第15回 次世代を担う若手のための医療薬科学シンポジウム

15th Young Investigator Symposium on Clinical Pharmaceutical Science

Seamlessな薬学界を創造する
基礎・臨床・実践の融合

要旨集

会期/会場

ライブ配信（一部講演はオンデマンド配信も予定）

2021年 10月23日（土）13:00～18:50
（終了後オンライン懇親会）

24日（日）9:00～15:05

ポスター掲示:2021年10月23日(土) 9:00～サイトオープン

実行委員長: 前田和哉(北里大学薬学部)
副実行委員長:鈴木陽介(明治薬科大学)
大会ホームページ　http://www.ycps.jp/15/
問い合わせ先 E-mail: ycps2021_office@pharm.kitasato-u.ac.jp

主　催　公益社団法人 日本薬学会 医療薬科学部会

【ご挨拶】

この度は、「第 15 回次世代を担う若手医療薬科学シンポジウム」にご参加いただきまして、誠にありがとうございます。昨年次が COVID-19 禍のために急遽オンライン開催に変更され、face-to-face のコミュニケーションができなかったこともあり、本年度は何とかオンサイトでの開催を目指しておりましたが、COVID-19 の予想以上のまん延もあり、毎年、相当数の医療従事者の先生方のご参加もいただく本シンポジウムの最適な開催方法について、組織委員の中で議論を重ねた結果、苦渋の選択として本年度も全面オンライン開催に踏み切ることといたしました。ただ、色々な会合がオンライン開催になる中で、新しいコミュニケーション手段も急速に開拓をされてきております。今回は新たな試みとして、ポスターセッションと懇親会において、リアルタイムでコミュニケーションしていただけるよう、Remo を導入し、できる限り対面での会話に近づけるような工夫をするなど、従来型の対面での会合でしかできなかったことをオンラインで極力、実現化してみたつもりです。

さて、本シンポジウムは、日本薬学会医療薬科学部会が主催しており、次世代の医療薬科学の発展を担う若手研究者の育成を目的としてスタートしました。第 4 回シンポジウム以降は、医療薬科学部会の若手世話人が実行委員長と副実行委員長を務め、若手が中心となって企画ならびに運営が行われてきました。

今回のシンポジウムは、『Seamless な薬学界を創造する基礎・臨床・実践の融合』をメインテーマにいたしました。薬学そのものは非常に学際的な学問領域で、カバーする範囲も、基礎研究が主体となる薬の探索から、創薬のための臨床研究、医療現場における薬の適正使用・育薬、行政の立場からの新薬の審査や安全管理等多岐にわたります。一方で、学問そのものもこれまでの細分化された領域の中での発展を超えて、領域融合型の新たな研究分野が次々と勃興するようになりました。そのような時代の中で、我々は「基礎」「臨床」「実践」の垣根をとっぱらい、seamless なコミュニケーションを通じて、薬学に新風を吹き込む気概を持って医療薬科学の進歩に邁進したいという思いを込めて今回のテーマを設定させていただきました。

その目的達成のために、今回は医療薬科学の領域を超えて、非常に内容的に多岐にわたる講演を用意いたしました。特別講演では、人工知能・ロボット研究の先駆者であり、システムズバイオロジーの概念を初めて提唱した北野宏明先生（システム・バイオロジー研究機構代表、ソニーコンピュータサイエンス研究所所長）と、長年の間、基礎と臨床を連結し、現場の立場から translational な薬学研究に従事されてきた本部会会長の崔吉道先生（金沢大学附属病院薬剤部長）にお願いをいたしました。また、教育講演では、企業での創薬研究、国内外での学術研究、そして学部長・学長として大学教育や運営、数多くの制度設計に関与し、薬学のあらゆる側面を体感してこられた伊藤智夫先生（北里大学名誉教授）にお願いいたしました。

今回のテーマの趣旨を達成するためには、シンポジウムの枠組み作り以上に、様々な研究分野や興味の方向性が異なる学生や基礎研究や臨床研究に携わる若手研究者が一堂に会して、freely に双方向なコミュニケーションを交わし、その緻密な web の中から新たな視点や発想が創出され、未来の医療薬科学が想像もつかなかった方向に駆動していくことが最も重要です。当日の議論と交流を通じて、新たなる医療薬科学の学問領域が思いがけず誕生する瞬間に立ち会えることを楽しみにしております。

第 15 回次世代を担う若手のための医療薬科学シンポジウム
実行委員長：前田　和哉（北里大学薬学部）
副実行委員長：鈴木　陽介（明治薬科大学）

【プログラム】

10 月 23 日（土曜日）

13:00～13:20　　開会式

13:20～14:35　　一般口頭演題（１）

14:45～16:00　　一般口頭演題（２）

16:10～16:55　　ポスター示説（奇数番号）

（Remo により行います）

17:10～18:00　　特別講演 1

北野　宏明　先生

（システム・バイオロジー研究機構代表、ソニーコンピュータサイエンス研究所所長）

「システムバイオロジーからノーベルチューリングチャレンジへ」

18:10～19:00　　教育講演

伊藤　智夫　先生

（北里大学名誉教授）

「若い医療薬科学研究者へのメッセージ : 日米の企業・大学での経験から」

19:00～21:00　　Online 懇親会

（Remo により行います）

10 月 24 日（日曜日）

9:00～10:30　　一般口頭演題（３）

10:30～12:22　　若手シンポジウム

「医療薬科学との融合が期待される最先端異分野研究」

・三浦　茜　先生

(成育医療研究センター成育遺伝研究部・研究員)

「原発性免疫不全症に対する CRISPR/Cas9 法を用いた新規遺伝子治療の開発」

・門之園　哲哉　先生

(東京工業大学生命理工学院・テニュアトラック助教)

「スマートデザインによる CD25 結合抗体代替ペプチドの創製」

・小松　徹　先生

(東京大学大学院薬学系研究科・助教)

「酵素のはたらきを網羅的に見て疾患を知る～１分子計測リキッドバイオプシー技術の確立を目指して～」

・竹下　潤一　先生

(産総研安全科学研究部門)

「安全性評価への数理科学的手法の応用」

12:22～13:15　　バーチャルランチョンセミナー

（富士通株式会社）

13:15～14:00　　ポスター示説（偶数番号）

（Remo により行います）

14:10～15:00　　特別講演２

崔　吉道　先生（金沢大学附属病院薬剤部長）

「基礎研究／臨床研究のアウトプット、アウトカム、ソーシャルインパクト」

15:00～15:20　　閉会式

【医療薬科学部会　若手世話人会】

荒木 拓也	群馬大学医学部附属病院・薬剤部
異島 優	徳島大学大学院・医歯薬
神崎 浩孝	岡山大学病院・薬剤部
小林 正紀	北海道大学大学院・薬
佐藤 洋美	千葉大学大学院・薬
座間味 義人	徳島大学大学院・医歯薬
首藤 剛	熊本大学大学院・薬
白坂 善之	金沢大学・薬
鈴木 雅美	大阪大学大学院・医
鈴木 陽介	明治薬科大学
高橋 有己	京都大学大学院・薬
舘 知也	岐阜薬科大学
中川 俊作	京都大学医学部附属病院・薬剤部
中瀬 朋夏	武庫川女子大学・薬
長野 一也	和歌山県立医科大学・薬
西村 周泰	京都薬科大学
平 大樹	京都大学医学部附属病院・薬剤部
平井 啓太	静岡県立大学・薬
前田 和哉	北里大学・薬
見野 靖晃	浜松医科大学病院・薬剤部
山田 勇磨	北海道大学大学院・薬

【YCPS2021　実行委員会】

前田 和哉	北里大学・薬（実行委員長）
鈴木 陽介	明治薬科大学（副実行委員長）
苅谷 嘉顕	東京大学医学部附属病院・薬剤部
齊藤 順平	国立成育医療研究センター・薬剤部
野口 幸希	慶應義塾大学・薬
奈良輪 知也	北里大学・薬
水野 忠快	東京大学大学院・薬

本シンポジウムに対して、以下の企業の方々の多大なるご支援を頂きました。心より御礼申し上げます。（五十音順）

アステラス製薬（株）
オリエンタル酵母工業（株）
（株）カネカ
木村情報技術（株）
サーモフィッシャーサイエンティフィック（株）
佐藤製薬（株）
シーメンスヘルスケア・ダイアグノスティクス（株）
（株）ジェノメンブレン　事業開発部
（株）じほう
（株）タカゾノ　病院営業部
高田製薬（株）
東和薬品（株）中央研究所（基盤技術本部）
日本ウォーターズ（株）
ノーベルファーマ（株）
ノボ ノルディスク ファーマ（株）
富士通（株）
フロイント産業（株）
理科研（株）
（株）Rhelixa

特　別　講　演　1

(10/23 17:10～18:00)

北野　宏明　先生

（システム・バイオロジー研究機構代表、
ソニーコンピュータサイエンス研究所所長）

「システムバイオロジーからノーベルチューリングチャレンジへ」

システムバイオロジーからノーベルチューリングチャレンジへ

○北野　宏明
[1] 特定非営利活動法人システム・バイオロジー研究機構、[2] 沖縄科学技術大学院大学、[3] 株式会社ソニーコンピュータサイエンス研究所
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システムバイオロジーは、生命をシステムとして理解する学問として提唱された[1,2]。分子生物学は、生命現象を分子の言葉で記述することで、極めて大きな成功を納めたが、生命現象は、それらの分子間のダイナミックな相互作用によって生み出されている。その背後には、システムレベルでの原理が存在し、それを理解することがより深い生命の理解へとつながるという考えが背後にある。その理論的支柱の一つとして生物学的ロバストネスの概念を提唱した[3-6]。また、これらの研究を推進する技術的基盤を形成するために、分子間相互作用の表記の国際標準(SBML, SBGN)の作成[7-9]、ソフトウエアプラットフォームの開発などを行なってきた[10]。その結果、システムバイオロジーは、生物学の重要な分野として認知されるに至った。

システムバイオロジーの提唱から25年近くの歳月が経ち、その成果と限界が明確になってきた。システムバイオロジーは、生物学にシステム論的思考を明示的にもたらし、生命現象の捉え方や研究の進め方に大きな変革をもたらした。さらに、創薬などの分野での応用が進み、システムバイオロジーの手法を利用した創薬が行われている[11]。しかし、極めて大規模で複雑なシステムにどれだけ切り込めているかに関しては極めて不十分であると言わざるを得ない。現在のシステムバイオロジーでは、大規模システムに関しては、大規模データからの統計解析とネットワーク解析を利用し、精密モデルは小規模なシステムを対象とするにとどまっている。大規模システムの精密モデルは、実現していない。この背後には、我々の認知的限界や現在の研究体制の社会学的・技術的制約が存在する[12]。この問題を打破するには、人間の認知の限界を突き破り、現在の研究の方法論を超えるアプローチを築き上げる必要がある。ノーベル・チューリング・チャレンジは、これを実現し、人工知能（AI）と人間の科学者の共生系として、かつてない速度で大きな科学的発見を連続的かつ高度な自律性をもって生み出していくシステムの開発を目指したグランドチャレンジである[13]。また、分散型の大規模サイエンスという新たな形態になるとも思われる[14]。このチャレンジは、科学のあり方を大きく変革させると考えている。

この背後の個人的な動機を簡単に述べさせていただく。私自身は、理論物理学を学んだ後、計算機科学の分野で活動を始め、米国の Carnegie Mellon University で、人工知能と超並列計算機の研究を行い、その後、ERATO プロジェクトでシステムバイオロジーとロボティックスのプロジェクトを開始した。その間、California Institute of Technology で、システム生物学と制御工学の境界領域研究を進めてきた。生命科学の最初のプロジェクトは、1993年頃に開始したワシントン大学セントルイス校の今井眞一郎教授（当時は慶應義塾大学）との細胞老化のメカニズムの解明であった[15,16]。この研究は、サーチュイン・ファミリーの発見にも結びつき[17]、20年経ってそこでの理論予測はほぼ全て正しかったことが分かった[18]。しかし、それまでに20年以上の歳月を要しており。また、その推論の過程では、多くの推測や科学的直感による判断が介入しており、我々はラッキーであったという感を免れない。AI が科学的発見を行うと言うと、必ず言及されるのが、重要なテーマをどうやって AI が判断するのかと言う点である。つまり、

Asking right questions が重要であるということである。しかし、これは、生身の科学者の現役期間とその間に利用できるリソースの限界からくるのである。この制約が大きく緩和されれば、Asking every questions, important answer is among them である。そもそも、何が重要な問いなのかを事前に予測すること自体が実は困難であることを理解し、謙虚になるべきであろう。このことを理解することは、好奇心に基づく基礎研究の重要さを理解することと同義である。このチャレンジは、Autonomous Scientific Discovery at Scale を実現しようと言うものであり、AI による科学的発見は、大きな発見を大規模に行うことを目指している。個人的には、私が研究してきた大規模 AI やロボット工学をシステムバイオロジーという対象領域で融合させる研究であり、サイエンスの形態を変革することを目指している。

略歴：

1984 年　日本電気（株）入社
1991 年　京都大学博士号（工学）取得
1993 年　ソニーコンピュータサイエンス研究所入社
2011 年　同代表取締役社長
2011 年　学校法人沖縄科学技術大学院大学学園教授
2001 年　特定非営利活動法人システム・バイオロジー研究機構を設立、会長
2016 年　ソニーグループ株式会社執行役員コーポレートエグゼクティブ
2020 年　同常務
2020 年　Sony AI Inc. CEO

その他：

1998 年 10 月～2003 年 9 月、科学技術振興事業団 ERATO 北野共生システムプロジェクト総括責任者兼務、2003 年 10 月～2008 年 9 月、同プロジェクトの発展継続プロジェクト、独立行政法人科学技術振興機構 北野共生システムプロジェクト（ERATO-SORST）の研究代表者

主な受賞：

1993 年　Computers and Thought Award
2000 年　Prix Ars Electronica
2009 年　ネイチャーメンター賞中堅キャリア賞
2021 年　米国人工知能学会（Association for the Advancement of Artificial Intelligence）AAAI フェロー

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特　別　講　演　２

(10/24 14:10～15:00)

崔　吉道　先生

（金沢大学附属病院薬剤部長）

「基礎研究／臨床研究のアウトプット、アウトカム、ソーシャルインパクト」

基礎研究／臨床研究のアウトプット、アウトカム、ソーシャルインパクト

○崔　吉道 [1,2]

[1] 金沢大学附属病院薬剤部、[2] 医薬保健研究域附属 AI ホスピタル・マクロシグナルダイナミクス研究開発センター

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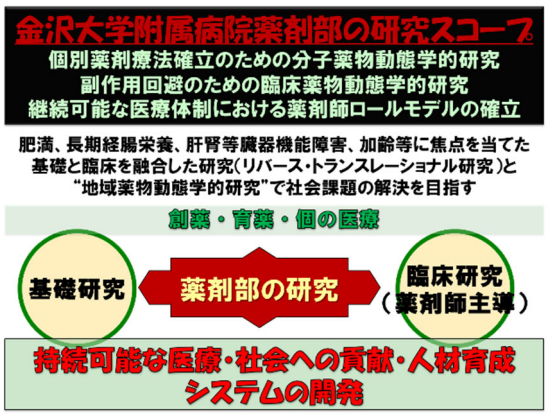
薬剤部職員や大学院生から「研究に興味があるけれど、何をどうすれば良いのか？」、「どうすれば研究テーマが見つかるのか？」、「クリニカルクエスチョンをリサーチクエスチョンに形作るにはどうすれば良いのか？」、「そもそも何のために研究をするのか？」といった質問をしばしば寄せられる。「医療薬科学のさらなる発展に向けて、異分野融合型の研究を推進することの重要性を啓発したい」との副実行委員長の鈴木陽介先生の熱意に触れ、前途輝く若手医療薬科学研究者の皆さんに医療薬科学部会の将来を託すために、この講演をお引き受けすることにした。本講演では、基礎（薬剤学、薬物動態学、細胞生物学、分子生物学）と臨床（医療薬学）の融合研究の経過と現在の医療と薬学、薬剤師を取り巻く環境を踏まえた今後の展望について演者の研究経過と経験を交えて概説したい。

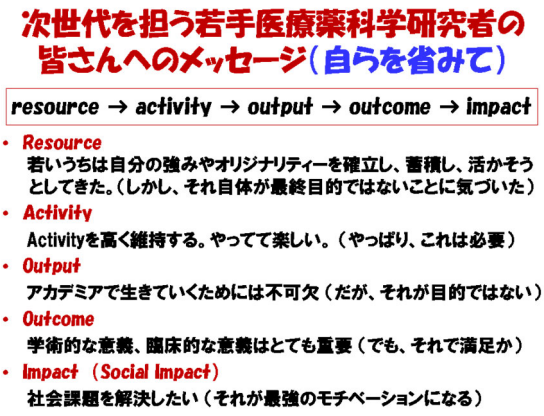
演者は、化学と医療との接点への興味と“博士”への漠然とした憧れから薬学部を選び、大学入学後はトランスポーター研究の第一人者の故辻彰教授の講義の魅力に引き込まれ製剤学研究室の門をたたき、生物薬剤学／薬物動態学の基礎研究の道を歩み始めた。卒業研究は、とにかく好きな実験がしたいというのが最大のモチベーションで、早朝、食肉センターに出向き牛脳検体の入手から脳毛細血管内皮細胞の単離と血液側および脳側細胞膜の分画、RI センターでの取り込み実験、細胞膜分画の酵素活性測定と続く 2 泊 3 日の実験に夢中になった。大学院は、リソソーム等の細胞内小器官を発見しノーベル賞を受賞した Christian de Duve の研究室で学んだ大熊勝治教授が主宰する生化学研究室に移りオルガネラの細胞分画、生体高分子の蛍光標識、共焦点レーザー顕微鏡、モノクローナル抗体の作成、細胞株のクローニングなど、細胞生物学と分子生物学の様々な手技を身に着け博士の学位を取得した。その後、助手として再び製剤学研究室に戻りアカデミアとしてのキャリアをスタートさせた。

この時代（昭和）は、carrier-mediated transport という現象を介在する担体は何か？という論争の真っ只中で、後に“Transporter”という言葉が生まれ薬物動態学研究の大きなパラダイムシフトがおこる中で、薬剤学領域に分子生物学や細胞生物学を持ち込んだ研究スタイルは自分自身の大きな強みとなり PEPT1、OCTN、OATP などの遺伝子クローニングや細胞内局在性の解明、SNP と薬物動態の個人間変動の解明等に貢献することができたと思う。



約 15 年の濃密な基礎研究期間を経て病院薬剤部へ異動し、必然として基礎研究と臨床研究の融合：リバーストランスレーショナルリサーチに取り組むことになったが、実はその間、共立薬科大学の中島恵美教授のもとで胎盤関門のトランスポーター研究に携わった 5 年間に、週に 1 度、短時間であるが、附属薬局

で行った薬剤師としての実務経験がその後の、臨床研究を行っていくのに大いに役立った。現在、病院薬剤部で約 12 年が経過し、薬剤部の教職員や研究室メンバーの頑張りが実り、いくつかの成果を得ることができた。一方、その間、医療を取り巻く社会の課題を目の当たりにし、臨床研究の先にあるものに気づかされた。アカデミアの研究者の使命である“新たな価値の創造と文化の継承”に加えて、社会の中の役割に応じた仕事が求められていくのである。そして、現在の演者の最大のモチベーションは“全ての世代が安心で持続的な医療体制の構築”という社会課題の解決とそれに必要な人材育成システムの開発である。



若いうちは自分の強み Resource を蓄積しオリジナリティーを確立したいと考えるのは自然で健全なことである。やがて、高い Activity を保ち、コンスタントに Output していくことは、アカデミアとしては不可欠であることに気づく。しかし、それ自体が最終目的ではない。次第に、明確なOutcomeを設定し学術的あるいは臨床的な意義がより高い研究を目指すべであり、さらに年齢と経験を重ね視野が広まるにつれて、Social Impact すなわち、目前のあるいは今後解決すべき社会課題の解決に貢献したいと考えるようになる。

皆さんも、自分の研究が社会をどのように変えることになるのか考えてみてはどうだろうか。私の経験が若い皆さんの将来に少しでも役に立てば望外の喜びである。

略歴：

1989 年　金沢大学薬学部卒業
1991 年　同　大学院薬学研究科修了
1994 年　同　大学院自然科学研究科修了　博士(薬学)
1994 年　金沢大学薬学部　助手
1997 年　米国 TUFTS 大学医学部生理学講座　Postdoctoral Fellow
2000 年　金沢大学大学院自然科学研究科　助手
2004 年　共立薬科大学　助教授
2008 年　慶應義塾大学薬学部　准教授
2009 年　金沢大学附属病院　准教授、薬剤部副部長
2014 年～現在　金沢大学附属病院　教授、薬剤部長、副病院長（2016 年～病院長補佐）
2020 年～現在　同　AI ホスピタル・マクロシグナルダイナミクス研究開発センター長兼任
主な社会的活動：(公社)日本薬学会　医療薬科学部会長、(公社)日本薬剤学会　理事、(一社)日本薬物動態学会　代議員、(一社)日本医療薬学会　理事、(一社)日本緩和医療薬学会　理事、(公社)日本薬剤師会　理事、(一社)日本病院薬剤師会　理事、(公社)薬剤師研修制度認証機構　理事、(NPO)薬学共用試験センター　理事、(公社)石川県薬剤師会　副会長、石川県病院薬剤師会　会長
趣味：模様替え
研究のモットー：あるべき姿を見極め、追求する

教　育　講　演

(10/23 18:10～19:00)

伊藤　智夫　先生

（北里大学名誉教授）

「若い医療薬科学研究者へのメッセージ：日米の企業・大学での経験から」

若い医療薬科学研究者へのメッセージ：日米の企業・大学での経験から

○伊藤　智夫
北里大学名誉教授
E-mail: itoht@pharm.kitasato-u.ac.jp

私は、1981 年に大学院修士課程を修了し、製薬企業に就職して経口徐放性製剤の研究開発に従事しました。在職中に2つの経口徐放性製剤の研究開発に関わりましたが、両者ともに上市され、現在でも市販されています。1つ目の製品は新入社員として計画通りに製品開発を進めただけでしたが、2つ目の製品は米国留学の経験（胃内滞留性製剤に関する基礎研究）を活かし当時利用可能になったばかりの PC を活用して、血中濃度の予測を重ねて自分が納得できる製品を開発することができました。ブロックバスターとなるような医薬品ではありませんでしたが、2つの医薬品の開発に関わることができたことは非常に幸運であったと思いますし、今でもこれらの医薬品を必要としている患者さんがいらっしゃることは、少しは社会貢献ができたのではないかという充実感を味わうことができています。

その後、博士の学位取得を目指し、製薬企業を辞して米国の大学院へ復学しました。大学院生あるいは博士研究員として大学に在籍しましたが、事実上は大学内のベンチャー企業の仕事をして学費・生活費を得ていました。上述の胃内滞留性製剤に関する基礎研究から2報の論文を発表しましたが、同時に米国の製薬企業が2つの特許を出願しました。また、博士研究員としては経皮吸収製剤の基礎研究に従事し、自分の研究の幅を広げることができました。米国の大学院生活で痛感したことは、博士の学位を有する者のみが研究者であり、学位を有しない者はテクニシャン止まりという現実です。一方、日本で取得した「博士」は世界中で通用しますが、多くの国の「博士」が欧米では通用しないことも知りました。足掛け5年半の米国生活でしたが、多くの国の様々なバックグラウンドを有する人と交流することができ、視野が広がると共に、人種・民族に対する考え方が身に付いたと思います。最近は海外留学が不要と考える方もいますが、米国のように様々な人種・民族が共存する環境に身を置くことは、日本では得られない貴重な経験になると今でも確信しています。

日本に帰国してからは私立大学に勤務しましたが、異性体医薬品の体内動態、トランスポーター、初回通過効果や薬物相互作用の定量的予測という様々な研究を行いました。振り返ってみると、ある意味その時々の流行りの研究で、学外研究費が得られる研究を行ってきたと思います。多くの著名な研究者が日本における基礎研究の低下を憂えていますが、普通の大学に勤務した経験からすると、学外研究費が得られないと学生の実験にも支障がでますので、どうしても流行りの研究をせざるを得ないという事情があります。企業では製品の研究開発が主ですが、大学では研究以上に教育、すなわち人材育成の比重が非常に大きくなります。私は私立大学に 31 年間勤務しましたが、この間に 620 名の学生が学部学生や大学院生として研究室を巣立って行きました。多くの学生さんが研究室を選んでくれたことに感謝するとともに、その責任の重さを感じながら仕事をしていました。今でも、多くの卒業生が社会で活躍しているのを見るのは喜びであると同時に、大学人として少しは責任を果たすことができたのではないかという安堵の気持ちもあります。

今回は、若い医療薬科学研究者を対象とした講演ですが、医療薬科学研究者の皆さんにも様々なバックグラウンドを持った方がいると思います。私は薬剤師の資格を有していますので、本来であれば実務（薬剤師業務）、教育、研究の3つを同時にこなすのが理想と思いますが、

3つを同時に均等にこなすことは不可能です。医療関連の資格を有しない方は、教育、研究の2つかもしれませんが、2つを同時に均等にこなすことも困難でしょう。おそらく、多くの若い方は研究が主で、その次に教育や実務になると思いますが、年齢を重ねると管理運営という新たな責任が加わります。多くの時間を自分のために使える若いうちに研究成果を挙げて、早めに博士の学位を取得して下さい。

日本や米国で勤めている時は、常に「企業はいつ潰れるか分からない」という思いを持って働いていました。最近は、日本の大学も同様の状況になりつつあると思います。自分のキャリアを確保するためにも、博士の学位は必須と思います。日本には、社会人大学院や論文博士の制度があります。前述のように、日本の学位は世界で通用します。世界で活躍するには、博士の学位を取得して、やっとスタートラインに立てるという現実を忘れないで下さい。

現在、COVID-19 が世界で猛威を振るっていますが、その背後には多剤耐性菌の問題が控えており、人類の将来に大きな影響を及ぼすと思われます。今回の COVID-19 に限らず、様々な面で世界は急速に狭くなっていると感じます。一方、日本は科学技術の面では、まだ世界のトップクラスに位置しており、恵まれた研究環境にあると思います。医療に関する研究は、患者さんへ還元され、人類に貢献すべきであると思います。若い医療薬科学研究者の皆さんは、是非、それぞれの立場で能力を発揮され、様々な形で人類に貢献する成果を挙げられることを期待しています。

略歴:

1981 年 3 月　東京大学薬学系大学院修士課程修了（製剤学教室）
1981 年 4 月　山之内製薬株式会社入社、経口徐放性製剤の研究開発に従事
1983～1984 年　カンザス大学出向、大学院在籍（M.S. 取得）
1986 年 10 月　山之内製薬株式会社退社、カンザス大学大学院復学
1987 年 6 月　カンザス大学大学院博士（Ph.D.）取得、カンザス大学博士研究員
1990 年 4 月　北里大学薬学部薬剤学教室・助教授
1997 年 4 月　北里大学薬学部薬剤学教室・教授
2008 年 7 月　北里大学薬学部長（2016 年 6 月まで）
2014 年 7 月　北里大学副学長（2016 年 7 月まで）
2016 年 8 月　北里大学学長（2020 年 6 月まで）
2021 年 3 月　北里大学薬学部定年退職、北里大学名誉教授

趣味: 人類の歴史に関する勉強
座右の銘:「得意の時に油断するな、失意の時に落胆するな」（山之内製薬の社訓）
大切にしている考え: “Drugs need to be designed with delivery components in mind.”
（by Takeru Higuchi in 1950s）

若手シンポジウム

「医療薬科学との融合が期待される最先端異分野研究」

(10/24 10:30～12:22)

三浦　茜　先生
(成育医療研究センター成育遺伝研究部)
門之園　哲哉　先生
(東京工業大学生命理工学院)
小松　徹　先生
(東京大学大学院薬学系研究科)
竹下　潤一　先生
(産総研安全科学研究部門)

原発性免疫不全症に対する CRISPR/Cas9 法を用いた新規遺伝子治療の開発

○三浦 茜[1]、内山 徹[1]、安田 徹[1]、中林 一彦[2]、枝澤 佳織[1]、安藤 由希子[1]、望月 微笑[1]、小野寺 雅史[1]

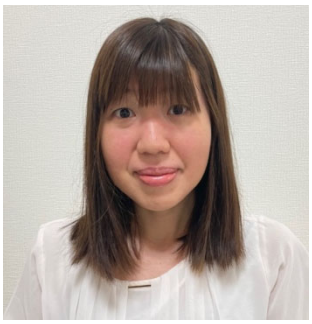
[1] 国立成育医療研究センター 成育遺伝研究部、[2] 国立成育医療研究センター 周産期病態研究部

uchiyama-t@ncchd.go.jp

1990 年代より実施されてきた原発性免疫不全症（PID）への遺伝子治療では、レトロ／レンチウイルスベクターによる遺伝子の恒常的発現により、免疫能の再構築という優れた効果が報告されてきました。一方で、一部の PID では、遺伝子の恒常的発現が発がん変化を引き起こすことから、従来の付加型遺伝子治療では安全性に大きな課題が存在しました。近年発展がめざましいゲノム編集技術では、変異遺伝子の直接修復が可能となり、修復後の遺伝子はゲノム上の内因性制御配列によって発現されます。そのため、厳密な生理的発現が可能となり、従来の方法では対応が困難とされていた疾患に対する遺伝子治療の開発が期待されています。

X 連鎖高 IgM 症候群(XHIM)は、活性化 T 細胞の表面に発現する CD40LG 遺伝子異常により発症し、B 細胞のクラススイッチ異常や T 細胞の機能不全を引き起こすことで、重症感染症を呈する疾患です。根本治療は造血幹細胞移植ですが、ドナーが不在の患者や感染による臓器障害を呈する患者に対しては、新たな治療法の開発が必要であり、T 細胞遺伝子治療の可能性が検討されてきました。CD40LG の強発現はリンパ腫の発生を引き起こすことから、生理的な遺伝子発現制御が必要であり、今回、我々が開発中である、CRISPR/Cas9 システムによるゲノム編集技術を用いた XHIM に対する T 細胞遺伝子治療法に関して最新の成果をご紹介します。

略歴：



2004 年 金沢大学医学部保健学科検査技術科学専攻 入学
2008 年 同 大学院医学系研究科 修士課程 進学
2010 年 信州大学医学部附属病院 臨床検査部 臨床検査技師
2011 年 信州大学大学院医学系研究科 博士課程 進学（社会人大学院生）
2016 年 国立研究開発法人国立成育医療研究センター 成育遺伝研究部 研究員
現在に至る
趣味：映画鑑賞、4 歳娘との工作
研究のモットー：研究も育児も欲張りに楽しむ

スマートデザインによる CD25 結合抗体代替ペプチドの創製

○門之園　哲哉
東京工業大学　生命理工学院　近藤・門之園研究室
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がんをはじめとする様々な疾患の分子標的治療において、標的に強く結合する中分子ペプチドは、抗体医薬の代替や抗体医薬を凌ぐ新たな創薬モダリティとしての利用が期待されている。このような標的結合ペプチドは抗体よりも組織浸透効率や体外排出効率が高く、細胞膜に発現する分子に限らず細胞内に局在する分子も標的として利用できるため、従来の抗体医薬とは異なる作用機序を持つ治療薬を開発することも可能である。そのため、臨床応用可能なペプチド医薬の創製を目指し、標的結合ペプチドのデザイン技術の高度化が進められている。

我々は、計算科学的手法と各種スクリーニング法を組み合わせた標的結合ペプチドの半合理的なデザイン技術「スマートデザイン」を提案し、基盤技術の構築を進めている [1,2,3,4]。スマートデザインは、既知情報を基にした構造計算や機械学習による最適配列予測などの、スーパーコンピューターによる計算技術を駆使し、広大な分子空間を効率よく探索することをコンセプトとしている。また、様々なタンパク質発現システムや分子ディスプレイシステムを活用し、候補分子を網羅的かつ迅速に評価することで、目的の機能を有する標的結合ペプチドを取得する。本講演ではスマートデザインの例として、CD25 受容体を抗原とする中和抗体医薬ダクリズマブから創製した T 細胞増殖促進ペプチドを紹介したい。

[1] T. Kadonosono, et al., "Design strategy to create antibody mimetics harbouring immobilised complementarity determining region peptides for practical use", *Sci Rep*, **10(1)**, 891 (2020)
[2] W. Yimchuen, et al., "Strategic design to create HER2-targeting proteins with target-binding peptides immobilized on a fibronectin type III domain scaffold", *RSC Adv*, **10**, 15154-15162 (2020)
[3] K. See, et al., "Reconstitution of an anti-HER2 antibody paratope by grafting dual CDR-derived peptides onto a small protein scaffold", *Biotechnol J*, e2000078 (2020)
[4] 特願 2021-097735 "T 細胞増殖促進ペプチド"

略歴:
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主な受賞:2018 年　平成 30 年度「東工大挑戦的研究賞」学長特別賞
目標:Protein designer になること

酵素のはたらきを網羅的に見て疾患を知る
～1分子計測リキッドバイオプシー技術の確立を目指して～

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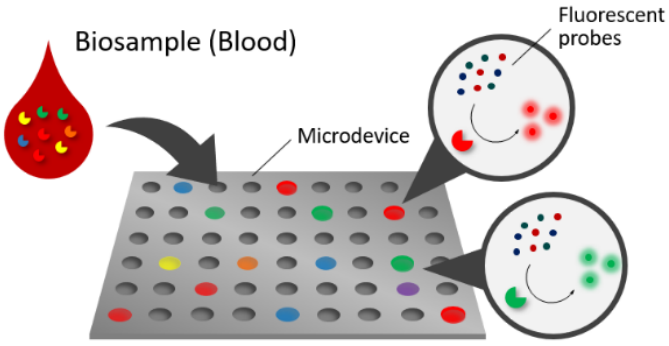
生体内には数千種類を超える酵素が存在し，これらの活性異常が疾患と関わる例が数多く知られています．血液中や疾患組織中の酵素活性の変化を検出することは，疾患の成り立ちに直結する病態の理解に繋がる診断の基盤となり得ることが提唱されていますが（Soleimany, A. P. et al., *Trends Mol. Med.* **2020**），血液中に存在する酵素のはたらきを網羅的かつ高感度に検出して疾患と関わる変化を効率的に探索する仕組みはこれまでに十分に確立されていませんでした．

このような背景の中，演者らは，血液中，生体サンプル中に存在する「酵素の機能」を「1分子ごとに」「網羅的に」解析することにより，疾患と関わる酵素の機能異常を理解し，かつこれに基づく疾患の早期診断法の開発を支える基盤技術を樹立することを目指した研究をおこなってきました．

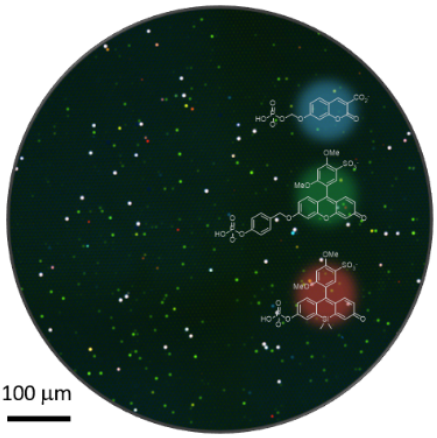
本手法は，微細加工技術によって調整された多数のマイクロチャンバーを有するデバイスに十分に希釈したサンプルをロードすることによって酵素分子を確率論的に1分子ずつ分画した状態で酵素の活性解析をおこなう1分子酵素活性計測法に基づいています．蛍光シグナルの変化によって特定の酵素活性を検出する「蛍光プローブ」を複数用いることで，これらに対する活性の違いからマイクロデバイス中にランダムに封入される1分子ごとの酵素種の違いを見分け，これらを網羅的に数える「1分子機能カウンティング」の方法論を考案し，これを用いて血液中の酵素活性を1分子計測により検出する技術の開発をおこないました（Sakamoto, S. et al., *Science Adv.* **2020**）．

はじめに，alkaline phosphatase（ALP），ectonucleotide pyrophosphatase/phosphodiesterase（ENPP）と呼ばれる酵素群に着目し，これらの活性を1分子レベルで計測可能な蛍光プローブ群を開発し，血液中の様々な酵素種の検出をおこないました．中でも，ENPP の特定のサブタイプの存在がすい臓がん患者の血液中で有意に増大していることが明らかになり，本方法を用いることにより，これまでのタンパク質解析法では見出すことが困難であった微少量のバイオマーカー候補を見出すことが出来ることが可能であることが確かめられました．

更に，より多様な酵素群の活性検出に本手法を利用するため，aminopeptidases，dipeptidyl peptidases，endopeptidases をはじめとする様々な酵素の活性を検出するプローブを効率的に開発する仕組みを開発し，種々のがん患者の血液サンプルで活性変化が見られる酵素を網羅的に評価するプラットフォーム構築を進めており，これらを用いて更なるバイオマーカーの探索が可能となることが期待されます．



Activities of single-molecule enzymes are read out by the set of fluorescent substrate probes



血液中の様々な生体分子の異常から疾患を診断する「リキッドバイオプシー」は，低侵襲性と繰り返し計測可能性などの利点をもって，従来の生検や画像診断に代わる次世代の疾患診断法として期待が集まっています．現在，各種モダリティーに基づく診断技術の開発が盛んにおこなわれている分野であるものの，セントラルドグマの下流に存在するタンパク質，特にその機能自体の変化に着目した診断手法の開発にはいまだ大きな可能性が残されていると考えられ，本研究を通じた新たなモダリティーのバイオマーカー，診断技術の開発の可能性についても併せて議論させていただけますと幸いです．

謝辞：本研究は，東京大学大学院薬学系研究科　水野忠快先生，名古屋市立大学　中川秀彦先生，川口充康先生，理化学研究所　渡邉力也先生，日本医科大学　本田一文先生をはじめとする諸先生方との共同研究成果であり，この場を借りて御礼申し上げます．

略歴：

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趣味：酒
研究のモットー：友人を大事に！

安全性評価への数理科学的手法の応用

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数理科学的手法を用いた化学物質や医薬品の安全性評価・予測手法として、定量的構造活性相関 (Quantitative Structure-Activity Relationship: QSAR) は広く知られた概念であると思う。QSAR とはインシリコ手法のひとつで、数理モデルを用いて化学構造などの化合物の特徴量をベースに、特定エンドポイントでの毒性を推計する手法であり、多くの既存研究がある。実際、私たちも一般工業化学物質を対象に、ラット肝毒性ポテンシャルの予測として血中 ALT 上昇の有無を統計的に予測する QSAR を構築した[1]。一方で、安全性評価で活躍し得る数理科学的手法は、QSAR 構築のための数理モデルだけではなく他にも色々とあるが、あまり紹介されることは少ないと感じる。そこで、本発表では、「探索」をキーワードとして、これまで講演者が取り組んだ研究から 3 つ紹介したい。1 つは QSAR 以外の文脈で統計手法を用いた研究、残り 2 つは数理最適化手法を用いた研究である。ここで数学分野での最適化とは、ある制約条件のもとで、何らかの評価関数を最大化もしくは最小化する解（最適解）を探すことをいう。

(1) 薬剤性肝障害 (DILI) 発症ポテンシャル評価のための分子記述子探索[2]

統計手法のひとつである決定木分析を利用した研究である。決定木分析は、木構造を用いて分類（場合によっては回帰）を行う手法である。最新の機械学習手法に比べると予測精度では劣るものの、分類ルールを可視化でき分類のキーとなる変数が分かりやすい特徴がある。そのため予測精度を求めることよりも、要因を分析したい場合には有効な手法であると考えられる。この研究では副作用データベースとして、米国環境保護庁 (EPA) が公開している DILIrank[3]を利用し、分子量を原子数で除した「平均分子量」のみでも DILI 発症ポテンシャルをある程度スクリーニング評価できる可能性を見いだした。

(2) ダイレクトリプログラミング (DR) を誘導する化合物組合せの探索[4]

DR とは、分化細胞から iPS 細胞を経ずに別の特異的な分化細胞に直接誘導する方法である。この研究は、DR を誘導する既知化合物組合せと同等の働きをし得る別の化合物組合せを、大規模データベースから探索する問題を、離散最適化問題として定式化し求解した研究である。離散最適化問題とは、最適化問題に含まれる変数の取り得る値が、整数や自然数など離散的である問題のことをいう。新たな化合物組合せの候補は KEGG DRUG[5]に含まれる承認薬約 5000 個とした。この候補化合物群から適当な化合物組合せを選択した際に、その化合物組合せがカバーする制御パスウェイと、既知化合物組合せがカバーする制御パスウェイとの類似性を評価関数とする離散最適化問題を定式化した。探索候補の化合物数が n 個の場合、候補となる組合せ数は約 2^n 通りとなり、n=10 で約 1000 通り、n=20 で約 100 万通り、n=30 で約 10 億通りとなる。これより本研究の n=5000 について総当たりで最適な組合せを求めることはほぼ不可能であるとわかる。そこで、それなりに良い解を現実的な時間で求めることができるメタ戦略とよばれる解法を利用し、最適な化合物組合せの候補を複数求めた。その結果、評価値が最適値の理論値に一致する組合せ候補や、それに極めて近い組合せ候補を複数抽出することができた。

(3) 化合物分類のための遺伝子抽出[6]

遺伝子発現データを用いて化合物をクラスタリングする際に、用いるデータの個体数（化合物数）よりも次元数（遺伝子数）が桁違いに多い問題に対して、クラスタリングに用いる遺伝子群を抽出する問題を離散最適化問題として定式化し求解した研究である。全遺伝子からクラスタリングに用いる適当な遺伝子群を選択した際の評価関数を、(i)同一化合物間の距離が近いほど、(ii)異なる化合物間の距離が遠いほど、(iii)持つ情報量が多いほど、良いとした。一般に評価関数が複数ある問題を多目的最適化問題とよび、評価関数が共存する場合には完全な最適解が存在するが、トレードオフの関係になっている場合はある評価関数に対しては最適であるが他の評価関数では最適ではない状況が生まれる。そのため、多目的最適化問題は適当な単一の最適化問題に変換して求解する必要が生じる。本研究では最も単純な方法ではあるが、元々の評価関数の線形和（加重平均）を評価関数とする単一の最適化問題に変換することを行い、求解した。その結果、全遺伝子データを用いてクラスタリングする時よりも、離散最適化問題の解として得られた一部の遺伝子群のデータを用いてクラスタリングした方が、より明確に分類されることがわかった。

謝辞: 本発表の一部は、静岡県立大学薬学部の吉成浩一教授、九州工業大学情報工学研究院の山西芳裕教授、筑波大学システム情報系の宮本定明教授と遠藤靖典教授、及び各研究室メンバーとの共同研究の成果です。

参考文献: [1]J. Takeshita *et al*, Comput Toxicol, 6 (2018), 64-70. [2]Y. Shimizu *et al*, PLoS ONE, 16(6) (2021), e0253855. [3]M. Chen *et al*, Drug Discov Today, 21(4) (2016), 648-653. [4]Nakamura *et al* (in preparation) [5] https://www.genome.jp/kegg/drug/ [6] J. Takeshita *et al*, Bull Inf Cybern, 53(4) (2021), 1-14.

略歴

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2011 年 4 月より現職
・法人格は 2015 年 3 月まで「独立行政法人」、2015 年 4 月より「国立研究開発法人」。役職は 2013 年 9 月まで「研究員」、2013 年 10 月より「主任研究員」。
趣味：プロ野球観戦で千葉ロッテマリーンズを応援している。一応、ファンクラブにも入っている。
研究について：数学以外に背景をもつ課題を数学的に解決することや、それに必要となる数学理論を構築することに興味を持ち研究してきている。上記で紹介した以外の研究として、新しい測定方法の精度を評価する統計手法（統計的品質管理手法）の構築などにも取り組んでおり、国際規格を策定する ISO の分科会のひとつである TC69（統計的方法の適用）の国際エキスパートや国内対応委員会の幹事を担当している。

バーチャルランチョンセミナー

(10/24　12:22～13:15)

富士通株式会社

「臨床薬物相互作用の評価に活用！

薬物動態パラメータ算出～薬物相互作用予測まで」

臨床薬物相互作用の評価に活用！
薬物動態パラメータ算出～薬物相互作用予測まで

中原　有沙
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ソーシャルデザイン事業本部デジタルラボ事業部
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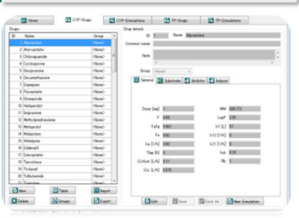
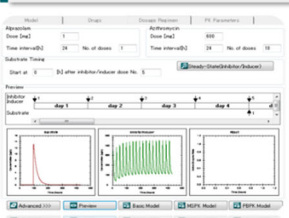
  トランスポーター阻害
  肝臓OATPs阻害
- Basic、MSPKモデル

パラメータデータベース
- PKパラメータ値の登録
- *in vivo* K_i値の収録
- 薬物データの編集機能



投与設計・評価
- 柔軟な投与設計
- バッチシミュレーション
- 各臓器の血漿中濃度推移の表示機能



一般口頭演題

O1-1～O1-5

10/23 13:20～14:35

O2-1～O2-5

10/23 14:45～16:00

O3-1～O3-6

10/24 9:00～10:30

O1-1

Factors influencing plasma coproporphyrin-I concentration as biomarker of OATP1B activity in patients with rheumatoid arthritis

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[INTRODUCTION] Organic anion transporting polypeptides (OATP)1B are drug transporters mainly expressed in the sinusoidal membrane. In previous reports, genetic factor, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) which is one of the uremic toxins, and inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) decreased OATP1B1 activity in vitro, but in vivo effects of these factors have not been elucidated. Plasma coproporphyrin-I (CP-I) is spotlighted as a highly accurate endogenous substrate of OATP1B. This study focused on patients with rheumatoid arthritis (RA) and evaluated the influence of several factors comprising gene polymorphisms, uremic toxins and inflammatory cytokines on OATP1B activity using plasma CP-I concentration. [METHODS] Disease activity score 28-C-reactive protein (DAS28-CRP) was used to evaluate disease progression. To investigate whether CP-I concentration is altered by the change of inflammatory status due to treatment, blood samples were collected at two points (at baseline and at the next visit). Plasma CP-I and CMPF concentrations were measured by ultra-high-performance liquid chromatography coupled to tandem mass spectrometry. Plasma concentrations of IL-6 and TNF-α were measured by ELISA method. To determine the OATP1B1 mutant alleles, all samples were analyzed for single nucleotide polymorphisms. [RESULTS] Thirty-seven patients were satisfied the selection criteria. Median DAS28-CRP and IL-6 were significantly lower at the next visit than at baseline, confirming reduced disease activity by treatment, but there was no significant difference in CP-I concentration. CP-I concentration tended to be higher in *OATP1B1*15* carriers than in non-carriers both at baseline ($p = 0.054$) and at the next visit ($p = 0.063$). A positive correlation was observed between plasma CP-I and CMPF concentrations (baseline: $r_s = 0.383$, $p = 0.019$; next visit: $r_s = 0.382$, $p = 0.021$), whereas no significant correlation was found between plasma CP-I and IL-6 or TNF-α concentration. Multiple logistic regression analysis by stepwise selection, plasma CMPF concentration was extracted as a significant independent factor affecting plasma CP-I concentration at baseline ($p = 0.029$), whereas *OATP1B1*15* allele was extracted at the next visit ($p = 0.027$). [DISCUSSION and CONCLUSION] Median IL-6 and TNF-α concentrations in patients with RA measured in this study were at approximately 10 pg/mL, whose concentrations were considerably lower than a previous in vitro study (IL-6: 10 ng/mL, TNF-α: 100 ng/mL). Therefore, it is possible that the discrepancy between the findings in this in vivo study and the previous in vitro study may be due to the differences in IL-6 and TNF-α concentrations. On the other hand, *OATP1B1*15* carriers and CMPF concentration were identified as an independent factor affecting the plasma CP-I concentration. In conclusion, the present findings suggest that inflammatory cytokines do not have clinically significant effects on OATP1B activity, whereas the effects of genetic polymorphisms and uremic toxins should be considered.

O1-2

Development of an Experimental Disease Model Suitable for the Analysis of Cancer Immunotherapy-Associated Myocarditis

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INTRODUCTION Immune checkpoint inhibitor (ICI)-induced myocarditis has a very high mortality rate; therefore, preventive and therapeutic agents are urgently required. Animal models are essential for developing new drugs. The analyzable period for the PD-1-KO-N10 model is short because it is a short-lived spontaneous myocarditis model. Therefore, it has been difficult to implement the model in the development of new drugs. In contrast, PD-1-KO-N12 is a similar model but with long-term survival and low myocarditis incidence. PD-1-KO-N12 could be used to create a long-lived and appropriately timed model for myocarditis using a myocarditis-inducing agent. METHODS The PD-1KO mice of a BALB/c background (PD-1-KO-N12[BALB/c]) were treated with the myocardial inducer myosin and pertussis toxin and dissected 21 days after administration to evaluate whether myocarditis was induced. Further, histological staining of the myocardium and analysis of inflammatory, fibrotic, and myocarditis-causing genes were performed. RESULTS and DISCUSSION Myosin-treated PD-1KO mice displayed cellular infiltration into myocardial tissue compared to that of untreated PD-1KO and wild-type mice and wild-type mice treated with myosin. In addition, the gene expression of inflammatory cytokines such as IL-6, IL-1b, and TNF α were upregulated in myosin-treated PD-1KO mice. Mice also showed an increase in levels of fibrosis and myocardium-related markers. CONCLUSION In conclusion, we have succeeded in creating an experimental model of ICI-associated myocarditis that can easily and reliably develop myocarditis.

O1-3

Development of an in vitro evaluation system to distinguish each process of absorption for the first time in the intestine-like epithelial cells

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[Introduction & Objective] Intestinal absorption has been extensively investigated so far by various in vitro evaluation systems but they all ignores distribution volume of the cell and differences of permeability between the apical and basolateral membranes which may affect on absorbability significantly especially for substrates of P-gp and CYP3A, thus never accounting for intracellular concentration. In this study, we established the in vitro method to evaluate each process of absorption and separated the contribution of P-gp and CYP3A in the intestine. The obtained parameters were also used to predict the FaFg of P-gp and CYP3A substrates. [Methods] In addition to conventional transport experiments, an efflux experiment was performed by using CYP3A forced expressed Caco-2 cells, for 13 drugs; midazolam, nifedipine, buspirone, nisoldipine, repaglinide, felodipine, terfenadine, sildenafil, alprazolam (CYP3A substrates), fexofenadine, digoxin (P-gp substrate), atorvastatin, and quinidine (CYP3A and P-gp substrates). The transport experiments were performed from both A and B sides in the presence and absence of P-gp or CYP3A inhibitor. For efflux experiments, these drugs were charged into the same cells under P-gp and CYP3A inhibition for 2 hours, washed with drug-free cold buffer, and then incubated at 37☒C for sampling from both sides over 60 minutes. LC-MS/MS was used to measure the concentrations of unchanged drugs and some of their metabolites, and the absorptive elementary process parameters were obtained by a simultaneous fitting analysis for various conditions using a three-compartment model. [Result & Discussions] The three-compartment model explained time-courses of drug concentrations satisfactorily for various conditions including the efflux experiments, and allowed reasonable estimation of the kinetic parameters and distribution volume for each drug. FaFg was also appropriately predicted. The permeability of fexofenadine, digoxin, atorvastatin, and repaglinide were 3.35, 4.3, 2.11, and 2.38 times more significant on the basolateral side than the apical side, suggesting possible contributions of facilitated exchange at the basolateral side. It was noted that the distribution volumes for felodipine and terfenadine were larger than other drugs which may suggest significant binding to the cell component. We confirmed that even though the clearance of efflux by P-gp and metabolism by CYP3A was large, the absorption was good if the permeability clearance to the basolateral side was also significant. For example, the efflux ratio of digoxin is twice that of fexofenadine. However, since the basolateral permeability of digoxin is 10 times greater than that of fexofenadine, the FaFg of fexofenadine is 0.3, and that of digoxin is 0.7. [Conclusion] With the new analysis method, the efflux by P-gp, metabolism by CYP3A, and permeability to the basolateral side in the intestinal epithelial cells were separately estimated and offered for prediction of FaFg. In the future, we will apply these data to our new physiologically based pharmacokinetic intestinal model, ATOM.

O1-4

The comparison of the MDR1 contribution to the drug distribution of the placental barrier and blood-brain barrier

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[INTRODUCTION] MDR1 at the blood-brain barrier and placental barrier functions to restrict drug distribution to the brain and fetus, respectively. Therefore, the fetal distribution of MDR1 substrate drugs is expected to be correlated with its brain distribution. However, the rodent placental barrier is formed by the syncytiotrophoblast bilayer frequently connected by gap junctional protein connexin26, and MDR1 is localized at the apical membrane of a fetal-facing layer. This indicates that placental MDR1 of rodents does not directly contact with the maternal blood, which may affect the functional role of MDR1. The purpose of this study was to quantitatively compare the contributions of single MDR1 protein to the fetal distribution of digoxin and paclitaxel with those to the brain distribution. [METHODS] The protein expression of MDR1A and MDR1B in the plasma membrane enriched fractions from murine placental labyrinth was quantified by LC-MS/MS-based quantitative targeted absolute proteomics. Paclitaxel or digoxin was continuously administered for 48-72 hr to pregnant *Mdr1a/1b* knockout or wild-type mice using an osmotic pump, respectively. The drug concentrations in maternal and fetal plasma and maternal brain were quantified by LC-MS/MS, and the drug concentration ratio (K_p) was calculated. The K_p ratio was calculated by dividing the K_p values of *Mdr1a/1b* knockout mice by that of wild-type mice. [RESULTS] The protein expression levels of MDR1A were almost constant from gestational days (GD) 13.5 to GD17.5, whereas MDR1B tended to decrease toward GD17.5. At GD17.5, the $K_{p,fetal\ plasma}$ ratio of paclitaxel was 7.5 while that of digoxin was 1.3. The $K_{p,brain}$ ratio of paclitaxel and digoxin was 28 and 41, respectively. The contribution of single MDR1 protein [(K_p ratio-1) / MDR1 protein expression amount] to fetal distribution of paclitaxel was calculated to be 98% of that to the brain distribution, while, in the case of digoxin, the MDR1 contribution to fetal distribution was 3% compared with the brain distribution. [DISCUSSION] Based on the pharmacokinetic model of murine placental barrier, the $K_{p,fetal\ plasma}$ ratio per single molecule of MDR1 is negatively correlated with the ratio of the PS product for the transfer mediated by gap junction (PS_{GJ}) to the PS product for the efflux across the apical membrane of SynT-II ($PS_{AP2,\ eff}$). The rate of passive diffusion of digoxin is lower than that of paclitaxel and thus PS_{GJ} / $PS_{AP2,\ eff}$ of digoxin is probably larger, causing the lower MDR1 contribution. [CONCLUSION] The contribution of single MDR1 protein at the placental barrier to fetal distribution of digoxin was marginal and much lower than that at the blood-brain barrier, while the contributions of single MDR1 protein were similar for paclitaxel. MDR1 at the rodent placental barrier is considered to work minimally for substrate drugs with low passive permeability.

O1-5

Improvement of insulin absorption by oral co-administration with small intestine-permeable cyclic peptide concatenated with an insulin-binding peptide

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【INTRODUCTION】Insulin is a 51-amino acid peptide hormone that is used to treat patients with diabetes mellitus (DM) and oral administration is an effective route for insulin treatment. We have recently developed a novel small intestine-permeable cyclic peptide (DNP peptide) and reported that oral co-administration of Zn-insulin with D-form DNP peptide (D-DNP peptide) enhanced blood glucose-lowering effect in mice. However, to reduce the effective amount of insulin required, a carrier peptide with increased insulin absorption has to be developed. The present study aimed at improving insulin absorption by oral co-administration of insulin with the novel D-DNP peptide concatenated with an insulin-binding peptide (D-DNP-V peptide). 【METHODS】A mixture of Zn-insulin with D-DNP-V peptide was administered by an *in situ* closed-loop method or orally in male ICR mice (7–10 weeks old). Blood glucose levels were measured using an ACCU-CHEK Aviva Nano meter. DM mouse models were generated by a single intraperitoneal injection of streptozotocin. The PA was. 【RESULTS and DISCUSSION】Using the *in situ* closed-loop method, co-administration of Zn-insulin and D-DNP-V peptide showed a significantly enhanced blood glucose-lowering effect compared to the D-DNP peptide. D-DNP-V peptide reduced the effective amounts of orally administered Zn-insulin (1/10) and D-DNP peptide (1/50). We optimized the concentration of $ZnCl_2$ to form hexamers and the molar ratio of insulin to D-DNP-V peptide. The optimized oral insulin administration method (M P.O. method) exhibiting the greatest blood-glucose lowering effect was the co-administration of insulin (10 IU/kg), D-DNP-V (1.2 μ mol/kg), $ZnCl_2$ (1 mM), and soybean trypsin inhibitor (STI, 1.25 mg/ml). The M P.O. method reduced blood glucose levels by 45% at 120 min and recovered to the initial level at 360 min. Additionally, oral administration of Zn-insulin at the lower dose (1 IU/kg) by M P.O. method reduced blood glucose levels in mice pre-treated with gastric degradation inhibitors (omeprazole and pepstatin A), and pharmacological availability relative to subcutaneous injection was estimated to be 34%. Finally, in DM model mice, oral co-administration of insulin by M P.O. method decreased the blood glucose levels by 64% at 240 min. 【CONCLUSION】The present study demonstrated that D-DNP-V peptide demonstrates enhanced blood glucose lowering effects by oral co-administration with Zn-insulin. We propose that by increasing the binding affinity of D-DNP peptide to insulin, intestinal absorption of insulin is facilitated in the mouse model. Cyclic D-DNP-V peptide shows great potential as a carrier peptide in the development of effective oral co-administration strategies.

O2-1

Development of Mitochondrial-targeted Nanocarrier for Photodynamic Therapy Using the Microfluidic Device

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[INTRODUCTION] Cancer photodynamic therapy (PDT) is a cancer-selective therapy that involves irradiating a photosensitizer (PS) with light in the presence of oxygen molecules. Tumor site-selective and intracellular organelle-selective drug delivery systems (DDSs) have recently attracted much attention to increase therapeutic effect and protect against photodermatosis, which is a side effect of PDT. Recently, mRNA-encapsulated lipid nanoparticle (LNP) preparations (COMIRNATY®), which are vaccines for use against the severe acute respiratory syndrome coronavirus 2 have been approved as pharmaceutical product and LNP have attracted much attention for DDSs. In this study, we report on attempts to prepare a π-extended porphyrin analog, rTPA-encapsulated MITO-Porter by using a microfluidic device. We focused on the ratio of rTPA to lipid (Drug/Lipid: D/L) as a condition for the preparation and prepare two types of LNPs with different D/L. We discuss the correlation between D/L and the internal structure of LNPs as well as the photoactivity. [METHODS] 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine/cholesterol/1,2-distearoyl-sn-glycerol-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2,000]/rTPA were dissolved in ethanol to prepare lipid solution. rTPA-encapsulated MITO-Porter was prepared by mixing the lipid solution and phosphate buffered saline (-) using a microfluidic device. The microfluidic device, which incorporates a baffle mixer, is referred to as invasive lipid nanoparticle production (iLiNP) [Kimura N et al, ACS Omega. 3 (2018) 5044-5051]. After the dialysis, the LNPs were modified with STR-R8. The prepared particles were then analyzed by Dynamic Light Scattering, electron microscopy and small angle X-ray scattering. In addition, the production of singlet oxygen and the cell-killing effect of the preparation on HeLa cells were confirmed. [RESULTS and DISCUSSION] In the preparation of rTPA-encapsulated LNPs using a microfluidic device, the D/L ratio did not alter the physicochemical properties and intracellular kinetics: both LNPs were delivered to the intracellular mitochondria. On the other hand, the difference in D/L ratio caused a change in the internal structure of the particles which led to changes in the localization of rTPA in the LNPs. rTPA in high D/L LNPs was reversibly inactivated and did not produce singlet oxygen. Only low D/L LNPs produced singlet oxygen and showed the cell-killing effect on HeLa cells when irradiated with light. [CONCLUSION] Our results indicate that control of the localization of porphyrin-based PS in the LNPs would optimize the drug efficacy. We observed a reversible inactivation with increasing D/L. Therefore, it would be possible to prepare (1) high D/L LNPs (inactivated LNPs), which would activate when PS break up after reaching the target site (2) activated LNPs even at high D/L, by controlling the localization of PS in LNPs. The technology to control the localization of drugs in LNPs would be an important issue in the development of LNP preparations that determine the drug potency. Further studies on this issue are underway.

O2-2

Formulation of sustained release microsphere containing Cu-ATSM nanoparticles for the treatment of Menkes disease

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[Purpose] Copper complex (Cu-diacetyl-bis [*N*⁴-methylthiosemicarbazone]; Cu-ATSM) is attractive drug candidate for Menkes disease which is an inherited disorder in which the body has a problem absorbing copper. The complex can distribute to the body tissue including brain *via* passive diffusion and its clinical trial is currently conducted for the treatment of malignant brain tumor and/or usage of PET contrast agent. In this study, Cu-ATSM was pulverized with an aqueous copolymer to prepare the nanoparticles to improve drug solubility and its bioavailability. In addition, we attempted to achieve the sustained release of Cu-ATSM from the microspheres consisting of biodegradable polymer, which is expected to reduce the burden on patients. [Method] Cu-ATSM (synthesized in our laboratory) was put into the milling vessel with polyvinyl alcohol-acrylic acid-methyl methacrylate copolymer (POVACOAT, Daido Chemical Corporation) aqueous solution (POVA aq.) and zirconia beads, and pulverized to prepare the nanoparticles using a planetary stirrer MAZERUSTAR KK-250S (Kurabo Industries Ltd.). The conditions for pulverization were designed using the statistical software JMP® Pro 15 (SAS Institute Inc.), and a design space was constructed for two types of Cu-ATSM suspensions with different concentrations. The nanoparticulate Cu-ATSM prepared by pulverization under the optimum conditions was dispersed into dichloromethane solution of lactic acid-glycolic acid copolymer (PLGA, Evonik Industries AG) with ice-cooling to obtain s/o emulsion. The emulsion was injected into an aqueous polyvinyl alcohol solution under high-speed stirring to prepare s/o/w emulsion. Finally, Cu-ATSM-encapsulated microspheres were obtained through vacuum filtration and freeze-drying treatment. The yield of microsphere and encapsulation rate of Cu-ATSM were compared in the cases of two concentrations of Cu-ATSM suspension as well as microscopic observation and the *in vitro* drug release test was also demonstrated. [Results and Discussion] To understand the suitable conditions for preparing suspensions containing Cu-ATSM nanoparticles using a planetary stirrer, the design space was constructed by the response surface methodology for 20 and 40 mg/mL of Cu-ATSM suspensions. The amount of zirconia beads, volume of POVA aq. and milling time were significantly affected to the target parameters, mean particle size of 200 nm or less and polydispersity index (PDI) of 0.3 or less in processing the nanoparticles. As a result, the preferable nanoparticles could be prepared within the design space with good reproducibility. The mean particle size and PDI in the optimal condition were 182.0 ± 4.57 nm and 0.205 ± 0.002, respectively. In addition, the estimated and experimental values were coincident well. For the preparation of PLGA microsphere, nanoparticulated Cu-ATSM suspension with 40 mg/mL indicated superior yield and encapsulation rate of Cu-ATSM compared to that of lower drug concentration. Also, the microsphere seemed to provide constant drug concentration during *in vitro* drug release test.

O2-3

Measurement of thiopurine metabolites by LC-MS/MS

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【INTRODUCTION】 Thiopurines are used in the treatment of various diseases such as leukemia, inflammatory bowel diseases, and autoimmune diseases. One of the metabolic enzymes, NUDT15, negatively regulates thiopurine activity by converting the active metabolites of thiopurine, thio-deoxy guanosine triphosphate (thio-dGTP) and thio-GTP, to thio-deoxy guanosine monophosphate (thio-dGMP) and thio-GMP, respectively. The NUDT15 polymorphism, which is common in Asian populations including Japanese, is associated with the development of severe myelosuppression when taking thiopurines. Furthermore, it is difficult to determine individual dosage of thiopurines even for patients with wild type NUDT15. However, to date, no method for directly measuring the metabolic activity of thiopurine nucleotides including the NUDT15 enzymatic activity in cells has been reported. In this study, we attempted to quantitatively measure the activity of purified recombinant NUDT15 by liquid chromatography tandem mass spectrometry (LC-MS/MS). 【METHODS】 Calibration curves were made with five different thiopurine metabolites: thio-GTP, thio-guanosine diphosphate (thio-GDP), thio-GMP, thioguanosine, and 6-thioguanine (6-TG). Recombinant NUDT15 was expressed in *E.coli* and purified. The enzyme was incubated with thio-GTP at 37° C. The reaction was terminated by heat treatment at 95° C for 10 min and the metabolites were purified on a stage-tip column packed with filter paper. Thymidine-$^{13}C_{10}$,$^{15}N_2$ 5'-monophosphate was used as an internal standard for the measurement. LC-MS/MS was used for calibration curve preparation and activity measurement of NUDT15, using electrospray ionization (ESI) positive mode and multiple reaction monitoring (MRM) mode. Samples were loaded onto an AQ-C18 metal-free column and separated with a linear gradient of 1–100% acetonitrile in 5 mM ammonium formate solution at 400 nl/min for 9min. 【RESULTS and DISCUSSION】 The calibration curves of the five thiopurine metabolites were made by the internal standard method and showed good linearity in the range of 1–100 μM for thio-GTP, thio-GDP, and thio-GMP ($r^2 \geq 0.995$), and also showed linearity for thioguanosine and 6-TG ($r^2=0.970$ and $r^2=0.917$, respectively). Under these conditions, we successfully detected the enzymatic activity of purified recombinant NUDT15 that converts thio-GTP to thio-GMP. We believe that direct measurement of the NUDT15 enzymatic activity by this method can be applied to dosage adjustment of thiopurines for personalized medication.

O2-4

Impact of serotonin-associated gut microbiota dynamics on drug-induced gastrointestinal toxicity

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[INTRODUCTION] Gastrointestinal (GI) toxicities (e.g. diarrhea and constipation) are among the most common adverse events leading to discontinuation of oral medication. Therefore, predicting GI toxicity as well as bioavailability is important to develop oral drugs having higher safety and effectiveness. However, drug-induced GI toxicity is not necessarily easy to assess and predict, because its mechanism is complicated by multiple factors. For instance, serotonin (5-HT), a major GI hormone, is associated with gut microbiota, which plays a role in various GI physiology, but its interaction with oral drugs has not been fully clarified yet. Therefore, we speculate that oral drugs may influence gut microbiota dynamics via change in GI disposition of 5-HT mediated by transporters and/or enzymes, resulting in the drug-induced GI toxicity. In the present study, we examined our hypothesis that changes in the transporter-mediated GI disposition of 5-HT due to orally administered drugs could influence gut microbiota dynamics, leading to disorders of the GI fluid regulation, using metformin which clinically causes diarrhea as a side effect. [METHODS] Influence of 5-HT and metformin on luminal fluid, 5-HT and chloride ion (Cl^-) levels were estimated by employing *in situ* GI experimental techniques in rats. Effect of metformin on GI 5-HT dynamics were estimated by uptake and transport study using *Xenopus laevis* Oocytes expressing serotonin transporter (SERT) and Caco-2 cells. The gut microbiota was analyzed by quantitative PCR using phylum-specific primers. [RESULTS and DISCUSSION] Administration of metformin into intestinal lumen significantly increased the GI fluid volume in rats, demonstrating diarrheal symptom as adverse effect of metformin. At the same time, elevated levels of 5-HT and Cl^- in the GI lumen was also observed. Since metformin inhibited SERT-mediated 5-HT transport in SERT-expressing oocytes and Caco-2 cells, these findings indicate that metformin increases the luminal 5-HT levels by inhibiting SERT-mediated intestinal uptake. Further analysis for fecal microbiota indicated that administration of metformin influence gut microbiota dynamics (mainly *Firmicutes* and *Bacteroidetes*) as well as 5-HT and Cl^- levels. A similar tendency was observed after long-term administration (twice a day for 7 days) of metformin. When transferring the feces (microbiota) of these rats into the intestinal lumen of another untreated rat, the recipient rat showed the same diarrheal symptoms as the donor rat. These results indicated that gut microbiota is linked indirectly with diarrheal symptom induced by metformin. [CONCLUSION] Our findings indicate that metformin-induced GI toxicity is caused by the change in gut microbiota dynamics via an increase of the luminal 5-HT levels by inhibition of SERT-mediated intestinal uptake. This phenomenon is applicable to other drugs which disturb gut microbiota by inhibiting SERT and is useful to develop a methodology for predicting drug-induced GI toxicity, which can contribute to drug development and clinical application as biomarkers.

O2-5

Site-directed connection of functional protein on cell membrane via click reaction

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[INTRODUCTION] Cell surface modification via covalent bond with the functional protein, such as fluorescence proteins, antibody etc., is a promising way for labeling or delivering of therapeutic cells. In order to maintain the protein function, the site-directed connection of proteins with cell membrane is necessary. Furthermore, in the preparation of the therapeutic cells, cell modification needs to be operated in cell suspension to avoid enzymatic cleavage at the detachment of cells. The purpose of this study is to modify the cell surface in suspension by the site-directed connection of protein. For the site-directed connection of protein, Asn20 of fluorescence protein mKO2 was substituted by azido-phenylalanine(AzF). Alkynyl group, which make covalent bond selectively to azide group, were introduced on membrane protein of mesenchymal stem cells by metabolic labeling. Then, mKO2(Az) were connected to cell membrane on MSC(Alk) by reacting in suspension. [METHODS] Expression and purification of mKO2(Az): mKO2(Az) was expressed in the E. coli strain BL21(DE3) co-transformed with pColdIII/mKO2(Az) and pCDF/AzAz, which expresses tRNA and enzymes to introduce AzF. Then, expressed mKO2(Az) were purified with Ni Sepharose resin. Introduction of alkynyl group on cell membrane: After MSCs were harvested for 24 h, cells were incubated in the culture medium containing 40 μM peracetylated N-(4-pentynoyl)mannosamine (Ac_4ManNAz) further 48 h. To detect alkynyl group, 5/6-Texas Red-PEG3-Azide (Texas Red-Az) were used. Cell surface modification of mKO2: Alkynyl group introduced cells were detached by incubating for 1 min with the mixture of accutase and 0.25% trypsin (ratio = 1:1). The detached cells and mKO2(Az) were reacted at 4° C for 2h in PBS including 50 μM mKO2(Az), 50 μM CuSO4, 300 μM BTTAA, and 2.5 mM ascorbic acid. [RESULTS and DISCUSSION] In SDS-PAGE analysis, a single band was observed at 30 kDa (mKO2) in CBB stained gel. Furthermore, fluorescence signal of DBCO-FAM was detected at the band, which indicates azide reactivity of mKO2(Az). After Texas Red-Az was reacted with the adherent MSCs, the fluorescence signal was observed in MSCs with Ac_4ManNAl treatment than in the cells without the treatment. Then, Texas Red-Az was reacted with the detached MSCs with or without metabolic labeling. Fluorescence signal was observed in MSCs with metabolic labeling, suggesting that alkynyl group were remained after cell removal by accutase. Finally, mKO2 and MSCs were reacted in PBS by rotary shaking. Fluorescence signal was observed in the combination of mKO2(Az) and MSCs (Alk), but not in mKO2 and MSCs, and mKO2 and MSCs (Alk). Unexpectedly, weak signal was observed in mKO2(Az) and MSCs. It may be explained by the fact that UV promote the connection of AzF to amin groups. [CONCLUSION] Using click reaction, mKO2 could be connected at a specific site to cell membrane in suspension.

O3-1

Disruption of circadian metabolic regulation of cysteine contributes to the rapid growth and malignancy of murine hepatic cancer cells

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[Introduction] Many types of cancer cells increase demand for specific amino acids, which is dependent on either exogenous supply or upregulated de novo synthesis. Consequently, such amino acid addictions of cancer cells have been recognized as potential target for development of therapies. Intracellular accumulation of cysteine (Cys) is often observed in cancer cells, which is thought to contribute to the elimination of oxidative stress induced by rapid cell proliferation and/or exposure to anticancer drugs. However, pathological role of Cys in cancer cells is not fully understood yet. In normal healthy cells, synthesis and catabolism of Cys are subject to circadian rhythm, so that its intracellular content is changed depending on the times of day. Circadian change in the Cys metabolism in normal cells is suggested to be significant for energy production and sustaining cell viability, but no previous study has investigated the circadian metabolic regulation of Cys in cancer cells. In this study, we examined the underlying mechanism of alteration of Cys metabolism in hepatocarcinoma by focusing on the circadian regulatory networks and also explored the pathological role of Cys for enabling rapid proliferation of cancer cells. [Methods] Mouse hepatocarcinoma cells were implanted on the back of male mice. Intracellular content of cysteine was determined by LC-MS/MS. The expressions for cysteine metabolism-related enzymes and cell cycle regulators were measured by real-time PCR or Western blotting. The cell cycle distribution of cancer cells was analyzed by FACs. [Results and Discussion] In the normal healthy liver of mice, the expression levels of genes responsible for synthesis and catabolism of Cys exhibited significant circadian oscillations, which causes the time-dependent variations in intracellular content of glutathione as well as Cys. On the other hand, circadian expressions for most of genes regulating Cys metabolism were disrupted in hepatocarcinoma implanted in mice. The levels for those genes were decreased in hepatic cancer cells, but Cys content was constantly increased throughout the day. Elevation of Cys content in hepatic cancer cells seemed to be caused by up-regulation of Slc7a11 gene encoding cystine/glutamic acid transporter. Exposure of cancer cells to Cys-deficient media prevented the cell cycle progression from G1 to S phase by decreasing the expressions of cyclins. These findings suggest that accumulation of Cys in hepatocarcinoma tumor cells is resulted from disruption of its circadian metabolic regulation and enhancement of exogenous supply. Elevation of intracellular Cys seemed to be involved in the cell cycle regulation. [Conclusion] Disruption of circadian Cys metabolism was detected in hepatocarcinoma tumor cells, which causes compensatory enhancement of extracellular uptake of Cys. Intracellular accumulation of Cys contributes to the cell cycle progression. The present findings indicate the potential of circadian metabolic pathways of Cys as a therapeutic target for treatment of cancers.

O3-2

Evaluation of mitochondrial dysfunction-induced hepatotoxicity in cryopreserved primary human hepatocytes using plate with high oxygen permeability and low drug adsorption

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[INTRODUCTION] Mitochondrial dysfunction is one of the main reasons for severe liver injury, so it is important to predict liver injury in the preclinical stage. The gold standard for predicting the risk of liver damage is the use of cryopreserved primary human hepatocytes (PHH), which is also desirable for predicting mitochondrial toxicity. However, it was difficult to properly assess, probably due to mitochondrial damage from cryopreservation. Our previous study suggested that an oxygen-permeable plate with low drug adsorption enabled sufficient oxygen supply for hepatocytes, which improved mitochondrial function, CYP activity and increased the sensitivity of mitochondrial dysfunction-induced toxicity in rat hepatocytes. Therefore, this study investigated whether the use of novel culture plate improved the performance of mitochondrial toxicity assessments with PHHs. [METHODS] PHHs were seeded on polystyrene (PS)-plate or novel culture plate and cultured in optimized William's Medium E added with ITS, GlutaMAX, dexamethasone, antibiotic-antimycotic mixed solution, and several compounds. Drug metabolize enzyme (DME) activity was measured using LC-MSMS. Phenformin and rotenone (these drugs have mitochondrial toxicity) were exposed for 24 hours, then cell death was evaluated by LDH release. [RESULTS] Compared to day 0 hepatocytes, DME activity was increased in association with culture irrespective of the plate type. However, CYP3A4 activity was more increased when cultured in novel culture plate than PS-plate. The sensitivity of phenformin toxicity was dramatically increased in novel culture plate compared to PS-plate. No toxicity with rotenone was observed on both plates, but when used in combination with 1-aminobenzotriazole (1-ABT, non-specific CYP inhibitor), toxicity was observed only in the novel culture plate. [DISCUSSION] We aimed to construct a new in vitro method to detect mitochondrial toxicity dysfunction-induced hepatotoxicity in PHHs using novel culture plate with good oxygen permeability and low drug adsorption. In the novel culture plate, the sensitivity of phenformin toxicity, a mitochondrial toxicant, was increased. On the other hand, the toxicity of rotenone, which is also mitochondrial toxicant, was not confirmed. However, previous report suggests that rotenone is metabolized to less-toxic form(s) by CYPs. So, the sensitivity of rotenone -induced toxicity was increased by 1-ABT. This suggests that the increased rotenone metabolism in the novel culture plate may have reduced apparent toxicity. These results indicate that novel culture plate is possible to evaluate mitochondrial toxicity considering metabolite(s) in PHHs. [CONCLUSION] The culture condition using novel culture plate proposed here improved the performance of mitochondrial toxicity assessment using PHHs compared to the standard culture condition using PS-plate.

O3-3

Basic Characterization of Drug-induced Gastrointestinal Toxicity Using Cultured Intestinal Stem Cells Originated from Region-specific Crypts in Monkeys, Dogs and Humans

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[INTRODUCTION] Drug-induced gastrointestinal toxicity (GIT) is one of the most common adverse effects that can limit dosing, which leads to the insufficient drug efficacy and patients' quality of life. Current *in vitro* experimental systems are inadequate for evaluating GIT with high accuracy, making it difficult to predict the occurrence of GIT before clinical use of drugs. Moreover, species differences in GIT among pre-clinical species also make it trouble to directly extrapolate the severity of drug toxicity to humans. These issues facilitate the need for appropriate *in vitro* systems which can quantitatively predict the risk of GIT in drug development process. Recent advances in 3D culture of intestinal organoids have enabled a long-term culture of intestinal stem cells. One of its advantages is that similar protocol for cell culture can be applied to various species. We focused that intestinal organoids from various species could be useful tools for evaluating the species-selective risk of GIT in the same platform. The present study aimed to establish intestinal organoids originated from region-specific crypts in monkeys, dogs and humans and characterize organoid cell viability by exposure of drugs with various risks of diarrhea. [METHODS] Isolated intestinal crypts in monkeys, dogs and humans were three-dimensionally cultured in L-WRN conditioned media. Organoid cell viability under drug treatment with known risks of diarrhea was semi-quantitatively evaluated by measuring cellular ATP and LDH release. [RESULTS] We successfully established monkey and dog intestinal organoid culture originated from crypts in different regions (duodenum, upper/lower jejunum, ileum, colon, and rectum) and human jejunal organoid culture in the unified culture protocol across species. Organoid cytotoxicity correlated with the reported incidence of diarrhea was confirmed by demonstrating that cell viability was decreased in the treatment of several chemotherapeutic agents and tyrosine kinase inhibitors (TKIs) with high risks of drug-induced diarrhea, while cytotoxicity was not observed by the exposure of drugs with no or negligible risk of diarrhea. Among EGFR-TKIs, susceptibility to toxicity of afatinib tended to be higher than that of lapatinib, gefitinib and erlotinib in each species, which recaptured the clinical observations that afatinib-induced diarrhea is an almost inevitable event compared with other EGFR-TKIs. Furthermore, afatinib is an irreversible EGFR-TKI, and unlike other reversible EGFR-TKIs, cell viability was not recovered even after drug removal from culture media, suggesting that afatinib-induced cytotoxicity was long-lasting. Moreover, organoid cultures showed that 5-FU-induced toxicity was ameliorated in the presence of oteracil, which reproduced clinical benefit of oteracil in TS-1 (a combination of tegafur/gimeracil/oteracil) to mask 5-FU-induced GIT. [CONCLUSION] Intestinal organoids could recapture the clinical risks of drug-induced GIT. These unified *in vitro* platforms may also be applicable to the rational explanation of species differences in GIT at the pre-clinical stage and its inter-individual differences in clinical settings.

O3-4

Effects of tea catechin (–)-Epigallocatechin-3-gallate on human and rat renal organic anion transporters OAT1 and OAT3

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[INTRODUCTION] Consumption of tea (*Camellia sinensis*) is a common practice throughout the world. (–)-Epigallocatechin- 3-gallate (EGCG) is the most abundant catechins of green tea. Organic anion transporter 1 (OAT1, *SLC22A6*) and 3 (OAT3, *SLC22A8*) are expressed on the basolateral membrane of renal proximal tubular cells and implicated both drug-drug interactions and nephrotoxicity. In this study, we characterized the fluorescent organic anion 6-carboxyfluorescein (6-CF) transport mediated by human (h) OAT1, hOAT3, rat (r)Oat1, and rOat3, and then examined the effects of EGCG on the OAT1, OAT3 and the urinary excretion in rat.

[METHODS] For in vitro assays, the uptake of 6-CF was measured using HEK293 cells transiently expressing transporter of interest. For in vivo assays, 6-CF was administered into the femoral vein of anesthetized rats and femoral arterial blood and urine were collected over time. 6-CF in the cell lysate, plasma, urine was quantified using a plate reader with excitation and emission wavelength of 484 and 535 nm, respectively.

[RESULTS AND DISCUSSION] 6-CF was transported in a time- and concentration- dependent manner by hOAT1, hOAT3, rOat1, and rOat3 with the K_m and V_{max} values of 6.94, 38.4, 6.68 and 2.52 μM and 125.1, 70.0, 131 and 35.3 pmol/mg/2 min, respectively. These transports were inhibited by known substrate and inhibitors and there were few species differences between human and rat counterparts while there was significant difference between OAT1 and OAT3 isoforms. EGCG inhibited hOAT1 in a mixed-type manner while it inhibited hOAT3, rOat1, and rOat3 in a competitive manner. The inhibitory constants (K_i) were estimated to be 334, 162, 595, and 56.5 μM for hOAT1, hOAT3, rOat1, and rOat3, respectively.

The renal clearance of 6-CF was higher than that of creatinine, showing active tubular secretion of 6-CF (18.3 and 3.29 mL/min/kg, respectively). Then we examined the effect of probenecid, a potent OAT inhibitor, D-malate, a reducing agent of intracellular α-ketoglutarate (a driving force of OATs), and EGCG. The coadministration of these compounds significantly decreased the renal clearance of 6-CF (2.8, 4.9, 7.4 mL/min/kg, respectively) without affecting creatinine clearance and blood urea nitrogen. By contrast, the area under the plasma concentration versus time curve of 6-CF was significantly increased by these compounds (34.4, 164, 62.4, 73.9 μg•min/mL, for control, probenecid, D-malate, EGCG, respectively). These results suggest that EGCG inhibits the urinary excretion mediated by OATs in rat.

[CONCLUSION] Our results suggest that 6-CF is useful for the assessment of food-drug interaction mediated by OAT1 and OAT3 *in vitro* and *in vivo*. EGCG has an antioxidant activity and may be useful for kidney protective agent as an inhibitor of renal OATs.

O3-5

Development of albumin-based DDS carriers with organ-specific distribution

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[Introduction] Human serum albumin (HSA) exists in not only human serum but also many organs and fluids. To control the HSA distribution in the body, many receptors such as gp18, gp30, cubilin, and megalin are engaged. It is well-known that each HSA receptor varies in the expression sites of organs, and some receptors recognize more oxidized or denatured HSA. However, pharmacokinetics of various denatured-HSA and the specific substrate recognition properties of various HSA receptors are still unclear. To elucidate the specific substrate recognition properties of various HSA receptors will lead to the construction of a specific HSA delivery system to organs and cells expressing the HSA receptors. Hence, we performed the pharmacokinetics experiment using either denatured-HSAs or ligand-bound HSA. [Methods] Denatured-HSAs were prepared by various reactions such as denaturation with heat, organic solvents, acid solvents, and oxidation. Ligand-bound HSA was prepared by incubation with fatty acid. Their organ distributions were evaluated by fluorescence intensity of FITC-labeled HSA. To examine the structural changes of each denatured-HSAs or ligand-bound HSA, we performed circular dichroism, intrinsic tryptophan fluorescence and the ligand binding experiments. [Results] The accumulations of heat-denatured HSA to the liver, lung and spleen were significantly greater than those of normal HSA. The kidney accumulation of oxidized HSA was significantly increased about 4-fold compared to normal HSA. Interestingly, the base-denatured HSA increased the half-life in blood about 2-fold compared to normal HSA. In addition, different structural changes were observed for each denatured or ligand-bound HSA. In particular, oleic acid-bound HSA showed a unique structure accompanied by the increasing binding capacity of Site I. [Discussion] Our data showed that the each denatured-HSA possesses individual pharmacokinetic properties, suggesting that the change in organ distribution may be due to different expression of HSA receptors in each organ. Previous studies showed that the enhanced kidney accumulation of oxidized HSA was related to its enhanced recognition by cubilin, megalin and CD36 which are abundantly expressed in the kidney. To clarify the binding property of either these denatured or ligand-bound HSAs to its receptors in various organs could lead to elucidate the mechanism for organ-specific distribution of these HSAs. [Conclusion] In this study, we could construct HSAs with organ-specific distribution properties by using various modification methods. These HSAs could be applied in a variety of disease as drug delivery carriers to a variety of target organs without severe adverse effect.

O3-6

The effect of intratracheal administration of triiodothyronine (T_3) to chronic obstructive pulmonary disease (COPD) mouse model.

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[INTRODUCTION] Thyroid hormone (T_3) regulates systemic metabolism and, in the lung, has long been known to act as an essential factor for development and growth. It has been shown that the intratracheal administration of T_3 suppressed lung fibrosis via improving mitochondrial function in mouse model of idiopathic pulmonary fibrosis (IPF). In the lung of chronic obstructive pulmonary disease (COPD) patients, mitochondrial function is decreased. Moreover, thyroid function and respiratory function in COPD patients were positively correlated, suggesting that T_3 may ameliorate the pathogenesis of not only IPF but also COPD. However, experimental evidence for the role of T_3 in the pathophysiology of COPD is lacking. Therefore, I aim to clarify the role of T_3 in COPD pathophysiology. [METODS] T_3 (40 or 80 μg/kg, for 3 weeks (elastase-induced model mice) or 12 days (βENaC-Tg mice), every other day) was intratracheally administered to two COPD model mice, elastase-induced COPD mice characterized by emphysema and βENaC-Tg mice characterized by clinical COPD symptoms (mucus stasis, chronic inflammation and emphysema). I analyzed its effects on pulmonary phenotypes such as respiratory function and emphysema and explore its mechanism. [RESULTS] T_3 (80 μg/kg) administration slightly improved the respiratory function (Crs; compliance, Ers; elastance) and significantly reduced the emphysematous parameter mean linear intercept (MLI) in elastase-induced model mice. Moreover, intratracheal administration of T_3 increased the mRNA expression level of *Ppargc1a*, which is the master regulator of mitochondrial biogenesis, and *Gclm*, which is an oxidative stress-related factor, in the lung of elastase-induced COPD mice. On the other hand, the intratracheal administration of T_3 to βENaC-Tg mice did not improve COPD pathology. [DISCUSSION] Intratracheal administration of T_3 improved COPD pathology of elastase-induced model mice, but not βENaC-Tg mice. The difference in the inhibitory effect of T_3 between the two COPD models may be due to the difference in the degree of inflammation and T_3 requirement. It has been reported that the expression of *Dio2* (the index of T_3 requirement) increases with inflammation. In fact, I found dramatically increased mRNA expression level of *Dio2* and inflammatory cytokines in elastase-induced model mice, but not βENaC-Tg mice. I think that elastase-induced COPD model mice simulate emphysema-dominant patients and βENaC-Tg mice simulate airway-dominant patients. In Japan, there are many emphysema-dominant patients, but there is no medicine that target emphysema. Therefore, T_3 may be a potential treatment for emphysema-dominant patients. [CONCLUSION] These data show that T_3 plays a protective role and suppresses the COPD pathology in the lung of elastase-induced COPD model. This effect may partly involve the improvement of mitochondrial function and/or reducing oxidative stress.

ポスター演題

示説時間

奇数番号：10/23　16:10～16:55

偶数番号：10/24　13:15～14:00

(P-4 は事務局都合の欠番です)

P-1

Inhibitory effect of a dimerization-arm-mimetic peptide on EGFR-dependent ERK signaling

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【INTRODUCTION】 Epidermal growth factor receptor (EGFR), which is a single spanning membrane protein with tyrosine kinase, is a major target for the development of novel anticancer drugs. The agonists binding to the extracellular domains of EGFR trigger the receptor activation through the receptor's dimerization, kinase activation and autophosphorylation. This activation is involved in the cell proliferation and differentiation through an intracellular MAPK/ERK signaling cascade. However, the overexpression or unregulated activation of the receptor is known to initiate cancers in various cells. Toward the development of novel EGFR inhibitors, several cyclic peptides which were designed based on the dimerization arm sequence of the EGFR ectodomain were reported. The first example of a dimerization arm mimic was a cyclic decapeptide (cyclic-CYNPTTYQMC) containing an intramolecular disulfide bond between the two cysteines. Certainly, they inhibited the EGFR autophosphorylation in the intact carcinoma cells. However, it was not clear whether they affected the ERK phosphorylation in the cascade. In this study, we examined inhibitory effects of the cyclic decapeptide and its derivatives on the ERK phosphorylation of EGFR-positive cancer cells. 【METHODS】 Cyclic peptides with an intramolecular disulfide bond were prepared by using Fmoc-based solid-phase peptide synthesis and air oxidation method according to the reported procedures. The crude peptide was purified by preparative HPLC. The desired fractions were identified by ESI-MS, and then were lyophilized. Each desired peptide was obtained as a white amorphous powder. The purity was confirmed to be >95% by analytical HPLC. In our biological assays for the peptides, we used human epidermoid carcinoma cell line (A431) which overexpressed EGFR on the surface. By treating the cells with each test peptide before the addition of the agonist EGF, the inhibitory effects on the ERK phosphorylation *via* the EGFR activation were evaluated by Western immunoblotting. 【RESULTS and DISCUSSION】 In the biological assay by using the intact A431 cells, the decapeptide decreased EGFR and ERK phosphorylation to about 62% and 55%, respectively, at the concentration of 5 μM. These results indicated that it could inhibit the EGFR-dependent ERK signaling in the cells. In addition, we found that several derivatives of the decapeptide showed the inhibitory activities against both EGFR and ERK phosphorylation. Therefore, structural optimization based on the decapeptide would be a useful strategy to develop novel anticancer agents having the inhibitory effect on the EGFR-mediated ERK signaling. 【CONCLUSION】 We demonstrated that the cyclic decapeptide inhibiting the EGFR blocked the intracellular MAPK/ERK signaling. Among the synthetic derivatives, we found new cyclic decapeptides having the inhibitory effects on the ERK phosphorylation induced by the EGFR activation on the intact A431 cells.

P-2

Association between MR-proADM concentration and treatment intensity of antihypertensive agents in chronic kidney disease patients with insufficient blood pressure control

Motoshi Iwao[1], Ryota Tanaka[1], Yosuke Suzuki[2], Takeshi Nakata[3], Kohei Aoki[3], Akihiro Fukuda[3], Naoya Fukunaga[3], Ryosuke Tatsuta[1], Keiko Ohno[2], Hirotaka Shibata[3], Hiroki Itoh[1]

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[INTRODUCTION] Response to antihypertensive drugs in patients with chronic kidney disease (CKD) has great interindividual variability. Adrenomedullin (ADM) is produced abundantly in hypertension, and increased blood ADM concentration has been associated with the development of hypertension, but clearance is very rapid. Mid-regional proADM (MR-proADM) produced from an ADM precursor is considered a surrogate biomarker for quantification of ADM. We investigated the association of MR-proADM with antihypertensive resistance in CKD patients with poor blood pressure (BP) control. [METHODS] This cross-sectional study analyzed 33 CKD patients with poor BP control defined as failure to achieve target BP despite at least two classes of antihypertensive drugs. Treatment intensity score was calculated to facilitate comparability of antihypertensive regimens across subjects taking different drugs. Plasma MR-proADM concentration was measured using ultra-performance liquid chromatography coupled with tandem mass spectrometry. The relations of plasma MR-proADM concentration with clinical data and treatment intensity score were evaluated. The relation of MR-proADM concentration with the treatment intensity score of each of the four drug classes (calcium-channel antagonists, ACE inhibitors and ARBs, β blockers and α β blockers, and diuretics) were also evaluated. Single and multiple regression analyses by stepwise selection were performed using treatment intensity score as the dependent variable. [RESULTS] Plasma MR-proADM concentration correlated with estimated glomerular filtration rate (eGFR) ($r=-0.777$, $p<0.001$). Treatment intensity score correlated positively with plasma MR-proADM concentration ($r=0.355$, $p=0.043$), and the correlation was further enhanced after correction by weight ($r=0.538$, $p=0.001$). Examining the relation of MR-proADM concentration with the weight-corrected treatment intensity score of each of the four drug classes, only the weight-corrected treatment intensity score for calcium-channel antagonists correlated positively with plasma MR-proADM concentration ($r = 0.456$, $p = 0.011$). Single and multiple regression analysis identified MR-proADM concentration ($p=0.005$) as independently associated with weight-corrected treatment intensity score. [CONCLUSION] This study suggests the usefulness of plasma MR-proADM concentration as a biomarker reflecting resistance to antihypertensive therapy in CKD patients with poor blood pressure control. The correlation between treatment intensity score for calcium-channel antagonists and plasma MR-proADM concentration may be explained that using their drugs acting directly on blood vessels reflects the vascular condition. For hypertensive patients at high risk of CVD, while early attainment of the target blood pressure is desirable to prevent onset of CVD, some patients with severe hypertension may need high-intensity antihypertensive therapy from the initiation of treatment, with a concern of adverse events. For these patients, safe and individualized antihypertensive therapy may be planned by selecting drugs based on the evaluation of resistance to antihypertensive drugs by MR-proADM in advance.

P-3

Development of a simple and rapid method for the derivation of dopaminergic neurons from human induced pluripotent stem cells by direct conversion

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[Introduction] Cell reprogramming by overexpression of region- and/or lineage-specific transcription factors has been explored to generate specific cell types including neurons by converting from another cell type. Recent advantageous of reprogramming technology can be applicable for development of new regenerative therapy by delivery of genes. For instance, mammalian somatic cells such as fibroblasts, astrocytes and Müller glia can be converted into functional dopaminergic (DA) neurons in vitro by the overexpression of particular transcription factors and reprogrammed-DA neurons have integrated into neural circuit to repair the lost neuronal function in vivo brain of parkinsonian models. For decades, numerous efforts are accumulated to establish robust induction protocols for generation of DA neurons from human induced pluripotent stem cells (hiPSCs) by precisely controlling cell fate using morphogens under optimized conditions. However, these protocols require fully trained techniques and take long-term (60 days<) to obtain matured functional DA neurons. Here we generated an inducible hiPSC line that can convert into DA neurons from hiPSCs and established simple and rapid protocol for generation of DA neurons.

[Methods] To generate an inducible hiPSC line, we used piggyBac vector to stably insert ASCL1 and LMX1A cDNAs into genome of hiPSCs. After transfection of vectors, we performed positive selection by 1 μg/mL puromycin and then picked ten hiPSC colonies. Two transgenes were overexpressed in response to 1 μg/mL doxycycline (DOX) treatment. Finally, we selected a clone that shows high neuronal conversion efficiency. We analyzed gene expression analysis and immunocytochemical analysis during conversion to reveal the neuronal conversion efficiency and DA phenotype on day 14, 21 and 28. Finally, electrophysiological analysis was performed multi-electrode array (MEA) system on day 28.

[Results & Discussion]

We generated a hiPSC line that can convert into DA neurons by DOX-inducible overexpression of minimal combinations ASCL1 and LMX1A. In response to DOX-treatment, hiPSCs rapidly acquired neuronal identity with expression of tyrosine hydroxylase (TH) and ventral midbrain markers such as FOXA2 and EN1 on day 14 and 21. On day 28, induced DA neurons showed expression of synaptic marker PSD-95 and exhibit electrophysiological feature recorded by multi-electrode array MEA. These results indicated that we succeeded in establishment of simple conversion method for generation of DA neurons from hiPSCs. Since hiPSC line can be infinitary expanded in culture condition, large scale preparation will be available for sustainable and scalable experiments. This hiPSC line is applicable as an in vitro model for pathology of disease and drug discovery with simple manipulation.

[Conclusion] We established a stable hiPSC line that can convert into DA neurons by DOX-inducible overexpression of ASCL1 and LMX1A. Using this cell line, we established a simple and rapid conversion method to generate DA neurons from hiPSC line.

P-5

Risk assessment of the use of antiepileptic drugs during pregnancy on placental trophoblastic functions

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[INTRODUCTION] Placenta, a crucial organ for proper fetal development and healthy pregnancy, has various functions, including nutrient supply and hormone secretion, aided by villous trophoblasts. Epilepsy is a common neurological complication in pregnant women. In utero exposure to certain antiepileptic drugs (AEDs) is associated with increased risks to fetus. Although retrospective studies have addressed the risks of AEDs, their effects during pregnancy have not been fully evaluated. We aimed to evaluate the reproductive effects of AEDs on trophoblastic functions: 1) transport mechanisms, 2) nutrient transport, 3) differentiation and hormone secretion. [METHODS] Human placental choriocarcinoma BeWo cells were used as a trophoblast model. The accumulation of AEDs was quantified using LC/MS/MS. Valproate (VPA, 400 mg/kg) was orally administered to pregnant Wistar rats for four days in *in vivo* assays. mRNA and protein levels were determined using qPCR and western blotting, respectively. [RESULTS and DISCUSSION] 1) The accumulation of six AEDs in BeWo cells at pH 7.4 was in this order: gabapentin (GBP) > lamotrigine (LTG) > levetiracetam = topiramate = lacosamide > VPA. Kinetic analysis showed that carrier systems were involved in the uptake of GBP (Km = 105.4 μM) and LTG (Km = 904.5 μM). PCR array analysis showed that approximately 70% of major genes involved in drug transport were expressed in BeWo cells. Inhibitors for amino acid transporter (LAT) and LAT1 siRNAs significantly decreased GBP uptake, suggesting that LAT1 contributes to the transport of GBP. Additionally, various amino acids (AA) *cis*-inhibited GBP uptake, whereas Met and His *trans*-stimulated GBP uptake. The results imply that GBP affect AA transport across placenta. A carrier sensitive to chloroquine, imipramine, quinidine, and verapamil was involved in LTG transport. 2) We evaluated the effects of AEDs, using *in vitro* assays, on the transport of folate, which is crucial for the development of fetus. Short-term exposure to 16 AEDs had no effect on folate uptake, whereas long-term exposure to VPA affected it. As VPA has an inhibitory effect of histone deacetylase, we focused on the effect via alteration of gene expression. VPA increased acetyl-histone H3 expression both in BeWo and rat placenta. In vivo, VPA changed the expression levels of nutrient transporters (Lat1, Octn1, and Oatp4a1) and the folate carrier Frα. 3) The effects of VPA or LTG on forskolin-stimulated BeWo cells were investigated. Exposure to VPA, and not to LTG, reduced differentiation markers (syncytin-1, -2) and hormone levels (hCG, hPL). [CONCLUSION] We showed that several AEDs were transported to BeWo cells via carrier-mediated pathway. It is suggested that GBP affect the transport of AA that are crucial for growth. Furthermore, VPA affects trophoblastic functions via the alteration of genes involved in nutrient transport, differentiation, and hormone secretion. The effects of AEDs on fetal growth and placentation should be a future research subject.

P-6

In vivo Evaluation of Adsorption of Doripenem and Ciplofloxacin to Different Hemofilters

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[INTRODUCTION] For the treatment of severe infections in intensive care unit (ICU), doripenem (DRPM) with a broad-spectrum antibiotic activity is selected as empiric therapy, and ciprofloxacin (CPFX) with potent antibacterial activity against *Pseudomonas aeruginosa* is selected for atypical pneumonia and *Pseudomonas aeruginosa* coverage. Since severe infections often cause acute kidney injury (AKI) due to factors such as hypercytokinemia, hemodynamic change, and renal tubular disorder, continuous renal replacement therapy (CRRT) is often initiated for cytokine removal and renal support in patients with AKI. Thus, it is necessary to decide the antibiotic dosage considering the CRRT clearance in addition to the residual renal function. On the other hand, since some of the hemofilters used in CRRT are known to adsorb antibiotics, the clearance of DRPM and CPFX may differ depending on the adsorptive characteristics of hemofilters. In this study, we evaluated the adsorption of DRPM and CPFX to different hemofilters *in vivo*. [METHODS] The patients who underwent CRRT while being treated with intravenous DRPM or CPFX at ICU of Oita University Hospital were recruited. Asymmetric cellulose triacetate (ATA) filter and polyethersulfone (PES) filter (both non-adsorptive hemofilters), as well as polymethyl methacrylate (PMMA) filter and AN69ST filter (both adsorptive hemofilters) were evaluated. The initial blood flow rate and filtration flow rate were set at 100 mL/min and 600 mL/h, respectively, (CRRT mode: continuous venovenous hemofiltration) and were adjusted appropriately according to clinical need. Blood samples and filtrate samples before and after passing through the hemofilter were collected 1 hour after infusion of the above antibiotics. The drug concentrations in plasma and filtrate were measured using ultra-high-performance liquid chromatography coupled with tandem mass spectrometry. The protocol for this study was approved by the Ethics Committee of Oita University Faculty of Medicine. [RESULTS] The adsorption rates (median [interquartile range]) of DRPM to the hemofilters were 1.88% [-5.31–9.08] (n=9) for ATA, 5.66% [0.88–10.43] (n=7) for PES, 0.78% [-1.82–3.39] (n=7) for PMMA, and 1.88% [-5.32–9.08] (n=9) for AN69AT. The adsorption rates for CPFX were 1.08% [-9.95–12.12] (n=7) for ATA, 17.59% [11.26–23.93] (n=6) for PES, 11.56% [6.86–16.24] (n=6) for PMMA, and 6.44% [-1.86–14.74] (n=6) for AN69AT. [DISCUSSION•CONCLUSION] Adsorption rates of DRPM to 4 types of hemofilters were low, with no significant difference among filters (p=0.696). On the other hand, adsorption of CPFX to PES and PMMA filters were high. When administered under CRRT, the dosage of DRPM can be decided without considering the type of hemofilter. On the other hand, the dosage of CPFX may need to be decided considering the type of filter used.

P-7

Prediction of drug discontinuation due to secondary non-response by serum infliximab and IL-6 levels in patients with rheumatoid arthritis

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[INTRODUCTION] Infliximab (IFX) therapy has considerably improved the outcome of treatment for rheumatoid arthritis (RA). However, in some patients, the efficacy of IFX therapy is gradually decreased, and secondary non-response eventually leads to discontinuation of treatment. The current challenge in IFX therapy is the optimization of long-term treatment. Previously, we showed that serum IFX levels were associated with therapeutic effects in clinical practice. Anti-drug antibody (ADA), tumor necrosis factor (TNF)-alpha and interleukin-6 (IL-6) levels were also the candidates of biomarker. However, it is still unclear whether we can predict the discontinuation of treatment due to secondary non-response using therapeutic monitoring of IFX and/or biomarkers. The purpose of this study is to investigate predictors of drug discontinuation by analyzing a Japanese cohort database. [METHODS] Data were collected retrospectively from the Kyoto University Rheumatoid Arthritis Management Alliance cohort from January, 2011 to December, 2020. Blood samples were randomly collected during IFX therapy. Serum IFX levels were measured using liquid chromatography-tandem mass spectrometry. ADA, TNF-alpha and IL-6 levels were measured using electrochemiluminescence. To define cut-off values for predicting discontinuation of IFX treatment, receiver operating characteristic curves were plotted for TNF-alpha or IL-6. We compared the crude risk of discontinuation for one year from sampling points using Kaplan-Meier analysis. This study was conducted with the approval of the Ethics Committee (R0357). [RESULTS] Out of the 310 RA patients receiving IFX, 84 were eligible for analysis. Twenty-one patients were classified into low-IFX group. Treatment persistence rates for one year were around 90% in these patients. Drug survivals were not significantly different between low-IFX and high-IFX groups. In addition, between two groups divided by ADA, TNF-alpha, or IL-6 levels, there were no significant differences in treatment persistence. Then, we focused on the combination of IFX level and other biomarkers, and compared one-year persistence rate among the four groups of each combination. Only in low-IFX/high-IL-6 group, the drug survival was shorter than in the other three groups. [CONCLUSION] In the present study, we demonstrated that the patients with low IFX and high IL-6 levels exhibited an earlier discontinuation of IFX treatment due to secondary non-response.

P-8

Safety Profiles of Oral Anticoagulants Using the Japanese Spontaneous Reporting Database

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[Introduction] The development of new direct oral anticoagulants (DOACs) has led to an alternative to treatment with warfarin. However, real-world data on comparing safety profiles of DOACs and warfarin are insufficient. The purpose of this study was to compare safety profiles of warfarin and DOACs using a spontaneous reporting system database. [Methods] Adverse event reports spontaneously submitted to the Pharmaceuticals and Medical Devices Agency (Japan) were analysed. We performed disproportionality analyses, calculating the reporting odds ratio (ROR) with 95% confidence interval (CI). [Results & Discussion] The database comprised 3445 reports associated with warfarin, and 14,269 reports with DOACs. A large number of bleeding complications were detected with the use of both warfarin and NOACs. As for cerebral hemorrhage, the signal scores were greater for DOACs as a class (ROR 25.1, 95% CI 23.3-27) and individual agents (edoxaban: ROR 23.6, 95% CI 18.6-29.9; rivaroxaban ROR 23.9, 95% CI 21.4-26.8; apixaban ROR 28.1, 95% CI 25.4-31.1) than for warfarin (ROR 18.9, 95% CI 16.4-21.7), but showed the lowest value for dabigatran (ROR 9.26, 95% CI 7.76-11). Gastrointestinal hemorrhage had stronger signals for DOACs (ROR 19.4, 95% CI 17.8-21.1) than warfarin (ROR 12.2, 95% CI 10.2-14.6). With respect to calciphylaxis, the association with warfarin was noteworthy (ROR 190; 95% CI, 126-287), but no reports were detected involving DOACs. [Conclusion] Our results may provide useful information for treatment with oral anticoagulants, although further studies with more data are needed.

P-9

Population pharmacokinetics of edoxaban in Japanese patients with atrial fibrillation

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[INTRODUCTION] Edoxaban, an oral direct inhibitor of activated coagulation factor X, is used to prevent stroke or systemic embolism in patients with non-valvular atrial fibrillation (AF). Its anticoagulant effects and safety were demonstrated to be equal or superior to those of warfarin, which has been the most commonly used anticoagulant. However, bleeding is still one of the most troubling adverse events during pharmacotherapy with edoxaban. Recently, exposure-response analyses showed that steady-state trough concentration of edoxaban is associated with the incidence of bleeding and venous thromboembolism, although the potential factors affecting inter-individual pharmacokinetic variability of edoxaban in AF patients have not been fully elucidated. In this study, we conducted the population pharmacokinetic analysis of edoxaban in Japanese AF patients to clarify intrinsic factors affecting pharmacokinetics of edoxaban. [METHODS] This study was approved by the Ethics Review Board of Ritsumeikan University Biwako-Kusatsu Campus, the Ethics Boards of Shiga University of Medical Science, Kyoto University and Kyoto Medical Center. One hundred thirty-one Japanese AF patients treated with edoxaban were enrolled in this study. The pharmacokinetic profiles of edoxaban were analyzed according to a 1-compartment model using non-linear mixed effect modeling (NONMEM^{TM}) program. Age, body weight (BW), serum creatinine (Scr), creatinine clearance (CLcr), estimated glomerular filtration rate (eGFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), concomitant CYP3A4 and/or P-glycoprotein inhibitors or substrates, and genetic polymorphisms of *CYP3A5* and P-glycoprotein (*ABCB1*) were used as candidates for the pharmacokinetic covariate of edoxaban. [RESULTS and DISCUSSION] The non-linear relationship between the apparent oral clearance (CL/F) of edoxaban and CLcr was observed. The population mean of CL/F for a typical patient (CLcr value of 61.8 mL/min) was estimated to be 28.3 L/h. In contrast, other covariates such as age, BW, AST, ALT, concomitant CYP3A4 and/or P-glycoprotein inhibitors or substrates, and*CYP3A5* and *ABCB1* genotypes did not affect the pharmacokinetics of edoxaban. Therefore, the inter-individual variability in CL/F of edoxaban in AF patients can be explained in part by CLcr. [CONCLUSION] Our results suggest that renal function is considered to be an intrinsic factor affecting edoxaban pharmacokinetics in Japanese AF patients. These findings may provide useful information for individualized anticoagulant therapy with edoxaban to prevent its adverse events.

P-10

Possible involvement of Nesfatin-1/NucB2 in xenin-induced anorexia in rats

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[INTRODUCTION] Xenin is a 25-amino acid peptide originally identified from human gastric mucosa. Xenin is known to inhibit acid secretion, induce pancreatic exocrine secretion, and affect small and large intestinal motility. Central and peripherally administered xenin also decreased food intake in rodent. Nesfatin-1/NucB2, newly identified as an anorexic neuropeptide, is widely expressed in the central nervous system and peripheral organ. The purpose of this study was examined associations between xenin and Nesfatin-1/NucB2. [METHODS] We examined the central effects of xenin on food intake, water intake and Nesfatin-1/NucB2 like immunoreactivity (Nesfatin-1/NucB2-LI) neurons in rats. 1. After intracerebroventricular (icv) administration of xenin (2 nmol/rat), we examined the Fos like immunoreactivity (Fos-LI) expression in the supraoptic nucleus (SON), paraventricular nucleus (PVN), arcuate nucleus (Arc), central amygdaloid nucleus (CAN), area postrema (AP) and nucleus of the solitary tract (NTS). 2. We also examined the Fos expression in nesfatin-1 neurons in the SON and PVN by double immunostaining for Fos and Nesfatin-1/NucB2. 3. We examined the functional role of the Nesfatin -1/NucB2 in xenin-induced anorexia (1 nmol/rat) using Nesfatin-1/NucB2 antisense. [RESULTS] 1. Fos-LI expressed in the SON, the PVN, the Arc, the LHA, the CAN, the AP, and the NTS after icv administration of xenin. 2. Icv administration of xenin caused significant increases the number of Fos-LI in expressing Nesfatin-1/NucB2-LI neurones in the SON and the PVN. 3. Icv administration of xenin significantly decreased food intake and water intake. Decreased food intake induced by central administered xenin was significantly attenuated by pretreatment with icv administration of Nesfatin-1/NucB2 antisense. [DISCUSSION] Previous study showed that xenin has high homology with neurotensin, which is known to be an anorectic peptide, and might have the similar biological effects with neurotensin by binding with the neurotensin receptor. However, the anorectic effect of xenin is stronger than that of neurotensin. Our obtained results suggest that the central administered xenin suppressed feeding partially via Nesfatin -1/NucB2 neurons. [CONCLUSION] We conclude that xenin-induced anorexia possibly involved with central Nesfatin-1/NucB2 neurons in rats.

P-11

Effects of a novel hepatitis B antiviral drug in organic acid transporters

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[INTRODUCTION] In treatment of hepatitis B virus (HBV), we usually need to care for drug-resistant HBV. Usually, it is difficult for us to control with emergence of drug resistance. Previous study showed that the number of patients with drug-resistant HBV have increased in Japan, and that has been about several thousands. In present first-line drugs for HBV, we usually use the entecavir and the tenofovir (TAF). These drugs have low rates of resistance mutations and side effects in the short term. However, we have some problems for using them for long term. Because HBV often reactive after treatment was stopped, patients have to keep them for long term. It is also unclear about emergence of drug-resistant mutant and safety of using for long term. Recently, our collaborating group has developed *E*-CFCP, as a candidate drug of HBV for patients with drug-resistant HBV. As it has high antiviral activity and the half-life also is longer, patients can take it in a once-weekly dosing. We expect that *E*-CFCP can greatly improve the quality of life of patients. However, effects of *E*-CFCP are unclear in renal. Therefore, the aim of this study is to clarify the effects of *E*-CFCP in the kidney, especially organic acid transporter（Organic anion transporters：OATs, Organic cation transporter：OCT）. [METHODS] 1. For cytotoxicity studies, we used mouse-derived renal cortex cell lines, the following. a) S2: Proximal tubule cells b) cTAL: Distal tubule cells c) CCD: Corticall collecting duct cells 2. For uptake studies using radioisotopes, we used the transporter stably expressing cell lines, the following. a) S2-hOAT1 b) S2-hOAT3 c) S2-hOAT4 d) S2-hOCT2 We used TAF as a control group in cytotoxicity studies and uptake studies. [RESULTS] In toxicity studies, *E*-CFCP has no cytotoxicity in all cell lines. We also examined the effect of drugs at high concentration using S2 cells. *E*-CFCP has no cytotoxicity even at high concentrations, while cytotoxicity of TAF was observed in a dose-dependent manner in S2 cells. In the substrate uptake assay, there was no inhibition of substrate uptake by *E*-CFCP. [DISCUSSION] Organic acid transporters involve in the uptake of drugs. As a mechanism of renal injury, drugs generally have been accumulated into proximal tubular cells via some transporters and caused renal cytotoxicity. In our present study, since *E*-CFCP did not show inhibition of substrate uptake by the transporter, the transporter is not involved in the intracellular transport of *E*-CFCP and is unlikely to cause cytotoxicity. [CONCLUSION] *E*-CFCP, a novel hepatitis B antiviral drug, is unlikely to cause renal damage. It may be a novel great candidate drug of HBV for patients with drug-resistant HBV.

P-12

Effect of the molecular state of loxoprofen sodium on the pharmaceutical properties of adhesive patches

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[Purpose] In an aging population, the demand for adhesive patches is increasing due to advantages of simplicity of administration, ease of management for the patients. However, there is an issue in formulation design of the patches to enhance the permeability of active pharmaceutical ingredient (API) through the stratum corneum of the skin. In this study, we prepared medical patches containing loxoprofen sodium hydrate (LP_Na), which has anti-inflammatory analgesic effects, with several acrylic polymers and investigated the interaction between LP_Na and acrylic base material as well as the formulation characteristics. [Method] Five types of acrylic polymers (Daido Chemical Industry Co.,Ltd) were used as base material, which contained 2% LP_Na (Hamari Chemicals, Ltd) and lactic acid (LA, Tokyo chemical industry Co.,Ltd). A free form of loxoprofen (LP_F) was also used for comparison of pharmaceutical properties with the LP_Na patch. The crystalline state of the API in the polymer was evaluated by polarizing microscopy and powder X-ray diffraction (PXRD) analysis. In addition, ^{1}H NMR was used to evaluate the molecular interaction between the polymer and LP_Na. Drug release test and *in vitro* skin permeation test were performed to evaluate the pharmaceutical properties. [Results and Discussion] Polarizing microscopy revealed precipitates in the patches prepared with the four polymers except for the polymer with derivatized with carboxy group (AO). The precipitates were anhydrides of LP_Na revealed from the measurement with PXRD. Whereas, no precipitates were observed in the patches containing LA and the patch prepared with LP_F. Therefore, it was suggested that the miscibility of LP_Na to the polymers was enhanced by induction of undissociated molecular form (LP_F). In the drug release test and *in vitro* skin permeation test, the AO patch without precipitates showed an excellent drug release and skin permeability. These properties of the other four polymers were improved by the addition of LA. In the ^{1}H NMR measurement, the chemical shift value of α-hydrogen of LP_Na was shifted to the same value as that of LP_F with increasing the amount of AO. Although no low field shift was observed in the other polymers despite the increased amount of polymer, a low field shift was observed by addition of LA, similar to the case of AO polymer. Thus, the H^{+} of the carboxy groups in the polymer and/or LA structure would be provided to LP_Na, and generated LP_F could likely distribute to the stratum corneum which have lipophilic properties, resulting in enhanced skin permeability of API. These results suggest that the pharmaceutical properties could be controlled by considering the interaction between LP_Na and the base polymer.

P-13

To clarify mechanism of neonatal hypoglycemia by ritodrine

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[INTRODUCTION] Ritodrine (RD) has been used as tocolysis, and hypoglycemia is a well-known side effect in neonates born to mothers receiving RD. However, the mechanism of neonatal hypoglycemia caused by RD has been unknown. Our previous study and a Japanese nationwide retrospective cohort study showed that risk factors of neonatal hypoglycemia due to RD were identified as follows; short-term interval to delivery, more than 2 days usage of RD, and maternal age over 35 years. The aim of this study is to clarify the mechanism of neonatal hypoglycemia using the rats model that reflects clinical studies based on the administration period of maternal RD. [METHOD] Phosphate buffered saline (PBS) as a control and 8 mg/kg/day of RD were administrated via osmotic pump subcutaneously to gestational day (GD) 14 of pregnant Sprague Dawley rats. On GD 21.5 of pregnant rats, fetuses were removed by C-section. Blood was collected from mothers before C-section and from neonates after birth to 6-hour of age. The maternal and neonatal plasma glucose concentration in each sample was measured. In addition, neonatal plasma insulin level at birth and hepatic glycogen content at birth and 3-hour of age were also measured. [RESULTS] Maternal plasma glucose concentration before C-section tended to be lower in the RD-treated group. Neonatal plasma glucose concentrations at birth were significantly reduced in the RD-treated group compared with the control. The changes of neonatal plasma glucose concentration from 1 hour to 2-hour of age were increased in the control group but remained low in the RD-treated group. Neonatal plasma insulin levels at birth were similar between the control group and the RD-treated group. Although there was no difference in the amount of neonatal hepatic glycogen at birth, those of 3-hour of age were significantly reduced in the RD-treated group compared with the control. [DISCUSSION] We established a rats model that reflected one of the risk factors, duration of maternal RD administration, obtained in clinical studies. It was clarified in the rats model that neonatal hypoglycemia occurred due to RD because neonates born to mothers receiving RD persisted in the low plasma glucose concentration after reaching a nadir at 1-hour of age. Since neonatal plasma insulin level and the amount of hepatic glycogen of neonates born to mother receiving RD at birth was almost the same as those of control neonates, suggesting that neonatal hypoglycemia by RD was not due to insufficient hepatic glycogen storage and hyperinsulinemia at birth. However, the hepatic glycogen at 3-hour of age was significantly decreased in the RD-treated group compared with the control. Thus, a part of the glucogenic pathway for maintaining the blood glucose concentration may be impaired, and hepatic glycogen is excessively degraded as an alternative pathway.

P-14

Evaluation of methylmalonic acid transport via transporters expressed in proximal tubules

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[INTRODUCTION] Methylmalonic acid (MMA), an abnormal metabolite of methylmalonyl CoA, is mainly produced in the liver of methylmalonic acidemia patients and excreted in the urine. Since the renal failure in methylmalonic acidemia is associated with elevated serum MMA level and the renal damage has been observed in proximal tubules but not in distal tubules, the uptake of MMA into the proximal tubule cells potentially causes renal toxicity. MMA has the dicarboxylic structure and is estimated to exist as a dianion in physiological pH. Thus, the purpose of this study was to evaluate the uptake of MMA by organic anion transporters (OATs) and sodium/dicarboxylate cotransporter NaDC1 expressed in human proximal tubule epithelia. [METHODS] The uptake of [^{14}C]MMA by tetracycline-inducible OAT1, 3, and 4 overexpressing HEK293 cells and NaDC1-transfected COS-7 cells were measured using the liquid scintillation counter. [RESULTS and DISCUSSION] Concerning the basolateral transporters in proximal tubules, cellular uptake of MMA by OAT1-overexpressing cells was time-dependently increased and higher than that by the uninduced cells, indicating that OAT1 recognizes MMA as a substrate. On the other hand, the uptake of [^{14}C]MMA was little affected by the overexpression of OAT3. As for the apical transporters in proximal tubules, [^{14}C]MMA uptake activity by OAT4-overexpressing cells was similar to that by the uninduced cells even in the presence or the absence of extracellular chloride. Since OAT4 uses chloride for anion exchanges, OAT4 is unlikely to be involved in both the uptake and efflux, namely, reabsorption and secretion, of MMA. The uptake of [^{14}C]MMA by NaDC1, a dicarboxylate transporter also localized at the apical membrane of proximal tubules, was then measured. The uptake of [^{14}C]MMA by NaDC1-overexpressing COS-7 cells and that by the mock cells were similar, while the uptake of [^{3}H]succinic acid, a typical substrate of NaDC1, was time-dependently increased in the NaDC1 overexpressing cells than that in the mock cells. Therefore, NaDC1 is not likely to be involved in the reabsorption of MMA as well. [CONCLUSION] Of transporters tested in this study, OAT1 is found to accept MMA as a substrate. Since OAT1 is localized at the basolateral membrane of proximal tubule cells, OAT1-mediated uptake of MMA from the plasma may be involved in the renal toxicity and urinary secretion of MMA in methylmalonic acidemia.

P-15

Searching for optimal attenuation methods for cisplatin-induced nephrotoxicity

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[INTRODUCTION] Cisplatin (CDDP) is often used as an anticancer drug in the treatment of several types of cancers. CDDP-induced nephrotoxicity (CIN) is one of the most serious adverse effects and occurs in about 30% of CDDP administered patients. The occurrence of CIN results in reduced use or discontinuation of CDDP administration for treatment, it is important to manage CIN. In this study, we conducted three verifications to attenuate CIN for implementation of safer CDDP administration: (1) elucidation of the mechanism of action of magnesium sulfate to attenuate CIN; (2) evaluation of the antioxidant activity effect of ascorbic acid on CIN; (3) examining whether non-steroidal anti-inflammatory drugs (NSAIDs) are a risk factor for CIN and affect the antitumor effect of CDDP. [METHODS] In an *in vitro* study, we used the epithelioid clone of normal rat kidney cells (NRK-52E cells), human lung adenocarcinoma cells (A549 cells), human small cell lung cancer cells (SBC-3 cells), and CDDP-resistant A549 and SBC-3 cells that were established in our lab. In an *in vivo* study, CDDP was administrated to male Wistar rats as a CIN model. A xenograft mouse model, in which CDDP-resistant A549 cells were transplanted into male BALB/cAJcl-*nu/nu* mice, was also used. In addition, we performed a meta-analysis and created a forest plot using previous studies to assess the clinical impact of NSAIDs on CIN. [RESULTS and DISCUSSION] (1) The co-administration of magnesium sulfate attenuated renal damage and reduced the accumulation of CDDP in the kidney. Moreover, magnesium sulfate was involved in altering the renal expression of OCT2, MATE1 and CTR1, which are transporters recognizing CDDP as a substrate.[1,2] (2) Multiple CDDP administration affected oxidative stress markers in the kidney, and co-administration of ascorbic acid, owing to its antioxidant effect, reduced kidney injury caused by CDDP.[(3)] Although meta-analysis showed that co-administration of NSAIDs is a risk factor for CIN,[4] it was revealed that diclofenac does not affect CIN and celecoxib attenuates CIN in basic study.[5] Moreover, diclofenac decreased cell viability of A549 and SBC-3 cells regardless of CDDP resistance and enhanced the antitumor effect of CDDP without affecting CIN in a xenograft mouse model.[6,7] [CONCLUSION] We examined three approaches to reduce CIN and found that the co-administration of magnesium sulfate, ascorbic acid, and diclofenac clinically helps to provide optimized cancer chemotherapy using CDDP. [REFERENCE] 1) Okamoto K (equally first author) *et al.* Eur J Pharmacol. 2017. 2) Okamoto K (equally first author) *et al.* Life Sci. 2017. 3) Okamoto K *et al.* Eur J Pharmacol. 2021. 4) Okamoto K *et al.* Anticancer Res. 2020. 5) Okamoto K *et al.* Eur J Pharmacol. 2020. 6) Okamoto K *et al.* Toxicol In Vitro. 2021. 7) Okamoto K *et al.* Drug Metab Pharmacokinet. 2021.

P-16

Nanoparticle processing of curcumin cocrystal in the solid state

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[Introduction]Curcumin (CCM) is a polyphenol contained in turmeric and has been reported to have pharmacological activities such as anticancer activity. However oral absorption of CCM in sufficient due to its poor aqueous solubility. To improve the solubility of insoluble drugs including CCM and its derivatives, formulation of nanoparticles or cocrystals would be promising approaches. Recently, Karashima et al. have successfully prepared the nano-cocrystals consisting of several poorly soluble drugs by processing with cellulose polymer and surfactant. In this study, we attempted the nanonization of CCM/pyrogallol (PYR) cocrystal by wet media milling. [Methods]An equimolar CCM and PYR were dissolved in acetone, and the solvent was evaporated to prepare the cocrystal. Obtained cocrystal was mixed and pulverized with hydroxypropyl methyl cellulose (HPMC) or polyvinylpyrrolidone (PVP)-K15 as stabilizer and sodium dodecyl sulfate as surfactant in designed ratio. The milled samples were measured with Zetasizer Nano ZS (Malvern Panalytical Ltd.) for particle size distribution and zeta potential, and Miniflex 600 (Rigaku Corporation) for powder X-ray diffraction. [Results and Discussion] The samples were milled with various the ratio of cocrystals or milling beads to a fixed amount of stabilizer. As a result, submicron particles were obtained in both polymers of HPMC and PVP-K15, and thus the nanoparticles were successfully prepared or CCM/PYR cocrystals. However, as the amount of added CCM/PYR cocrystals increased, the cocrystals dissociated and then CCM metastable crystals (form II) appeared. Preferable inhibitory effect to the dissociation of CCM/PYR cocrystals was observed in the case of PVP-K15 compared to HPMC, suggesting the PVP has higher affinity to the surface of CCM/PYR cocrystals. On the other hand, PVP-K90 with higher molecular weight provided interestingly different crystal form of CCM. Namely, the stable crystal (form I) was precipitated during milling process where the cocrystal dissociated. Generally speaking, the metastable crystals would precipitate in advance of the thermodynamically stable crystals when precipitating from highly concentrated solution according to the Ostwald's step rule. PVP-K15 acted as a solubilizer for CCM/PYR cocrystal, and it was considered that increasing the CCM concentration promoted the precipitation of metastable form according to the Ostwald step rule. In addition, the stable form tends to precipitate when the rate of crystallization is slow. PVP-K90 has a higher molecular weight than that of PVP-K15, which indicated to reduce the diffusion rate of CCM molecules on the surface of particles. Thus it was considered that the stable form was precipitated in the combination of PVP-K90 and CCM/PYR cocrystal. These results suggest that the dissociation tendency of the cocrystals differs depending on the type and molecular weight of the polymer used as a stabilizer in the preparation of nano-cocrystals.

P-17

Effects of antiemetic 5-HT$_3$ receptor antagonists on cisplatin-induced renal injury

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INTRODUCTION: Although cisplatin has been used as a key drug for standard anticancer treatment, nausea, vomiting, and renal injury are common adverse effects associated with it. A study using a mouse model of acute kidney injury (AKI) suggested that ondansetron, a 5-HT3 receptor antagonist used as an antiemetic agent, may be a risk factor for the development of cisplatin-induced AKI; however, the effects of various 5-HT3 receptor antagonists currently used clinically on cisplatin-induced AKI has not been elucidated. Therefore, in this study, the effect of various 5-HT3 receptor antagonists on cisplatin-induced AKI was examined. METHODS: C57BL/6 mice were intraperitoneally administered with cisplatin or saline 30 minutes after administering various 5-HT3 receptor antagonists. The degree of renal damage was assessed by serum creatinine, BUN, and histopathological evaluation. Cisplatin accumulation in the kidney to be quantified using a polarized Zeeman atomic absorption spectrophotometer. Changes in the number of reported renal injuries due to the combination of cisplatin and various 5-HT3 receptor antagonists were validated using medical big data analysis of more than 14 million reports and a survey of 3000 hospital medical records. RESULTS: The concomitant use of a first-generation 5-HT3 receptor antagonist (ondansetron, granisetron, or ramosetron) significantly increased cisplatin accumulation in the kidneys and worsened renal damage. Conversely, the concomitant use of palonosetron had no effect on renal function compared with the use of cisplatin alone. Furthermore, an analysis of data from the US Food and Drug Administration Adverse Event Reporting System and retrospective medical records revealed that the combined treatment of cisplatin and a first-generation 5-HT3 receptor antagonist significantly increased the number of reported renal adverse events compared with the combined treatment of cisplatin and a second-generation 5-HT3 receptor antagonist. CONCLUSIONS: These results suggest that compared with the first-generation antagonists, second-generation 5-HT3 receptor antagonist does not worsen cisplatin-induced acute kidney injury.

P-18

Exploration of prophylactic drugs against doxorubicin-induced cardiomyopathy using large-scale medical databases

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[INTRODUCTION] Doxorubicin, an anthracycline antitumor agent, is an essential chemotherapeutic drug; however, its associated adverse events, including cardiotoxicity, prevent patients to discontinue treatment. In this study, we explored existing approved drugs with potential preventative effects against doxorubicin-induced cardiac events by analyzing three medical information databases. We also determined the efficacy and mechanism of action of the candidate drugs. [METHODS] The Gene Expression Omnibus (GEO), Library of Integrated Network-based Cellular Signatures (LINCS), and Food and Drug Administration Adverse Events Reporting System (FAERS) databases were used to extract candidate prophylactic drugs. Doxorubicin-induced cardiac event model mice were generated by an intraperitoneal administration of 20 mg/kg of doxorubicin on day one, and an oral administration of prophylactic candidate drugs for six consecutive days, beginning on the day before doxorubicin administration. On day six, mice hearts were extracted and examined for the mRNA expression of apoptosis-related genes, inflammatory cytokine genes, and biomarkers related to cardiac fibrosis. [RESULTS and DISCUSSION] The GEO analysis showed that doxorubicin administration upregulated 490 genes and downregulated 862 genes. LINCS identified sirolimus, verapamil, minoxidil, prednisolone, guanabenz, and mosapride as drugs capable of counteracting these genetic alterations. In addition, the effects of these drugs on cardiac toxicity were examined using FAERS, and sirolimus and mosapride were identified as new prophylactic drug candidates. For the in vivo study, we evaluated the effects of the administration of doxorubicin and the candidate drug on Bax and Bcl-2 expression, which relates to cardiac toxicity. We found a significant increase in the Bax/Bcl-2 mRNA expression ratio in the cardiac cells of mice with doxorubicin-induced heart failure; however, a trend toward Bax/Bcl-2 suppression was observed in the mosapride and sirolimus combination groups, compared to the doxorubicin only group. Similar results were obtained for the expression of inflammatory cytokines, Il1b and Il6, and markers related to cardiac fibrosis, LGAL3 and TIMP-1. These results suggest that treatment with mosapride and sirolimus may improve prognosis after the onset of cardiac disease. The inflammatory response causes fibrosis, which leads to cardiac dysfunction, and the suppression of the inflammatory response by mosapride and sirolimus may suppress doxorubicin-induced cardiomyopathy. [CONCLUSION] Doxorubicin-induced cardiac events may be suppressed by the administration of the candidate drugs, mosapride and sirolimus.

P-19

Effects of Muscat and Grape Juice on Folate Transport by PCFT

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[Purpose] Folic acid (FA) is a water-soluble vitamin that plays an important role in cell growth, differentiation, and maintenance of cell functions. FA is absorbed from the small intestine by proton-coupled folate transporter (PCFT). Recently, the opportunity of the intake of FA as a supplement has been increasing (e.g. for the safe childbirth), and thus the effects of various beverages on the intestinal absorption of FA must be considered. In our laboratory, we have shown that various flavonoids can inhibit FA transport via PCFT. In the present study, we investigated whether co-ingestion of muscat juice and grape juice affects PCFT-mediated FA transport or not. [Methods] Inhibition study on the uptake of [^{3}H]-FA in the presence of a H^{+} gradient (pH 6.0) was performed using HEK293 cells stably expressing human PCFT. Inhibitors were added to the cells, and after the designated period, uptake study was performed in the absence of inhibitors. Muscat juice and grape juice, each diluted to a fixed concentration in Hank's balanced salt solution (HBSS), were used as inhibitors. [Results and Discussion] While in the presence of muscat juice (1-10%), no change in FA uptake was observed, in the presence of grape juice (1-10%), FA uptake decreased in a concentration-dependent manner. These results suggested that grape juice may inhibit the absorption of FA via PCFT. After pretreatment with muscat juice and grape juice (1-10%) for 60 min, FA uptake was evaluated in the absence of inhibitors. Muscat juice did not show any effect of pretreatment, while grape juice showed a concentration-dependent decrease in FA uptake. Furthermore, FA uptake was measured after pretreatment with 5% grape juice for 60 min and incubation with HBSS (pH 7.4) for 10 and 30 min, and a time-dependent recovery of FA uptake was observed. These results suggested that the inhibitory effect of grape juice may be sustained. The distinct inhibition profiles of FA uptake by muscat juice and grape juice may be due to the difference in the contents of polyphenols such as anthocyanins and flavonoids.

P-20

Development of a novel module detection method in gene co-expression network and its application to clinical data

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[INTRODUCTION] Co-expression patterns derived from omics data form a complex network. The modules, sub-networks, in a gene co-expression network (GCN) contain not only information about grouping but also the relationships between individual genes, which indicates that a module in GCN retains more information than that of gene sets such as gene ontology (GO) and contributes to describe disease states. However, the methods to extract modules from GCN are diverse and not optimized with regard to biological meanings. In this study, we developed a novel module detection method that returns biologically diverse modules and confirmed its usefulness in analysis of human clinical data. [METHODS] Human clinical gene expression data of lung adenocarcinoma (LUAD), glioblastoma (GBM) and liver hepatocellular carcinoma (HCC) were downloaded from TCGA. We calculated the correlation coefficients between each gene about these clinical datasets and constructed GCNs using planar maximally filtered graph (PMFG). Next, we proposed to evaluate the correspondence between modules and GOs from the viewpoint of biological diversity and developed a novel module detection method using Node2Vec. Finally, we obtained differentially expressed genes (DEG) from other datasets and mapped them to the extracted modules to elucidate the relationships between DEG and its surrounding genes. [RESULTS] Biological process of GOs, which is often used as a reference to evaluate modules in network analysis, contains duplications among many groups of genes. To avoid overestimation of a particular group of genes, first, we devised a system to evaluate the biological diversity by calculating the coverage rate at a specific depth in the hierarchical structure of GOs. Next, we developed a novel module detection method using Node2Vec, tested its correspondence with GOs using Fisher's exact test (FET), and compared its performance with existing methods from the viewpoints of the number, percentage, and biological diversity about the significant modules. As a result, the novel method showed higher diversity than the existing methods while maintaining the number of modules that show significant correspondence with GOs. Finally, we confirmed this framework reflected the clinical information. For the LUAD data, 742 DEG defined in other microarray datasets were mapped to the generated GCN and the correspondence with the detected modules was tested by FET. Within the modules that showed significant overlap, DEG maintained coherent relationships rather than being scattered, and many of the central hub genes, such as MFAP4, KIF2C and AGER, were confirmed to be associated with LUAD by literature survey. These good correspondences with existing knowledge were also found in other datasets such as GBM and HCC. [CONCLUSION] We proposed a new perspective, diversity, to evaluate biological validity of module detection from GCN. Based on this evaluation metrics, we developed a novel module detection method and confirmed its good correspondence with clinical information.

P-21

Cocoa extract inhibits the transport activity of organic anion transporting polypeptide (OATP) 2B1

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[INTRODUCTION] Organic anion transporting polypeptide (OATP) 2B1 is expressed in the intestine and thought to contribute to the gastrointestinal absorption of various drugs, including lipid-lowering HMG-CoA reductase inhibitors (statins) and antiallergic fexofenadine. Cocoa (*Theobroma cacao L.*) is a rich source of polyphenols such as (+)-catechin, (-)-epicatechin, and oligomers of these monomeric base units, namely procyanidins, and anthocyanidins. The consumption of cocoa is associated with decreased risks of coronary artery disease, stroke, and diabetes. However, the effects of cocoa on the function of drug transporters in intestinal drug absorption have not been reported. In the present study, we examined the effect of cocoa on OATP2B1-mediated transport. [METHODS] Transport activity of OATP2B1 was evaluated by uptake of [^{3}H] estrone-3-sulfate (E_1S) into HEK293 cells stably expressing OATP2B1 (HEK-2B1 cells). The effect of co-incubation or pre-incubation of HEK-2B1 cells with cocoa extract on the OATP2B1-mediated transport of E_1S was examined. Cellular localization of OATP2B1 was assessed by immunocytochemistry. [RESULTS & DISCUSSION] Co-incubation with cocoa extract markedly reduced the OATP2B1-mediated E_1S uptake in a concentration-dependent manner, indicating that the gastrointestinal absorption of OATP2B1 substrate drugs may be decreased when taking these drugs with cocoa. Pre-incubation (2-60 min) of HEK-2B1 cells with cocoa extract significantly inhibited the OATP2B1-mediated E_1S uptake in a concentration-dependent manner, indicating that the gastrointestinal absorption of OATP2B1 substrate drugs may also be decreased when cocoa was ingested before taking these drugs. The inhibitory effect after pre-incubation with cocoa extract was sustained for at least 4 h, suggesting the long-lasting inhibition of OATP2B1-mediated E_1S uptake by cocoa extract. The cellular localization of OATP2B1 was not altered by incubation with cocoa extract, indicating that internalization is not involved in the reduction of its transport activity. [CONCLUSION] Cocoa extract effectively inhibits the OATP2B1-mediated transport in both its co-incubation and pre-incubation, suggesting that cocoa inhibits the gastrointestinal drug absorption via OATP2B1, which may lead to the decrease in bioavailability of orally-administered OATP2B1 substrate drugs. These results provide an important information on proper ingestion of cocoa and drugs.

P-22

Factors associated with CYP3A activity in patients with rheumatoid arthritis using plasma 4β-hydroxycholesterol

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[INTRODUCTION] Cytochrome P450 (CYP) 3A activity has been reported to be decreased by some physiologic factors such as indoxyl sulfate, an uremic toxin, and the inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). However, these effects on CYP3A activity in vivo have not been fully elucidated. An endogenous substrate 4β-hydroxycholesterol (4β-OHC) has been focused as an indicator of CYP3A activity. When assessing CYP3A activity between individuals cross-sectionally, plasma 4β-OHC concentration, 4β-OHC/total cholesterol (TC) obtained by dividing 4β-OHC by TC, and 4β-OHC/4α-hydroxycholesterol (4α-OHC) obtained by dividing 4β-OHC by 4α-OHC are used. In this study, we evaluated the effects of several physiologic factors such as inflammatory cytokines and uremic toxins on CYP3A activity in patients with rheumatoid arthritis (RA) using three CYP3A activity indicators. [METHODS] Patients with RA attending Oita University Hospital were included in the study. Disease activity score 28-C-reactive protein (DAS28-CRP) was used to evaluate disease progression. Plasma 4β-OHC, 4α-OHC, and indoxyl sulfate concentrations were measured by ultra-high-performance liquid chromatography coupled with tandem mass spectrometry. TC was measured by the enzymatic method. Plasma concentrations of IL-6 and TNF-α were measured by ELISA. *CYP3A5*3* (6986A>G) were evaluated by real-time PCR. This study was approved by the ethics committee of Meiji Pharmaceutical University (approval number: 202017) and Oita University Hospital (approval number: 1433). [RESULTS] Thirty-six patients were satisfied the selection criteria. Plasma 4β-OHC concentration, 4β-OHC/TC and 4β-OHC/4α-OHC [median (range)] were 35.0 (15.2-126.3) ng/mL, 0.17 (0.091-0.76) and 6.3 (1.7-21.6), respectively. There were no significant differences in plasma 4β-OHC concentration, 4β-OHC/TC and 4β-OHC/4α-OHC between *CYP3A5*1* carriers (n = 11) and non-carriers (n = 25). There were no significant correlations between plasma 4β-OHC concentration, 4β-OHC/TC or 4β-OHC/4α-OHC with DAS28-CRP, plasma indoxyl sulfate, IL-6 or TNF-α concentrations. Interestingly, a significant negative correlation was observed between 4β-OHC/TC and plasma indoxyl sulfate concentration in patients treated with TNF-α inhibitors (n = 7, r_s = -0.82, p = 0.034). [DISCUSSION and CONCLUSION] In the entire patient population of this study, there were no significant factors associated with plasma 4β-OHC concentration, 4β-OHC/TC or 4β-OHC/4α-OHC, which might be due to the fact that the disease activity of RA was in clinical remission to moderate in most of the patients in this study. On the other hand, accumulated indoxyl sulfate was suggested to be associated with reduced CYP3A activity in condition with suppressed inflammation by TNF-α inhibitors. In conclusion, our findings suggest that inflammatory cytokines and uremic toxins do not affect CYP3A activity in the entire patient population of this study. Meanwhile, indoxyl sulfate may be a significant physiologic factor associated with interindividual variability in CYP3A activity in RA patients treated with TNF-α inhibitors.

P-23

Involvement of endoplasmic reticulum stress in HLA-B*57:01 polymorphism-dependent abacavir skin hypersensitivity

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[INTRODUCTION] HLA-B*57:01 polymorphism is known to be associated with abacavir hypersensitivity. However, the detailed mechanism has not been clarified, for example, what leads to skin inflammation, or what leads to infiltration of inflammatory cells in abacavir hypersensitivity. Therefore, in this study, we examined that endoplasmic reticulum (ER) stress induced in keratinocytes (KCs) was involved in cutaneous symptoms in abacavir hypersensitivity, using chimeric HLA-B*57:01 transgenic mice (B*57:01-Tg) and PD-1 knock-out B*57:01-Tg (B*57:01-Tg/PD-$1^{-/-}$), which are mouse models capable of reproducing HLA polymorphism-dependent skin hypersensitivity by abacavir constructed in our laboratory (Susukida *et al*, Arch Toxicol, 2018; Susukida & Kuwahara *et al*, Commun Biol, 2021). In addition, previous studies in our laboratory suggested that HLA-B*57:01 transfected HeLa cells expressed abnormal HLA complexes on the cell surface by abacavir exposure (Shirayanagi *et al*, Biol Pharm Bull, 2020). Therefore, we considered that changes in the intracellular behavior of the HLA-B*57:01 complex could cause ER stress in KCs, and aimed to capture the changes in the intracellular behavior of HLA. [METHODS] Abacavir was exposed to KCs isolated from B*57:01-Tg, and ER stress response was evaluated by immunoblotting of p-IRE1. After single oral dose of abacavir, the ER stress response was evaluated by immunohistochemistry of p-IRE1 in the auricular tissue. B*57:01-Tg/PD-$1^{-/-}$ was depleted of $CD4^{+}$ T cells and orally administered of abacavir for 5 days to evaluate skin disorders. Furthermore, the skin symptoms were evaluated when 4-phenylbutyric acid (4-PB) was intraperitoneally administered to relieve ER stress. In these experiments, the interaction between HLA and abacavir was evaluated by comparing each Tg mice with the littermates and the vehicle-administered mice. In addition, the localization of HLA in KCs was evaluated by immunocytochemistry. [RESULTS] Three hours after abacavir administration, higher phosphorylation of IRE1 was observed in B*57:01-Tg KCs in both isolated cultured KCs and auricular skin. Daily administration of abacavir to B*57:01-Tg/PD-$1^{-/-}$ for 5 days resulted in redness of the auricle and elevation of the serum TARC, and these symptoms were alleviated by 4-PB administration. In B*57:01-Tg KCs, HLA was observed to be uniformly localized in the ER in the vehicle-exposed group, but intracellular aggregates in which HLA had accumulated were appeared 1 hour after ABC exposure. Some of the aggregates co-localized with calnexin and were presumed to be part of the ER. [DISCUSSION] As an initial response to ABC, an ER stress response occurs in keratinocytes, which could lead to skin inflammation in abacavir hypersensitivity. The appearance of HLA-accumulated vesicles could be associated with the onset of ER stress. [CONCLUSION] These results suggested ER stress could be a factor to induce HLA-B*57:01 polymorphism-dependent abacavir skin hypersensitivity.

P-24

Characterization of human jejunal spheroid-derived intestinal epithelial cells for the evaluation of human intestinal absorption properties of substrates of drug-metabolizing enzymes and transporters

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[INTRODUCTION] Small intestine express various drug-metabolizing enzymes and transporters that play a major role in determine the oral absorption of drug. The 3D culture system, known as spheroids or organoids, allows the long-term culture of intestinal stem cells with differentiation capability into multiple lineages including absorptive enterocytes. Furthermore, the 2D monolayers that is easy to perform pharmacokinetics drug transport studies can be generated from intestinal spheroids/organoids. However, there is little information on the quantitative prediction performance of the human intestinal absorption of drug-metabolizing enzyme and transporter substrate drugs by in vitro assays with the differentiated cells derived from human intestinal spheroids/organoids. [PURPOSE] This study aimed to characterize the human intestinal spheroid-derived intestinal epithelial cells as a novel in vitro model for investigating the impact of intestinal drug-metabolizing enzymes and transporters on the intestinal absorption of substrate drugs in humans. [METHODS] Human jejunal spheroids were established from surgical human jejunum specimens and expanded using the conditioned media that contained Wnt, R-spondin and Noggin. Human jejunal spheroids were enzymatically dissociated into single cells and plated on Matrigel-precoated culture plates or culture inserts. [RESULTS] The mRNA expression levels of typical intestinal pharmacokinetic-related genes in human jejunal spheroid-derived intestinal epithelial cells were increased drastically over a 5-day period after seeding compared with those in human jejunal spheroids and maintained at approximately the same levels as in human jejunum tissue at least until 13 days after seeding. Activities of typical drug-metabolizing enzymes (CYP3A, CYP2C9, UGT1As, and CES2) and uptake/efflux transporters (PEPT1, P-gp, and BCRP) in the differentiated cells were confirmed. Furthermore, intestinal availability (Fg) estimated from the permeation clearance in the apical-to-basolateral direction (CLA to B) across the cell monolayers showed a good correlation with the reported ones in humans for five CYP3A substrate drugs, whose Fg ranged from 0.35-0.98. [CONCLUSION] The functions of major intestinal drug-metabolizing enzymes and transporters could be maintained in human jejunal spheroid-derived intestinal epithelial cells. This system would be useful for the quantitative evaluation of the impact of intestinal drug-metabolizing enzymes and transporters on the intestinal absorption of substrate drugs in humans.

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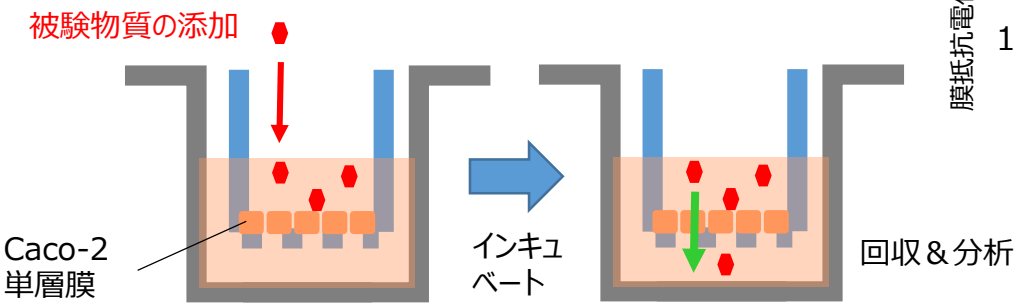

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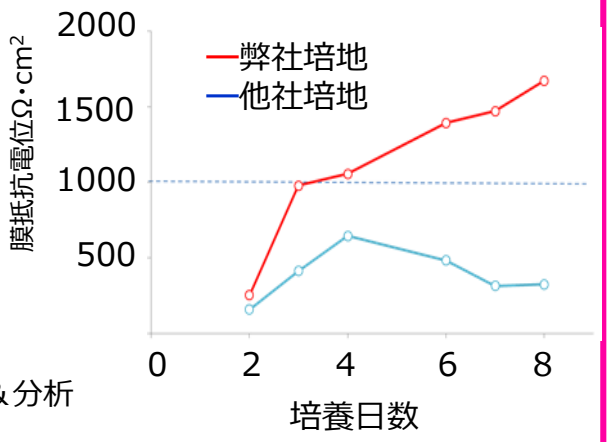


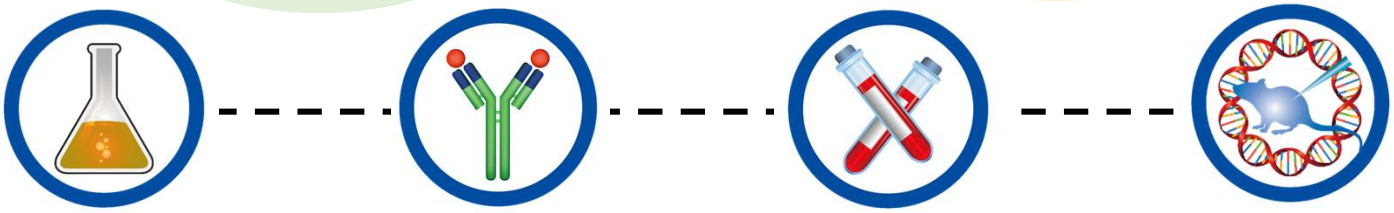
***in vitro* から *in vivo* まで、幅広い研究支援サービスを提供しております。**
研究課程のあらゆるシーンでサポートいたします。

■ *in vitro* 関連サービス

- 遺伝子解析
- 微生物培養
- 細胞培養
- 抗体開発 /生産
- 組換えタンパク質開発 /生産
- ADME /Tox試薬
- 研究用試薬
  (サイトカイン /抗体 /酵母エキス他)
- 生体試料

■ *in vivo* 関連サービス

- 実験動物用飼料、特別注文飼料
- 実験動物、飼育用器材
- 遺伝子改変動物作出
- SPF / 無菌化
- 動物検査
  (生化学 / ホルモン / ステロイド他)
- 受託飼育
- レンタルラボ
- 薬効薬理 / 安全性試験



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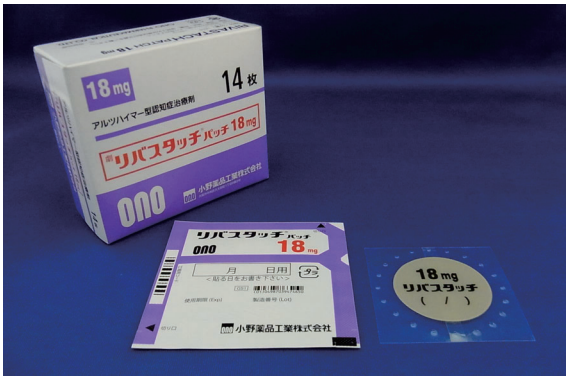
The adhesive base-ingredient technology of KM Transderm, a member of Kaneka Group, was adopted to a formulation containing a new base-ingredient for the treatment of Alzheimer's Disease Dementia

Kaneka Corporation
June 27, 2019



A formulation containing a new base-ingredient[*1] using adhesive technology of KM Transderm Ltd. (Headquarters: Kita-ku, Osaka; President: Haruki Tanabe; "KM Transderm"), affiliate company of Kaneka Corporation (Headquarters: Minato-ku, Tokyo; President: Mamoru Kadokura; "Kaneka"), was approved on March 13, as a partial change in the approved items of the manufacturing and marketing approval[*2].

This formulation adopted the technology of KM Transderm as a partial change to the transdermal formulation[*3] for the treatment of Alzheimer's Disease Dementia, sold as Rivastach® Patch and Exelon® Patch[*4] (generic name: rivastigmine), marketed by Ono Pharmaceutical Co., Ltd. (Headquarters: Chuou-ku, Osaka; President: Gyo Sagara; "ONO") and Novartis Pharma K.K. (Headquarters: Minato-ku, Tokyo; President: Kazunari Tsunaba; "Novartis Pharma"), in order to improve the current formulation.

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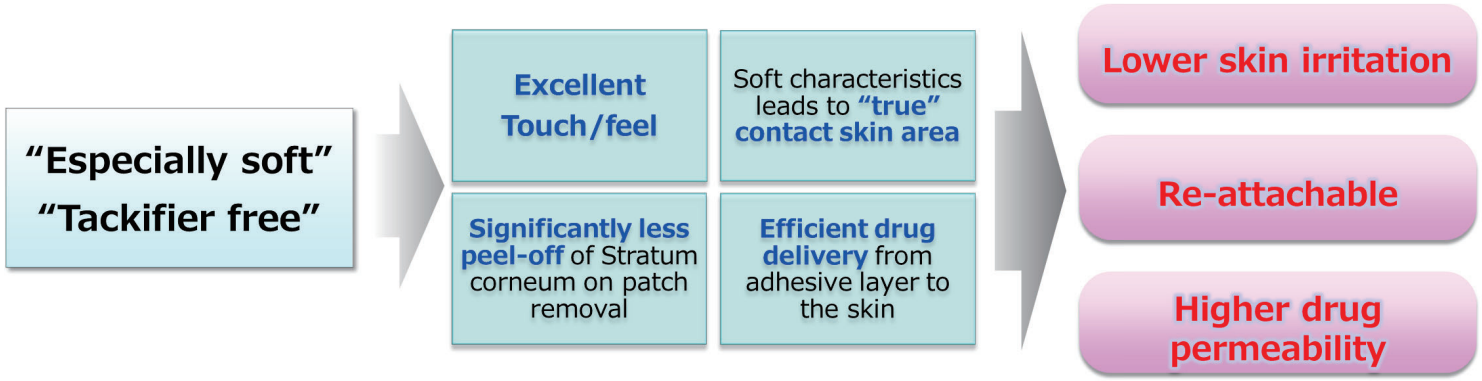

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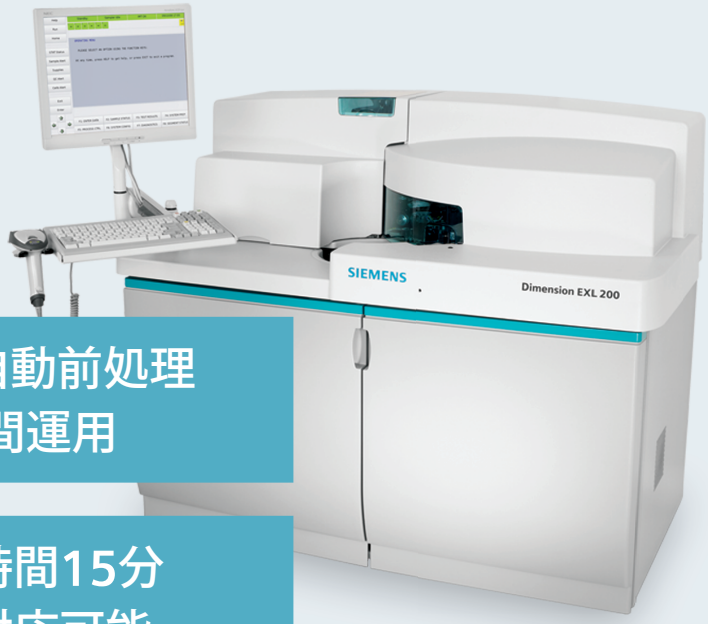

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1 ベシクル・試薬

【ABC Transporter Vesicles Products 】

バキュロウィルス発現系により ABC Transporter を大量発現させた Sf9 細胞膜画分を、当社独自の技術で高純度に精製した製品です。

ABC vesicles　Reagent Kit

2 安定発現細胞・一過性発現細胞

【SLC Transporter 培養細胞プレート 】

納品後そのままお使いいただけるReady-to-useの製品です。

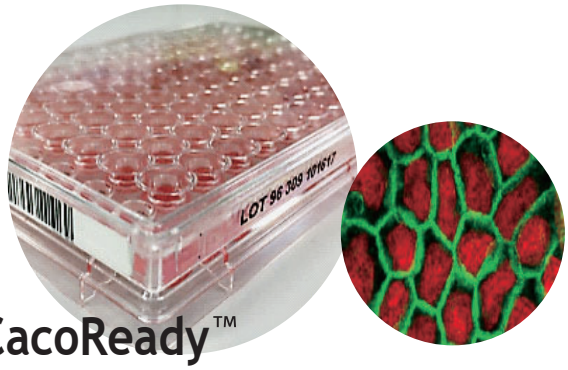
【TRANSiPORT(G) Cells】

柔軟な実験計画が可能で、トランスポーター試験が 2日間で行えます。

SLC 培養細胞プレート　TRANSiPORT(G) Cells

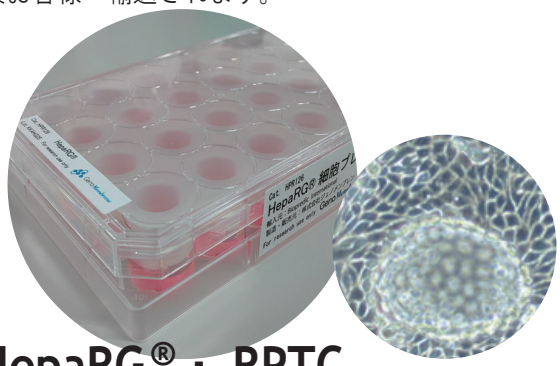
3 TransFlex™

MDCK Ⅱ 細胞に取込もしくは排出型トランスポーター又はその両方を一過性発現させた 96-well plate フォーマットです。自由なレイアウトが可能なReady-to-useの製品です。



4 CacoReady™

CacoReady™ は CACO-2細胞をTranswell®プレートに播種した状態でお届けする透過性試験用のReady-to-useタイプの製品です。スペインの ReadyCell 社が特許を有する Shipping medium（輸送時はゲル状）を用いて、ReadyCell社から直接お客様へ輸送されます。



5 HepaRG® ・ RPTC

【HepaRG® 細胞プレート 】

BIOPREDIC社（フランス）の凍結HepaRG®をプレートに播種したReady-to-useタイプの製品です。

【RPTC 凍結細胞・細胞プレート 】

BIOPREDIC社（フランス）のRPTC凍結細胞（バイアル）に加え、Transwell®プレートに播種した状態でお届けするReady-to-useタイプの製品もご用意しております。

6 受託試験サービス

トランスポーター試験の詳細については
お問合せ下さい。

株式会社ジェノメンブレンは薬物輸送性トランスポーターの研究・開発に特化した企業です。

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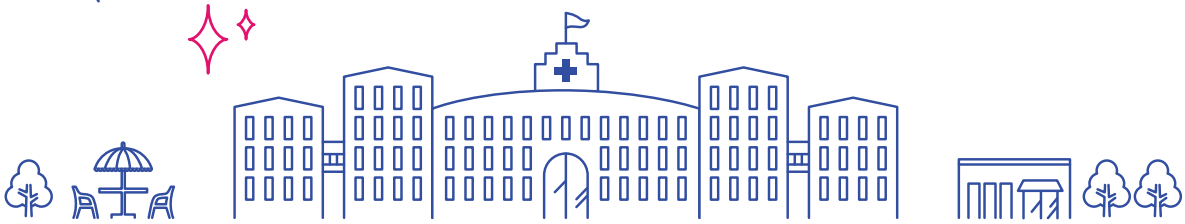
ISBN：978-4-8407-5369-2



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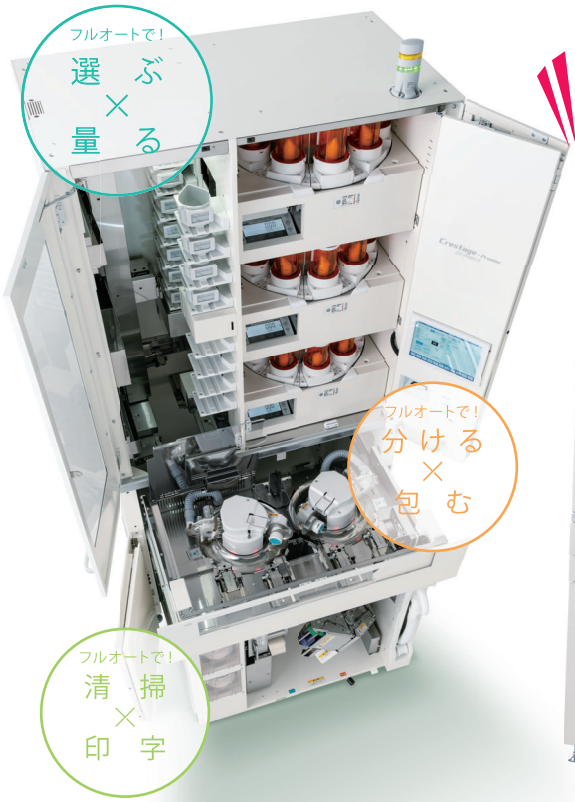
※ オプションです。



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それまで手作業であった製造工程の自動化を実現し、製剤技術の新たなページをひらきました。
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次世代シーケンス データ取得受託サービス

※下記は.fastqファイル+md5.txtファイルのみ納品する場合の税抜料金です。

Illumina Platform NovaSeq 6000	価格（1検体税抜）	受入サンプル	リード長 データ量	参考納期 検体受領時から	サンプル要件
真核生物RNA-seq poly-A選択法, Strand-specific	¥32,000	total RNA	150PE 4Gb	4~6週	total RNA, 1μg以上 (> 20μL), 50ng/μL以上 OD260/280 = 1.8-2.2 , OD260/230≧1.8
原核生物RNA-seq rRNA除去法, Strand-specific	¥39,000	total RNA	150PE 2Gb	5~7週	total RNA, 3μg以上 (> 20μL), 50ng/μL以上 OD260/280≧1.8-2.2, OD260/230≧1.8
真核生物RNA-seq 微量サンプル, Non-stranded	¥60,000	total RNA	150PE 4Gb	5~8週	total RNA, 20ng ~ 100ng (> 20μL), 0.1 ~ 10ng/μL以上 OD260/280≧2.0, OD260/230≧1.0
WGS ヒト 30xカバレッジ	¥110,000	DNA	150PE 90Gb	4~6週	DNA, 500ng以上 (> 20μL), 20ng/μL以上 OD260/280≧1.8, OD260/230≧1.0
WGS 細菌・真菌	¥28,000	DNA	150PE 1Gb	4~6週	DNA, 500ng以上 (> 20μL), 20ng/μL以上 OD260/280≧1.8, OD260/230≧1.0
WES ヒト	¥40,000	DNA	150PE 6Gb	4~6週	DNA, 800ng以上 (> 20μL), 20ng/μL以上 OD260/280≧1.8, OD260/230≧1.0
ChIP-seq ChIP-DNA受入プラン	¥29,000	ChIP-DNA	150PE 6Gb	6~8週	ChIP-DNA, 50ng以上, (>20 uL), 2ng/μL以上, 断片サイズ 100~500 bp (ピークトップ:200~300bp), OD260/280 = 1.8-2.0
シングルセルRNA-seq	業界最安水準 お問い合わせ	凍結細胞	お客様ご指定	問合せ	詳細はお問い合わせください

ライブラリーシーケンス	価格（1検体税抜）	受入サンプル	リード長 データ量	参考納期 検体受領時から	サンプル要件
シングルセル3' RNA-seq シーケンス+Cell Ranger	¥200,000	調製済み ライブラリ	150PE 120Gb (8億リード)	6~9週	調製済み Library 詳細はお問い合わせください
Illumina HiSeq X Ten 1レーンシーケンス	¥180,000	調製済み ライブラリ	150PE 110Gb	3~6週	調製済み Pooled Library 詳細はお問い合わせください

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お薬が苦手な方やお子さまにも飲みやすく。
さらに、お薬と飲食物との飲み合わせも研究しています。

+α 見分けやすい

お薬の名前を印刷して、分割しても何のお薬か
見分けやすい錠剤や、飲み間違いを防ぐパッケージなど、
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+α 原薬からのこだわり

お薬の効き目のもととなる原薬からこだわり、高い品質で、
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光・熱・湿気による影響を抑えてお薬の品質を
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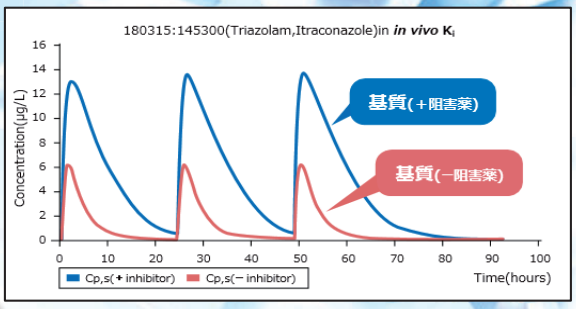

注目

独自の*in vivo* K_i 値 データベースを構築

**北里大学薬学部・前田和哉　教授、
武蔵野大学薬学部・伊藤清美　教授、
の監修により、複数の臨床試験データから算出。
独自のデータベースとして収録しています。**

シミュレータ

- PBPKモデル
- 肝代謝阻害(競合阻害・MBI)／誘導
- 小腸代謝阻害(競合阻害・MBI) ／誘導
- トランスポーター阻害　●肝臓OATPs阻害

薬物データベース

- *in vivo* K_i 値の収録
- 薬物PKパラメータ値の収録
- データの編集機能

投与設計・評価

- 柔軟な投与設計
- バッチシミュレーション
- 各臓器の血漿中濃度推移の表示機能

フィッティングツール

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- 非線形最小二乗法による当てはめ計算
- コンパートメントモデル、PBPKモデルを搭載

※フィッティングツールはオプションです。

詳細情報は ▶ DDI Simulator 検索

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富士通株式会社

第１５回次世代を担う若手のための医療薬科学シンポジウム
要旨集
2021 年 10 月 20 日　公開