tokyo Univ. Agricul
[2)] Department of Nutritional Science and Food Safety, Faculty of Applied Bioscience, Tokyo University of Agriculture
[3)] Department of Nutritional Science and Food Safety, Graduate School of Agriculture, Tokyo University of Agriculture
[4)] Advantec Co.,Ltd. Pathology Department, [5)] Division of Pathology, National Institute of Health Science
[6)] Faculty of Animal Health Technology, Yamazaki University of Animal Health Technology

[Aim] This study aimed to clarify whether Sox9 expression is involved in the progression of NASH. Sox9 expression was sequential analyzed in an animal model of NASH. **[Materials and Methods]** In the experiment, 6-week-old male C57/BL6J mice were fed a basal diet or a choline-defiant, methionine-lowered, L-amino acid-defined, high fat diet (CDAA-HF) (45 kcal fat, 0.1% methionine) for 2, 13, 26, 52 and 63 weeks. Livers were obtained and used for the analysis of Sox9 expression. **[Results]** In the 2 week-CDAA-HF group, there were marked steatosis, slight fibrosis, and expression of Sox9 in the extra-bile duct epithelium. At the end of week 13, fibrosis became prominent, and the Sox9 expression was marked and diffuse. Double staining for α-SMA and Sox9 showed the partial co-expression and the adjacent expression. Sox9 expression was observed in hepatocytes of nodular lesions in the 26-week or longer experiment groups. In hepatocellular adenomas and carcinomas occurred in the 52- and 63-week groups, both Sox9 positive and negative areas were observed. In addition, the high expression of Sox9 was observed in cholangiofibrosis in the 52- and 63-week groups. **[Conclusion]** Sox9 was highly expressed in the periphery of fibrosis, suggesting that Sox9 is involved in the fibrosis of NASH. The expression of Sox9 was also observed in hepatocytes within the nodular lesions, indicating that Sox9 expression may also be involved in NASH-associated hepatocarcinogenesis.

P-68 *

Tumor promoting effect of iron (III) - tannic acid nanoparticles in diethylnitrosamine - induced hepatocarcinogenesis in rats

○Chi Be Hlaing[1)], Arpamas Chariyakornkul[1)], Chalermchai Pilapong[2)], Rawiwan Wongpoomchai[1)]

[1)]Department of Biochemistry, Faculty of Medicine, Chiang Mai University
[2)]Center of Excellence for Molecular Imaging (CEMI), Department of Radiologic Technology, Faculty of Associated Medical Sciences, Chiang Mai University

[Background] Metal-polyphenol nanoparticles gain attention in cancer nanotheranostics in recent years. Ferric-tannic acid nanoparticles (Fe-TA NPs) presented antiproliferative effect via enhanced autophagic cell death and MRI signal in the liver cancer cells. Our previous study suggested it was not genotoxic using Ames test and liver micronucleus test. **[Aim]** This study aimed to investigate the effect of Fe-TA NPs on DEN-induced hepatocarcinogenesis in rats. **[Materials and Methods]** DEN was intraperitoneally injected to male Wistar rats at 100 mg/kg bw once a week for 3 weeks, followed by partial hepatectomy. Then, 0.55, 1.75 and 17.5 mg/kg bw of Fe-TA NPs were injected intraperitoneally once a week for 10 weeks. Immunohistochemical studies of glutathione *S*-transferase placental form (GST-P) positive foci as the endpoint preneoplastic marker, proliferating cell nuclear antigen (PCNA) positive cells and TUNEL assay for apoptotic cells were performed in liver tissues collected 24 hours after last injection. **[Results]** Fe-TA NPs did not induce hepatic preneoplastic lesion in rats but 1.75 mg/kg bw of Fe-TA NPs enhanced both number and area of GST-P positive foci together with increased number of PCNA-positive cells in GST-P positive foci, and decreased apoptotic cells, compared to DEN alone group. It indicated Fe-TA NPs promoted DEN-induced hepatocarcinogenesis. **[Conclusion]** The non-genotoxic Fe-TA NPs would act as non-genotoxic carcinogen and exhibited tumor promoting action.

P-69 *

Pathological analysis of pancreatic lesions induced by Zinc Maltol in rat

○Sakura Fujiwara, Takayasu Moroki, Masaya Hitomi, Makoto Satou, Yui Terayama, Tsuyoshi Yoshikawa

Otsuka Pharmaceutical Co., Ltd. Tokushima Research Institute, Nonclinical Research Center, Department of Drug Safety Research

[Aim] We conducted detailed pathological analysis focusing on pancreatitis-like lesions observed in 4-week repeated oral dose toxicity study of Zinc Maltol in rats. **[Materials & Methods]** Zinc Maltol was orally administered by gavage for 4 weeks to male SD rats at 1000 mg/kg/day. HE and Masson-Trichrome stain, immunohistochemical analysis and transmission electron microscope observation were conducted to pancreas tissue. **[Results]** Acinar atrophy, interstitial fibrosis and infiltration of mononuclear cells were observed in Zinc Maltol dosing animals. As acinar cells decreased, the SOX9 positive duct-like structures were increased. The fibrotic lesion was composed of vimentin positive cells and collagen fibers. Although myofibroblasts positive for α -SMA and desmin were often observed, pancreatic stellate cells positive for GFAP were rarely observed. The most of infiltrated mononuclear cells were positive for Iba-1. Ultrastructurally, the atrophied acini were composed of ductal epithelium and acinar cells without Zymogen granules. **[Conclusion]** It was considered that inflammation might have occurred following acinar injury as acinar atrophy were prominent. The fibrotic lesion might be predominantly comprised of fibroblast and myofibroblast which were not originated from pancreatic stellate cells. Although acinar necrosis and acute pancreatitis induced by zinc ion compounds dosing were reported in rodents, we obtained the different characteristics in current study.

P-70

Comprehensive evaluation of general toxicity, genotoxicity, and carcinogenicity of 3-acetyl-2,5-dimethylfuran using *gpt* delta rats

○Shinji Takasu, Yuji Ishii, Moeka Namiki, Kenji Nakamura, Takehiko Nohmi, Kumiko Ogawa

Division of Pathology, National Institute of Health Sciences

[Introduction] 3-Acetyl-2,5-dimethylfura (ADF), a flavoring agent containing a furan ring, was predicted as an Ames mutagenic compound by QSAR analysis and showed positive results in Ames test. However, there were no toxicological information including *in vivo* genotoxicity and carcinogenicity. In the present study, to determine the general toxicity, genotoxicity and carcinogenicity of ADF, we carried out comprehensive toxicity study using *gpt* delta rats. **[M&M]** Six-week-old male F344 *gpt* delta rats were given 0, 30 and 300 mg/kg of ADF by gavage for 13 weeks to examine the general toxicity. *gpt* assay and GST-P immunohistochemistry were performed in the liver because changes in organ weight, histopathology, and cell proliferation were observed in the liver of rat given ADF. **[Results]** In general toxicity, body weight gain at the 300 mg/kg group and serum triglyceride, total cholesterol, and phospholipid at the 30 and 300 mg/kg group were significantly decreased. Histopathological examination showed that centrilobular hepatocellular hypertrophy, necrosis and respiratory metaplasia of olfactory epithelium were observed at the 300 mg/kg group. *gpt* mutant frequency and number and area of GST-P positive foci were significantly increased at the 300 mg/kg group. **[Conclusion]** Changes in the general toxicity parameters revealed systemic toxicological effects of ADF in rats. The results of *gpt* assay and GST-P immunohistochemistry suggest that ADF is a genotoxic hepatocarcinogen in rats.

P-71

Chronic toxicity and carcinogenicity study of diphenylarsinic acid in C57BL/6J mice

○Takashi Yamaguchi[1)], Min Gi[2)], Masaki Fujioka[1)], Shugo Suzuki[1)], Yuji Oishi[1)], Hideki Wanibuchi[1)]

[1)]Department of Molecular Pathology, Osaka City University Graduate School of Medicine
[2)]Department of Environmental Risk Assessment, Osaka City University Graduate School of Medicine

[Background] Diphenylarsinic acid (DPAA), a neurotoxic organic arsenical, is present in the groundwater and soil in some regions of Japan due to illegal dumping after World War II. The purpose of this study is to evaluate the chronic toxicity and carcinogenicity of DPAA in mice. **[Methods]** DPAA was administered to male and female C57BL6/J mice at concentrations of 0, 6.25, 12.5, and 25 ppm in their drinking water for 52(chronic toxicity study) and 78(carcinogenicity study) weeks. **[Results]** Chronic toxicity study: In the liver, the relative weights were significantly increased in males treated with 25 ppm DPAA, and the absolute weights were significantly decreased in the female 25 ppm DPAA group. The incidences of cholangitis and simple bile duct hyperplasia were significantly increased in the female 25 ppm group compared to the control groups. Proteomics analysis showed overexpression of the CYP2E1 protein in the female 25 ppm group. Carcinogenicity study: no treatment-related significant increases in tumor incidence was found in any organ or tissue of mice administered DPAA. **[Conclusion]** These results suggest that DPAA is toxic to the bile duct epithelium and hepatocytes, and CYP2E1 is involved in DPAA metabolism and toxicity in C57BL6/J mice. The NOAEL of DPAA were estimated to be 12.5 ppm for males and 6.25 ppm for females under the conditions of chronic toxicity study. The carcinogenicity study demonstrated that DPAA is not carcinogenic in male or female C57BL/6J mice.

P-72＊

28-day repeated inhalation toxicity study of 1,2-dichlorobenzene in fischer 344 rats

○Hee-Seon Park, Hye-Yeon Choi, Yong-Soon Kim, Mi-Ju Lee

Pathology Department, Inhalation Toxicity Research Center, Chemical Research Bureau, Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency

[Background] 1,2-Dichlorobenzene is widely used around the world as solvent for various substances and degreasing agent for metals, leather, and paper. It has aroused concern since inhalation of mist or vapor may result in damage to several organs including lung, liver and kidneys. **[Aim]** The quantitative and available data is limited to make toxicity profile of 1,2-dichlorobenzene. Therefore, we performed 28-day repeated inhalation toxicity using F344 rats. **[Materials and Methods]** Each sex of animals was randomly divided to four groups consisting of five rats. 1,2 dichlorobenzene was exposed in whole body chamber at concentration of 0, 50, 150 and 450 ppm 6 hours per day, five times per week for 28 days and followed by organ weight measurement, hematology, serum biochemistry, and histopathologic examination. **[Results]** Body weight was decreased in rats exposed to 1,2-dichlorobenzene. APTT and PT were elongated in rats exposed to 1,2-dichlorobenzene. Total protein, albumin, and ALT concentration were increased in rats exposed to 1,2-dichlorobenzene. Absolute and relative liver weights were increased in rats exposed to 150 and 450 ppm 1,2-dichlorobenzene. Histopathologically, karyomegaly and vacuolation in the liver were noted in rats exposed to 1,2-dichlorobenzene. **[Conclusion]** Taken together, these results suggest that liver was the major target organ of 1,2-dichlorobenzene.

P-73

Study on the pathological features and biomarkers of CCl4 induced non-alcoholic fatty liver disease in rat

○Jin Yi[1)], Jing Li[2)], Lv Aizhen[2)], Li Ming[2)], Jin Zhihu[2,3)]

[1)] Shenzhen Institute for Drug Control, [2)] Sunshine Lake Pharma Co., Ltd, [3)] Shenzhen Jinzhi Techmology Co., Ltd

[Background] Make a rat model of non-alcoholic fatty liver disease induced by subcutaneous injection of carbon tetrachloride (CCl4) that appear different pathological features from intraperitoneal injection or gavage. **[Aim]** To investigate the pathological features and changes of plasma metabolites in CCl4-induced NAFLD rat model, explore the pathogenesis of NAFLD and study the specific biomarkers in the metabolic pathway. **[Materials and Methods]** Male rats were divided into the blank control group, CCl4-induced NAFLD model group, prevention group and treatment group, and last two groups Traditional Chinese medicine Tongluo Quzhuo Fang were administrated. Liver tissues were observed by microscopes,and venous blood was withdrawn in the ninth week to investigated by high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (HPLC-QTOF/MS). **[Results]** It was significant different from other administration route of CCl4 that remarkable fatty changes in liver tissue was remarkable, and linoleic acid and phosphatidylcholine PC(0:0/18:0)showed significant difference ($P<0.05$) between groups. **[Conclusion]** The metabolites linoleic acid and phosphatidylcholine PC(0:0/18:0) may be the potential biomarkers of CCl4-induced NAFLD. The intervention and treatment of traditional Chinese Medicine Tongluo Quzhuo Fang on the NAFLD rat models were effective, which can decrease the liver fat accumulation in NAFLD rats.

P-74

Establishment of mouse orthotopic transplantation tumor models of human hepatoma and comparison of their characteristics

○Jun Yin[1)], Du Mu[3)],Dingsha Lijing[1)], Huiming Zhang[2)], Ruiping She[2)], Conglin Zuo[2)]

[1)] JOINN LABORATORIES (Beijing) Inc., [2)] China Agricultural University College of Veterinary Medicine
[3)] JOINN LABORATORIES (Suzhou) Inc

[Objective] Three human hepatoma cell lines were injected into livers of four mice with different immune function defects to establish orthotopic xenograft models of human hepatoma for comparison. **[Methods]** Human HepG2, HUH-7, and QGY-7703 cell suspensions were injected in BALB/c nude, NOD SCID, NOG and NPG mice liver. Survival time, mortality, liver weight, B-mode ultrasound, and histology were used to analyze and compare the characteristics of liver cancer models in the mice. **[Results]** All experimental animals showed tumor nodule formation in livers. All animals injected with a HepG2 cell suspension into livers died at about 20 days. The survival time of NOG and NPG mice was significantly shorter than that of BALB/c and NOD SCID mice. Experimental groups with injected HUH-7 and QGY-7703 cell suspensions into livers were autopsied at day 92 and 104. The liver volumes of NOG and NPG model mice were increased significantly and formed large tumor masses, whereas BALB/c nude and NOD SCID mice showed only small tumor nodules in livers. The weights of NOG and NPG mouse livers were significantly higher than those of BALB/c nude and NOD SCID mouse livers. **[Conclusion]** Compared with BALB/c nude and NOD SCID mice, hepatoma cells grew more rapidly in the liver of NOG and NPG mice, and the survival time was short, the liver volume was large, and the weight was increased.

P-75＊

Attempt to make a drug-induced liver injury model using humanized mouse

○Sho Fujiwara, Takeshi Izawa, Miyuu Tanaka, Mitsuru Kuwamura

Laboratory of Veterinary Pathology Osaka Prefecture University

[Background & Aim] PXB-mouse has a humanized liver expressing human metabolizing enzymes and is useful for prediction of human pharmacokinetics, but less is known on its susceptibility to hepatotoxicity. Here we investigated hepatic lesions of PXB-mice induced by hepatotoxicants acetaminophen (APAP), carbon tetrachloride (CCl_4), or allyl alcohol (AA). **[Materials & Methods]** Male PXB-mice were intraperitoneally injected with CCl_4 (0.75, 1.25, 2 ml/kg), AA (35, 50, 70 mg/kg), APAP (500 mg/kg) or saline for single or 3 consecutive days, and sampled at 18 or 24 hours post-last injection for blood biochemistry, histopathology, and immunohistochemistry for hepatic zone-specific markers. **[Results]** In the CCl_4 model, serum ALT increased mildly at 1.25 ml/kg dose; focal necrosis of mouse hepatocytes was observed while necrosis of human hepatocytes was absent. The AA and APAP models lacked elevation of hepatic enzymes or necrosis. The human hepatocytes expressed ASS1 in Zone 1, CYP2E1 in Zones 2-3, and glutamine synthetase in Zone 3, suggesting the presence of metabolic zonation relevant to human liver. **[Conclusion]** Liver injury was not evident in the humanized liver even at the obviously-hepatotoxic doses of rodents, suggesting that PXB-mice are less susceptible to hepatotoxicity. Further investigation is in progress to clarify the mechanism, focusing on metabolic enzyme activity, detoxification pathways, and anti-stress responses.

P-76

Influence of diabetes induction on rat NAFLD model

○Takeshi Izawa, Eri Mizuguchi, Jyoji Yamate, Mitsuru Kuwamura

Laboratory of Veterinary Pathology, Osaka Prefecture University

[Background & Aim] Diabetes is reported to progress nonalcoholic fatty liver disease (NAFLD); however, the detailed mechanism is unknown. Here we report the influence of diabetes induction on liver pathology of rat NAFLD model. **[Materials & Methods]** 1) Zucker+WD model: Six-week-old male ZDF-Lepr^{fa}/CrlCrlj rats were fed a normal (ND; 4% fat) or Western diet (WD; 21% fat & 34% fructose diet with sugar water drinking) for 13 weeks. 2) STZ+WD model: Six-week-old male F344/DuCrlCrlj rats were fed a Western diet for 20 weeks; at week 6, rats were intraperitoneally injected with streptozotocin (20 mg/kg) for 3 days. **[Results]** 1) Zucker+WD group had an increased serum total cholesterol, decreased triglyceride, and increased hepatic microvesicular steatosis with increased transaminases, compared with Zucker+ND group. 2) STZ+WD groups with hyperglycemia had an increased serum triglyceride, decreased insulin, and increased hepatic Zone-3 macrovesicular steatosis, compared with WD group. Increase in serum transaminases and hepatic inflammation was minimal in both groups. **[Conclusion]** Feeding of WD to Zucker rats promotes hepatic microvesicular steatosis and hepatocellular injury based on hypercholesteremia; the Zucker+WD model can be used for study on fatty liver-induced fibrosis. STZ treatment with WD feeding promotes hepatic macrovesicular steatosis based on hypertriglyceridemia; further induction of oxidative stress and inflammation is required to induce steatohepatitis in the STZ+WD model.

P-77＊

Participation of CD44 in hepatic fibrosis of non-alcoholic steatohepatitis in rats

○Kinuko Uno[1)], Katsuhiro Miyajima[2,3)], Marika Toma[3)], Noriko Kemuriyama[2)], Dai Nakae[2,3)]

[1)] Dept. Food and Nutri. Sci., Fac. Agricul., Graduate School of Tokyo Univ. Agricul
[2)] Dept.Nutri. Sci. Food Safety, Fac. Applied Bioscience, Undergraduate School of Tokyo Univ. of Agricul
[3)] Dept. Nutri. Sci. Food Safety, Fac. Applied Bioscience, Graduate School of Tokyo Univ. Agricul

The prevalence of Non-alcoholic steatohepatitis (NASH) is increasing among the patients of metabolic syndrome. The curative drugs are required all over the world. CD44 was reported contribution to hepatic inflammation in NASH. Major ligand of the CD44 was hyaluronic acid which one of the extracellular matrixes. It seems to be a main factor in controlling the hepatic lesion. In this study, the contribution of CD44 in hepatic fibrosis was analyzed in NASH model. Male, 6 weeks of age, Fischer 344 (F344) rats were fed choline-deficient, methionine-lowered amino acid diet (CDAA diet) for two to 26 weeks. At autopsy, blood and liver were collected. The CDAA diet was induced hepatic injury as indicated by increasing blood AST and ALT activities, enhancement of hepatic gene expressions in TNF α and MCP-1. In histopathology, CDAA diet was induced fatty change in hepatocytes, accumulation of macrophage and fibrosis. CDAA diet augmented hepatic CD44 expression, CD44 positive cells were increased accordingly progress of hepatic fibrosis. Intrahepatic bile ducts were increased with progressed of hepatic lesion. Positive reaction of CD44 was exhibited in the part of bile ductal epithelium. Hyaluronic acid binding protein (HABP) was seen consistent with CD44-positive bile ducts, suggesting that CD44-positive bile ducts were associated with hepatic fibrosis. Therefore, the contribution of CD44 to NASH was suggested not only in hepatic inflammation but also in fibrosis.

P-78＊

Investigation of the usefulness of liver-type fatty acid binding protein (L-FABP) as a biomarker for early stage of nonalcoholic fatty liver disease (NAFLD)

○Marika Tohma[1)], Katsuhiro Miyajima[1,2)], Keiichi Ohata[3)], Kinuko Uno[4)], Ayaka Horiuchi[2)], Noriko Kemuriyama[2)], Dai Nakae[1,2)]

[1)] Department of Nutritional Science and Food Safety, Graduate School of Applied Biosciences, Tokyo University of Agriculture
[2)] Department of Nutritional Science and Food Safety, Faculty of Applied Biosciences, Tokyo University of Agriculture
[3)] L-FABP Business Department, CMIC Holdings Co., Ltd
[4)] Department of Food and Nutrition Science, Graduate School of Agriculture, Tokyo University of Agriculture

The mechanism leading to the onset and progression of nonalcoholic fatty liver disease (NAFLD) remains unclear, and no curative treatment has been established. It is necessary to establish accurate biomarkers that contribute to diagnosis from the early stage of NAFLD. L-FABP has already been reported to be useful as a biomarker for NASH. However, the information as a biomarker from early phase of NAFLD is limited. The purpose of this study is to investigate the role of L-FABP as an early phase of biomarker for NAFLD, the liver lesions were compared induced by the choline-deficient methionine reduced amino acid (CDAA) diet or a high fat diet (HFD). Sixteen-week-old male hL-FABP Tg mice were fed with CDAA or HFD for 1, 3, or 7 days, respectively. After each feeding period, the mice were dissected for histopathological observation of the liver, blood biochemical examination, and measurement of hL-FABP concentration by ELISA. A control group was fed a standard diet (SD) for 7 days. Blood levels of hL-FABP were highest after 1 day of feeding with CDAA and HFD. Histopathological observation showed that on day 1, diffuse fatty changes of hepatocyte in CDAA or focal change in marginal zone in HFD. The area of fatty change became wider over time on 3 or 7-days feeding. The concentration of hL-FABP was detected at an earlier stage than the increase in blood AST and ALT activities, indicating that they should be useful as a biomarker in the early stages of NAFLD.

P-79＊

Involvement of glucagon in pathophysiology of type 2 diabetic animal model

○Kouhei Mandai[1)], Katsuhiro Miyajima[1,2,3)], Kana Watanabe[1)], Kana Isizuka[1)], Kinuko Uno[4)], Noriko Kemuriyama[2)], Masami Shinohara[5)], Tomohiko Sasase[5)], Toshihisa Watanabe[6)], Hideki Ito[6)], Masami Shinohara[7)], Takeshi Ohta[5,8)], Dai Nakae[1,2,4)]

[1)] Department of Nutritional Science and Food Safety, Faculty of Applied Bioscience, Graduate School of Tokyo University of Agriculture
[2)] Department of Nutritional Science and Food Safety, Faculty of Applied Bioscience, Tokyo University of Agriculture
[3)] Department of Nutritional Science and Food Safety, Graduate School of Agriculture, Tokyo University of Agriculture
[4)] Department of Food and Nutrition Science, Graduate School of Agriculture, Tokyo University
[5)] Tokyo Animal & Diet Dept. CLEA Japan, Inc., [6)] CLEA Japan, Inc. Fuji Breeding Facility, [7)] CLEA Japan Inc. Business Promotion Dept
[8)] Laboratory of Animal Physiology and Functional Anatomy, Graduate School of Agriculture, Kyoto University

[Background] Type 2 diabetes is a major health problem and patients is in hyperglycemic condition with insulin resistance, and it has also been suggested that hyperglucagonemia is associated with the progression of diabetes. To investigate the involvement of glucagon in the condition of diabetes in type 2 diabetic animals.

[Materials and Method] Male five-week-old SDT fatty rats (SDTf), an obese type 2 diabetes model, were fed CE-2 (BD: basal diet) or Quick Fat (QF: high fat diet) ad libitum for 21 or 23 weeks. After feeding period, rats were dissected and collected the blood and organs to analysis. Male SD rats (SD) were set as a control group.

[Results] A tendency of increase in BW was shown in both strains fed QF and the BW in SDTf was lower than SD. Blood glucose level were higher in SDTf than SD. Insulin level in SDTf was lower than SD. A tendency to increase of TG and TC was showed in both strains fed QF. In histopathological analysis of the islet, irregular and atrophy, increased glucagon positive cells and decreased insulin positive cells were observed in SDTf. In gene expression analysis in the liver, up-regulation in gluconeogenesis related genes and PGC-1 α, which expression is increased in response to glucagon, were noted in SDTf, and glucose metabolism related genes in SDTf was lower than SD.

[Discussion] It was suggested that up-regulation of gluconeogenesis due to enhanced action of glucagon might be associated with progress of diabetic condition.

P-80

LRG-1 is a promising blood marker for pancreas cancer

○Katsumi Fukamachi[1)], Nahida Sultana[1)], Harutoshi Matsumoto[1)], Hiroyuki Tsuda[2)], Masumi Suzui[1)]

[1)] Nagoya City University Graduate School of Medical Sciences, [2)] Nagoya City University

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal types of cancer, with a mortality rate closely approaching the incidence rate. The survival rate of pancreas cancer patients can increase with early detection. Many approaches have been taken to identify new biomarkers of pancreatic cancer. Since animal models can be sampled under controlled conditions, better standardization is possible compared to heterogeneous human studies. Transgenic rats with conditional activation of oncogenic RAS in pancreatic tissue develop PDAC that closely resembles the biological and histopathological features of human pancreas cancer. In this study, we found that Leucine-rich α 2-glycoprotein-1 (LRG-1) was overexpressed in rat PDAC compared to normal pancreas tissue of the control rats. Serum levels of LRG-1 were also significantly higher in rats bearing PDAC than in controls. Importantly, chronic pancreatitis in male Wistar Bonn/Kobori rats, which is a widely accepted as a model of chronic pancreatitis, did not cause serum levels of LRG-1 to become elevated. These results suggest that serum LRG-1 may be a candidate biomarker for non-invasive diagnosis of PDAC. Our findings indicate that the rat models of pancreas cancer used in the present study provide a useful strategy to identify candidate markers applicable to human cancer.

P-81 *

Precision-cut liver slice (PCLS) as a model for evaluation of hepatotoxicity

○Yoshitaka Katoh, Naofumi Takahashi, Chinatsu Fujiwara, Shinya Miyazaki, Tsuyoshi Ito, Aya Koyama, Atsushi Shiga, Ryoichi Ohtsuka, Makio Takeda, Takanori Harada

The Institute of Environmental Toxicology

[Background] The advantages of PCLS include high reproducibility of *in vivo* cellular environment, availability for histopathology, and contribution to the 3Rs principle including reduction and replacement. Thus, we attempted to establish an evaluation method with PCLS for toxic response to [1] chemicals and [2] its modification by CAR-siRNA (CsR).
[Materials/Methods] Rat liver slice sections were prepared using a Krumdieck slicer and incubated at 95% O_2/5% CO_2 for up to 72h with [1] Phenobarbital (PB, 100μM), Acetaminophen (APAP, 2.5mM), or Lipopolysaccharide (LPS, 100μg/mL) and [2] PB + CsR. These samples were analyzed molecular pathologically.
[Results] [1] In the PB group, hepatocellular hypertrophy was not observed, while *Cyp2b1* expression was markedly increased. In the APAP group, hydropic degeneration was seen along with PCNA-positive hepatocytes. In the LPS group, AST, ALT, and LDH significantly increased and hepatocellular necrosis and oval cell proliferation were observed. [2] In the PB + CsR group, *Car* expression was knocked down by 70% and *Cyp2b1* expression was suppressed to 5% compared to the PB group. Immunostaining with anti-CYP2B1 antibody showed centrilobular localization of CYP2B1 in the PB group and a reduced positivity rate in the PB + CsR group.
[Conclusion] PCLS is a useful model to reproduce *in vivo* responses and capture histological changes that are difficult to detect with conventional *in vitro* systems such as hepatocyte primary culture.

P-82 *

Deep learning-based Image analysis algorithm for classification and quantification of multiple histopathological lesions of the rat liver

○Taishi Shimazaki[1)], Kyotaka Muta[1)], Naohito Yamada[1)], Yuzo Yasui[1)], Deshpande Ameya[2)], Hajra Anindya[2)], Thomas Tijo[2)], Toshiyuki Shoda[1)]

[1)] Yokohama Research Center, Central Pharmaceutical Research Institute, Japan T obacco Inc., [2)] AIRA Matrix Private Limited

[Introduction] Recently, AI-based image analysis has been intensively investigated in the field of healthcare diagnostics. The development and implementation of this technology is still in progress for preclinical safety assessment studies in the pharmaceutical industry. In this study, we present an AI-based solution for application in preclinical toxicology studies. **[Materials and Methods]** We trained an algorithm to learn and quantify multiple typical histopathological findings in whole slide images (WSIs) of the livers of young SD rats by using a U-Net-based deep learning network. The trained algorithms were validated using 255 liver WSIs to detect, classify and quantify 7 types of histopathological finding (vacuolation, bile duct hyperplasia, single-cell necrosis, etc.) in the liver. **[Results]** The algorithms showed consistently nice performance for the detection of abnormal areas. The results of the quantitative analysis and the classification of the diagnosis based on the threshold values between "no findings" and "abnormal findings" correlated well with the histopathological diagnoses by the pathologists. **[Conclusion]** This study suggests that Deep Learning-based algorithms can detect, classify and quantify multiple findings simultaneously on a WSI of rat liver. The algorithms could be a useful supportive tool for histopathological evaluation, especially for the primary screening of early screening rat toxicity studies when the speed for go or no-go decision is critical.

P-83

Quantification of hepatic fibrosis in Sprague-Dawley rats using deep learning instance segmentation focused on H&E staining whole slide level

○Ji-Hee Hwang[1)], Hyun-Ji Kim[1,2)], Heejin Park[1)], Byoung-Seok Lee[1)], Hwa-Young Son[2)], Yong-Bum Kim[3)], Sang-Yeop Jun[4)], Jong-Hyun Park[4)], Jaeku Lee[4)], Jae-Woo Cho[1)]

[1)]Toxicologic Pathology Research Group, Toxicology Mechanism Research Divison, Department of Advanced Toxicology Research, Korea Institute of Toxicology
[2)]College of Veterinary Medicine, Chungnam National University
[3)]Department of Advanced Toxicology Research, Korea Institute of Toxicology
[4)]Research & Development team, LAC Inc

[Background] The exponential development in artificial intelligence since the advent of deep learning has affected clinical and non-clinical studies attempting the application of the technology to pathological diagnosis.
[Aim] We applied 'Mask R-CNN', one of the image segmentation algorithms, to test whether the deep learning technique can be applied to detect the toxicologic pathology lesion, hepatic fibrosis.
[Materials and Methods] Hepatic fibrosis in SD rats was induced by NDMA, and H&E stained Whole slide image(WSI)s were used for data preparation. Total 2,011 cropped images were collected from 51 WSIs, and hepatic fibrosis was annotated using VGG 2.0.1.0. Training and detection of hepatic fibrosis via Mask R-CNN were performed by Tensorflow 2.1.0, powered by an NVIDIA 2080 Ti GPU. The trained model validation at the WSI level was conducted by comparing the model predictions in 18 WSIs at 20X and 10X magnifications with ground truth annotations and board-certified pathologists.
[Results] 95% of model accuracy was observed from the test process using tile images. The validation at the WSI level showed a high correlation between ground truth annotation and model prediction (R2 = 0.9660). Furthermore, the predictions at 20X showed a good correlation with the average fibrosis rank by pathologists (R2 = 0.8887).
[Conclusion] We confirmed the possibility of quantification and automatic diagnosis of hepatic fibrosis of SD rats in H&E stained WSIs using a deep learning algorithm.

P-84＊

Role of DPYD expression in pancreatic cancer and the mechanism of its suppression

○Hiroyuki Kato, Aya Naiki-Ito, Masayuki Komura, Satoru Takahashi

Department of Experimental Pathology and Tumor Biology Nagoya City University Graduate School of Medical Sciences

[Background] We have reported that Luteolin (Lut), a flavonoid, suppresses pancreatic carcinogenesis via suppression of dipyrimidine dehydrogenase (DPYD). Although DPYD is known to be an enzyme that degrades 5-FU, its contribution to pancreatic cancer is unclear. In this study, we investigated the difference in sensitivity to 5-FU in pancreatic cancer cells depending on DPYD expression, its contribution to cancer progression, the regulatory mechanism of DPYD, and the structure of Lut that is important for DPYD inhibition. **[Methods and Results]** We transfected DPYD or LacZ genes into low DPYD pancreatic cancer cell lines (AsPC1, 8988T). The proliferation was significantly higher, and the susceptibility of 5-FU was significantly lower in DPYD-transfected cell than that in LacZ-transfected cell. For the regulation of DPYD, miR-494 was identified as common miRNA between upregulated miRNAs by Lut treatment and miRNAs that can bind to DPYD. As for the Lut structure, 19 kinds of Lut analogues including flavonoids were examined the inhibitory effect on DPYD expressions. Quercetin and one substance that maintain the 3',5'-OH structure of flavone inhibited DPYD expression. **[Conclusion]** The expression of DPYD decreases the sensitivity to 5-FU and promotes the proliferation and may be regulated by miR-494. We found that it was important to maintain at least the 3' and 5' -OH of the flavone to suppress DPYD.

P-85

Relationship between urinary bladder carcinogenicity and urinary metabolites of occupational urinary bladder cancer-related aromatic amines

○Shugo Suzuki, Min Gi, Masaki Fujioka, Anna Kakehashi, Hideki Wanibuchi

Dept. Mol. Pathol. Osaka City Univ. Grad. Sch. Med.

[Aim] The occupational exposure to aromatic amines is one of the most important risk factors for urinary bladder cancer. Recently, occupational bladder cancer occurred in a plant using aromatic amines in Fukui Prefecture. In this study, we evaluated the carcinogenic effects of four aromatic amines that were used at the plant, and analyzed the relationship with urinary metabolites. **[Materials and Methods]** Six-week-old rats were treated with 0.6% anilinium chloride (ANL), 0.3% p-toluidine hydrochloride (PT), 1.5% acetoaceto-o-toluidide (AAOT) or o-toluidine(OTD) for 4 weeks. Fresh urine samples were collected at the fourth week of treatment and urinary aromatic amines and metabolites were determined by liquid chromatography-mass spectrometry (LC-MS/MS). Rats were sacrificed and urinary bladder was removed. Histological, immunohistochemical and TUNEL analyses were performed. **[Results]** Incidences of simple hyperplasia and cell proliferation were induced by AAOT and OTD treatments in the bladder urothelium, but not by ANL or PT treatment. There was no difference in TUNEL positivity among the groups. In the AAOT and OTD groups, OTD was the most abundant substance in the urine, and its metabolites were also present. In contrast, in the ANL and PT groups, the respective administered substances and metabolites were identified. **[Conclusion]** In AAOT and OTD groups, OTD and its metabolites could be important for induction of cell proliferation on rat bladder urothelium.

P-86

Effects of repeated oral administration of *o*-toluidine and *o*-anisidine metabolites on the rat urinary bladder

○Takeshi Toyoda[1)], Takuma Kobayashi[2)], Noriyuki Miyoshi[2)], Kohei Matsushita[1)], Hirotoshi Akane[1)], Tomomi Morikawa[1)], Kumiko Ogawa[1)]

[1)] Division of Pathology, National Institute of Health Sciences
[2)] Laboratory of Biochemistry, University of Shizuoka

Although *o*-toluidine (*o*-Tol) and *o*-anisidine (*o*-Ans) are known as aromatic amines with bladder carcinogenicity, the specific metabolites involved in carcinogenesis are still unclear. We examined the effects of head-to-tail dimers of *o*-Tol (MMBD) and *o*-Ans (MxMxBD) on the rat urinary bladder. Six-week-old male F344 rats were administered MMBD, MxMxBD, *o*-Tol, and *o*-Ans at a dose of 100 mg/kg/day for 28 days. The 400 mg/kg *o*-Tol and 600 mg/kg/day *o*-Ans groups were also set as high-dose groups for comparison. Histopathology and immunohistochemistry for γ-H2AX and bladder stem cell markers (KRT14, ALDH1A1, and CD44) were performed. The high-dose *o*-Tol and *o*-Ans groups induced bladder lesions such as hyperplasia of urothelium, whereas the low-dose and MMBD/MxMxBD groups showed no obvious lesions, except mononuclear cell infiltration in the 100 mg/kg *o*-Tol group. Although γ-H2AX formation was significantly increased by *o*-Tol and *o*-Ans treatment, remained at the same level in the MMBD and MxMxBD groups as in the control group. Notably, immunostaining for bladder stem cell markers showed increased expression of ALDH1A1 in the bladder urothelium of the MMBD and MxMxBD groups as well as in the *o*-Tol and *o*-Ans groups, suggesting that these metabolites might be associated with the bladder carcinogenesis of *o*-Tol and *o*-Ans. Higher doses of MMBD and MxMxBD were considered necessary to induce bladder lesions and increase γ-H2AX formation by oral administration.

P-87＊

The potential effect of Thymoquinone and *Nigella sativa* crude oil extract on experimental urinary bladder cancer model

○Areeg M. Khalifa, Elsayed I. Salim

Department of Zoology, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University

[Background] *Nigella sativa* oil and its main constitute Thymoquinone are both known for being effective on a broad spectrum of the biological pathways in living organisms. **[Aim]** The present study aimed to investigate the effect of both *Nigella sativa* and Thymoquinone on the urothelial lesions induced by *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) in male Wistar rats. **[Materials and Methods]** A six-week-old male Wistar rats were divided into four groups: The 1st group received no treatment as -ve control, the 2nd was treated with 0.05% BBN and 5% Sodium ascorbate as +ve control. The 3rd was treated the same as the 2nd group then was post treated with 200 mg/kg/b.wt. *Nigella sativa* by inter-gastric luminal gavage (i.g.) respectively until the end. The 4th also was the same as the 2nd group but was post treated with 10 mg/kg/b.wt. Thymoquinone by inter-peritoneal (i.p.) also until the end after 32 weeks. **[Results]** *Nigella sativa* and Thymoquinone treatments inhibited the incidence and multiplicities of bladder tumours. The immunohistochemical proliferating cell nuclear antigen labeling index (PCNA LI %) was significantly inhibited in bladder tissues and tumours by both treatments. While, Nigella sativa treatment has caused *p53* gene down regulation as compared with control. Furthermore, the results of blood biochemical analysis revealed that *Nigella sativa* ameliorate lipid, liver and kidney functions. **[Conclusion]** In conclusion, *Nigella sativa* has a sufficient therapeutic effect against bladder carcinogenesis through their free radical scavenging, inhibition of cellular proliferation and modulation of anticancer genetic pathways.

P-88＊

Analysis of cardiovascular lesions associated with acyclovir crystal-induced nephropathy

○Junichi Sugiyama, Hideki Tanaka, Shota Yoshida, Shohei Kanie, Kazuhiko Besshi

Toxicology Laboratory, Taiho Pharmaceutical Co., Ltd.

[Background] Crystal-induced nephropathy (CN) with acyclovir is characterized mainly by deposited drug crystals in the distal tubules, urinary stagnation, and interstitial disorders. In this study, we found unreported cardiovascular lesions in rats with acyclovir-induced CN. **[Materials and Methods]** Acyclovir was administered to 6 week-old SD rats at 250 mg/kg (i.v., 1 mL/min) once a day at a volume of 10 mL/kg for up to 3 days. **[Results]** Some alterations associated with CN were observed grossly or histopathologically. Accumulation of substances in the distal tubules and collecting tubules that show polarization under polarized light were also observed histopathologically. There were no histopathological changes in the bones and parathyroid glands. In addition to typical CN pathological findings, significant increases in creatinine, urea nitrogen, and inorganic phosphorus were detected on the blood chemistry. Conversely, blood calcium tended to be decreased. Animals with particularly high inorganic phosphorus levels presented cardiovascular irregularities and perivascular inflammation. Marked cardiovascular calcification was observed in a dead animal. **[Conclusion]** The cardiovascular lesion observed in this study was ectopic calcification associated with hyperphosphatemia, suggesting that it was induced from an early stage of renal dysfunction.

P-89

Potential of CD44 as a biomarker capable of predicting chronicity of drug-induced kidney injury

○Kohei Matsushita, Takeshi Toyoda, Hirotoshi Akane, Tomomi Morikawa, Kumiko Ogawa

Division of Pathology, National Institute of Health Sciences

[Aim] Maladaptive repair of renal tubule after acute kidney injury leads to chronic kidney disease. We have shown CD44 expression in renal tubules in maladaptive repair using several rat models. Here, we examined the potential of boy fluid diagnosis using CD44 to predict chronicity of drug-induced kidney injury (DIKI).
[Methods] Six-week-old male SD rats were intraperitoneally injected 0, 2 and 6 mg/kg of cisplatin and necropsied at 1, 3, 5, 7, 10, 14, and 28 days after injection. Kidneys were histopathologically examined. Serum CD44 level was measured by ELISA at day 5, 7, and 28.
[Results] From day 1 to 5, there were degeneration/necrosis of renal tubules in 2 and 6 mg/kg groups. In 2 mg/kg group, kidneys were repaired from day 5 to 28. In 6 mg/kg group, dilated tubules were detected after day 5, and there was fibrosis with dilated/atrophic tubules after day 10. CD44 was expressed in dilated/atrophic tubules in 6 mg/kg group. Serum CD44 level was significantly increased in 6 mg/kg group at day 5, 7, and 28. There was positive correlation between serum CD44 level and the number of CD44-positive renal tubules in the kidney.
[Discussion] CD44 expressed in dilated/atrophic tubules in maladaptive repair, which may affect serum CD44 level. In 6 mg/kg, serum CD44 level was increased prior to fibrosis, suggesting potential of CD44 as a biomarker to predict chronicity of DIKI. The results of pathway analysis by microarray related to function of CD44 will be presented in the meeting.

P-90 ＊

Effect of high sucrose/high fat diet on the kidneys in obese type 2 diabetes model SDT fatty rats

○Kana Watanabe[1)], Katsuhiro Miyajima[1,2)], Kouhei Mandai[1)], Keita Sekiguti[2)], Kinuko Uno[3)], Noriko Kemuriyama[2)], Tomohiko Sasase[6)], Toshihisa Watanabe[4)], Hideki Ito[4)], Masami Shinohara[5)], Dai Nakae[1,2)], Takeshi Ohta[6)]

[1)] Dept. Nutri. Sci. Food Safety, Fac. Applied Bioscience, Graduate School of Tokyo Univ. Agricul
[2)] Dept.Nutri. Sci. Food Safety, Fac. Applied Bioscience, Undergraduate School of Tokyo Univ. of Agricul
[3)] Dept. Food and Nutri. Sci., Fac. Agricul., Graduate School of Tokyo Univ. Agricul
[4)] CLEA Japan, Inc. Fuji Breeding Facility, [5)] CLEA Japan Inc. Business Promotion Dept
[6)] Laboratory of Animal Physiology and Functional Anatomy, Graduate School of Agriculture, Kyoto University

Diabetic nephropathy is a major complications of diabetes mellitus, and when the pathological condition progress, dialysis is required and a decline in QOL of patients is predicted. In this study, the possibility of a new animal model as a diabetic kidney disease (DKD) was analyzed in SDT fatty rats with obese type 2 diabetes by feeding a high sucrose/high fat diet (Quick Fat: QF).Four-week-old SDT fatty rats in males were fed standard diets (CE-2) or QF (CLEA Japan, Inc) ad libitum. During the feeding period, body weights, food intake and blood glucose levels were measured. At 27 weeks of age, animals were necropsied, and organ weights were measured, and blood and kidney were sampled. Blood biochemistry, histopathological observation in kidneys and gene expression analysis were conducted using the collected materials. The group of SD rats was set as the control group.In CE-2 group in SDT fatty rats, mild to moderate histopathological findings were observed as follows; enlargement and atrophy of glomerulus, formation of urinary cast, inflammatory cell infiltration, moderate dilation, regeneration and Armani-Ebstein lesions in tubules. In the QF group in SDT fatty rats, these lesions were enhanced. In addition, fatty droplets in the proximal tubule and an increase of ED-1 positive cells in interstitial areas were observed in QF group.From these results, QF feeding exacerbates renal lesions in SDT fat rats and it might be served as a new DKD model.

P-91 *

Application of urinary liver-type fatty acid-binding protein (L-FABP) on the mice DIC (disseminated intravascular coagulation) models in COVID-19 study

○Nguyen Hanh Nhung[1)], Katsuhiro Miyajima[1,2)], Keiichi Ohata[3)], Yuka Kawaguchi[1)], Yuri Hatanaka[1)], Ayaka Horiuchi[1)], Kinuko Uno[4)], Marika Tohma[2)], Karin Arai[1)], Teppei Uechi[1)], Noriko Kemuriyama[1)], Dai Nakae[1,2)]

[1)]Dept.Nutri. Sci. Food Safety, Fac. Applied Bioscience, Undergraduate School of Tokyo Univ. of Agricul
[2)]Dept.Nutri. Sci. Food Safety, Fac. Applied Bioscience, Undergraduate School of Tokyo Univ. of Agricul
[3)]Dept. Nutri. Sci. Food Safety, Fac. Applied Bioscience, Graduate School of Tokyo Univ. Agricul
[4)]L-FABP Business Department, CMIC Holdings Co., Ltd
[5)]Dept. Food and Nutri. Sci., Fac. Agricul., Graduate School of Tokyo Univ. Agricul

The increase of serious cases of COVID-19 has brought the medical system to nearly its breaking point, which urges the demand of developing an effective biomarker for diagnosing patients with high risk of getting severe. Taking it into consideration, we used 12-13 week-old male human L-FABP gene induced Tg-mice to reproduce COVID-19-associated thrombosis, then studied the relation between urinary L-FABP and histopathological changes in kidney. The results revealed that concentration of urinary L-FABP significantly correlated with histopathological findings in histone administration tests. LPS and histone administration caused the increase in urinary L-FABP at the time of observation. In the groups with underlying disease, the concentration of urinary L-FABP further increased after being administered with histone, compared to the control group. In histopathology, LPS administration caused inflammatory cell infiltration and histone administration caused urinary casts. Urinary casts are also observed in the groups with underlying disease in different levels, which showed the impact of each factor on DIC models. Overall, we suggest that urinary L-FABP could be used as a potential biomarker reflecting hemodynamic change. This research is hoped to contribute to develop treatments and prevention methods for COVID-19.

P-92 *

Karnovsky's fixative prevents artifacts appearing as vacuolation derived from tissue processing in kidneys treated with antisense oligonucleotide

○Hironobu Nishina, Satomi Nishikawa, Akane Kashimura, Mao Mizukawa, Tetsuya Sakairi

Safety Research Laboratories, Mitsubishi Tanabe Pharma Corporation

[Background] In kidneys treated with antisense oligonucleotides (ASOs), vacuoles, in addition to basophilic granules, are often observed in the proximal tubules. Some reports have described that these vacuoles are likely to be a secondary phenomenon resulting from the extraction of ASOs during tissue processing. To prove that the vacuoles are secondary changes, we compared renal morphology after fixation with Karnovsky's fixative or 4% paraformaldehyde phosphate buffer (PFA) with that of 10% neutral-buffered formaldehyde solution (NBF). **[Materials and methods]** 4-week-old female Sprague-Dawley rats, intravenously treated four times with 50 mg/kg locked nucleic acid containing ASOs for 1 or 2 weeks, were examined. **[Results]** Vacuoles and basophilic granules in the proximal tubules were observed in the kidneys fixed with NBF. Immunohistochemically, the majority of the vacuolated epithelia were negative for KIM-1. In kidneys subjected to Karnovsky's fixation, vacuoles were not observed, although basophilic granules were observed. In kidneys subjected to PFA fixation, vacuoles and basophilic granules were observed, similar to those in samples subjected to NBF fixation. **[Conclusion]** The possibility of overestimation of vacuolation due to artifacts during tissue processing when using conventional NBF fixation was suggested. Karnovsky's fixative is considered a useful alternative for distinguishing artificial vacuoles from true nephrotoxicity.

P-93

Pathological study for chronic progressive nephropathy in rats

○Beibei Wang, Mu Du, Yanan He, Jun Yin, Wenyu Wu, Rui Zhang, Sucai Zhang, Huiming Zhang

JOINN LABORATORIES (Beijing) Inc.

[Background and Aim] To observe the incidence and characteristics of chronic progressive nephropathy (CPN) in rats in 104 weeks of continuous feeding, and to accumulate valuable data for the study of rats CPN. **[Materials and Methods]** 4 weeks of age 60 imported SD rats, 120 domestic SD rats and 120 domestic Wistar rats were given feeding import food and domestic food. In the same feeding conditions, the animals were taken for euthanasia after feeding for 104 weeks. Kidney was collected for conventional slide and staining. The incidence and pathological lesion were analyzed in different strains, different gender and different food feeding for CPN. Results The total incidence of CPN is 31.87%, of which male rat is 48.54% and female rat is 15.12%. The CPN incidence in Wistar rats is higher than that of SD rats. The CPN incidence in domestic food feeding rats is higher than that of imported food feeding rats; Glomerular basement membrane and mesangial hyperplasia with segmental sclerosis are first mover lesions of CPN, nevertheless degeneration and regeneration of renal tubular epithelium with renal interstitial fibrosis are secondary changes. **[Conclusion]** There is a higher incidence of CPN in rat, and there are differences for gender and fodder in incidence. The change in Glomerulus came first, which leading to secondary tubule change.

P-94

Detection of glomerulosclerosis using Halo AI in a mouse model of anti-glomerular basement membrane glomerulonephritis

○Atsuko Murai[1)], Saori Matsuo[1)], Shoko Usami[2)], Natsuko Hada[2)], Masakazu Kanamori[2)], Masaki Yamazaki[1)], Shinichi Onishi[1)], Atsuhiko Kato[1)]

[1)] Translational Research Division, Non-clinical Safety Assessment Dept., Chugai Pharmaceutical Co., Ltd.
[2)] Research Division, Discovery Pharmacology Dept., Chugai Pharmaceutical Co., Ltd.

[Background and Aim] Anti-glomerular basement membrane nephritis mice model (anti-GBM mice) which induced by anti-GBM antibody develops glomerulosclerosis and crescent formation. Halo AI, an image analysis platform added AI, is used for training and analyzing of pathological images. We detected glomerulosclerosis in anti-GBM mice by Halo AI. **[Materials and Methods]** Seven-weeks-old female C57BL/6JJcl mice were pre-sensitized by subcutaneously injection with sheep IgG. After five days pre-sensitization, nephrotoxic serum (NTS) containing anti-GBM antibody was injected intravenously for 3 days. Kidneys were collected 14 days after the first NTS injection. A classifier (DenseNet AI V2 (Plugin)) of Halo AI was used to create the glomerular classification model by training of annotated sclerotic and non-sclerotic glomeruli in some mice and then was applied for all mice. **[Results]** Under histopathological analysis, glomerulosclerosis was found in 18.5% of total glomeruli on average using PAM staining. By Halo AI, glomerulosclerosis including segmental sclerosis was detected in 20.4% of total glomeruli by PAM staining, whereases only 8.9% was detected by PAS staining. In some cases, two glomeruli were counted as one glomerulus by Halo AI. **[Discussion]** Glomerulosclerosis was appropriately detected by Halo AI using PAM staining. The detection could be influenced by staining type. We are going to show some tips for glomerular detection in the meeting.

P-95

Anticarcinogenic effect of chitosan oligosaccharide supplementation on breast cancer in a rat model.

○Masahiro Yoshioka[1)], Momoka Chatani[2)], Rio Matama[3)], Mayu Miyoshi[3)], Yuichi Kinoshita[4)], Yoshiharu Okamoto[5)], Katsuhiko Yoshizawa[2,3)]

[1)] Department of Nutrition, School of Nutritional Science, Koshien University
[2)] Graduate School of Human Environmental Sciences, Mukogawa Women's University
[3)] Department of Innovative Food Sciences, School of Food Sciences and Nutrition, Mukogawa Women's University
[4)] Wakayama Medical University Hospital, [5)] Joint Department of Veterinary Medicine, Faculty of Agriculture, Tottori University

[Background] Chitosan oligosaccharide (COS) is a functional food which possess many bioactivities including anticancer activity. Previously, we reported that oral administration of COS suppressed breast cancer in rat model. However, the mechanism of its inhibitory effect is not yet understood.
[Aim] In order to uncover the mechanism of the inhibitory effect through which COS suppresses breast cancer, animal and in vitro experiment were carried out.
[Materials and Methods] 1. SD rats aged 6 weeks were divided into 4 groups(CTR, COS, MNU, MNU+COS). At 7 weeks, animals received a single 50 mg/kg intraperitoneal dose of MNU or saline. After 4 weeks, 1%COS was fed for 3 weeks, followed by 2%COS for 2 weeks, and 4%COS for 2 weeks. Test subjects were then euthanized at 18 weeks. Inguinal breast tissues and breast tumors were then collected and evaluated histopathologically.
2. MCF-7 cells were plated at an initial cell concentration of 1×10^3 cells per well of a 96-well plate for 24h and treated with COS for 120h. After 120h, the cell growth rate was measured.
[Results] Unlike our previous study, the oral administration of COS after MNU treatment did not cause significant variations on the number of tumor occurrences between MNU alone and MNU+COS groups. Histological differences in tumors were not observed. Furthermore, the suppression of breast cancer cells by COS was not observed.
[Conclusion] These results support that COS suppresses breast cancer by inhibiting the tumor initiation.

P-96＊

Identification of fusion genes in radiation-induced rat mammary carcinomas using RNA sequencing

○Hikaru Watanabe[1,2)], Kazuhiro Daino[1)], Atsuko Ishikawa[1)], Tatsuhiko Imaoka[1,2)], Mayumi Nishimura[1)], Masaru Takabatake[1,2)], Kazumasa Inoue[2)], Masahiro Fukushi[3)], Shizuko Kakinuma[1)]

[1)] Dept. Radiat. Effects Res., NIRS, QST, [2)] Dept. Radiol. Sci., Grad. Sch. Human Health Sci., Tokyo Metropolitan Univ.
[3)] Dept. Radiol. Tech., Tsukuba International Univ.

[Aim] The mammary gland is one of the most susceptible organs to radiation carcinogenesis, but the genetic abnormalities involved therein still remain unclear. Since most of the fusion genes are generated by chromosomal rearrangements such as translocation and inversion, in this study, we aimed to identify fusion genes in rat mammary carcinomas induced by γ-rays using RNA sequencing.
[Methods] RNA sequencing was performed using total RNAs extracted from 6 mammary carcinomas of female Sprague-Dawley rats irradiated with 4 Gy of γ-rays at 7 weeks of age. To discover the fusion transcripts, the RNA sequencing data were analyzed by the STAR-Fusion software. The expression of fusion transcripts was confirmed by RT-PCR and Sanger sequencing.
[Results] In 3 of the 6 mammary carcinomas, 3 candidate fusion genes containing kinase domains were identified based on functional annotations of transcripts fused in frame. The fusion transcripts were not detected in matched normal mammary gland tissues. By adding 3 more carcinoma samples, we detected 2 fusion transcripts each in different carcinoma and the remaining 1 fusion transcript in 2 of 9 carcinomas. Furthermore, those fusion transcripts were not detected in 9 mammary carcinomas developed in the non-irradiated group. We are currently investigating downstream targets of the fusion transcripts by immunohistochemical analysis.
[Conclusion] These results suggest the existence of fusion genes induced by ionizing radiation in mammary cancer.

P-97

Effects of testosterone on rat placental development

○Satoshi Furukawa[1)], Naho Tsuji[1)], Sego Hayashi[1)], Yusuke Kuroda[1)], Masayuki Kimura[1)], Chisato Hayakawa[1)], Kazuya Takeuchi[1)], Akihiko Sugiyama[2)]

[1)] Biological Research Laboratories, Nissan Chemical Corporation, [2)] Faculty of Veterinary Medicine, Okayama University of Science

We investigated the morphological effects of testosterone on placental development in a rat model of polycystic ovarian syndrome. Testosterone propionate (TP), which was subcutaneously administered to pregnant rats with 5 mg/animal from gestation day (GD) 14 to GD 18, induced a maternal weight reduction without mortality or clinical signs from GD 19 onwards. A decrease in fetal and placental weight, an increase in intrauterine growth retardation (IUGR) rates, and histological changes in the placenta were observed on GD 21 but not on GD15 or 17. Histopathologically, on GD 21, the trophoblastic septa were thickened by an increased trophoblasts and the maternal sinusoids were narrowed in the labyrinth zone, resulting in a small placenta. Additionally, the placental weight, thickness, number of cells in the trophoblastic septa, and histological morphology in the labyrinth zone on GD 21 in the TP-treated group were nearly identical to those on GD 17 in the control and TP-treated groups. Therefore, it was assumed that the testosterone-induced small placenta was induced in association with the developmental inhibition of the fetal part of the placentas from GD 17 onwards. An increased IUGR in the testosterone-induced rat was attributable to insufficient blood supply for rapid fetal development from GD 17 onwards, as a consequence of the narrowing of maternal sinusoids and the thickening of trophoblastic septa in the labyrinth zone.

P-98 *

Development of an automated rat estrus cycle classification model using an AI image analysis platform

○Shinichi Onishi[1)], Riku Egami[2)], Yoshinobu Nagashima[2)], Yuya Nakamura[2)], Kaori Nishihara[1)], Saori Matsuo[1)], Atsuko Murai[1)], Shuji Hayashi[1)], Masaki Yamazaki[1)], Mizuno Hideaki[2)], Atsuhiko Kato[1)]

[1)] Translational Research Division, Chugai Pharmaceutical Company
[2)] Research Division, Chugai Pharmaceutical Company

[Background and Aim] In toxicologic studies on the effects of test articles on the estrous cycle of the female reproductive organs (ovary, uterus, and vagina), it is necessary to histologically classify the cycle into diestrus, proestrus, estrus, and metestrus. For efficient pathological assessments, we investigated whether AI can automatically evaluate the uterine and vaginal estrus cycles of rats using whole slide images (WSIs). **[Materials and Methods]** Five toxicologic pathologists classified uterine and vaginal estrus cycles and cases with more than four matching judgements were isolated. Those WSIs were then compressed to less than 2000 × 2000 pixels and divided into training data and validation data. Using IBM® Visual Insights, an AI-image analysis platform, we created an automatic object detection model by training it on the data of each uterus and vaginal estrus cycle. Finally, the correct answer rates were verified by the validation data. **[Results]** The model was 90% correct for the uterus and 62% for the vagina. **[Conclusions]** An automated estrus cycle detection model of the uterus of rats was sufficiently accurate and helpful. On the other hand, the vaginal detection model did not have a sufficiently accurate answer rate. The difference in the accuracy may be influenced by the difference in the observed magnification of the uterus and vagina. Therefore, large WSIs must be divided into small images before analysis to increase the accuracy of vaginal classification.

P-99 *

ACTH-induced stress in weaned sows impairs LH receptor expression steroidogenesis capacity in the ovary

○Zhu Huaisen[1,2], Tan Rongrong[1], Xiu Xiaoyu[1], Lu Henglei[1]

[1] AnLing Biomed (ShenZhen) Co., Ltd
[2] Centre for Drug Safety Evaluation and Research (CDSER), Shanghai Institute of MateriaMedica (SIMM), Chinese Academy of Sciences (CAS)

[Background] Endocrine disruption, which is closely related to the persistent follicles, is possibly one of the results of stress. Since luteinizing hormone receptor (LHR) in ovarian follicular wall and concentrations of steroid hormone in follicular fluid are related to the development of persistent follicles, this study is designed to evaluate the effect of administered adrenocorticotrophic hormone (ACTH) to weaned pigs on their ovarian steroidogenesis capacity and LHR expression. **[Aim]** To explore the effects of changes in ovarian LHR and steroidogenesis capacity on ovarian ovulation during stress. **[Materials and Methods]** Ten multiparous sows were weaned and randomly divided into two groups (n = 5 each). Sows received 1 IU/kg ACTH or saline every 8 h from days 3-9 after jugular vein intubation. Blood samples were collected throughout the experiment, and ovaries were collected after slaughter on day 10. **[Results]** The plasma cortisol concentration was significantly elevated after ACTH injection. The E2 and ASD concentrations in FF were significantly lower in the ACTH group. The LHR, 3β-HSD, P450arom, and P450c17 mRNA levels were significantly reduced in the ACTH group. Immunohistochemical staining showed significant differences in the distribution of 3β-HSD, P450c17, LHR, and P450arom between the two groups. **[Conclusions]** These findings indicated that ACTH significantly diminished the LHR expression and steroidogenesis capacity of the ovaries of weaned sows.

P-100

An exploration of novel carcinogenic mechanisms by DMBA treatment in mouse normal mammary tissue-derived organoids

○Toshio Imai[1,2], Rikako Ishigamori[1], Ruri Nakanishi[1], Yukino Machida[3], Mie Naruse[1]

[1] Central Animal Division, National Cancer Center Research Institute
[2] Department of Cancer Model Development, National Cancer Center Research Institute
[3] Laboratory of Veterinary Pathology, Nippon Veterinary and Life Science University

[Background] An oral dose of 7,12-dimethylbenz[*a*]anthracene (DMBA: 50 mg/kg b.w.) induced mammary carcinomas with *Hras* mutations at high frequency and typical biphasic structures in heterozygous BALB/c-*Trp53* knockout female mice. In parallel, we report a model using DMBA (0.6 μ M)-treated mammary tissue-derived organoids generated from the same strain mouse to induce tumors after injection into the nude mouse subcutis. **[Aim]** To clarify whether phenotypes and genotypes of the tumors in the organoid-based model resemble to the carcinomas in the DMBA-treated mouse model. **[Materials and Methods]** Histopathological and immunohistochemical studies of the both models and whole exome sequencing (WES) of the organoid-basis model were conducted. **[Results]** Tumors in the organoid-based model consisted of mixed cytokeratin (CK) 18-positive luminal and α -smooth muscle actin-positive myoepithelial cells, and they partly changed to CK14-positive squamous cell carcinomas after passages to nude mouse subcutis. WES revealed no mutations in *Hras*, and mutations in other genes, e.g. *Tgfbr2*. **[Conclusion]** Tumors with different pathological properties from the mouse model, possibly due to the unique genetic alterations, were observed in the organoid-based model. Although further studies using various chemicals in the organoid-basis model are needed, the organoid-based model would be expected to explore novel mechanisms of chemical carcinogenesis, which have not been observed in animal models.

P-101＊

Assessment of the molecular and physiological role of micro RNA in chemically-induced mammary gland carcinoma in rats

○Fatma A. Elmalah[1)], Mona M. Hegazi[1)], Doha M Beltagy[2)], Elsayed I. Salim[1)]

[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis, Faculty of Science, Tanta University
[2)]Biochemistry Department, Faculty of Science, Damanhour University

[Background] Breast cancer is the leading cause of death among all cancers types in women. Recent advances in expression biology have shifted in identifying and developing specific and sensitive biomarkers, such as micro RNAs (*miRNAs*) for cancer diagnosis and prognosis. **[Aim]** We attempted to provide a comprehensive profile of key *miRNAs* involved in experimental breast cancer to establish a more reliable non-invasive clinical biomarkers for early detection. **[Materials and Methods]** In this experiment, three groups of female Sprague-Dawley rats were administered either 0.09% saline, Methylnitrosourea (MNU) or MNU+Doxorubicin to evaluate the expression role of *miR-21*, *miR-155*, *miR-195*, *miR-122* and *miR-17-3p* in mammary tumors and after treatment with Doxorubicin. **[Results]** The results showed that *miR-21, miR-155* and *miR*-195 were up-regulated in breast cancer, while *miR-122* and *miR-17-3p* were downregulated. This expression was modified by Doxorubicin. Other investigations such as blood biochemistry, histopathology, immunohistochemistry and antioxidant enzymes activities were demonstrated to correlate with the changes occurred. **[Conclusions]** The study explained that *miR-21*, *miR-155*, *miR-195*, *miR-122* and *miR-17-3p* expressions differed in the normal mammary tissue, mammary gland tumors and after treatment with chemotherapy, this encourages the promising use of *miRNAs* as new prognostic biomarkers for breast cancer.

P-102＊

Promoting effect of sunset yellow at low doses on *N*-methyl *N*-nitrosourea-induced rat mammary gland carcinogenesis

○Malak I. Elbassuny[1)], Magdy E. Mahfouz[2)], Elsayed I. Salim[1)]

[1)]Zoology Department, Research Lab. for Molecular Carcinogenesis. Faculty of Science, Tanta University
[2)]Zoology Department, Faculty of Science, Kafrelsheikh University

[Background] Sunset Yellow (Yellow 6: SY (E110)) a food coloring linked to health risks in animal models. **[Aim]** We investigated the role of SY during chemically-induced mammary carcinogenesis in rats. **[Materials and Methods]** *N*-methyl *N*-nitrosourea (MNU) was injected into female rats then they were divided into 3 groups. Group 1 were set on high fat diet after MNU. Group 2 were administered SY at 161.4 mg\kg\day, Group 3 were given lower dose of SY (80.7 mg\kg\day) after MNU. The SY doses were chosen below the human acceptable daily intake (ADI) of the WHO/FAO guidelines. Group 4 were control. Groups 5 and 6 were administered SY at the same doses as groups 2 and 3 respectively but without MNU. **[Results]** After 22 weeks, SY in both doses significantly increased tumor incidences, multiplicities, volumes, and average tumor burden, as well as it decreased tumor latency as compared with positive control. Estrogen and progesterone hormones levels significantly increased in SY-treated groups, also oxidative stress parameters especially MDA as well as ERα, PR and PCNA immunohistochemical indexes were elevated in groups treated with SY vs. control. *ERα* and *EGFR* mRNA expression was upregulated in SY-treated groups vs. control. **[Conclusions]** SY significantly promoted incidence and multiplicities of mammary tumors in rats, therefore may have strong potency for breast cancer development in humans.

P-103

The histopathologic changes in lungs of mice and cynomolgus monkeys administrated intravenously with human umbilical cord-derived mesenchymal stem cells

○Yanjun Cui, Xu Zhu, Yi Zhou, Xuezhou Cai, Yichao Tian, Li Zhou

Hubei Topgene Biotechnology Co. Ltd Wuhan Branch

[Objective] Effects of human umbilical cord-derived mesenchymal stem cells (HUC-MSCs) were evaluated in single and repeated dose toxicity studies using mice and Cynomolgus monkeys (macaca fascicularis).
[Materials and Methods] KM mice (40 mice for the single dose toxicity study) and Cynomolgus monkeys (four monkeys for the single dose study, eighteen monkeys for the two-week repeated-dose toxicity study), were intravenously administrated with HUC-MSCs.
[Results] In the single dose studies, six mice (30%) were dead and thrombosis was found, and thrombosis comminated with inflammation in the was observed in one monkey(25%) in the vessel of lung. In the repeated-dose of toxicity studies, alveolar septum thickened that may be caused by the HUC-MSCs infilled were observed in two monkeys (33%) of low dose group and three animals (50%) of high dose group. Additionally, thrombosis and inflammatory nodular formation in and around pulmonary vessel was found in one animal (17%) of high dose group.
[Conclusions] Treatment-related pathological changes in pulmonary vessel were found in both mice and monkeys. Special attention should be paid for thrombosis induced by HUC-MSCs in further non-clinical and clinical studies.

P-104

Histopathological investigation of islets in SD rat by subcutaneous injection with a repeat dose new hypoglycemic compound

○Du Mu, Qi Wei, Guo Jin, Zhang Rui, Guo Hui, Liu Xiangjiang, Wang Beibei, He Yanan, Yin Jun, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc.

[Background] and Aim There are many drugs for the type 2 diabetes included insulin, linsulin analogs and GLP-1 receptor agonists, but there is not report on the effect of islet in SD rat. This report describes the lesion of islets in SD rat with a repeat dose new hypoglycemic compound. **[Materials and Methods]** 6-9 weeks SD rat were administrated new hypoglycemic compound 4 weeks by subcutaneous injection at 60, 120 and 180 nmol/kg respectively. The rats were euthanized after 4 weeks on Day 29 and 4-week recovery on Day 57. The blood was collected for clinical chemistry. The pancreas was weighted and fixed in 10% neutral buffered formalin for HE staining, immunohistochemistry was performed with Insulin and Glucagon. **[Results]** There was no difference in the pancreas weight in all dose group. Dose dependent blood glucose decreased was observed in all dose groups. The HE and IHC staining showed that the islets of each dose group on Day 29 were small in size, A cells increased, A cells mitosis and B cell atrophy. After a 4-week recovery on Day 57, minimal A cell increased was observed in high dose group, but the severity and incidence was significant lower, other findings were recovery. **[Conlusion]** Because the blood glucose decreased caused by the test article, A cell increased, A cell mitosis and B cell atrophy were considered to be a secondary pathological changes caused by a pharmacological effects rather than adverse lesion.

P-105＊

Comparison of histopathological and immunohistochemical methods with blood hormone levels in detection of chemical-induced antithyroid effect in rats

○Hirotoshi Akane[1)], Takeshi Toyoda[1)], Kohei Matsushita[1)], Tomomi Morikawa[1)], Tadashi Kosaka[2)], Hitoshi Tajima[2)], Hiroaki Aoyama[2)], Kumiko Ogawa[1)]

[1)] Division of Pathology, National Institute of Health Sciences, [2)] Toxicology Division, Institute of Environmental Toxicology

Although blood hormone levels are useful for detection of antithyroid chemicals in rodent toxicity studies, there are several difficulties such as large individual differences and limited sample volume. We performed the comparison of histopathology and immunohistochemistry with blood hormone levels to determine certain parameters for more efficient evaluation of antithyroid effects in short-term tests. Propylthiouracil (PTU) and methimazole (MMI), which are both antithyroid drug, were administered by gavage to six-week-old male and female SD rats (5 rats/group) at 0.03 to 3 mg/kg/day and 0.3 to 10 mg/kg/day, respectively, for 28 days. Results of organ weights, histopathology, and immunohistochemistry were compared with changes of serum thyroid hormone levels. Decreases in serum T3 and T4 were detected in 1 mg/kg or higher PTU and 3 mg/kg or higher MMI groups, and thyroid weights were increased at almost same doses. Follicular hypertrophy/hyperplasia in the thyroid was found in all groups except for female PTU lowest dose group. Immunohistochemistry revealed a dose-dependent decrease in thyroid T4 expression in all groups with histological lesions. TSH-positive area in the anterior pituitary gland was increased in same groups as decreased serum T4. Histopathological findings and decreased T4 expression in the thyroid were observed from lower doses without significant decrease in serum T4, suggesting that they can be more sensitive parameters for detecting antithyroid drugs.

P-106

Histopathological changes in the thyroid of tadpole in the positive control group of the Amphibian Metamorphosis Assay (AMA).

○Mika Nagaike, Itaru Yamamoto, Yuta Baba, Eito Ikeda, Akiko Okada, Naoko Hongo, Kosei Inui

Ishihara Sangyo Kaisha, LTD., Central Research Institute, Safety Science Research Laboratory

[Background] AMA (OECD TG231) is an assay for endocrine disruption (ED) on environmental organisms. European authorities often require it in order to detect ED effects with thyroid-modality for pesticide registration. In amphibians, thyroid hormones promote development of the limbs during metamorphosis. We examined in-life data and thyroid pathology of African clawed frogs (*Xenopus laevis*) treated with sodium perchlorate (Sodium Iodide Symporter inhibitor). **[Materials and Methods]** In accordance TG231, tadpoles were exposed to sodium perchlorate in the test water for 21 days from developmental stage 51 (17 days old). After euthanasia in Tricaine, wet body weight, snout vent length (SVL), and hind limb length (HLL) were measured. After fixation and paraffin embedding, serial sections in coronal of the head was prepared. Furthermore, the same substance was administered via drinking water (1% w/v) to ICR mice for 90 days. The thyroid was examined histopathologically. **[Results]** In tadpoles exposed, there was no effect on survival rate, wet weight, or SVL, while HLL was significantly shortened. Histopathologically, thyroid glands markedly enlarged and contacted with each other. Follicular epithelial cells displayed diffuse hypertrophy/hyperplasia, increased mitosis, and decreased follicular colloid. In mice, hypertrophy/hyperplasia of follicular epithelial cells and loss of follicular colloid were observed with much severe than those in tadpoles.

P-107 *

Neoplastic mass of ganglionic origin seen at the base of the brain

○Qi Wei, Du Mu, Guo Jin, Guo Hui, Zhang Rui, Liu Xiangjiang, Yasuhiko Hirouchi, Li Zheng

JOINN LABORATORIES (Suzhou) Inc.

[Aim] Edematous mass with approximately 0.4cm diameter was observed grossly of the brain base in a SD rat. Because this lesion was significantly different from other brain tumors, it was considered to be a neoplastic lesion occurring in the peripheral ganglia, therefore, its histopathological features were reported. **[Material and methods]** A male Sprague-Dawley from control rat dissected for 26 weeks of repeated dosing, edematous mass of the brain base was collected, after fixation with 10% neutral formalin, slides were prepared and stained with HE, and antibodies for immunohistochemical staining for histopathological examination. **[Results]** The cells that make up the ganglion are mainly large nerve cells, satellite cells, and nerve sheath cells (Schwann cells) that make up the myelin sheath. Histological examination of the present case did not reveal proliferation of large neural cells. Significant proliferation of oval cells lacking cytoplasm and had abundant chromatin, were observed, even some cells form vesicle-like structures, mixed with round lighter stained cells were also seen. Nearly all myelin sheaths of myelinated nerve were accompanied by swelling and degeneration. Immunohistochemical staining results showed that myelin S100 was positive, partially cytoplasmic of oval cell were positive. **[Conclusion]** Immunohistochemical results showed dense proliferation of oval cells with vesiculation, it was considered to be a benign Schwannoma(Antoni type B) of the trigeminal ganglion.

P-108

A spontaneous benign meningioma in an ICR mouse

○Hu Yiwen, Kong Qingxi, Lv Ai

Pharmaron Inc.

[Background] A spontaneous meningioma is rare in the brain of ICR (Crj: CD-1) mouse. To the best of our knowledge, this might be the first report concerning the spontaneous benign meningioma in a strain ICR mouse in China. **[Aim]** To introduce the feature of a spontaneous benign meningioma of fibroblastic type occurring in an aged ICR mouse. **[Materials and Methods]** The brain sample was from a 77-wk-old found dead ICR (Crj: CD-1) mouse in a 78-wk carcinogenicity study. Study animals were purchased from Jihui Laboratory Animal Technology in Shanghai. Grossly, meningeal thickening was observed in the brain at necropsy. After collection, brain tissues were trimmed, dehydrated, cleared, infiltrated with paraffin, embedded, sectioned into 5μm thick sections, mounted onto glass slides, and stained with hematoxylin and eosin stain. **[Results]** Microscopically, the normal surface of the brain was covered by multifocal masses of delicate spindle-shaped cells with pale eosinophilic cytoplasm, and small elongated hyperchromatic nuclei. The cells formed loosely interwoven bundles and exhibited myxomatous areas. **[Conclusion]** For the tumor appeared well demarcated and was characterized by rare mitotic figures and expansive growth compressing the adjacent brain, but without any invasion of the underlying brain parenchyma, the tumor was diagnosed as a benign meningioma of fibroblastic type.

P-109＊

A case of cartilaginous metaplasia in the sclera of a Kbs:JW rabbit

○Kotaro Yamada, Yoshinori Yamagiwa, Miki Masatsugu, Yu Haranosono, Masaaki Kurata

Central Research Laboratories, Research & Development Division, Senju Pharmaceutical Co., Ltd.

[Introduction] Cartilaginous metaplasia in the sclera has not been reported in rabbits. Here, we report a case of spontaneous cartilaginous metaplasia in the sclera of a young Japanese white rabbit. **[Methods]** The animal was a 14-week-old male Kbs:JW rabbit that had received a single ocular instillation of isoproterenol (IP) at a concentration of 20% one day before necropsy. No abnormalities were observed in clinical signs, ophthalmology and necropsy. A hyaline cartilage-like tissue was focally observed in the sclera in the histopathological examination of the IP-administered eye. Then, additional specimens treated with Alcian blue staining and immunohistochemistry for vimentin were prepared. **[Results]** In H&E staining specimens, a focal cartilage-like tissue was observed between the scleral fibers on the posterior pole of the eye, and it consisted of a pale basophilic cartilage-like matrix with vesicles and oval or polygonal chondrocyte-like cells within the vesicles. The cartilage-like matrix was stained in pale blue by Alcian blue staining. Immunohistochemistry showed that chondrocyte-like cells were positive for vimentin. **[Discussion]** Based on the histological features, we diagnosed this lesion as a cartilaginous metaplasia in the sclera in a Kbs:JW rabbit. The location of the lesion was distant from the IP administered site, suggesting that this lesion was not caused by administration of IP, but was spontaneous due to abnormal differentiation of neural crest-derived cells.

P-110＊

Pulmonary hypoplasia in a Beagle dog

○Mai Todoroki, Sousuke Masuda, Hisashi Yoshimi, Makoto Furuya, Shigeyuki Mori

Department of Drug Discovery R&D Center., Zenyaku Kogyo Co., Ltd.

[Case] The animal was a 28-month-old female beagle dog allocated to a toxicity study. Deterioration of the general condition and body weight loss due to drug administration were noted. At necropsy, multiple white foci were observed in the cranial lobe of right lung. Organs were fixed in 10% neutral buffered formalin, and routinely stained with hematoxylin and eosin. For the lung, Masson's trichrome (MTC) staining was performed. **[Results]** The lesion macroscopically observed as white foci exhibited pulmonary hypoplasia. The alveoli were small, sparse, and collapsed, and the septa were thick and lined with cuboidal epithelial cells suggestive of type II cells. There was marked fibrosis around the bronchi (MTC staining: blue) and immature tubular structures resembling terminal bronchi were scattered. No significant findings were observed in other organs. **[Conclusion]** Pulmonary hypoplasia is a type of developmental dysplasia histologically characterized by dysplasia of the terminal bronchioles and alveoli, and predominance of type II cells. In this case, there were no alveoli around the bronchi and the lung parenchyma was dysplastic. Additionally, there were immature tubular structures resembling terminal bronchioles, which morphologically corresponded to the pseudoglandular stage of lung development. Based on these characteristics, this case was diagnosed as pulmonary hypoplasia. Immunohistochemical and electron microscopic examinations are currently ongoing.

P-111＊

Inflammation of the cardiac coronary artery in ICR mice

○Kyohei Yasuno[1)], Masako Imaoka[1)], Tetsuya Ohsawa[1)], Keiko Okado[2)], Kiyonori Kai[1)], Yoshimi Tsuchiya[1)]

[1)] Medicinal Safety Research Laboratories, Daiichi Sankyo Co., Ltd
[2)] Department of Translational Research, Daiichi Sankyo RD Novare Co, Ltd

Inflammation of the cardiac coronary artery in Crlj:CD1(ICR) mice is occasionally observed in toxicity studies. In this study, we collected background information on this lesion of 6 to 8 weeks old ICR mice. As a result, ten of 144 (7.0%) mice showed vasculitis of the coronary arteries. Lesion was commonly found in the right ventricular wall. In histopathological examination, hypertrophy of vascular smooth muscle cells (VSMCs) and perivascular infiltration of macrophages were observed in mild cases. In moderate to marked cases, vasculitis was accompanied by single cell necrosis of VSMCs, hemorrhage of the tunica media, and/or fibrinoid necrosis of the vessel wall. Electron-microscopic examination of the lesion showed rupture of the internal elastic lamina and VSMCs below the rupture showed degeneration.

These results suggest that this lesion is caused by rupture of the internal elastic lamina and necrosis of VSMCs, leading to leakage of plasma components, which progress toward vasculitis and perivascular inflammation. In ICR mice, mineralization is rarely seen which is predominantly observed in the right ventricle. The onset of this lesion is focal calcification at the same site as necrosis of myocardial fibers and the pathogenesis of mineralization is considered to be ectopic calcification. Since mineralization was not seen in any part of the heart in this lesion, coronary artery inflammation seen in young ICR may be a different pathophysiology from that in ICR mice.

P-112＊

Spontaneous lymphangioma in a young SD rat

○Rena Ishikawa, Aya Goto, Yuki Seki, Kota Nakajima, Etsuko Ohta

Global Drug Safety, BA Core Function Unit, Medicine Development Center, Eisai Co.,Ltd.

[Background] We report the histological and immunohistochemical characteristics of the spontaneous cervical and thoracic lesion observed in a rat. **[Materials and Methods]** In a 9-week-old male Crl:CD(SD) rat sacrificed terminally, edema of connective tissue around trachea in the thoracic cavity and a red nodule (7 mm in diameter)in submaxillary subcutis were grossly noted. HE and Masson-Trichrome stain sections were prepared. Immunohistochemistry for CD31, LYVE-1, Cytokeratin(CK) AE1/AE3, Ki67, α-SMA was also performed. **[Results]** Grossly edema-like lesion was composed of dilatation of vascular-like structure that are lined by flattened cells without any compression to surrounding tissue, mitosis or cellular atypia. In addition, there were valve like structure and continuity to normal mandibular lymph node. Flattened cells were positive for CD31 and LYVE-1, but negative for CK AE1/AE3 and Ki67 and considered to be lymphatic endothelial cells. α-SMA positive cells lined beneath endothelial cells. **[Conclusion]** Since this lesion consisted of vascular-like structure composed by lymphatic endothelial cells with continuity to normal mandibular lymph node, we diagnosed the lesion lymphatic malformation(lymphangioma). Although there is no active proliferation, lymphangioma in human is also known to no significance proliferation. Recently, lymphangioma in human is included in Lymphatic malformation in ISSVA classification.

P-113

Gastric carcinoid tumors in rats with parietal cell atrophy in a long-term carcinogenicity study

○Norimitsu Shirai, Choudhary Shambhunath, Houle Christopher

Pfizer Inc. Drug Safety R&D, Pathology

Gastric carcinoids are very rare as spontaneous tumors in rats, but can be induced through a feedback loop via increases in the plasma gastrin levels following administration of agents that block gastric acid for prolonged periods. We aim to present microscopic data from a long-term carcinogenicity study of a small molecule antagonist against the cannabinoid-1 receptor in which carcinoids and parietal cell atrophy coincided, focusing on a causal link. Test article was administered to 60 rats/sex/group once daily by oral gavage at low, mid or high dose for 2 years. Two separate groups of rats received vehicle only and served as controls. Microscopic examination was performed on H&E sections of stomach from all animals. Sevier-Munger silver stain for neuroendocrine tissues was used to aid diagnosis. Carcinoid and neuroendocrine cell hyperplasia occurred in 2/60 females and 1/60 females, respectively, only at the high dose. Parietal cell atrophy was increased in incidence at the high dose (11/60 males, 22/60 females) compared to controls (2/120 males only). Carcinoids exhibited expansive growth obliterating normal mucosal architecture and infiltrating into the submucosa. Tumor consisted of densely packed nests of round to polygonal cells delineated by fine fibrovascular stroma. Sevier-Munger staining revealed argyrophil granules in cell cytoplasm. Carcinoids are rare in control rats, and in this case, were likely secondary to test article-related parietal cell atrophy.

P-114

A case of giant esophageal diverticula filling the thoracic cavity in a SD rat

○Junko Fujishima, Hiroki Yamashita, Yuji Sasaki, Kinji Kobayashi, Hiroshi Maeda

Drug Safety Research Laboratories, Shin Nippon Biomedical Laboratories, Ltd.

Diverticula are known to occur anywhere of in the wall of the alimentary tract, including the esophagus. This case study describes the histopathological features of a giant esophageal diverticulum filling the thoracic cavity of an untreated rat.

An untreated female rat [Crl:CD(SD), 11 weeks old] showed no abnormalities in clinical observations. A mass (35x25x20 mm) filling the thoracic cavity, involving other thoracic organs, and adhering to the thoracic wall and diaphragm was observed grossly. No fluid or food residue was observed in the thoracic cavity. The mass was examined histopathologically and immunohistochemically.

Microscopically, the mass was lined with collagen fibers and was partly lined with squamous epithelium lacking lamina muscularis mucosae. The mass was filled with pus and foreign bodies such as the food. Although the esophagus, aorta, trachea, and lungs were observed in the proximity of the mass, these were all well demarcated. However, the esophageal adventitia was connected to the connective tissue in the mass, and Desmin-positive cells were observed in this connective tissue.

Based on the above findings, this case was diagnosed as a giant esophageal diverticulum. A congenital esophageal diverticulum was suggested to possibly have become enlarged due to accumulation of food residue since, although the mucosa and muscle layer were incomplete, this was a naive animal that was only 11 weeks old.

P-115*

Case report: Cystic nodular lesion in the jejunum of a rat.

○Yuta Baba, Eito Ikeda, Akiko Okada, Naoko Hongou, Kosei Inui, Mika Nagaike

Safety Sciences Group, Safety Science Research Laboratory, Central Research Institute, Ishihara Sangyo Kaisha, Ltd.

[Aim] We report a case of cystic nodular lesion lined by small intestinal mucous on the mesenteric side of the jejunum in an aged rat.
[M & M] An animal is a female BrlHan:WIST@Jcl(GALAS) rat used for a control group of a carcinogenic study. It was euthanized at 111 week-old as planned. At necropsy, a milky white, about 6 mm in diameter, nodular mass was found at mesenteric side of the jejunum adjacent to a pancreas.
[Results] Histopathologically, the nodule is a cyst-like tissue similar to the adjacent jejunum, consisting of mucous membrane, smooth muscle layer, and a serosa from the luminal side. The smooth muscle layer revealed thin and disrupted running, and shared with it of the adjacent jejunum. The muscularis mucosae and enteric plexus are absent as far as we searched. Mucosa in the cyst consists by the area with taller and branched villi indicating hyperplasia and also the flattened area without villi. Generally, mucosa is lined by absorptive epithelial cells with brush border and goblet cells. Severe vacuolation was observed mainly at the flattened area. Osseous metaplasia was noted in the proper lamina. The lumen was filled by basophilic granular materials with eosinophilic flocculent materials.
[Discussion] Differential diagnoses of cystic nodular lesion on the small intestine are Meckel's diverticulum, other diverticulum, enteric duplications and tumors. We are going to discuss pathogenesis based on the macroscopic and the histopathological findings of this lesion.

P-116

Study on pathomorphological changes of liver in Beagle dog with spontaneous hepatocirrhosis

○Hu Jian-ting, Qiu Bo, Ying Yong

New Drug Evaluation Center of Shandong Academy of Pharmaceutical Sciences

[Background] During repeated toxicity tests, one dog in the control group developed severe liver cirrhosis. **[Aim]** To study the liver pathomorphological and serum biochemical Changes in Beagle dog with spontaneous hepatocirrhosis and establish the background information of experimental animals for GLP. **[Materials and Methods]** The ALT, AST, TP, ALB, ALP, TBIL, TC, TG and GGT were detected by automatic biochemical analyzer, compared the differences of above index between blank control and diseased animal. The histopathological feature of liver was described with optical microscope. **[Results]** Compared with blank control, the ALT, AST, ALP, TBIL and GGT of diseased animal were increased significantly, and the ALB decreased significant. Compared with normal, the liver cells were nodular regeneration and arranged irregularly and False leaflets formation. The false leaflets were packaged with collagen fiber. **[Conclusion]** It is suggested that spontaneous lesions should be monitored so as to provide experimental animals histopathological background information for drug safety evaluation.

P-117＊

A case of renal mesenchymal tumor observed on kidney

○Guo Jin, Du Mu, Qi Wei, Zhang Rui, Guo Hui, Liu Xiangjiang, Yasuhiko Hirouchi

JOINN LABORATORIES (Suzhou) Inc.

[Background] A kidney nodule was observed in a female animal of a 26-week toxicity evaluation study in Sprague-Dawley rat. A few renal tumors of ductal or nephroblast origin has been reported. For this time, we reported a histopathological case of an incidental renal tumor with mesenchymal features. **[Methods]** In this case, the animal was found dead on 23th week, and a kidney nodule was observed during necropsy. The collected renal tissue was embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E), immunohistochemical stain and specific stain for microscopic examinations. **[Results]** Microscopically, the nodule was located in the cortex of kidney without infiltrative growth. The nodule characteristics included a round nodular formation with well-defined boarder, and arranged in swirl by smooth muscle cell mixed with collagenous fibers. Meanwhile, the tumor cells composed of very pleomorphic cells without cell mitosis. A few scattered neutrophil cells infiltrated in, and scattered with high density of glandular cells. Moreover, Cells characterized by a circular nucleus and an eosinophilic and foamy cytoplasm were observed in a paving stone.Since the tumor was not identified glomerular-like structures, a nephroblastoma was ruled out. And, the tumor morphology derived from the renal tubule was not observed. In conclusion, it was considered a mesenchymal tumor formed by smooth muscle cells and collagenous fibers.

P-118＊

A mortal case of 9-week-old CBA/J mouse due to ovarian choriocarcinoma.

○Toshio Kobayashi, Yutaka Oshima, Kimika Yamamoto, Hisako Morioka, Masafumi Horiuchi, Yasuhiro Tsubokura, Katsumi Miyata, Satsuki Hoshuyama

Chemicals Evaluation and Research Institute

[Background] Ovarian choriocarcinoma is one of the rarest tumors in mice. According to the National Toxicology Program data, only seven cases out of 41,102 animals were reported in B6C3F1 mice, and the age ranged from 29 to 94 weeks old. Recently a case of ovarian choriocarcinoma has been reported in 8-week-old ICR mouse although, there is no report in CBA/J mice. **[Case]** A 9-week-old female CBA/J mouse receiving vehicle on the ear for 2 days was found dead on the 3rd day. The animal showed no abnormal clinical conditions during the life period, nor did it the body weight change. Necropsy revealed that approximately 0.6 mL of hemoperitoneum, which considered to be a cause of death, and the left ovary was enlarged with dark reddish change. Histopathologically, most of the ovary was occupied by hematocyst, and residual parenchyma was composed of tumor cells with bizarre giant nucleus and small spindle shape cells resembling cytotrophoblast. Therefore, the ovarian tumor was diagnosed as choriocarcinoma. This is the first report of ovarian choriocarcinoma in CBA/J mice. Results of other organs and special staining will be shown at the presentation.

P-119＊

Malignant tumour of ovary in a young Rhesus monkey - Case Report

○Wang Haoan[1)], He Yang[1)], Chen Ke[1)], Qiu Shuang[1)], Yang Kaixuan[2)], Cen Xiaobo[1,3)], Hu Chunyan[1)]

[1)] Westchina-Frontier Pharma Tech Co., Ltd (WCFP)
[2)] West China Second University Hospital, Sichuan University
[3)] National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy and Cancer Center, Sichuan University, and Collaborative Innovation Center for Biotherapy

[Background] Right ovarian mass with nodules in the lung were found in a 3.5-year old female Rhesus monkey in control group of a toxicity study during the necropsy. **[Aim]** To determine the histopathological classification of the ovarian tumor and investigate the relationship between the ovarian tumor and nodules noted in the lung. **[Materials and Methods]** Tumor tissues were embedded in paraffin, 4-μm slides were stained with hematoxylin and eosin, and immunohistochemistry labeling for CK18, CK-p, P27, α-inhibin, HPL, SALL4, Ki67, and CD117 were also performed. **[Results]** Microscopically, the tumors of the ovary mainly composed of three components. In most parts of the tumor, neoplastic cytotrophoblasts and syncytiotrophoblasts were arranged around blood vessels; some parts existed vesicular or cystic structure containing a large amount of mucus, hyaline droplets were found in the cytoplasm of the lining tumor cells; in addition, small foci of embryonal carcinoma component were present. Tumor cells were positive for CK18, CK-p, P27, α -inhibin, HPL, Ki67 and SALL4, but negative for CD117. For the lung, the tumor contained cytotrophoblasts and syncytiotrophoblasts as well as vesicular or cystic structure, and the tumor cells in the lung were positive for CK18, Ki67 and SALL4. **[Conclusion]** Malignant mixed germ cell tumor originated from the ovary was diagnosed based on the histologic and immunohistochemical features, and partial components of the tumor were metastases to the lung.

P-120

A case of spontaneous pituitary gland adenocarcinoma in a nineteen-week-old female Sprague-Dawley rat

○Duyeol Kim, Jong-Il Shin, Hyun Kyung Song, Byung-Woo Lee, Hyun-Woo Kim, Han Kyul Lee, Sun-Hee Park

Biotoxtech Co.

Pituitary gland tumors have been known as one of the most common tumors occurring in aging rats, with arising from pars distalis, but they are rare in young rats.

[Aim]

We describe an adenocarcinoma from the pituitary gland and the cancer within hypothalamus in a young female SD rat.

[Materials and Methods]

The masses in the pituitary gland and hypothalamus of 19-week-old female SD rat were prepared for histopathology. In addition, the masses were analyzed by staining with antibodies against cytokeratin (CK), vimentin, S-100b, ED-1, RM-4 and GFAP, and stained with PAS.

[Results]

At necropsy, white nodule is located in the pituitary gland and the mass pressed the hypothalamus. The mass is characterized by abundant eosinophilic matrix and severe invasion to the hypothalamus. Small islands composed of neoplastic cells are scattered in the abundant matrix. Round to oval tumor cells showed high N/C and two-three mitotic figures (hpf). In the hypothalamus, it is also observed that the tumor cells cluster is located within meninges and hypothalamus, and the histological characteristics are similar to those in the pituitary gland.

On IHC and histochemical staining, the cells stained positive for only CK antibody in the cytoplasm and the matrix was positive for PAS staining.

[Conclusion]

Taken together, the pituitary tumor was diagnosed as adenocarcinoma derived from basophil and the tumor in the hypothalamus was the result of invasion of the pituitary tumor.

P-121 *

Spontaneous tumor resembling human clear cell sarcoma of the planta in a female SD rat

○Tsubasa Saito, Hiromu Okano, Moeko Aoki, Yumiko Kamiya, Shiori Fujiwara, Osamu Hashiguchi, Yuko Yamaguchi

BoZo reserch center Inc.

In human pathology, clear cell sarcoma is classified as a tumor of uncertain differentiation. We report histopathological features resembling human clear cell sarcoma developed in the footpad of a rat.

A female SD rat was euthanized as moribund states at 85-week old in a 2-year feeding trial to obtain the background data for 2-year carcinogenicity studies. After necropsy, all tissues were fixed in 10% NBF and a leg was decalcified with K-CX, and sections were subjected to special stains and immunohistochemistry (IHC) in addition to hematoxylin and eosin stain.

The lesion was macroscopically observed as swelling of the left planta. In microscopy, tumor cells proliferated massively from the subcutis of the plantar region to the metatarsal bone and were continuous with the plantar aponeurosis. The neoplastic cells were divided into nests or trabecular patterns by collagenous framework. They had small round nuclei with fine chromatin and clear to pale cytoplasm with eosinophilic fine granules, and mitotic figures were rare. These cells were negative for PAS reaction, but positive for S100 and vimentin in IHC. Desmin, α-SMA and Iba-1 were negative. Ki-67 and PNL2 failed to demonstrate appropriate reactions due to the decalcification procedure. Other than the above, although this case exhibited various age-related lesions, there were no lesions related to this plantar neoplasm.

This is an extremely rare spontaneous tumor that has a morphological resemblance to human clear cell sarcoma.

発表者索引

W

X

Y

Z

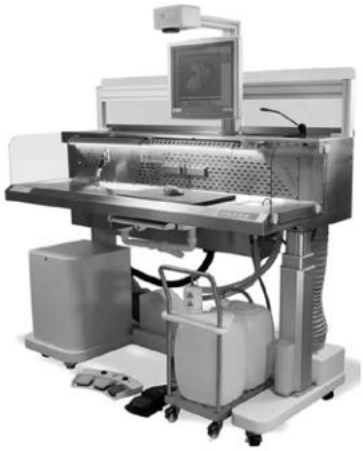
第 38 回日本毒性病理学会総会及び学術集会
第 1 回アジア毒性病理学連盟学術集会
講演要旨集

編　　集　第 38 回日本毒性病理学会総会及び学術集会
第 1 回アジア毒性病理学連盟学術集会　事務局
大阪市立大学大学院医学研究科 分子病理学
〒 545-8585　大阪市阿倍野区旭町 1 丁目 4 番 3 号
責任者　鰐渕　英機

印刷・製本　株式会社プロアクティブ

広　告

病理・解剖分野は白井松にお任せ下さい



eGROSS pro-x

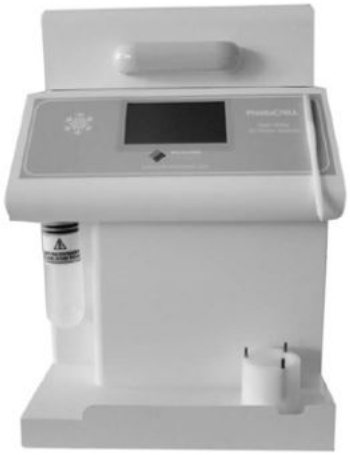
肉眼診断 / 切出し ワークステーション

- 切出し、撮影、ホルマリン分注が一元化できる局所排気装置です
- 撮影、ホルマリン分注はフットスイッチで操作可能
- ホルマリンを廃液することができます（※満水警報付）
- ご使用のホルマリンタンクがセット可能です
- 撮影装置は病理システムとの連携が可能です
- 前面開口部からの風速は 0.7 ～ 1.0m/s です
- 作業台の高さは 90 ～ 120cm の間で調整可能です

LOGOS

オールインワンハイブリット型ティシュープロセッサー

- 自動運転により、キシレンを使用しない包埋処理や夜間運転などの
  従来の処理方法や迅速処理に対応
- フレキシブルなカセットのセット数量
- 約 5L の専用試薬タンクを使用することにより、最大 210 カセットを処理
- スプリットラック（140 ～ 210 カセット処理可能）、
  ランダムバスケットラック（300 カセット処理可能）では、
  5mm の厚さまで各種組織の処理が可能
- スーパーメガカセットラック（24 カセットの処理が可能）では、
  8mm の厚さまで各種組織の処理が可能



PrestoCHILL

完全ドライ型 迅速凍結包埋システム

- 液体窒素やドライアイス、ヘキサン等を使用しない、完全ドライシステム
- 氷晶形成を防止した凍結システム
- わずか 60 秒で平坦なアイスブロックを作製
- プログラムにより一定条件で凍結でき、作業の標準化が可能
- サンプルの角度を調整、凍結させることが可能
- フラット表面凍結により、トリミング回数を減らすことが可能
- フェイスダウン技術による最適なオリエンテーション

HANDEX 白井松器械株式会社
HP: http://www.handex.jp/ http://www.shiraimatsu.co.jp/

大 阪: 〒540-0003 大阪市中央区森ノ宮中央 1-19-16
Tel 06-6942-4181(代)

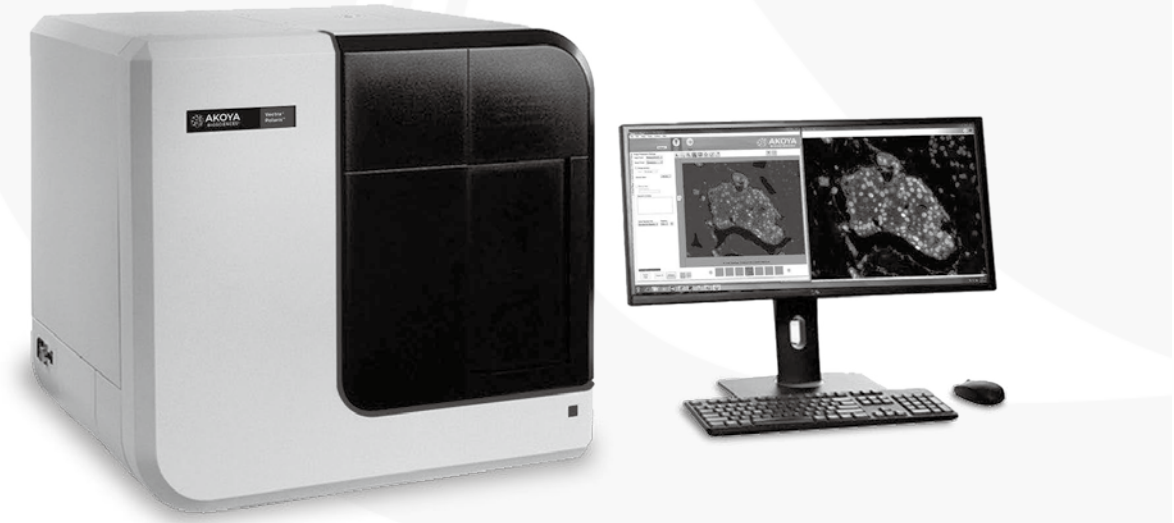
東 京: 〒123-0873 東京都足立区扇 2-14-32
Tel 03-5647-1570(代)

北関東: 〒133-0051 東京都江戸川区北小岩 5-6-9
Tel 03-6458-0697(代)

九 州: 〒811-2115 福岡県糟屋郡須恵町佐谷1447-1
Tel 092-687-8710(代)

キコーテック株式会社

組織定量解析
組織定量イメージングシステム
Vectra Polaris



Vectra Polarisは、スペクトルイメージング機能を搭載し、優れた定量性を有するスライドイメージングシステムです。スペクトルイメージングは染色した色素成分を正確に分離・定量できるので、免疫染色から特殊染色まで様々な組織標本の定量が可能です。またマシンラーニングによる学習機能は、組織形態の定量解析や特定の領域内の染色の定量が可能です。

- 色素染色の染色強度の定量
- 特定の形態面積の分離・計測
- 細胞単位のシグナル定量
- 陽性細胞のスコアリング評価
- 細胞表現型解析（フェノタイピング）

AKOYA BIOSCIENCES®

輸入販売元

キコーテック株式会社

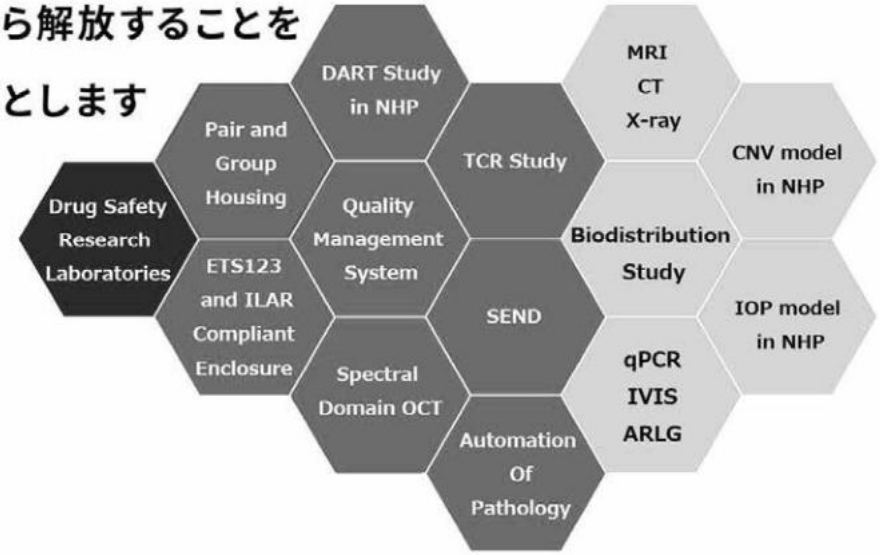
本　　社 大阪府箕面市船場西三丁目10番3号
〒562-0036　TEL　072(730)6790　FAX　072(730)6795
東京支社 東京都世田谷区駒沢二丁目11番1号駒沢ﾌｫｰﾗﾑｶﾞｰﾃﾞﾝ
〒154-0012　TEL　03(5787)3323　FAX　03(5787)3324
つくば営業所 茨城県つくば市竹園2丁目3番17号第一・ISSEIビル
〒305-0032　TEL　029(850)3771　FAX　029(856)3881
神奈川営業所 神奈川県藤沢市藤が岡一丁目8番14号田中ビル1F
〒251-0004　TEL　0466(55)4110　FAX　0466(55)4120

http://www.kiko-tech.co.jp/

Shin Nippon Biomedical Laboratories, Ltd.

創薬と医療技術の向上を支援し、
人類を苦痛から解放することを
絶対的な使命とします

SNBL



（株）新日本科学は60年以上にわたる
豊富な経験と実績に裏付けされた確かな技術力により
質の高いサービスとニーズに合わせたソリューションを提供します

●学会期間中はぜひ新日本科学のオンラインブースにお立ち寄りください！●

- **各種窓口（営業，Pathologist，標本作製担当，etc）にオンラインで相談可能**
- **オンラインラボツアーもご相談ください**

●New Service●

レビューの際に複数拠点で画像を同期して
カンファレンスを実施できるようになりました！

NanoZoomer S360
©Hamamatsu Photonics K.K.

●Locations●

鹿児島
本店 / 安全性研究所
東京
本社, 病理センター
大阪
病理センター
和歌山
薬物代謝分析センター, 病理分室

SUSTAINABLE DEVELOPMENT GOALS

株式会社　新日本科学
https://www.snbl.co.jp　　mail: info@snbl.co.jp

「食の安全」を科学する

食品安全委員会

日本毒性病理学会に所属する先生方にも
様々なハザードの毒性の評価にご活躍いただいています

食品安全委員会は、食品の安全を確保するため、国民の健康の保護が最も重要であるという基本的認識の下、規制や指導等を行うリスク管理機関（厚生労働省、農林水産省、環境省、消費者庁）から独立して、科学的知見に基づき客観的かつ中立公正にリスク評価を行う機関です。
食品安全委員会は7名の委員により構成されています。また、添加物、農薬、動物用医薬品、汚染物質、かび毒 ・自然毒等のハザードごとに専門調査会が設置され、約200名の専門委員が在籍しています。

＝食品安全委員会の業務＝

リスク評価
食品に含まれる微生物や化学物質が人の健康に与えるリスクを科学的知見に基づいて評価しています。主にリスク管理機関からの要請を受けて行います。

調査・研究
リスク評価を行うために必要なデータや情報を得るための研究・調査を実施しています。

[食品健康影響評価技術研究]
リスク評価やそのガイドライン策定などに必要な知見を得るための研究
　募集形態 ： 公募型委託研究
　募集開始時期 ： ９月頃

[食品安全確保総合調査]
リスク評価等を行うために必要な情報とデータの収集・整理・解析等
　募集形態 ： 入札による委託調査
　募集開始時期 ： 随時

リスクコミュニケーション
食品の安全性に関する科学的知識の理解をより一層促進するため、意見交換や情報交換を行っています。
SNS等による情報発信も行っています。

国内外の情報の収集・発信
国内外の情報を収集して整理・分析・データベース化し、リスク管理機関と共有するとともに、「食品安全関係情報」としてウェブサイトで公開しています。
オンラインジャーナル「Food Safety」を刊行し、ヒトの健康に関わる食品安全分野の科学技術情報を発信しています。PubMedやJ-Stageに収載されています。

国際協調
リスク評価の手法や個別の課題について、定期会合やシンポジウム等を通じて情報交換・意見交換を行い、海外の関係機関と連携強化を図っています。

食品安全委員会ホームページ
https://www.fsc.go.jp/

内閣府 食品安全委員会
Food Safety Commission of Japan

新しい発見を変わらない品質で

私たち日本クレアは、生命のあらゆる可能性を探求し発展させる基盤として、動物愛護のグローバルな視点に立った世界最高品質の実験動物を提供して参ります。

マウス・ラット・マーモセット

●クローズドコロニー

マウス　Jcl:ICR

ラット　Jcl:SD, Jcl:Wistar
BrlHan:WIST@Jcl(GALAS)

●近交系

マウス　C3H/HeNJcl, C3H/HeJJcl※
C57BL/6NJcl, C57BL/6JJcl※
BALB/cAJcl, BALB/cByJJcl※
FVB/NJcl, DBA/2JJcl※, 129^{+Ter}/SvJcl

ラット　F344/Jcl

●ハイブリッド系

マウス　B6C3F1/Jcl, B6D2F1/Jcl,
MCH(ICR)/Jcl (Multi Cross Hybrid)

●疾患モデル

免疫不全モデル

マウス　BALB/cAJcl-*nu*
C.B-17/Icr-*scid* Jcl
NOD/ShiJic-*scid* Jcl
ALY®/NscJcl-*aly*

ラット　F344/NJcl-*rnu*

1型糖尿病モデル

マウス　NOD/ShiJcl

2型糖尿病モデル

マウス　KK/TaJcl, KK-A^{y}/TaJcl
BKS.Cg-*m*+/+*Lepr*^{db}/Jcl※

ラット　GK/Jcl, SDT/Jcl, SDT fatty/Jcl

アスコルビン酸合成能欠如モデル

ラット　ODS/ShiJcl-*od*

●疾患モデル

網膜変性疾患モデル

ラット　RCS/Jcl-*rdy*

関節リウマチモデル

マウス　SKG/Jcl

外用保湿剤・外用殺菌消毒薬効果検証モデル

マウス　NOA/Jcl

ヒトDuchenne型筋ジストロフィーモデル

マウス　C57BL/10-*mdx*/Jcl

●遺伝子改変動物

短期発ガン性試験モデル

マウス　CByB6F1-Tg(HRAS)2Jic

乳腺がん高感受性モデル

ラット　Hras128/Jcl

膵がん短期発がんモデル

ラット　Kras301/Jcl

生体恒常性維持機構解析モデル

マウス　α-Klotho KO/Jcl

マウス　*klotho*/Jcl

アレルギーモデル

マウス　OVA-IgE/Jcl (卵アレルギー)
TNP-IgE/Jcl (化学物質アレルギー)

●Germ free

マウス　MCH(ICR)/Jcl[Gf], C57BL/6NJcl[Gf]
BALB/cAJcl[Gf]

●コモンマーモセット

Jcl:C.Marmoset(Jic) (国内生産)

その他の取り扱い動物

●(公財)実験動物中央研究所維持系統

●フェレット(輸入販売)

生産地 : 中華人民共和国/輸入販売代理店
((株)野村事務所)を通じて国内販売

実験動物用飼料

一般動物用飼料/家畜・家禽試験用飼料/放射線滅菌飼料/特殊配合飼料/成分分析

器具・器材

飼育ケージ/飼育機・ラック/自動飼育システム/クリーンエアーシステム/バイオハザード対策システム/空調設備・排水処理システム/管理・実験機器/施設計画コンサルティング

受託業務

微生物学的クリーニング/遺伝子改変マウスの作製/モノクローナル抗体作製/受精卵採取・凍結処理/凍結受精卵の供給/系統維持及び生産/各種処置動物作出/マイクロバイオーム研究のサポート(無菌動物・ノトバイオートマウス作製および受託試験)/各種受託試験 他

関連業務

動物輸出入/微生物モニタリング/遺伝モニタリング/各種データ/情報サービス

業務提携

Physiogenex社(仏): 代謝性疾患領域に特化した薬効薬理試験受託サービス
(株)ジーピーシー研究所 : イメージングマウスの作製サービス

※ "This substrain is at least (a number>20 by definition) generations removed from the originating JAX® Mice strain and has NOT been re-infused with pedigreed stock from The Jackson Laboratory."

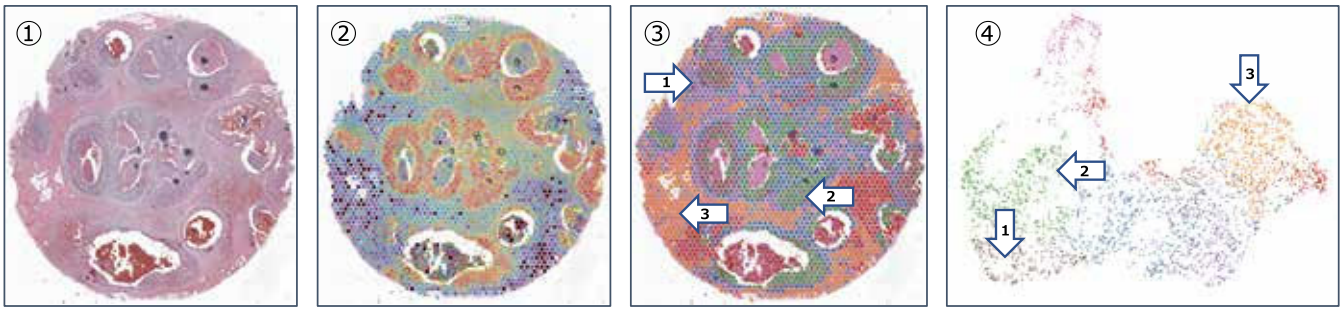
日本クレア株式会社
CLEA
www.CLEA-Japan.com

東京AD部　〒153-8533 東京都目黒区東山1-2-7　TEL.03-5704-7050
大阪AD部　〒564-0053 大阪府吹田市江の木町6-5　TEL.06-4861-7101
【動物・飼料のご注文先: AD受注センター TEL.03-5704-7123】
東京器材部　〒153-8533 東京都目黒区東山1-2-7　TEL.03-5704-7600
大阪器材部　〒564-0053 大阪府吹田市江の木町6-5　TEL.06-4861-7105
札幌出張所　〒063-0849 北海道札幌市西区八軒九条西10-4-28　TEL.011-631-2725
仙台出張所　〒983-0014 宮城県仙台市宮城野区高砂1-30-24　TEL.022-352-4417
名古屋出張所　〒465-0093 愛知県名古屋市名東区一社3-121-1　TEL.052-715-7580

位置情報があるTranscriptomics
Visium Spatial Gene Expression

組織のどこでどの様な遺伝子が発現しているのかをノンターゲットに解析

凍結サンプル、FFPEサンプルに対応



ヒト乳がん組織。①：HE染色、②：HER2遺伝子発現、③：Transcriptome情報からのクラスタリング、④：③のクラスターのUMAPプロット。腫瘍や周辺の環境に不均一性が確認できる。

シングルセル解析プラットフォーム Chromiumシリーズ

Chromium iX / X

Chromiumコントローラー

	Chromium X	Chromium iX	Chromium Controller
1レーンあたりの回収可能数 (Cellplex使用時)	20,000細胞 (60,000細胞)	10,000細胞 (30,000細胞)	10,000細胞 (30,000細胞)
1ランあたりの細胞数 (Cellplex使用時)	320,000細胞 (960,000細胞)	80,000細胞 (240,000細胞)	80,000細胞 (240,000細胞)
ご使用いただけるアプリケーション			
3' 遺伝子発現解析 (RNA-seq)	✓	✓	✓
3' 遺伝子発現解析 HT（ハイスループット）	✓	要アップグレード	非対応
イムノプロファイリング（TCR/BCR）	✓	✓	✓
イムノプロファイリング HT	✓	要アップグレード	非対応
ATAC	✓	✓	✓
マルチオーム (ATAC+3' 遺伝子発現)	✓	✓	✓

輸入元

株式会社スクラム

本社　〒135-0014 東京都江東区石島2-14 Imas Riverside 4F
Tel. (03)6458-6696 Fax. (03)6458-6697

西日本営業所　〒532-0003 大阪市淀川区宮原5-1-3 NLC新大阪アースビル403
Tel. (06)6394-1300 Fax. (06)6394-8851

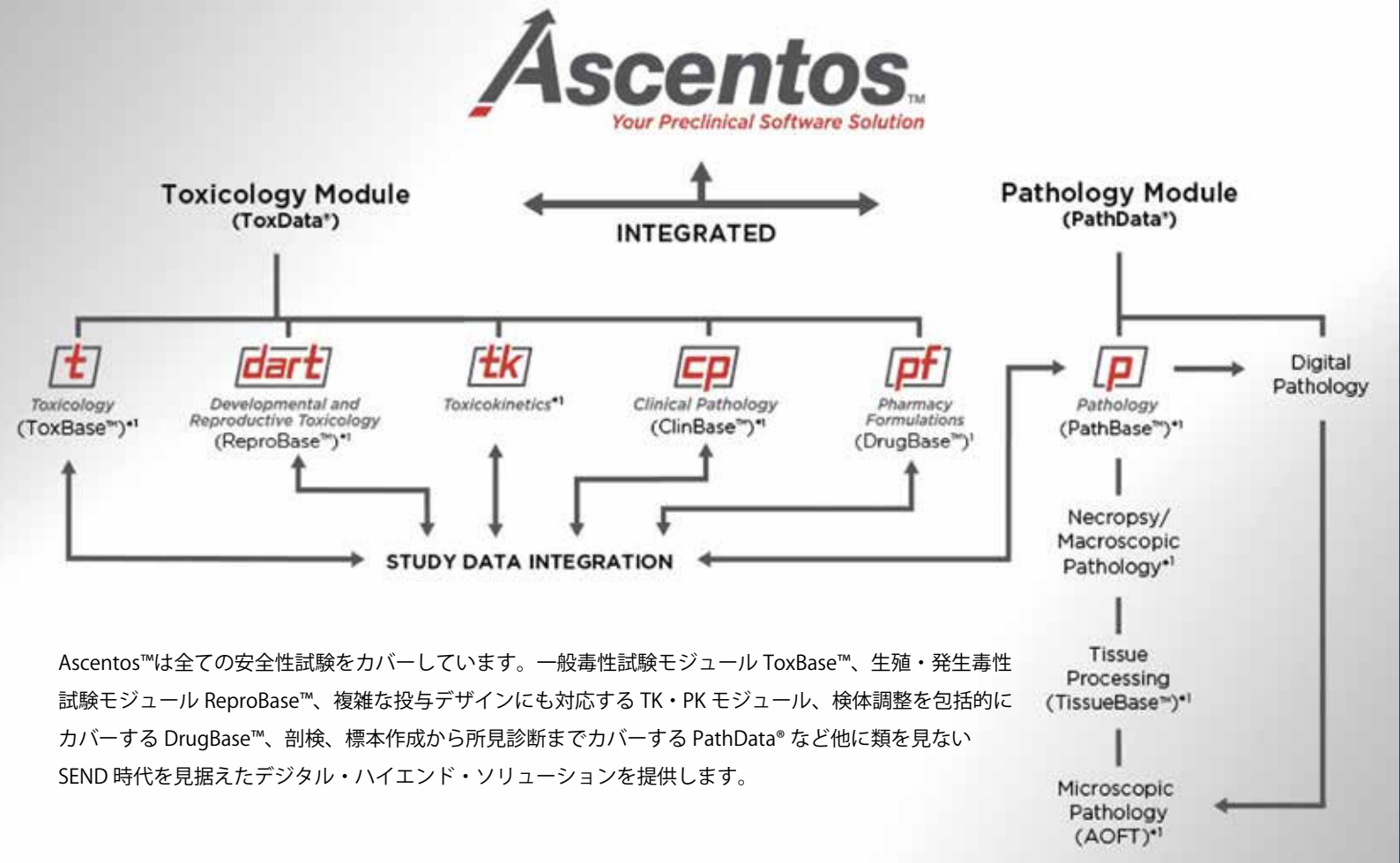
Web Site www.scrum-net.co.jp

Ascentos™
Your Preclinical Software Solution

Instem
Information Solutions For Life™

世界の一流パソロジストが愛用する Ascentos™ PathData®

世界で最も進んだ病理システム PathData® は一流のパソロジスト集団によって作り上げられたパソロジストが作ったパソロジストのためのシステムです。毒性試験の所見画像、剖検画像データを効率的に利用でき、レポーティングと有機的に結びつける最新の機能である ImageBase™もトータル・ソリューションである Ascentos™に含まれています。また、病理モジュールのみの導入も可能で、人数単位の廉価な導入も可能です。



Ascentos™は全ての安全性試験をカバーしています。一般毒性試験モジュール ToxBase™、生殖・発生毒性試験モジュール ReproBase™、複雑な投与デザインにも対応する TK・PK モジュール、検体調整を包括的にカバーする DrugBase™、剖検、標本作成から所見診断までカバーする PathData® など他に類を見ない SEND 時代を見据えたデジタル・ハイエンド・ソリューションを提供します。

Instem
Information Solutions For Life™

GSENDサポーター
G SEND

お問い合わせは ジャパンオフィスまで
e-mail pds.japan@pdslifesciences.com
電話 053-415-8917 Fax 053-522-9854