LSACJ2023
23rd Annual Conference of LSACJ

International Conference on Interdisciplinary Life Sciences 2023（ILS2023）

DATE: January 20 (Sat), 2024
VENUE: Masukawa Hall, Kyoto University
Oiwake-cho, Kita-Shirakawa, Sakyo-ku, Kyoto, 606-8267, Japan

PROGRAM COMMITTEE

CHAIR
Quan WU
Kyoto University

PRESIDENT of LSACJ (2023)
Biao MA
RIKEN R-CCS

LSACJ COUNCIL

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Homepage: https://lsacj.org

LSACJ 2023 Academic Committees

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Greetings from the Chair of LSACJ2023

In a world where knowledge is expanding at an exponential rate, the boundaries between traditional disciplines are blurring, and we find ourselves at the nexus of an exciting era. Indeed, the progress of biotechnology owes much of its success to the close collaboration with fields such as physics, chemistry, and computer science. For example, breakthroughs in microscopy and sequencing technologies have paved the way for incredible advancements in biology. More recently, the integration of AI into predicting protein structures, and conducting pathological analysis based on image data has triggered a paradigm shift within the biological sciences.

On the other hand, the complexity of life, shaped by billions of years of evolution, continues to astound us. Indeed, biology stands as a testament to nature's intricate and interwoven web. This complexity extends beyond our imaginations, presenting us with multifaceted challenges that necessitate a multidisciplinary approach.

Therefore, we have adopted the theme of LSACJ 2023 as “Crossing Boundaries, Exploring New Frontiers in Life Sciences”. We extend a warm invitation to every one of you to participate actively and engage wholeheartedly in this gathering. We encourage you to sign up, be part of this transformative experience, and let your curiosity and expertise shine as we embark on this expedition into uncharted territories.

知識が指数関数的な速度で拡大している世界では、伝統的な学問分野の境界が曖昧になりつつあり、私たちは新たな時代の結節点にいます。実際、バイオテクノロジーの日進月歩は、物理学、化学、計算科学といった分野との緊密な連携によるところが大きいです。例えば、顕微鏡や シークエンシング技術の飛躍的進歩は、生物学における驚くべき進歩への道を開きました。さらに最近では、タンパク質の構造予測や画像データに基づく病理解析に AI が統合され、生物科学におけるパラダイムシフトが起きています。

一方、何十億年もの進化によって形作られた生命の複雑さは、私たちを驚かせ続けています。実際、生命が複雑に絡み合う自然のネットワークから生まれました。この複雑さは私たちの想像を超えており、その解明には学際的なアプローチが必要です。

そこで、LSACJ2023 のテーマを「Crossing Boundaries, Exploring New Frontiers in Life Sciences」といたしました。私たちは、この集まりに積極的に参加し、心をこめて取り組んでいただけるよう、皆様を温かくお招きいたします。この未知の領域への探検に乗り出すにあたり、あなたの好奇心と専門知識を存分に発揮してください。

在这个知识量以指数增长的世界里，传统学科之间的界限正在变得模糊，我们正处于一个激动人心的时代的中心。事实上，生物技术日新月异地进步在很大程度上要归功于与物理、化学和计算机科学等领域的密切合作。例如，显微镜和测序技术的突破为生物学的惊人进步铺平了道路。最近，人工智能与预测蛋白质结构以及根据图像数据进行病理分析的结合，引发了生物科学领域的范式转变。

另一方面，经过数十亿年进化而形成的生命的复杂性继续令我们震惊。事实上，大自然错综复杂、相互交织的网络孕育了生命。这种复杂性超出了我们的

想象，给我们带来了多方面的挑战，需要采取多学科的方法。

因此，我们将 LSACJ 2023 的主题定为 "跨越边界，探索生命科学的新前沿"。我们诚挚地邀请大家积极参与，全身心地投入到这次盛会中来。我们期待您报名参与到这一变革性体验中来，让您的好奇心和专业知识在我们踏上未知领域的征程中大放异彩。。

Quan WU

Graduate School of Medicine, Kyoto University

Senior Lecturer.

Greetings from the President of LSACJ (2023)

The Life Science Association of Chinese in Japan (LSACJ) was established in 1995 as a multidisciplinary and comprehensive academic society focusing on life sciences by Chinese scientists and Chinese students in Japan with a history of 28 years. The association was founded in 1995 as the Kansai Region Chinese Students' Association for Molecular Biology, and later developed into the Kansai Chinese Life Sciences Association, which was renamed to the present Life Sciences Association for Chinese Residents in Japan in 2005 on the occasion of the 10th anniversary of the association. Since its foundation, the association has been committed to the spirit of openness, tolerance, friendship, unity, and endeavor to improve communication and cooperation among its members, and to pursue scientific and technological innovation. The Association is also committed to promoting exchanges and cooperation between China and Japan in the field of life sciences.

In LSACJ 2022, we will focus on the theme of "Bench to Bedside", and experts and researchers will be invited to share the latest cutting-edge research results from basic to clinical stages. We will also invite experts who are familiar with pharmaceutical policies in China and Japan to explain the regulations and application process of clinical research in China and Japan. It is hoped that this conference will promote the translation of basic research into clinical applications and provide a platform for communication and interaction between Chinese and Japanese colleagues in different research fields.

We sincerely hope that all of you will participate.

在经历了近四年的新冠疫情挑战之后，我们非常荣幸地宣布，第 23 届留日中国人生命科学协会年会（LSACJ2023） 暨国际多领域生命科学年会 2023(ILS2023) 将作为自疫情以来的第一次线下活动举行。这次面对面的会议不仅是一个科学交流的盛会，更是我们共同克服困难、重新聚集的象征。

在此，我要特别感谢本次年会的主席，京都大学的吴泉老师和年会筹备委员会的各位老师。各位老师的专业知识和热情投入对于本次会议的成功举行起到了关键作用。

同时，我们感谢所有赞助企业、团体以及后援团体。你们们的慷慨支持和坚定信任是本次年会得以成功举行的重要基石。每一位赞助者的贡献都对促进科学交流和合作，以及推动生命科学领域的进步具有不可估量的价值。

本年会以“跨越科学边界，探索生命科学的新境界”为主题，致力于汇聚来自不同背景和领域的科学家，共同探讨和分享生命科学领域的最新进展和研究成果。在这样一个特殊的时刻，我们期待与会的专家学者进行深入的交流和探讨。

自 1995 年成立以来，LSACJ 始终致力于增进会员间的交流与合作，并在推动中日两国在生命科学领域的发展中扮演了重要角色。尤其在疫情期间，我们的会员们不仅在科学研究领域取得了显著成就，还积极参与到疫情防控和科学研究中，为全球抗击疫情做出了重要贡献。

此次年会不仅是一个学术交流的平台，也是庆祝我们团结一致、共克时艰的时刻。我们鼓励每位参会者积极参与，分享你们在疫情期间的经验和见解，以及如何将这些经验转化为未来科研工作的动力。

最后，衷心感谢每位会员、嘉宾、赞助企业、团体及后援团体的参与和支持。在这个特殊的时刻，让我们共同期待这次年会能够为大家带来启发性的学术体验，并为我们未来的合作和发展奠定坚实的基础。

希望大家在 LSACJ2023 会议上有所收获！。

コロナパンデミックの試練から 4 年近くを経て、COVID-19 流行後初のオンサイト開催イベントとして、第 23 回留日中国人生命科学協会年会(LSACJ2023) と国際学際生命科学年会 2023(ILS2023) が開催されることを大変嬉しく思います。 この顔合わせは、学術交流のイベントであると同時に、困難を乗り越え再集結するための共通の努力の象徴でもあります。

年会長である京都大学の呉泉先生と、年会準備委員会の先生方に感謝の意を表したいと思います。彼らの専門知識と熱意が、この会議の成功に欠かせなかった。

また、すべてのスポンサー、組織、支援団体に感謝いたします。 皆様の惜しみないご支援と揺るぎない信頼が、この会議の成功の礎となりました。 皆様お一人お一人の貢献は、科学的交流と協力を促進し、ライフサイエンス分野を発展させる上でかけがえのないものです。

Crossing Scientific Boundaries, Exploring New Frontiers in the Life Sciences (科学の境界を越え、生命科学の新たなフロンティアを探求)」というテーマのもと、この年次大会は、さまざまな背景や分野の科学者が一堂に会し、生命科学の最新の進歩や研究成果について議論し、共有することを目的としています。 私たちは、この特別な機会に参加される専門家や学者たちの深い交流と議論を楽しみにしています。

LSACJ は 1995 年の設立以来、常に会員間の交流と協力の強化に努め、日中間の生命科学の発展に重要な役割を果たしてきました。 特に伝染病の流行期には、会員が科学研究の分野で目覚ましい成果を上げただけでなく、伝染病の予防と制御、科学研究にも積極的に参加し、世界的な伝染病との闘いに大きく貢献しました。

この年次大会は学術交流の場であるだけでなく、私たち共に困難を乗り越える時でもあります。 私たちは、すべての出席者が積極的に参加し、COVID-19 流行中の経験や見識を共有し、それらを将来の科学研究にどのように反映させることができるかを分かち合うことを奨励します。

最後に、ご参加とご支援を賜りました会員、ゲスト、スポンサー、団体、支援グループの皆さまに心より御礼申し上げます。 この特別な機会に、私たち全員がこの年次大会で啓発的な学術的経験をし、私たちの将来の協力と発展のための強固な基礎となることを期待しましょう。 LSACJ2023 が皆様にとって実り多きものとなりますよう、心よりお祈り申し上げます。

Biao MA

President of LSACJ (2022-)

Research Scientist

HPC- and AI-driven Drug Development Platform Division, RIKEN Center for Computational Science

About LSACJ

List of the Presidents of LSACJ

Period	Chairpersons
2022 ~	Biao Ma, Ph.D.
2020 ~ 2022	Li Sun, Ph.D.
2018 ~ 2020	Yu-Shi Tian, Ph.D.
2016 ~ 2018	Tao Yu, Ph.D.
2008 ~ 2016	YuQuan Lu, Ph.D.
2008 ~ 2008	Xin Zhao, Ph.D.
2007 ~ 2008	Jitian Zhang, Ph.D.
2006 ~ 2007	Cho Azuma, Ph.D.
2005 ~ 2006	Lei Shi, Ph.D.
2004 ~ 2005	Guolong Zhang, Ph.D.
2002 ~ 2004	Yi Dai, PhD.
2000 ~ 2002	Gang Huang, Ph.D.
1999 ~ 2000	Ping Zou, Ph.D.
1998 ~ 1999	Wei Shi, Ph.D.
1997 ~ 1998	Kai Chen, Ph.D.
1996 ~ 1997	Zhihua Zou, Ph.D.
1995 ~ 1996	Jun Sheng, Ph.D.

LSACJ Committee in 2023

President: Biao MA

Vice Presid. in Charge: Dan Ohtan WANG

Vice Presidents: Xiangji JIANG, Yi ZHOU

Secretariats: Yi ZHOU, Lu CHEN

IT Director: Xiangji JIANG, Zixuan WANG

Financial Director & Cashier: Xiaochun ZHANG, Duligengaowa WUERGEZHEN

External Contactor: Ning LI

Public Relation: Yidan ZHU

Guidance /参加者へのご案内/会议一般说明

1. Registration / 登録 / 报名

Registration includes but not limited to 1) on-site registration, 2) paying the participation fee, and 3) getting conference proceedings, participant cards, and recipes.

当日参加の申し込み、事前参加の申込者の参加費のお支払い及び領収証の発行、要旨集の配布は総合（参加）受付で行います。

当日参会报名以及事先报名参会者的参会费缴纳，收据发行和摘要集的发放将在登记处进行。

Attention: Registration time / 受付時間 / 登记处的工作时间: **9:30-15:00, January 20, 2024**

2. Fees / 登録費 意見交換会費/ 参加费 意见交换会费

Category (区分)	Early-bird Registration (事前参加登録)	On-site Registration (当日参加登録)
Students 学生	JPY 0	JPY 0
OEM (Students) 意見交換会(学生)	JPY 1000	JPY 1000
Others その他	JPY 0	JPY 0
OEM (Others) 意見交換会(その他)	JPY 3000	JPY 4000

3. Wi-Fi is not available.

There is no Wi-Fi during the conference.

Wi-Fi を提供しておりません。

会场内不提供 Wi-Fi 服务

Instructions

Every speaker has 15-40 minutes (including 5 min questions) to give the presentation. Please check the slides or data at least 30 minutes in advance. Waiting seat is prepared for the next speaker, who will give a talk in 15 minutes.

Please bring your laptop or submit your slides or data (by USB memory stick) to the conveners. Macintosh users are recommended to check the device connection in advance.

Data submission time: coffee break or at registration

Presentation:

If you will use your personal laptop,

* The PowerPoint (2013 or later versions) is recommended for your presentation; but not limited to it.
* If your presentation contains a movie file, we recommend using your own laptop.
* Please bring your presentation data on media (e.g. USB stick) for backup, with all links restored in the same back up file.
* Appliances in Japan run on 100V A.C. and plug in to a 2-flat pin, type A socket. Since it is difficult to find sockets compatible with 3-pin plugs or supplying 120V, 200V, and 220V electricity, we highly recommend that you bring an adaptor.
* The secretariats will prepare laptop cable connector of MiniD-sub 15 pin and HDMI. If your laptop is not compatible with these cables, please bring an adaptor to connect your laptop and the MiniD-sub 15 pin cable or HDMI.
* Please make sure to turn off the screening saver and power saving function before you give the presentation.

If you would like to use our laptop,

* The secretariats will only prepare laptop with Windows (OS: Windows 10, PowerPoint 2013 or previous versions). Please bring your presentation data on USB Memory Stick. No floppy, CD-ROM, or MO is acceptable.
* Presentation data accepted at the PC Registration Desk will be copied to the secretariat's PC for the presentation. All the copied data will be deleted after the conference.
* All the presentation data are required to be backed up in media and be brought to the conference room in case of any malfunction or damage of your submitted data.
* Please check the files by using anti-virus software before your submission to the desk.

座長・発表者へのご案内

座長の方へ

・ご担当のセッション開始 15 分前までに、次座長席にお座りください。時間内でのセッション進行にご協力ください。

発表者の方へ

・発表時間は 15-40 分（質疑応答 5 分）です。
・データに動画をご使用の方、また Mac での発表をご希望の方は、必ずご自身の PC をご持参の上、PC センターにて、動作確認を行ってください。

当日の流れ

・ご発表の 30 分前までにデータ受付へお越しください。
・お持込の PC 本体または、 USB メモリをご提出いただき、必ず動作確認を行ってください。
・受付での編集作業をお断りいたします。
＊お預かりしました発表用データは、一旦コピーさせていただきますが、学会終了後、責任をもって完全消去いたします。
PC データ受付: 会場の前方に設置しております。 受付時間：参加受付時または、各休憩時間。

発表のデータ作成について

・発表データの持ち込みについて
学術集会準備の PC は OS Windows10 でアプリケーションソフトは Microsoft PowerPoint 2013 以降のものがご利用いただけます。 Macintosh のご利用をご希望の場合はご自身で本体をご持参下さい。ご利用可なメディアは USB フラッシュメモリのみとなります。それ以外の媒体を受付できません。動画をご利用の場合はご自身の PC をご持参下さい。発表データはご自身の PC 以外でも文字化け等がなく、PowerPoint に設定された標準的なフォントをご使用ください。お持込みのメディアは、事前にウイルスチェック駆除ソフトでチェックを行って下さい。持込メディアに発表データ以外は入れないようにお願いいたします。

・PC の持ち込みについて
持ち込みの PC (Winodws, Macintosh) は試写用モニターに接続し外部出力状況を確認してください。D-Sub15 ピン（ミニ）と HDMI のケーブルをご用意いたします。 PC によっては本体付属のコネクタが必要な場合がありますので、その場合には、必ずご持参ください。動画も利用可能ですが、実際に持ち込む PC で再生できることを事前にご確認ください。本体の液晶画面に動画が表示されても、 PC の外部出力に接続した画面には、表示できない場合があります。講演に使用する PC の外部出力に、モニターあるいはプロジェクターを接続して、事前にご確認ください。音声の利用はできません。スクリーンセーバー並びに省電力設定はあらかじめ、解除してください。

致演讲者和主席

各位主席（chair）

・请在各自负责的会议区分开始前 15 分钟到达“下一座长”的座位。请严格按照时间掌控会议区分的进行

各位演讲者

・讲演的时间为 15-40 分钟（包括讨论 5 分钟）。请遵守时间。

・如果您的讲演资料（PPT 等）里含有动画，或者您使用苹果电脑，请自行携带电脑参加本次会议，并且请在发表前确认您的资料可以正常播放。

当天的流程

・请在发表前 30 分钟，把您的讲演资料交给放映工作人员。

・讲演资料可以放在您自带的电脑或者 USB 盘，请您在提交前仔细确认。

・提交给工作人员后，禁止再次修改讲演资料。

☆如果您把讲演资料交给我们的工作人员，我们保证在学会结束后，彻底删除会场电脑里的您的资料。

放映工作人员将坐于会场前方。 资料的受理时间：可在您参会报名时或茶歇等休息时间。

讲演资料的准备

・使用学会准备的电脑

学会准备的电脑系统为 windows 10，幻灯片播放软件为 Microsoft PowerPoint 2013。如果您使用苹果系统，请自行携带电脑参会。提交可能的媒体仅限于 USB 盘，其他媒体不予接受。如果您的讲演中含有动画，请尽可能使用您自己的电脑，以免造成播放不出的情况。您的 USB 盘请一定在事先使用杀毒软件查杀病毒。演讲资料以外的内容请不要放入提交的 USB 盘里。

・自行携带电脑

如果您自行携带电脑请确认您的电脑的外部接口。会场将准备 D-Sub15 和 HDMI 的连接线。如果您的电脑需要转换头，请自行准备。动画是可以在会场播放的，不过请您一定事先确认，因为有可能会出现动画画面可以显示但是动画不被播放的情况。演讲者自行携带电脑时，请事先测试是否可以连接会场的投影仪。不可使用声音的媒体。请取消屏保和省电模式。

Program

Opening	10:00-10:10

Symposium 1: Molecular Imaging and Radiotheranostics

Masukawa Hall	10:10-12:00

Convener **Zhouen Zhang, Shanghai JankoVita Biosciences Co. Ltd.**

S1-1
10:10-10:45

Radiopharmaceuticals for Positron Emission Tomography and Targeted Radionuclide Therapy: The Experience in QST

Prof. Mingrong Zhang, Ph.D.

Director, Department of Advanced Nuclear Medicine Sciences, National Institutes for Quantum Science and Technology (QST)

S1-2
10:45-11:20

Current Status and Future Prospects of Preclinical Development of Targeted Alpha Particle Therapy using Astatin-211 at Fukushima Medical University

Prof. Songji Zhao, M.D., Ph.D.

Fukushima Global Medical Science Center Advanced Clinical Research Center, Fukushima Medical University (FMU)

S1-3
11:20-11:40

Novel Theranostic Radiopharmaceuticals Targeting Metabotropic Glutamate Receptor 1 for Precision Medicine in Oncology

Lin Xie, M.D., Ph.D.

National Institutes for Quantum Science and Technology (QST)

S1-4
11:40-12:00

Innovation of 11C-Labeling Chemistry for the Visualization of Pharmaceuticals and Medicine

Zhouen Zhang, Ph.D.

General Manager, Shanghai JankoVita Biosciences Co. Ltd.

Photograph

Masukawa Hall	12:00-12:15

Luncheon Seminar & Sponsored Seminar

Seminar Room	Exhibition Hall	12:15-13:15

Convener Biao Ma, RIKEN Center for Computational Science (R-CCS)

12:15	**LS-1 上海南方模式生物科技股份有限公司美国分公司 Shanghai Model Organisms Center(USA) LLC.**	**SS-1: 深圳市瑞沃德生命科技有限公司 RWD Life Science (Sponsored Seminar) Theme: Application of Laser Speckle Technology in Medicine and Microcirculation**
12:35	**LS-2 北京深势科技 DPTechnology**	
12:55	**LS-3 EPS 株式会社（EPSHD）**	**LS-4 上海国际人才交流协会日本大阪联络处**
13:05		**LS-5 鎂伽日本株式会社**

Symposium 2: Frontiers of Basic Life Sciences

Masukawa Hall	13:30-15:00

Convener Quan Wu, Graduate School of Medicine, Kyoto University

S2-1
13:30-14:00

Tissue pattern emergence through boundary-driven ordering

Takafumi Ichikawa, Ph.D.

Assitant Professor, Department of Developmental Biology, Graduate School of Medicine, Kyoto University

S2-2
14:00-14:30

Unraveling the dynamic 3D genome architecture through single-cell DNA replication profiling

Ichiro Hiratani, Ph.D.

Team Leader, Laboratory for Developmental Epigenetics, RIKEN Center for Biosystems Dynamics Research (RIKEN BDR)

S2-3 **14:30-15:00**	**Programmed activation of Autophagy preserves body structure for a long-term diapause period** Masayuki Oginuma, Ph.D. Assitant Professor, Research Institute for Microbial Diseases, Osaka University

Break	**15:00-15:10**

Symposium 3: Translational Medicine and Clinical Science

Masukawa Hall	**15:10-16:40**

Convener	**Yuemin Zhou, HuaiHe Hospital of Henan University** **Yuquan Lu, Osaka University**

S3-1 **15:10-15:40**	**Translation medicine in plastic surgery** Prof. Yuemin Zhou, Ph.D. Professor, HuaiHe Hospital of Henan University
S3-2 **15:40-15:55**	**Development of new bioabsorbable implants with de novo adipogenesis** Qiannan Zhao, Ph.D. Kyoto University
S3-3 **15:55-16:10**	**Treatment of keloid** Ruoxuan Liu, Ph.D. HuaiHe Hospital of Henan University

S3-4 16:10-16:25	**Clinical application of PRP in refractory wounds** Yuepu Wang, Ph.D. HuaiHe Hospital of Henan University
S3-5 15:25-16:40	**3D technique-based nonsurgical correction of congenital auricular deformities** Xin Zhao, Ph.D. HuaiHe Hospital of Henan University

Break **16:40-16:50**

Symposium 4: Computing and Artificial Intelligence for Life Science

Masukawa Hall **16:50-18:00**

Convener **Biao Ma, RIKEN Center for Computational Science (R-CCS)**

S4-1 16:50-17:30	**Data integration and curation as a basis for Artificial Intelligence-based drug discovery** Prof. Kenji Mizuguchi, Ph.D. Professor of Computational Biology, Institute for Protein Research, Osaka University Director, Artificial Intelligence Center for Health, Biomedical Research (ArCHER), NIBIOHN
S4-2 17:30-18:00	**High-throughput single-cell profiling methods for microbiota and mammalian cells** Prof. Jianshi Jin, Ph.D. Professor, State Key Laboratory of Integrated Management of Pest Insects and Rodents Institute of Zoology, Chinese Academy of Sciences

Poster **18:00-19:00**

Opinion Exchange Meeting **19:00-21:00**

Symposium 1

Molecular Imaging and Radiotheranostics

Masukawa Hall

10:10-12:00

International Conference on Interdisciplinary Life Sciences 2023

α線放出核種アスタチン - 211を用いた標的α線核医学的治療開発の現状と将来展望—福島県立医科大学の取組—

趙　松吉

Keywords: 核医学，トレーサー情報分析

2011 年 3 月 11 日の東日本大震災、それに続く福島第一原子力発電所事故から、そろそろ13年になる。福島県立医科大学では、震災、原発事故後の福島の復興のため、先端臨床研究センターを創立した。当センターの使命は、核医学診断と放射性アイソトープ治療を含むがん治療法を開発することで、放射線科学を生かして地域社会に希望をもたらすことである。

当センターは、2016 年 6 月に本格的な稼働を開始し、現在では日本国内でアスタチン-211 (211At) を用いた標的α線治療（TAT）を開発する中心の 1 つとなっており、新しい 211At 標識化合物の臨床応用に向けた治療戦略を開発している。→アルファ線放出核種は、線エネルギー付与が高く、組織内飛程が短い特徴を有するため殺細胞効果が大きく、癌治療、特に微小転移癌や白血病の治療において非常に魅力的である。211At は、中型サイクロトロンで製造でき、適切な半減期（7.2時間）を有するため、副作用の制御の面からも治療に適したα線放出核種として期待されている。当センターには医療専用のMP-30加速器（住友重機械工業株式会社）が設置され、2016年から211Atの生産を開始し、2017年から本格的に稼働している。現在、2 時間の照射で 1 GBq 以上を生産でき、安定的に前臨床研究に提供している。

当センターには独自の非臨床研究施設を設けており、2016 年 11 月に本格的な稼働を開始した。本施設は、特定の病原菌が存在しない環境（SPF）下での非密封ラジオアイソトープ（RI）を用いたイメージングによる薬物動態・薬効薬理試験ならびに治療効果を評価する非臨床試験を信頼性基準下で運用するアカデミアでは国内初の施設として211At標識薬剤を用いた新規放射線治療法の開発などを行っている。数多くの211At標識医薬品候補について研究開発を進めており、その中の1つはすでに臨床試験へ繋げることができた。そのほかいくつかの候補については、動物の体内動態実験及び抗腫瘍効果評価に関する試験を実施しており、抗腫瘍効果のproof of concept (POC）を獲得し前臨床評価段階に進んでいる。

Meta-211At-astato-benzylguanidine （ 211At-MABG）は悪性褐色細胞腫の治療薬として期待されている。2017年から、211At-MABGを用いたTATの臨床応用を目指すため、量子科学技術研究開発機構と共同研究の契約を締結し、211At-MABGの自動合成から薬物動態・薬効薬理試験、治療効果及び非臨床毒性予備試験を行ってきた。医薬品医療機器総合機構（PMDA）との対面助言に基づいて褐色細胞腫の治療薬としての安全性を確認するため、信頼性基準に適合した211At-MABGの拡張型単回投与毒性試験を独自に実施した。PMDAとの対面助言と非臨床毒性試験を経て、2022年10月から福島県立医科大学附属病院で211At-MABGの第I相治験（First in Human）を開始した。

本発表では、臨床試験へ向けた福島県立医科大学における211Atを用いた標的α線核医学的治療開発の現状と将来展望について紹介する。

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Field

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Education Experiences

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1990年　吉林大学白求恩医学部　医学修士号取得
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2003年　北海道大学　医学博士号取得

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1996年　京都大学大学院医学研究科・核医学科　研修生
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2011年　北海道大学医学研究科・トレーサー情報分析学分野　教授
2016年　福島県立医科大学・先端臨床研究センター　教授・受託研究部門長

Radiopharmaceuticals for Positron Emission Tomography and Targeted Radionuclide Therapy: The Experience in QST

Ming-Rong Zhang✉

Keywords: Radiopharmaceuticals, Positron emission tomography, Targeted Radionuclide Therapy, Radiosynthesis

Radiopharmaceuticals are a group of pharmaceutical drugs containing radioactive isotopes. Radiopharmaceuticals can be used for positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging, and for targeted radionuclide therapy (TRT)), emit radiation (alpha, beta, auger etc.) themselves. The processes for producing radiopharmaceuticals for human use include the following steps: **1)** production of radioactive nuclide or isotope by cyclotron, reactor, or generator etc., **2)** radiolabelling for drug candidates (small molecule, peptide, antibody, nano particle etc.), **3)** evaluation of usefulness, safety, and toxicity **4)** GMP production and quality control, **5)** regulation and approval.

In 1974, the first medical cyclotron was set up in National Institute of Radiological Sciences (now, QST) of Japan for fast neutron therapy and production of positron emission tomography (PET) radionuclides. Since then the number of cyclotron-PET facilities was gradually increased for nearly 30 years and rapidly began to increase in 2002 when fluorine-18 (^{18}F, half life: 109 min) labelled fluorodeoxyglucose ([^{18}F]FDG) was approved for tumor imaging by health insurance. At the moment, the number of cyclotron has counted about 220. In this time, I will introduce the development and production of radiopharmaceuticals for PET and TRT in our institute.

1) Development of irradiation and production methods of radioisotopes

To synthesize radioprobes that are useful for diagnostic and therapeutic purposes, we have developed an automated target handling system, vertical irradiation station, and target vessels made of ceramic to facilitate the production capacity of radioactive metals and halogens. Nowadays, we are not only producing isotopes (^{64}Cu (half time: 12.7 h)) and ^{89}Zr (78.4 h) etc.) for diagnostic imaging, but also producing alpha- (^{211}At (7.2 h) and ^{225}Ac (14.9 d)) and auger (^{91}Pt (2.8 d) and ^{103}Pd (17 d))-emitters for possible applications in TRT.

2) Development of radiolabeling techniques

We have built a technology platform to develop various synthetic methods and systems for producing radiolabeling agents with many chemical functional groups. In order to synthesize radioactive compounds that have diverse physiological functions and chemical structures, we are 1) developing and making practical use of ^{11}C (20.2 min)- or ^{18}F-labeling agents, such as [^{11}C]CH_3I, [^{11}C]$COCl_2$, [^{11}C]CO, [^{11}C]HCN, [^{11}C]CS_2, [^{18}F]F^-, [^{18}F]FEBr and [^{18}F]epifluorohydrin, 2) designing new labeling reactions and achieving them with high radiochemical yields and sufficient radioactivity using automated synthesis systems

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developed in house, 3) developing labeling techniques to reach ultra-high molar activity (> 7400 GBq/micromole) and radiochemical yields, 4) constructing a platform for labelling small molecules, peptides, antibodies, and nano particles with radiohalogens (^{18}F, ^{34m}Cl (32 min), ^{76}Br (16 h), ^{124}I (4.2 d)) and ^{211}At) and radiometals (^{64}Cu, ^{89}Zr, ^{225}Ac etc.).

3) Development of useful pharmaceuticals for PET and TRT studies

Using various labeling techniques, we have developed many new radioactive probes for imaging and quantitative measurement of diverse biological targets, functions, and disorders. The targets include receptors, transporters, and enzymes in brain, tumor, and peripheral systems. These probes are designed based on principles for exploring the biological functions and molecules and evaluated using cells and normal and model animals (ischemia, tumor, and senescence etc.). In this time, I will introduce some radiopharmaceuticals for PET imaging of human dementia and neuroinflammation. These drugs include radioactive probes targeting brain acetylcholinesterase, translocator protein 18 kDa (TSPO), metabotropic glutamate receptor, acylglycerol lipase and abnormal protein aggregators (Tau, alpha-synuclein etc.).

On the other hand, instead of just diagnosis, we are developing ^{211}At, ^{64}Cu, ^{89}Zr, ^{225}Ac-labeled compounds, including small molecules, peptides, proteins (antibodies), and nano-sheet for radiotheranostic and TRT studies on tumor.

4) Production of radiopharmaceuticals for clinical use

We are routinely producing more than 120 PET radiopharmaceuticals for imaging of brain and tumor etc. in clinical use and are producing 10 quality-assured radiopharmaceuticals according to the guidelines for in-house radiopharmaceuticals standards authorized by the Japanese Society of Nuclear Medicine (JSNM GMP). To transfer 1~3 new radiopharmaceuticals for clinical use of first-in-human (patient) every year, we are developing production, preparation, formulation, and analysis methods for reproducible yields and quality of new drug candidates.

In addition to PET imaging use, we have also started to produce [^{64}Cu]Cu-ATSM (> 22 GBq per irradiation) for TRT in clinical use.

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Education Experiences

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Work Experiences

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1998.4-2000.3 National Institute of Radiological Sciences; Postdoctoral Researcher

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2006.4-2016.3 Department of Molecular probes, Molecular Imaging Center, National Institute of Radiological Sciences; Team Leader, Director

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Major Publications

1. Xie L, et al. ***Cell Rep Med*** 2023;4:100960. 2. Hu K, et al. ***Acta Pharm Sin B*** 2022;12:1363-76. 3. Kikuchi T, et al. ***Chem Sci*** 2022;13:3556-62. 4. Nagatsu K, et al. ***Eur J Nucl Med Mol Imaging*** 2021;49:279-89. 5. Xie L, et al. ***J Immunother Cancer*** 2021;9:e002616. 6. Yamasaki T, et al. ***J Med Chem*** 2020;63:11469-83. 7. Nagai Y, et al. ***Nat Neurosci*** 2020;23:1157-67. 8. Hu K, et al. ***Nat Commun*** 2020;11:2778. 9. Miyazaki T, et al. ***Nat Med*** 2020;26:281-8. 10. Xie L, ***J Nucl Med***. 2020;61:242-8. 11. Terashima Y, et al. ***Nat Commun*** 2020;11:609. 12. Hu K, et al. ***Chem Commun*** (Camb) 2019;55:4162-5. 13. Fujinaga M, et al. ***J Med Chem*** 2017;60:4047-61. 14. Nagai Y, et al. ***Nat Commun*** 2016;7:13605. 15. Kikuchi T, et al. ***J Med Chem*** 2016;59:5847-56. 16. Shimoda Y, et al. ***J Med Chem*** 2016;59:3980-90. 17. Yamasaki T, et al. ***J Neurosci*** 2016;36:375-84. 18. Fujinaga M, et al. ***J Med Chem*** 2015;58:1513-23. 19. Hashimoto H, et al. ***J Nucl Med*** 2014;55:1532-8. 20. Maruyama M, et al. ***Neuron*** 2013;79:1094-108. 21. Yui J, et al. ***Stroke*** 2013;44:2567-72. 22. Xie L et al. ***J Hepatol*** 2012;57:1076-82. 23. Yamasaki T, et al. ***J Nucl Med*** 2012;53:1601-7. 24. Fujinaga M, et al. ***J Med Chem*** 2012;55:2342-52. 25. Kumata K, et al. ***J Med Chem***. 2011;54:6040-9. 26. Yui J, et al. ***Neuroimage*** 2011;54:123-30. 27. Yui J, et al. ***J Nucl Med*** 2010;51:1301-9. 28. Zhang MR et al. ***J Nucl Med*** 2007;48:1853-61. 27. Zhang MR et al. ***J Med Chem*** 2007;50:848-55. 28. Zhang MR, et al ***J Med Chem*** 2006;49:2735-42. 29. Zhang MR, et al. ***J Med Chem*** 2004;47:2228-35.

Novel Theranostic Radiopharmaceuticals Targeting Metabotropic Glutamate Receptor 1 for Precision Medicine in Oncology

Lin Xie✉

Keywords: Metabotropic glutamate receptor 1, Small-molecule radiopharmaceutical, Positron emission tomography, α–radiopharmaceutical therapy, Pan-cancer, Precision medicine

Cancer remains a significant global health challenge, with projections suggesting that nearly 20 million new cancer cases will be diagnosed annually by 2025. Substantial progress is underway in cancer drug development, especially in the field of radiotheranostics medicines ─ combination of molecular imaging with targeted radionuclide therapy. These advancements play pivotal roles in the fight against cancer, offering the potential of precision medicine through the utilization of paired diagnostic and therapeutic radionuclide labeled compounds known as radiopharmaceuticals. These radiopharmaceuticals enable the selective and targeted "seeing" and "killing" of cancer cells, customized to each patient's unique condition. With the FDA approval of several radiopharmaceuticals, the market is poised to expand from $6.60 billion in 2022 to $7.57 billion in 2023 and is anticipated to surge to $12.85 billion by 2027, maintaining an annual growth rate of 14.1%.[1] The exponential, global expansion of radiotheranostics in oncology is driving the identification of promising targets and the development of novel theranostic radiopharmaceuticals. Here, I will introduce our research group's newly developed theranostic radiopharmaceuticals targeting metabotropic glutamate receptor 1, which are found in various types of cancers.

Metabotropic glutamate receptor 1 (mGluR1), a crucial mediator in glutamatergic signaling, is typically expressed in the central nervous system. However, it is aberrantly overexpressed as an oncoprotein in various human tumors, while being absent in normal peripheral organs.[2] This makes mGluR1 a widely applicable target for theranostics in oncology. Unfortunately, conventional mGluR1-targeting strategies, primarily focused on modulating mGluR1 activity through antagonistic binding, prove ineffective in achieving durable remission across various cancer types due to the presence of metabolic compensatory regulation. To address this challenge, we have investigated an mGluR1-based radiotheranostic strategy as a potential

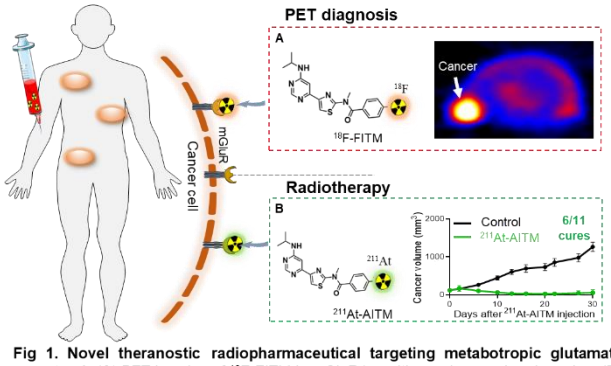

Fig 1. Novel theranostic radiopharmaceutical targeting metabotropic glutamate receptor 1. (**A**) PET imaging of ^{18}F-FITM in mGluR1-positive melanoma bearing mice. (**B**) Therapeutic efficacy of ^{211}At-AITM in mGluR1-positive pancreatic cancer bearing mice.

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solution to the limitations encountered in early clinical trials of conventional molecular targeted therapy (Fig.1)

Initially, we developed ^{18}F-FITM to visualize and quantify mGluR1 expression in melanomas (Fig.1A).[3] This small-molecule radiotracer, a specific mGluR1 antagonist with a half maximal inhibitory concentration (IC_{50}) value of 5.1 nM, exhibited excellent selectivity for mGluR1 compared to other subtypes (IC_{50} > 7 μM). Using ^{18}F-FITM with positron emission tomography (PET), we successfully visualized and quantified mGluR1 expression in melanomas and metastasis with high selectivity and specificity. Furthermore, rapid clearance from non-target organs after intravenous injection demonstrated the potential of the small-molecule carrier for developing therapeutic radiopharmaceuticals.

Next, a small-molecule alpha (α)-emitting radiopharmaceutical, ^{211}At-AITM, was developed by replacing the smaller fluorine atom with the α-emitting halogen nuclide ^{211}At (Fig.1B).[4] Importantly, the bulky ^{211}At atom prevented ^{211}At-AITM from entering the mGluR1-rich brain, avoiding detrimental radiation to the central nervous system—a significant concern in the clinical translation of mGluR1-targeted radiotherapies. Simultaneously, it maintained high tumor uptake and specificity for mGluR1. In therapeutic studies,[5] a single dose of ^{211}At-AITM (2.96 MBq) in mGluR1$^+$ cancers exhibited long-lasting *in vivo* antitumor efficacy across 7 subtypes of the 4 most common tumors, including breast cancer, pancreatic cancer, melanoma, and colon cancers, with minimal toxicity. Moreover, approximately 50% of tumor-bearing mice showed complete regression of mGluR1$^+$ breast cancer and pancreatic cancer. Mechanistically, the functions of ^{211}At-AITM were uncovered in downregulating the mGluR1 oncoprotein and inducing senescence of tumor cells with a reprogrammed senescence-associated secretory phenotype. These findings suggest that α-radiopharmaceutical therapy with ^{211}At-AITM can be a useful strategy for mGluR1$^+$ pan-cancers, irrespective of their tissue of origin.

The success of our theranostic radiopharmaceuticals holds the potential to provide an accurate imaging-based method for efficiently detecting the oncoprotein mGluR1 expression in multiple types of cancer for diagnosis, patient screening, and treatment monitoring. Additionally, it introduces a novel mGluR1-based α-radiopharmaceutical therapy, paving the way for precision medicine in cancer patients.

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4. Xie L, Hanyu M, Fujinaga M, et al. ^{131}I-IITM and ^{211}At-AITM: Two Novel Small-Molecule Radiopharmaceuticals Targeting Oncoprotein Metabotropic Glutamate Receptor 1. *J Nucl Med.* 2020; 61:242-248.
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Education Experiences

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Major Publications

1. **Xie L**, Zhang L, Hu K, et al. A ^{211}At-labelled mGluR1 inhibitor induces cancer senescence to elicit long-lasting anti-tumor efficacy. *Cell Rep Med* 2023, 4:100960.
2. **Xie L**, Hu K, Duo Y, et al. Off-tumor IDO1 target engagements determine the cancer-immune set point and predict the immunotherapeutic efficacy. *J Immunother Cancer* 2021, 9.
3. **Xie L**, Hanyu M, Fujinaga M, et al. ^{131}I-IITM and ^{211}At-AITM: Two Novel Small-Molecule Radiopharmaceuticals Targeting Oncoprotein Metabotropic Glutamate Receptor 1. *J Nucl Med* 2020,61:242-8.
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放射性核素高速高效标记关键核心技术的研究开发

张周恩

Keywords: 核医学,放射性药，核素标记技术

放射性核素标记技术是实现疾病诊治和药物体内的核心技术，也是目前制约放射药物和核医学发展关键瓶颈之一。同位素碳元素是生物药物分子中最普遍存在的同位素，如果能将药物分子中的同位素12C置换成放射性同位素11C, 我们就能实现绝大多数药物分子的可视化。将半寿命仅20.4分钟的同位素11C高速高效导入到药物分子中，是合成化学前沿领域最具挑战性的难题之一。为此我们开发了一系列高速高效C-11C标记新方法，包括靶介导的芳香硼和芳香锡的C-[11C]氰基化、镍介导的芳香氟和芳香氯的C-[11C]氰基化和C-[11C]羰基化，杂环内碳素的11C标记法等。如下图所示，我们这些世界领先的基本标记核心技术的突破，大大拓宽了可利用的放射性标记前驱体和可放射标记的药物分子范围（超过16类基本化学结构）。

我们开发的标记技术实用性强，能胜任结构复杂医药分子可视化的标记合成，能用适用各种功能性成像探针的创制。结合药物化学的生物等价体策略，我们成功创制了30多种结构功能各异的分子成像探针。这些放射性标记方法为今后药物和医疗可视化的开拓发展，奠定了更扎实的放射性标记化学基础。

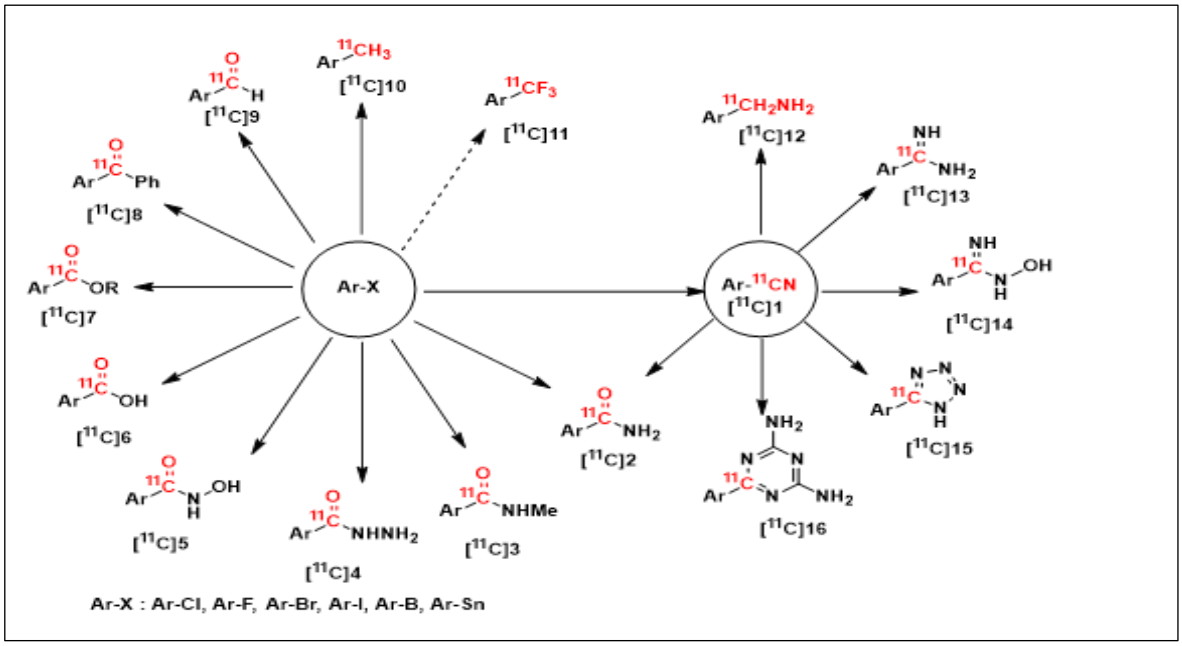

Fig1. 我们先进的11C-标记化学创新技术，为各种结构药物可视化提供可能。

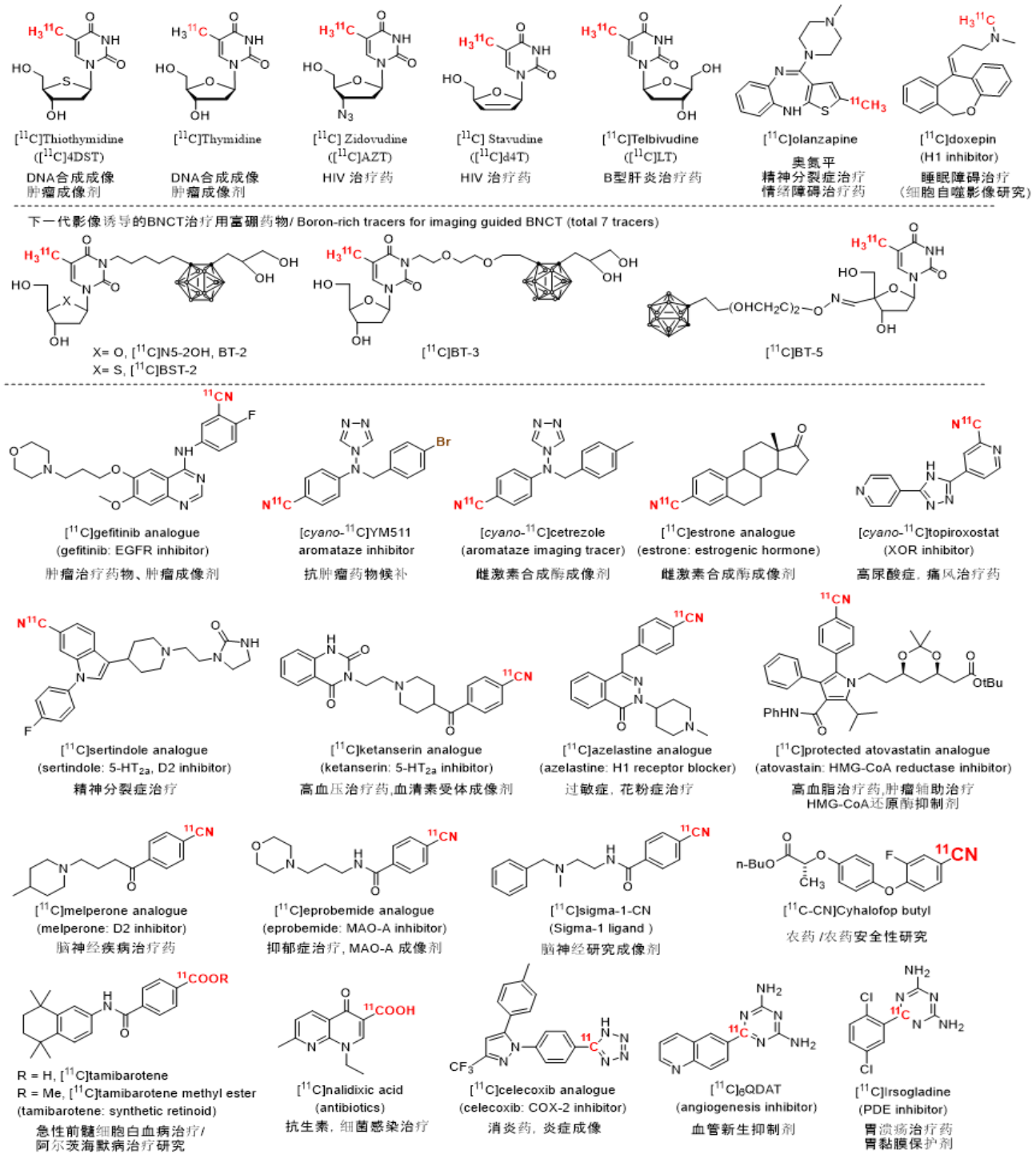

Fig2. 利用我们原创的 11C-标记技术成功开发的代表性放射性药物（分子成像探针）。

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Field

核医学，生物医药

Education Experiences

2001-2004年就读京都大学工学研究科博士课程，

2005年 获京都大学工学博士

Work Experiences

2005-2008年任京都大学医工联合博士后，京都高度技术研究所研究员；

2008-2023年任理化学研究所研究员；

2023年任上海君康立泰生物医药科技有限公司总经理

Symposium 2
Frontiers of Basic Life Sciences

Masukawa Hall

13:30-15:00

Tissue pattern emergence through boundary-driven ordering

Takafumi Ichikawa[1, 2✉], Shuchang Hu[1, 2], Pamela Guruciaga[3], Steffen Plunder[1], Mei Makino[1], Anniek Stokkermans[4], Anna Erzberger[3], Takashi Hiiragi[1,2,4]

Tissue patterning, mouse epiblast, tissue-tissue boundary

Multi-cellular living systems exhibit self-organizing properties and entail feedback regulations across scales from molecular to tissue level to achieve a functional pattern. We aim to understand the principles of tissue pattern emergence in mouse peri-implantation epiblast, which develops into a cup-shaped structure with a lumen inside and eventually gives rise to our body. To this end, we established a 3D *ex vivo* system that recapitulates mouse peri-implantation embryo development. Light-sheet microscopy reveals dynamic cellular coordination underlying epiblast order emergence. We also find that tension release in the polar trophectoderm allows its development into the extra-embryonic ectoderm, which later guides epiblast growth and patterning through mechano-chemical interactions. This culture system offers unprecedented access to the embryos for monitoring, measurement, and manipulation [1]. We will further discuss recent findings about the role of tissue boundary in driving epiblast patterning and propose a physical model accounting for it.

1. Ichikawa, T., Zhang, H. T., Panavaite, L., Erzberger, A., Fabrèges, D., Snajder, R., Wolny, A., Korotkevich, E., Tsuchida-Straeten, N., Hufnagel, L., Kreshuk, A., & Hiiragi, T. (2022). An *ex vivo* system to study cellular dynamics underlying mouse peri-implantation development. *Developmental cell*, *57*(3), 373–386.e9.

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Education Experiences

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2010-2012 Graduate School of Agriculture, Kyoto University. Master
2012-2015 Graduate School of Agriculture, Kyoto University. Ph.D (received in 2017)

Work Experiences

2017-2021 Postdoctoral Fellow, European Molecular Biology Laboratory (EMBL), Germany.
2021-2023 Program-specific Assistant Prof., Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University.
2023- Assistant Prof., Graduate School of Medicine, Kyoto University.
.

Major Publications

1. Ichikawa, T., Zhang, H. T., Panavaite, L., Erzberger, A., Fabrèges, D., Snajder, R., Wolny, A., Korotkevich, E., Tsuchida-Straeten, N., Hufnagel, L., Kreshuk, A., & Hiiragi, T. (2022). An ex vivo system to study cellular dynamics underlying mouse peri-implantation development. Developmental cell, 57(3), 373–386.e9.

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3. Yamashita, H., Ichikawa, T., Matsuyama, D., Kimura, Y., Ueda, K., Craig, S. W., Harada, I., & Kioka, N. (2014). The role of the interaction of the vinculin proline-rich linker region with vinexin α in sensing the stiffness of the extracellular matrix. Journal of cell science, 127(Pt 9), 1875–1886.

Unraveling the dynamic 3D genome architecture through single-cell DNA replication profiling

Ichiro Hiratani[1,✉]

Keywords: DNA replication timing, Hi-C, mouse embryogenesis

The Hi-C (high-throughput chromosome conformation capture) technology has revolutionized genome biology, revealing that mammalian chromosomes are composed of a series of megabase-sized topologically associating domains (TADs). In the 3D space of the nucleus, each TAD is assigned to either the transcriptionally active (A) nuclear compartment or the inactive (B) compartment. The A and B compartments correlate well with early and late S-phase DNA replication timing, respectively. We recently developed a single-cell genome-wide DNA replication profiling technology (scRepli-seq), which has allowed us to analyze DNA replication timing in single cells, estimate the A/B compartment profile based on scRepli-seq data, and explore their developmental dynamics at the single-cell level in mouse embryonic stem cells and early embryos. In this talk, I would like to introduce our ongoing efforts to understand the developmental regulation of DNA replication and the organizing principles of the 3D genome architecture by taking advantage of our homemade scRepli-seq technology.

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Field

Molecular Biology, Epigenetics, Single-cell Genomics

Education Experiences

1998 B.S., Biological Sciences (Zoological Science), University of Tokyo

2000 M.S., Biological Sciences, Graduate School of Science, University of Tokyo

2003 Ph.D., Biological Sciences, Graduate School of Science, University of Tokyo (Supervisor: Masanori Taira)

Work Experiences

2003	Postdoctoral Associate, Department of Biological Sciences, Graduate School of Science, University of Tokyo (Associate Prof. Masanori Taira)
2003–2006	Postdoctoral Associate, Department of Biochemistry and Molecular Biology, SUNY Upstate Medical University (Prof. David M. Gilbert)
2006–2010	Postdoctoral Associate, Department of Biological Science, Florida State University (Prof. David M. Gilbert)
2010–2013	Assistant Professor, National Institute of Genetics (Prof. Kazuhiro Maeshima)
2013–2018	Team Leader, Laboratory for Developmental Epigenetics, RIKEN Center for Developmental Biology (CDB)
2018–present	Team Leader, Laboratory for Developmental Epigenetics, RIKEN Center for Biosystems Dynamics Research (BDR)

Major Publications

1. †Takahashi S, †Miura H, †Shibata T, Nagao K, Okumura K, Ogata M, Obuse C, *Takebayashi SI, *Hiratani I. Genome-wide stability of the DNA replication program in single mammalian cells. ***Nat Genet*** 51:529-540 (2019)

2. Miura H, Takahashi S, Poonperm R, Tanigawa A, Takebayashi SI, *Hiratani I. Single-cell DNA replication profiling identifies spatiotemporal developmental dynamics of chromosome organization. ***Nat Genet*** 51:1356-1368 (2019)

3. †Miura H, †Takahashi S, †Shibata T, Nagao K, Obuse C, Okumura K, Ogata M, *Hiratani I, *Takebayashi SI. Mapping replication timing domains genome wide in single mammalian cells with single-cell DNA replication sequencing. ***Nat Protoc*** 15:4058-4100 (2020)

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Programmed activation of Autophagy preserves body structure for a long-term diapause period

Masayuki Oginuma✉,

Keywords: Diapause, Turquoise killifish, embryo, metabolism

The African turquoise killifish (N. furzeri) lives in ephemeral ponds that completely dry up for ~6 months each year. In dry season, they enter diapause which is the state of arresting the embryonic development and protecting organisms from extreme environments. How diapause arrest development and protect o organisms are largely unknown. To understand the molecular mechanism of diapause, we generated transgenic reporter lines, which can monitor cellular activities of the metabolic process for cellular resolution. Using these reporter lines, we found diapause is the highly organized biological process correlated with the programmed process of embryogenesis, they did not suspend the metabolic activity of all cells together but gradually arrested from the anterior to posterior direction with the axial elongation process of the embryo. Furthermore, some cells were still active even in the long-term diapause period. Interestingly this programmed process strongly induces an autophagy pathway in the diapause embryo, and autophagy activity in suspended cells is required for the protection of body structure in the long-term diapause period. In this meeting, we wish to discuss the significance of this unique activation of autophagy during the N. furzeri's diapause.

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2005-2008 SOKENDAI, National Institute of Genetics. Ph.D.

Work Experiences

2008-2009 Post Doc. National Institute of Genetics.
2009-2015 Post Doc. Institut de Génétique et de Biologie Moléculaire et Cellulaire
2015-2018 Post Doc. Harvard Medical School
2018-2020 Assistant Professor. Institute for Molecular and Cellular Regulation, Gunma university
2020- Assistant Professor. Research Institute for Microbial Diseases, Osaka University

Major Publications

1. Oginuma M, Nishida M, Ohmura-Adachi T, (….), Matsui H, Ishitani T: Rapid reverse genetics systems for N. furzeri, a suitable model organism to study vertebrate aging, Sci Rep 12:11628, 2022.
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4. Oginuma M, Takahashi Y, (….), Saga Y*: The oscillation of Notch activation, but not its boundary, is required for somite border formation and rostral-caudal patterning within a somite. Development 137,1515-22, 2010
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Symposium 3
Translational Medicine and Clinical Science

Masukawa Hall

15:10-16:40

Translation medicine in plastic surgery

Yuemin Zhou [1,✉]

Keywords: Plastic surgery (整形外科学), translation medicine (转化医学), cell and tissue engineering (细胞与组织工程), reconstructive medicine (再生医学).

1. 【整形外科学】（医学科学）

整形外科（Plastic and Reconstructive Surgery），也称整形修复外科，日语为形成外科。是以通过修复各种原因所造成的组织缺损或畸形，改善或恢复生理功能和外貌，从而提高患者的QOL(quality of life)为目的的现代医学科学在外科学领域的一个专业分支学科。主要包括：重建外科（reconstructive）和美容外科（aesthetic surgery）。

2. 【转化医学】

随着医学科学和生物技术的发展，学科分工越来越细。大量基础研究成果的临床应用以及不同专业领域的合作显得越来越重要。因此，跨学科合作和转化医学应运而生。这是近年来国际医学健康领域出现的新理念，是医学研究的一个新分支。目的是在基础研究与临床医疗之间建立更直接的联系。其核心内容是将医学基础研究成果及时有效的转化，应用于临床。主要包含两个方面:bench to bedside（实验室到临床）以及bedside to bench（临床到实验室），简称B2B过程。前一个B2B（bench to bedside）是指将实验室的研究成果应用到临床、转化为医药产品或者诊疗技术的过程，第二个B2B是指通过临床观察分析为基础医学研究提供思路、指导实验设计的过程，二者相辅相成，构成了转化医学的双向循环。在整形外科学领域，同样积累了大量的分子细胞生物学、动物实验和相关领域研究成果。但大多止步于论文发表及学术交流阶段，并未及时有效的服务于临床。转化医学的发展，为加速相关学科技术成果在整形外科学中的转化提供了契机。通过跨界协作、整合资源，共同探索前沿技术的多元化应用与成果转化方式，建立多学科跨界交流合作生态，搭建从前沿技术、临床转化、多元应用的高效协同平台，提升整形外科的创新力与竞争力，推动整形外科学领域的发展。是转化医学在整形外科领域发展的必然趋势。

河南大学淮河医院整形修复外科创建于2015年，同时开创有河南省细胞工学国际联合实验室。基于上述转化医学理念，积极开展瘢痕的综合治疗、创面治疗、各类先天或后天畸形的修复重建；同时为广大求美者提供面部年轻化综合治疗、体形雕塑与脂肪再生医学等医疗美容服务。

以下是我们的部分实践经验。

3. 【转化医学在整形外科的具体应用】

整形外科区别于传统的按解剖部位或系统划分科。它是一个与许多不同组织器官或系统都有横向联系，还与非医学领域有广泛交叉的特殊学科。其涉及领域包括人文（心理、美学）、生物科技（分子细胞、基因细胞组织工程）、材料学、高分子化学、物理学、计算机科学等等。

河南大学淮河医院整形修复外科，应用综合大学多学科及拥有“河南省细胞工学国际联合实验室”优势，建立了“基础-临床 -转化”研究领域模式，主要开展了以下几个方面的工作。

(1) 瘢痕疙瘩的个体化动态综合治疗
(2) 慢性难愈合性创面治疗
(3) 医学激光的临床应用
(4) 畸形矫正
(5) 心理健康与整形外科
(6) 数据医学

1 Department of Plastic and Reconstructive Surgery, Henan University; International Joint Laboratory of Cell Medical Engineering in Henan Province..

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(7) 细胞组织工程临床应用

Reference

略

Author Information

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Field

Plastic surgery, Regenerative medicine

Education Experiences

1979-1984 Zhengzhou Univ. Bachelor
1990-1993 Fudan Univ. Master
1999-2003 Osaka Metropolitan Univ. Ph.D.

Work Experiences

1984-1990 Department of Surgery, Dongjing Hospital, Henan Univ. Surgeon
1993-1998 Department of Surgery, Tongji Hospital, Tongji Univ. Surgeon
2003-2012 Department of Bioengineering, Department of Artificial Organs, Advanced Medical Engineering Center, National Cardiovascular Center Research Institute, Researcher
2012-Present Department of Plastic and Reconstructive Surgery, Huaihe Hospital, Henan University. Professor.

Major Publications

1. Liu ZN, Li YL, Zhang T, Xu XQ, Zhou YM. Clinical effects of pulsed dye laser in dynamic treatment of fresh trauma scars after facial cosmetic suture. China Medical Cosmetology, 2023,13(10):22-26. DOI:10.19593/j.issn.2095-0721.2023.10.006.
2. Liu ZN, Zhou YM, Liu RX, Li YL, Li Q, Zhang T, Zhang SM. Clinical effects of pulsed dye laser dynamically combined with triamcinolone acetonide in the treatment of keloids. Zhonghua Shao Shang Za Zhi. 2022 Sep 20;38(9):822-829. Chinese. doi: 10.3760/cma.j.cn501225-20220620-00249. PMID:36177586.
3. Liu ZN, Zhao QN, Han HH, Zhou YM. Research progress in the treatment of keloid with lasers. Chin J Aesth Plast Surg. 2022,33(11):287-290. Chinese. doi: 10.3969/j.issn.1673-7040.2022.11.000.
4. Liu ZN, Zhou YM. Research advances on the application of pulsed dye laser in the early treatment of post-traumatic scars. Zhonghua Shao Shang Za Zhi. 2021 Jul 20;37(7):688-691. Chinese. doi: 10.3760/cma.j.cn501120-20200315-00164. PMID: 34304412.
5. Han HH, Zhao QN, Liu ZN, Zhang FM, Liu RX, Chen SQ, Zhou YM. Experience in the application of integrated medical care treatment model in the treatment of refractory wounds. Journal of Henan Univ（Medical Science）,2021,40(03):225-229.
6. Zhao QN, Zhou YM, Ma YY, Han HH. [Research advances on the effect of early intervention on post-traumatic scar formation] [J]. Zhonghua Shao Shang Za Zhi. 2021 Jul 20;37(7):697-701. Chinese. doi:

10.3760/cma.j.cn501120-20200315-00169. PMID: 34304414.

7. Zhao QN, Zhou YM, Ma YY, Han HH. [Research advances on the effect of early intervention on post-traumatic scar formation] [J]. Zhonghua Shao Shang Za Zhi. 2021 Jul 20;37(7):697-701. Chinese. doi: 10.3760/cma.j.cn501120-20200315-00169. PMID: 34304414.
8. Zhao Q, Zhou Y, Liu Z, Zhang S, Sun C. [Application of minimally invasive scar release combined with autologous microfat graft in the treatment of facial depressed scar] [J]. Chinese Journal of Plastic Surgery,2021,37(4), 371-375. doi: 0.3760/cma.j.cn114453-20200616-00372.
9. Zhao Q, Ma Y, Lu Y, Chai Y, Zhou Y. Successful Treatment of Chronic Lower Extremity Ulcers with Allogeneic Platelet-Rich Plasma and Artificial Dermis: A Case Report[J]. Adv Skin Wound Care. 2019 Dec;32(12):550-552. doi: 10.1097/01.ASW.0000604176.47082.60. PMID: 31764145; PMCID: PMC7328864.
10. Zhao Q, Liu R, Zhang S, Zhou Y, Lu Y. [Mechanism and Progress of Hydroxyurea-Induced Lower Limb Ulcer. Journal of Henan University (Medical Science)] [J]. 2018, 37(1), 69-72.

Development of new bioabsorbable implants with de novo adipogenesis

Qiannan Zhao[1,✉], Shuichi Ogino[1], Naoki Morimoto[1]

Keywords: Bioabsorbable implant, Adipogenesis, PGA nano sheet, PLLA, Collagen sponge

【Introduction】

In recent years, the incidence of breast cancer has increased as the most commonly diagnosed malignancy [1]. The most common breast reconstruction methods include the use of silicone implants, skin flaps, and autologous fat injections, each of which has its limitations. The development of tissue engineering has brought new hope for breast reconstruction. In our previous study, we regenerated adipose tissue using a combination of a poly-L-lactic acid (PLLA) mesh and collagen sponge (CS). This novel absorbable implant can regenerate autologous adipose tissue without the addition of ASCs or growth factors[2]. However, the amount of regenerated adipose tissue is small, and we need to investigate superior materials in terms of their adipogenesis ability.

【Method】

In this study, we used poly(lactic-co-ε-caprolactone) (P(LA/CL)), PLLA, and low-molecular-weight PLLA (LMW-PLLA) as the external frames and polyglycolic acid (PGA) nanosheets and CS as the internal fillings. We investigated the optimal external frames and internal fillings for adipose tissue regeneration. We prepared six types of implants with spheroidal prolate shapes: P(LA/CL) with PGA nano, PLLA with PGA nano, PLLA with CS, PLLA with 1/2 CS, PLLA with 1/4 CS, and LMW-PLLA with CS using a rat inguinal model. We evaluated the weight and volume of the fat pad, formed tissue and adipose tissue inside implants and the collagen fibers inside implants at 6 and 12 months.

【Result and conclusion】

The internal spaces in the P(LA/CL) and LMW-PLLA implants collapsed at 6 months, whereas those in the other four implants collapsed at 12 months. Adipose tissue regeneration was not significantly different between the groups implanted with PLLA at 6 and 12 months, and it was greater than that in the P(LA/CL) with PGA nano and LMW-PLLA with CS groups. The PGA nanosheet inside PLLA was comparable to the CS inside the PLLA in terms of adipose tissue regeneration. In summary, PLLA is a promising external frame material, as the internal space can be replaced with adipose tissue. In addition to CS, PGA nanosheets are promising materials for internal filling. Implants combined with these materials could be ideal for breast reconstruction without the cells or growth factors.

Reference

1) Shan Z, Liu L, Shen J, et al. Enhanced UV Resistance Role of Death Domain-Associated Protein in Human MDA-MB-231 Breast Cancer

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Cells by Regulation of G2 DNA Damage Checkpoint. Cell Transplant. 2020;29:963689720920277.

2) Ogino S, Morimoto N, Sakamoto M, et al. Development of a novel bioabsorbable implant that is substituted by adipose tissue in vivo. J Tissue Eng Regen Med. 2018;12(3):633-641.

Author Information

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Field

Tissue engineering, Regenerative medicine

Education Experiences

2012-2017 Henan univ. Bachelor
2017-2020 Henan univ. Master
2021-2025 Kyoto univ. Ph.D.

Major Publications

1. Zhao Q, Ogino S, Lee S, Kato Y, Li Y, Sakamoto M, Yamanaka H, Nakano T, Sawaragi E, Morimoto N. Development of new bioabsorbable implants with de novo adipogenesis[J]. Regen Ther. 2023, 24: 311-317. https://doi.org/10.1016/j.reth.2023.07.008.
2. Zhao QN, Zhou YM, Ma YY, Han HH. [Research advances on the effect of early intervention on post-traumatic scar formation] [J]. Zhonghua Shao Shang Za Zhi. 2021 Jul 20;37(7):697-701. Chinese. doi: 10.3760/cma.j.cn501120-20200315-00169. PMID: 34304414.
4. Zhao QN, Zhou YM, Ma YY, Han HH. [Research advances on the effect of early intervention on post-traumatic scar formation] [J]. Zhonghua Shao Shang Za Zhi. 2021 Jul 20;37(7):697-701. Chinese. doi: 10.3760/cma.j.cn501120-20200315-00169. PMID: 34304414.
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Treatment of keloid

Ruoxuan Liu[1,✉]

Keywords: Keloid; Dynamic treatment algorithm; Early intervention

【Introduction】

Keloid is a special type of pathological keloid. Keloid grow above the surface of normal skin and beyond the edge of the initial wound, appearing as continuous growing mass with hard texture that is less flexible, itchy or painful. They manifest tumor-like features, such as being refractory to therapy and having a high probability of recurrence. Currently, there is no unified standard for the treatment of keloid, either domestically or internationally. The treatment mainly include surgery, radiation therapy, laser therapy, intralesional injections, and compression therapy. The recurrence of keloid remains a difficulty in treatment. Therefore, establishing a reasonable follow-up system and diagnosing and intervening in the early stages of recurrence can achieve twice the result with half the effort, which is of great significance in the prevention and treatment process of keloid.

【Dynamic treatment algorithm based on surgery】

At present, comprehensive therapy, including surgery, postoperative adjuvant radiation and compression therapy, is the main treatment for keloid. A large body of clinical practice experience and therapeutic results have shown that early surgical excision combined with other methods, such as radiotherapy, intralesional injections and dressing compression, has good efficacy, and the 5-year recurrence rate is significantly reduced. Treating keloid is a long and progressive process, requiring persistent and adequate treatments. Regular assessment is a key factor in the whole treatment process, which includes assessing the growth of the keloid and the efficacy of prior treatments. A persistent and dynamic treatment algorithm，should be developed based on these assessments until treatment satisfaction is achieved.

1. Surgical excision

Clinical investigation found that the recurrence rate of keloid resection alone was 50% -100%. The Chinese expert consensus on clinical prevention and therapy of keloid pointed out that surgical therapy is used as the first-line therapy for medium and large keloid. Currently, tension suture technique improves the tensile resistance of incision and effectively reduces the recurrence rate of postoperative keloid.

2.Postoperative radiotherapy

Several studies have shown that postoperative adjuvant radiotherapy can reduce the keloid recurrence rate to less than 10%. The mechanism by which radiotherapy works is likely to directly kill fibroblasts, leading to the destruction of collagen structure, and to balance the proliferation and apoptosis of fibroblasts by increasing the apoptosis rate of fibroblasts. At present, the common radioactive sources include isotopes, brachytherapy and superficial X-ray. Isotope therapy causes serious adverse reactions such as radiation dermatitis and

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hypopigmentation, and is gradually being phased out in clinical practice. Brachytherapy can be used to accurately regulate the irradiation depth and has little influence on deep tissues or organs. The superficial X-ray has a low cost, is simple and easy to operate, and can also achieve the purpose of preventing keloid recurrence.

3. Compression therapy

The mechanism of action of pressure on keloid may be to block the blood flow through the pressure, reduce the transport of inflammatory cytokines, oxygen and nutrients, and effectively reduce the recurrence of keloid.

【Conservative treatment】

1. Agents therapy

Keloid agents now available include topical preparations, intralesional injections and oral medicines. Among them, the topical agents are mainly silicone agents, onion extract and hormone agents. It is reported that oral medicines such as snow glycoside tablets and Tranilast Capsules are also used in the therapy of keloid, and have achieved good clinical results. Among the injected agents, the Recommended Guidelines for the Clinical therapy of Keloid in China preferentially recommended glucocorticoids and 5-fluorouracil as the main injections. With the continuous progress of research, botulinum toxin A injection is also considered as an innovative and effective therapy for keloid. Compared with the hormone agents injection, it has the advantages of definite efficacy and no obvious adverse reactions, and is expected to become an alternative to hormones.

2. Laser therapy

In 1993, Alster et al. first proposed the application of pulsed dye laser for keloid, and it was then rapidly applied in the therapy of keloid. The principle of pulsed dye laser action mainly aims at hemoglobin in keloid, so that hemoglobin can produce heat and produce coagulation necrosis, cause tissue hypoxia, and achieve the effect of inhibiting keloid tissue hyperplasia. In addition, CO2 dot array laser is also gradually applied in keloid, but its therapeutic effect and recurrence rate still need to be further studied.

3. Other therapy

Conventional cryotherapy also has some effect on keloid, but it has been gradually replaced. Some immunomodulators such as γ interferon have immunomodulatory effects in the therapy of keloid because they accelerate collagenolysis and inhibit the proliferation of fibroblasts.

At present, the therapy of keloid is still preferred. With the deeper understanding of the molecular level of keloid, and the continuous clarification of the etiology and pathological mechanism, the therapy of keloid will also make a breakthrough progress.

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Clinical application of PRP in refractory wounds

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Keywords: Platelet-rich plasma, Chronic refractory wounds,Growth factors,Fibroblasts,Reduction rate of wound area

【Introduction】

Refractory wounds are characterized by long treatment cycles and recurrent conditions, which hazard patients' health and even endanger their lives, and often bring great mental pressure and huge economic burden to patients and their families, while consuming a large amount of medical resources. Although there are many traditional clinical methods to treat refractory wounds, traditional treatment methods often fail to achieve satisfactory results for complex chronic and refractory wounds. In recent years, with the development of the understanding and application of Platelet Rich Plasma Therapy(PRP), PRP treatment has been gradually applied to various difficult wounds (such as pressure ulcers, diabetic ulcers, venous and arterial vascular ulcers, and other refractory wounds), and its effectiveness and safety have been widely recognized. The aim of this study was to investigate the biological activity and clinical efficacy of PRP on refractory wounds, ,which is reported as follows.

【Method】

1) Peripheral blood of healthy volunteers was extracted, and PRP was prepared by secondary centrifugation legal system, and PRP growth factor contents (PDGF, VEGF, FGF, EGF) were detected in 7, 14 and 28 days stored at 4° C, -20° C and -80 ° C respectively. Analyzed under different storage conditions, 0.5%, 1%, 5% concentrations of PRP on the proliferation and migration of human fibroblasts to determine the optimal storage conditions for PRP.
2) According to the diagnostic criteria included in the refractory wounds (disease duration more than 3 months), Patients received individualized sequential comprehensive treatment therapy for 3 weeks after first registration,Patients with wounds still not healed were enrolled for treatment for the second time, and their own blood was used to prepare PRP (Blood collection amount is determined by the area of the wound). PRP was divided into 4 parts after activation. The first part was applied to fresh PRP for wound treatment. The remaining 3 parts were frozen at －20C° .PRP treatment was treated once a week and healing effect was evaluated at 7, 14, 21 and 28 days of treatment, respectively.

【Result】

1) After 7 days of storage, the growth factors in PRP stored at all temperatures do not decrease significantly; The contents of PDGF and VEGF in PRP stored at 4 ℃ for 14 days are significantly lower than those of fresh PRP（$p<0.01$）,The contents of VEGF in PRP stored at 4℃ was significantly lower than that of PRP stored at -20℃ and -80℃ ($P<0.05$); The contents of four growth factors in PRP stored at 4 ℃ for 28 days

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are significantly lower than those of fresh PRP, PRP stored at-20 ℃ and PRP stored at-80 ℃ ($p < 0.01$). Compared with PRP stored at-80 ℃ for 14 days, 28 days and-20 ℃, the four growth factors do not decrease significantly ($p > 0.05$)

2) The proliferative effect of 1% and 5% fresh (0 day) PRP group is significantly higher than that of the 10% FBS group ($p < 0.05$).The effect of PRP stored at-20 ℃ and-80 ℃ on fibroblast proliferation is significantly better than that of PRP stored at 4 ℃ and 10% FBS ($p < 0.05$), but there is no significant difference between-20 ℃ and-80 ℃ on fibroblast proliferation ($p >0.05$).
3) The cell mobility of PRP cells stored at-20 ℃ or-80 ℃ for 12 hours is significantly higher than that of PRP stored at 4 ℃ and 10% FBS groups (all $p < 0.01$).
4) 28 days after PRP treatment, the area of chronic refractory wounds is significantly reduced compared with that before treatment ($p < 0.01$). The VAS score drops from 6.68 ± 1. 32 before treatment to 1.86 ± 1. 67 ($p < 0.01$). There is no significant difference in wound reduction rate and wound bed improvement rate between fresh PRP treatment for 28 days and storage PRP treatment for 28 days ($p > 0.05$).No adverse events related to PRP treatment has occurred during treatment.

【Conclusion】

5) PRP still has biological activity when stored at-20 ℃ and-80 ℃ for 4 weeks, and there is no difference in its effectiveness when stored between these two temperatures.
6) Both fresh autologous and storage PRP can effectively treat chronic refractory wounds,and the effective storage application of PRP expands the application of PRP and provides new ideas and means for the treatment of refractory wounds.

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3D technique-based nonsurgical correction of congenital auricular deformity

Xin Zhao[a,b], Yuemin Zhou[a,b]✉

Key words: Congenital auricular deformity, Nonsurgical correction, 3D printing, Correction bracket

【Introduction】

Congenital auricular deformitie (CAD) is a common postpartum malformation that not only affects the physical health of the infants, but also causes psychological damage to the infants and their families, which in turn affects their social interactions. Induction of CAD could be due to multiple factors like mother's delivery situation, mother's hepatitis history, abnormal pregnancy, and so on.CAD can be classified as malformational and deformational anomalies, which resulted from embryologic maldevelopment and in utero or ex utero deformational forces, respectively.

The treatment of auricular deformities includes both surgical and non-surgical treatment.Surgical treatment is mainly aimed at patients with malformation anomalies and older auricular deformities, while non-surgical treatment is currently the best treatment option for auricular deformities in infants. Mainly for: Surgical tape or bandages, curved orthoses and clip-on earmoulds, integrated ear orthoses,and so on. Integrated orthoses from various brands (e.g. Earwell, LiangEar, etc.) are basically of uniform specifications and often cause complications such as unsatisfactory correction and skin pressure damage due to inappropriate size and shape, and are expensive, so their application is limited and difficult to popularise.

With the continuous popularization of 3D printing technology,it has been gradually applied in the biomedical field, such as neurosurgery, maxillofacial surgery and other fields. In plastic surgery, it is now mostly used in the modeling of ear reconstruction and maxillofacial repair.

In this study, we introduced a 3D technique-based nonsurgical correction (3D-NSC) method for deformational CAD. Patients with different deformational CAD types were nonsurgically corrected by constructing wearable correction bracket under the help of 3D scanning, modeling and printing technique. The clinical efficacy of the 3D-NSC approach is summarized in this paper.

【Purpose】

To analyze the clinical efficacy and explore the feasibility of 3D-NSC for CAD in infants and children.

【Method】

1.The clinical data of 49 cases (80 ears) of infants with auricular deformities treated at the Department of Plastic and Reconstructive Surgery, Huaihe Hospital of Henan University from September 2015 to August 2022 were retrospectively analyzed. According to the inclusion and exclusion criteria, 34 patients with 55 auricular deformities, including 18 males and 16 females, were finally included in the study. All infants

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were treated with 3D-NSC.

2.The infants were grouped according to their initial treatment age (divided into A1, A2 and A3 groups), gender (divided into B1 and B2 groups) and type of auricular deformity (divided into C1, C2 and C3 groups), and were classified as excellent (Effectiveness and cure), good (improvement) and poor (no improvement) according to the effectiveness of corrective treatment, and the differences in treatment effectiveness and treatment duration in terms of age at initial treatment, type of auricular deformity and gender were assessed. A caregiver questionnaire was used to measure the subjective satisfaction of the infant's family.

【Results】

1.55 ears with auricular deformities were treated and all showed improvement with a clinical efficiency of 100%. The overall efficacy and cure rate was 83.6%.

2.The effectiveness and cure rates for the different initial treatment age groups were 96% for Group A1, 80% for Group A2 and 40% for Group A3, with statistically significant differences (P = 0.01). The median length of treatment for the 3 groups was: Group A1: 7 (7,14) d, Group A2: 21 (11,30) d and Group A3: 105 (10.5,150.5) d. The differences were statistically significant (P = 0.001).

3.The effectiveness and cure rates for male and female were 81.3% for group B1 and 87% for group B2, respectively, with no statistically significant difference (P = 0.85). The median length of treatment for the 2 groups was 21 (7,30) d for group B1 and 10 (7,14) d for group B2, respectively, with a statistically significant difference (P = 0.012).

4.The effectiveness and cure rates for the different auricular deformity types were 64% (16/25) for group C1, 100% (23/23) for group C2 and 100% (7/7) for group C3, with statistically significant differences (P = 0.002). The median length of treatment for the 3 groups was: Group C1: 21 (7,52.5) d, Group C2: 14 (10,21) d and Group C3: 7 (5,42) d. The difference was not statistically significant (P = 0.159).

5.Age at initial treatment was positively correlated with length of treatment (r = 0.519, P < 0.001) and negatively correlated with treatment outcome (r = -0.378, P = 0.004)

6.4 ears had complications (3 ears with skin breakdown and 1 ear with dermatitis) and there was no correlation between age at initial treatment, sex, type of auricular deformity, or length of treatment for complications (r=0.049, P=0.723; r=0.046, P=0.736; r=0.058, P=0.674; r=-0.081, P=0.557).

7.The satisfaction rates for the effectiveness and cure and effective groups were 4 (4,5), 3 (2,3), (b=1.142, t=4.363, P<0.001) respectively, and the differences were statistically significant.

【Conclusion】

1.3D printing correction brackets are safe and effective in the treatment of auricular deformities in infants and provide an individualized and precise treatment for auricular deformities in infants.

2.The earlier the age of initial treatment, the better the outcome and the shorter the duration of treatment; the type of auricular deformity has an influence on the outcome, with helical rim deformity and Stahl's ear being treated better than constricted ear.

3. The type of auricular deformity and the treatment outcome affected the satisfaction of the infant's family, with the treatment outcome being the most important factor.

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Symposium 4

Computing and Artificial Intelligence for Life Science

Masukawa Hall

16:50-18:00

Data integration and curation as a basis for Artificial Intelligence-based drug discovery

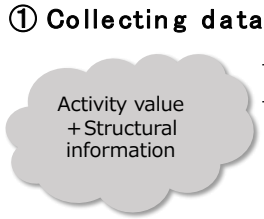
Kenji Mizuguchi[1,2]✉

Keywords: Database, Machine-learning, Bioinformatics

Advances in Artificial Intelligence (AI) critically depend on the availability of a large amount of data in a computer-friendly format. In some application areas including disease biology and drug discovery, this issue can be a major impediment in utilizing a wealth of data from public sources. For example, a commonly used parameter that defines drug metabolism and pharmacokinetics (DMPK) may be called by different names, obtained in slightly different experimental conditions, and shown in different units (Fig. 1). As a result, the naïve compilation of available data could lead to a noisy training dataset and the AI models with misleading predictive performance[1-2].

Similar problems arise in many areas of healthcare and biomedical research. We argue that data curation and integration play key roles in tackling this issue. Unlike other big data, biomedical data are inherently "small"; they tend to be produced by many small studies or experiments, and they become "big" only after the careful examination of the metadata and integration from multiple data sources.

Based on the standardized databases, predictive models can be built, typically with machine-learning

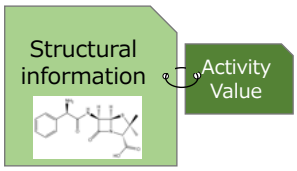


① Collecting data from public sources (ChEMBL, CTD, IF)

n = 18,257

Parameter	Value	Unit	Species	SMILES
PPB	0.995		Human	NC1=NC2=C..
fup	0.04		Rat	CC(C)[C@H]..
fu,p	0.132		Human	CS(=O)(=O)..
fup	15.8	%	Human	CCCCC(=O)..

② Curation



n = 2738

Parameter	Value	Unit	Species	SMILES
fup	0.005		Human	NC1=NC2=C..
fup	0.132		Human	CS(=O)(=O)..
fup	0.158		Human	CCCCC(=O)..

Fig. 1 An example of data collection and curation

Measurements for the pharmacokinetic parameter fraction unbound in plasm (f_{up}) can be obtained from public sources including the ChEMBL database, the Common Technical Document (CTD) or the Interview Form (IF) but they need manual curation for use in machine learning.

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techniques, for a wide range of problems including protein structures and interactions, and pharmacological properties of chemical compounds. Also, often required are mathematical models based on certain general principles for complementing the data-driven approaches. Note that these principle-based approaches will still benefit from high-quality databases.

In my research group, we aim to establish computational systems approaches to rational drug discovery. Such an attempt should be based on the three key components described above (Fig. 2), namely, databases, data-driven modelling, and principle-based modelling techniques. Again, the first component, out of the three, is the most important.

In some research areas, sharing data in a computer-friendly format is yet to be established as common practice. In developing a machine-learning model for predicting nano-particle toxicity from particle-design and assay parameters, we performed extensive literature data mining and curated the obtained data[3].

In DMPK research, measurements for a number of relevant experimental parameters are widely available, either from public databases or as electronic files associated with publications. However, they are not necessarily standardized (Fig. 1). We have performed extensive manual curation on a dataset of chemical structures and associated pharmacokinetic parameters, and demonstrated that predictive models trained on a curated dataset outperformed those trained on a non-curated dataset[4]. By capitalizing on those achievements, we have developed DruMAP (Drug Metabolism and pharmacokinetics Analysis Platform)[5]. This system consists of 1) a curated database of DMPK parameters for about 30,000 chemical compounds and 2) a web interface to a range of predictive models, built based on those data.

Databases are also important for assessing the performance of predictive models. We have developed

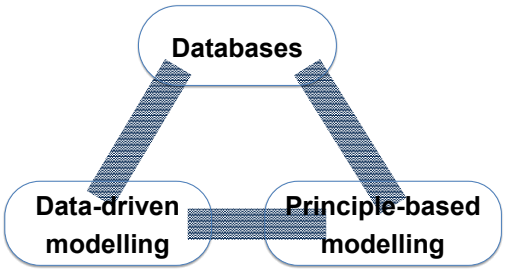

Fig. 2 Computational approaches to rational drug discovery

The three basic elements shown here complement each other and play key roles in any modeling studies.

a transformer-based model for predicting the interaction between a T-cell receptor (TCR) and its cognate peptide presented by the Major Histocompatibility Complex[6]. It performed well on a standard benchmark dataset. However, it performed poorly on new (and more realistic) datasets that we compiled from newer databases and a recent publication. This observation highlights the challenges in predicting unseen data. While attempts have been made to address this issue by improving machine-leaning algorithms, we believe that more data will be necessary and are exploring new collaborations with immunologists.

In this talk, I will discuss the interplay between databases and data-driven modelling, with specific applications described above.

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High-throughput single-cell profiling methods for microbiota and mammalian cells

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Keywords: microbiota, scRNA-seq, live-cell imaging

Abstract

The commensal bacterial microbiota is essential for the health or disease of the host, e.g., human. To comprehensively understand how the microbiota contributes to health or disease, the composition of the microbiota as well as the host cells should be accurately characterized. Here, I will present two recently developed high-throughput single-cell profiling methods.

First, I will describe a method named BarBIQ (Barcoding Bacteria for Identification and Quantification)[1,2], which classifies single bacterial cells into taxa—named herein cell-based operational taxonomy units (cOTUs)—based on cellularly barcoded 16S rRNA sequences with single-base accuracy, and quantifies the cell number for each cOTU in the microbiota in a high-throughput manner. BarBIQ opened a new window to visualize both the microbiota characterization and individual constituent bacteria including unknown bacteria, which is a basis for further understanding of the mechanism of microbiota-host interactions. Thus, BarBIQ is extremely suitable to study a microbiota which have a large number of unknown bacteria.

Second, I will describe a robot named ALPS (Automated Live-imaging and cell Picking System)[3], which can perform whole transcriptome analysis (RNA-seq) for microscopically observed single cells, e.g., peripheral blood mononuclear cells. Using these datasets, we firstly predicted the transcriptome-defined cell types from the label-free live cell images (dynamics) by deep learning with high accuracy, and showed that the accuracy was higher than that of cell type identification based on morphological and dynamical features extracted using conventional image analysis methods. This noninvasive and unbiased determination of live-cell molecular phenotypes will be useful for cell dynamics studies.

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Posters

Nesprin-2 coordinates opposing microtubule motors to drive nuclear movements during neuronal migration

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Keywords: Nesprin-2, Kinesin-1, Dynein, Neuronal migration

Neuronal migration is a fundamental process during mammalian brain development to establish the correct positioning of neurons. In migrating neurons, the nucleus undergoes active movements driven by microtubule motors. The nuclear membrane protein Nesprin-2 serves as a linker by recruiting microtubule motors, dynein and kinesin-1/KIF5, onto the nuclear envelope (Zhang et al., 2009). Dynein is widely recognized as the major driving force of forward neuronal nuclear translocation, but the role of kinesin-1 is still poorly understood (Vallee et al., 2009; Wu et al., 2018; Gonçalves et al., 2020). Due to the opposite directionalities of dynein and kinesin-1 motilities, novel mechanisms are needed to elucidate how opposing motors drive nuclear transport.

We used mouse cerebellar granule cells (CGCs) in organotypic and in vitro primary cultures to observe nuclear dynamics during neuronal migration. We found that nuclear translocation was severely impeded upon dynein or kinesin inhibition, suggesting a co-dependent interplay between opposing motors. In the developing cerebellum of Nesprin-2 knockout mice, nuclear migration of CGCs was also delayed. While exogenous expression of Nesprin-2 rescued the delayed nuclear translocation in knockout CGCs, the non-kinesin-binding or non-dynein-binding mutants of Nesprin-2 failed to support nuclear translocation, indicating that Nesprin-2 is an important adaptor for coordinated transport by dynein and kinesin-1. By utilizing an intracellular cargo-trafficking assay, we demonstrated that Nesprin-2 could generate active bidirectional transport along microtubule tracks. Our results together implicate that kinesin-1 functions coordinately with dynein via Nesprin-2 to facilitate forward nuclear movements in migrating neurons.

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Major Publications

1. Chuying Zhou, Mineko Kengaku (2022). Possible mechanisms of bidirectional nuclear transport during neuronal migration. BIOCELL. Doi: 10.32604/biocell.2022.021050.

Chinese Medicine Constitution that Influences Sleep Quality and Fatigue among Chinese Nurses Working in Shifts in Japan and China

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Keywords: Japan-China comparison, Chinese nurses who work in shifts, sleep quality, fatigue, Chinese medicine constitution

Abstract

Nurses who work in shifts may face poor sleep quality and oppressive fatigue. The purpose of this study was to clarify Chinese medicine constitution that influences sleep quality and fatigue among Chinese nurses engaged in shift work. Considering that these conditions might differ according to living environments, studies were conducted both in Japan and China.

Data were gathered using the attributes of nurses, the Pittsburgh Sleep Quality Index to evaluate sleep quality, the *Jikaku-sho shirabe* to evaluate fatigue, and the Constitution in Chinese Medicine Questionnaire, which evaluates Chinese medicine constitution according to nine criteria. The survey was conducted via internet, with data analyzed from 100 Chinese subjects in Japan and 100 Chinese subjects in China.

Table1. Variables that cause lower sleep quality and fatigue

the object variable	causal factors	SPRC
sleep quality	Age (years)*	0.141
	Country of residence (Japan = 1, China = 0)**	-0.287
	QDC*	0.190
	BSC**	0.268
	Coefficient of determination (R^2) = .301	
	Adjusted coefficient of determination (adjusted R^2) = .264	
fatigue at the end of the day shifts	No. of years engaging in shift work*	0.109
	YIDC**	0.202
	QSC*, ISC*	0.161
	Coefficient of determination (R^2) = .485	
	Adjusted coefficient of determination (adjusted R^2) = .461	
fatigue at the end of night shifts	Country of residence (Japan = 1, China = 0)**	0.240
	Sleep quality*	0.141
	QDC**	0.218
	YADC*	0.135
	Coefficient of determination (R^2) = .301	
	Adjusted coefficient of determination (adjusted R^2) = .464	

Note:Qi-deficiency constitution = QDC;Blood-stasis constitution = BSC;Yin-deficiency constitution = YIDC; Inherited special constitution = ISC;Yang-deficiency constitution = YADC;SPRC = standardized partial regression coefficient.
*p < .05, **p < .01

The results of the multiple regression analysis with sleep quality or fatigue (at the end of the day shift and at the end of night shifts) as the object variable are shown in Table 1.Increase in age, living in China, Qi-deficiency constitution and Blood-stasis constitution were causal factors for lower sleep quality. Sleep quality was significantly lower among nurses in China than those in Japan. The following factors were observed to be causal factors for increased fatigue: longer histories of working in shifts, living in Japan, poorer quality sleep, Qi-deficiency constitution, Yang- and Yin-deficiency constitution, Qi-stagnation constitution and Inherited.special constitution. Nurses in Japan showed significantly greater fatigue at the end of a night shift than did those in China. It is suggested that adjustments of Qi-deficiency constitution and Blood-stasis constitution can improve sleep quality in nurses who work in shift.

We believe that improving sleep quality and making adjustments to the five types of Chinese medicine constitution can work to reduce fatigue.

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Major Publications

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Lymphocyte-specific protein tyrosine kinase inhibitor depletes effector Tregs and enhances anti-tumor immunity

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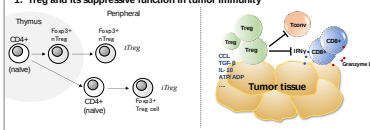
Keywords: Immunotherapy, Treg, Tumor immunity

Abstract

High infiltration of regulatory T cells (Tregs) in various tumor tissues correlate with poor prognosis in cancer patients. Tregs are specialized in immunosuppression and indispensable for preventing autoimmunity, however, their presence in tumors hampers cancer immunity. Thus, how to specifically target and deplete Tregs for augmenting anti-tumor immunity while evading autoimmunity in vivo is important for its therapeutic application. We have shown that Tregs are physiologically lower in the expression of lymphocyte-specific protein tyrosine kinase (LCK), compared with other T cells including CD8+ T cells, thus having differential sensitivity to LCK inhibition. We show that orally-available small molecule with LCK specific inhibition activity effectively reduced Ki-67+ effector Tregs in vitro and in vivo in a dose-dependent manner. This reduction in effector Tregs conversely expanded tumor-specific CD8+ T cells and effectively reduced tumor growth in mice without autoimmune side-effects. The results suggest that LCK-specific inhibition is a promising strategy to safely augment tumor immunity by selectively targeting effector Tregs.

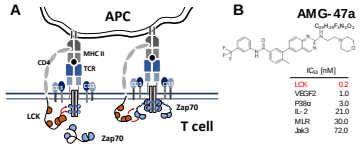
Introduction

1. Treg and its suppressive function in tumor immunity



Regulatory T cells (Tregs) are a subset of CD4+ T cells expressing CD25 and Foxp3 molecules (left) with suppressive functions, which are indispensable for the maintenance of immune homeostasis. However, high level of Treg infiltration has been associated with poor prognosis in many cancers. Trafficking of Treg cells into tumor microenvironment may be exploited by tumors to escape from immunosurveillance, leading to the tumor progression (right).

2. Lymphocyte- specific protein tyrosine kinase (LCK) and LCK inhibitor AMG47- a

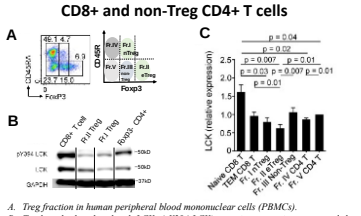


A. LCK is a member of Src kinase family and plays an essential role in the selection and maturation of developing T-cells in the thymus. LCK is important for the activation of the T-cell receptor signaling in both naive T cells and effector T cells. Once ZAP70 binds CD3, the coreceptor associated with Lck binds the MCH stabilizing the TCR-MCH-peptide interaction.
B. AMG-47a is a potent and orally bioavailable LCK inhibitor, with an IC_{50} of 0.2 nM. Meanwhile AMG-47a has anti-inflammatory activity, with an ED_{50} of 11mg/kg.

Question

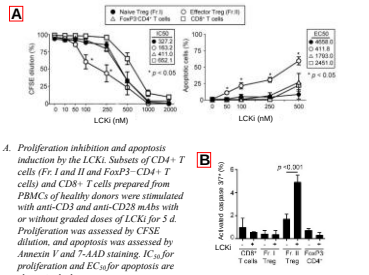
Is LCK inhibitor (LCKi) / AMG- 47a a promising strategy to deplete Treg thus augmenting tumor immunity?

Figure 1: Treg expressed lower LCK level than CD8+ and non-Treg CD4+ T cells



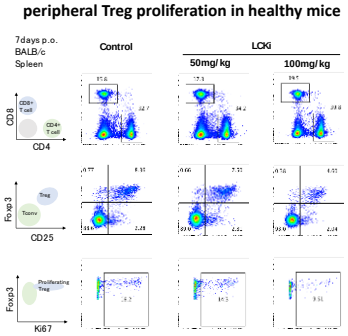
A. Treg fraction in human peripheral blood mononuclear cells (PBMCs).
B. Total and phosphorylated LCK (pY394-LCK) protein expression measured by Western blotting.
C. LCK mRNA expressions in naive CD8+ T cells, Fr. I naïve Treg cells, Fr. II effector Treg cells, and naïve CD4+ T cells prepared from PBMCs of healthy donors.

Figure 2: LCKi down-regulated LCK expression in Treg and enhanced Treg apoptosis *in vitro*



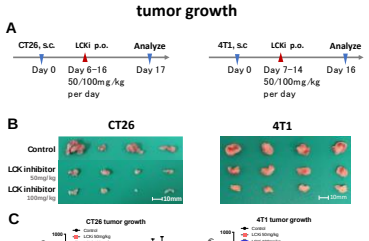
A. Proliferation inhibition and apoptosis induction by the LCKi. Subsets of CD4+ T cells (Fr. I and II and FoxP3−CD4+ T cells) and CD8+ T cells prepared from PBMCs of healthy donors were stimulated with anti-CD3 and anti-CD28 mAbs with or without graded doses of LCKi for 5 d. Proliferation was assessed by CFSE dilution, and apoptosis was assessed by Annexin V and 7-AAD staining. IC_{50} for proliferation and EC_{50} for apoptosis are shown in the boxes.
B. The frequencies of cells with activated caspase 3 and 7, prepared from PBMCs of healthy donors, after treatment with or without 250 nM LCKi for 4 d with anti-CD3 and anti-CD28 mAbs. Caspase 3/7+ cells negative for SYTOX AADvanced cell impermeant nucleic acid stain were measured.
Data are pooled from more than two independent experiments.

Figure 3: Oral administration of LCKi inhibited peripheral Treg proliferation in healthy mice



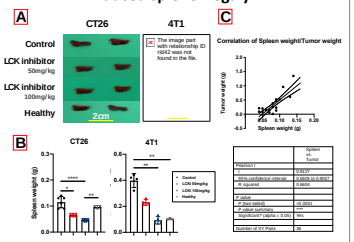
Representative plots of flow cytometry in splenocytes collected from healthy mice (Balb/c, 7-week-old, ♀). LCKi was given once a day with a dose of 50mg/kg or 100mg/kg by p.o. for 7 days. Mice were sacrificed for analysis. Frequency of CD4+ and CD8+ among CD3+ in spleen (Top); Frequency of Treg cells among CD4+ T cells (middle); Frequency of Ki-67+ proliferating Treg cells among total Treg cells (bottom). LCKi inhibited peripheral Treg and suppressed proliferation of Treg in a dose-dependent manner.

Figure 4: Oral administration of LCKi suppressed tumor growth



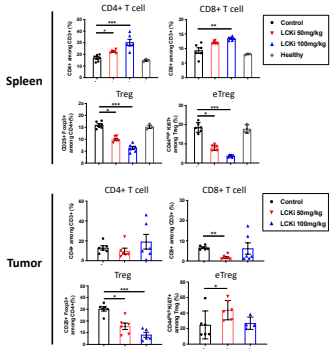
A. Murine colon cancer cell line CT26 (10^6 cells/mouse) and murine breast cancer cell line 4T1 ($5x10^5$ cells/mouse) were injected subcutaneously (Balb/c, 7-week-old, ♀) to generate tumors. Once tumor diameter has reached 5mm, LCK inhibitor was given once a day by p.o. for 11 or 8 days and mice were sacrificed for analysis.
B. Representative tumors from each treatment conditions are shown.
*C. Tumor size was measured everyday. The tumor volume was calculated by formula (1^2*Length*width^2/2). Tumor growth curve are shown. LCKi presented a therapeutic effect for tumor on tumor-bearing mice in a dose-dependent manner.*

Figure 5: LCKi treatment relieved tumor-induced splenomegaly



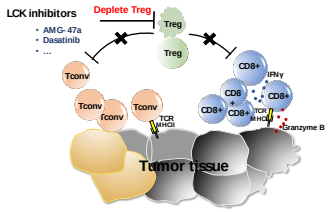
A. Spleens were taken from mice in Figure 4.
B. Spleen weight was presented as shown. Spleen weight increased in CT26 or 4T1 tumor-bearing mice without LCKi treatment. In 4T1 tumor-bearing mice, severe splenomegaly was observed, however this symptom was relieved by LCKi in a dose dependent manner.
C. Correlation analysis was conducted between Spleen weight and Tumor weight recorded from CT26 tumor-bearing mice. Tumor volume was found positively associated with spleen weight.

Figure 6: Oral administration of LCKi suppressed peripheral and tumor infiltrated Treg



The frequencies of lymphocytes taken from CT26-bearing mice in Figure 4. Spleen and tumor are analyzed by flow cytometry. In spleen, LCKi increased CD4+/CD8+ population and decreased Treg/eTreg in a dose-dependent manner. In tumor, Treg was also suppressed significantly in a dose-dependent manner.

Summary and Prospect



We have verified targeting LCK might be a practical strategy to augment tumor immunity. In murine tumor-bearing models, tumors were efficiently suppressed and Treg populations were decreased in a dose dependent manner by using existing compound AMG-47a. Our results provided evidence that supported effectiveness of Treg depletion mediated-immunotherapeutic strategies. We are also looking forward to develop more novel compounds that targets LCK.

COI Disclosure Information

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- I have no financial relationships to disclose.

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Major Publications

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iMSC-mediated delivery of ACVR2B-Fc fusion protein reduces heterotopic ossification in a mouse model of fibrodysplasia ossificans progressiva

Pan Gao[1,2], Yoshiko Inada[2], Akitsu Hotta[2], Hidetoshi Sakurai[2], and Makoto Ikeya[2,] ✉

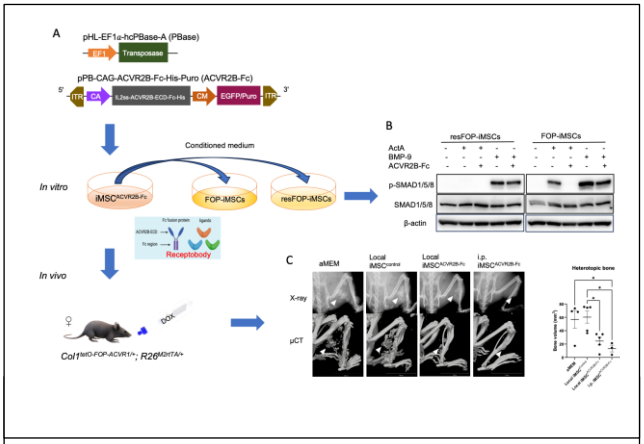
Keywords: fibrodysplasia ossificans progressiva, heterotopic ossification, induced pluripotent stem cells, mesenchymal stem/stromal cells, ACVR2B-Fc fusion protein

Background: Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease caused by a gain-of-function mutation in ACVR1, which is a bone morphogenetic protein (BMP) type I receptor. Moreover, it causes progressive heterotopic ossification (HO) in connective tissues. Using FOP patient-derived induced pluripotent stem cells (FOP-iPSCs) and mouse models, we elucidated the underlying mechanisms of FOP pathogenesis and identified a candidate drug for FOP.

Methods: In the current study, healthy mesenchymal stem/stromal cells derived from iPSCs (iMSCs) expressing ACVR2B-Fc (iMSC$^{ACVR2B-Fc}$), which is a neutralizing receptobody, were constructed (Fig. 1A). Furthermore, patient-derived iMSCs and FOP mouse model (ACVR1^{R206H}, female) were used to confirm the inhibitory function of ACVR2B-Fc fusion protein secreted by iMSC$^{ACVR2B-Fc}$ on BMP signaling pathways and HO development, respectively.

Results: We found that secreted ACVR2B-Fc attenuated BMP signaling initiated by Activin-A and BMP-9 in both iMSCs and FOP-iMSCs *in vitro* (Fig. 1B). Transplantation of ACVR2B-Fc-expressing iMSCs reduced primary HO in a transgenic mouse model of FOP (Fig. 1C). Notably, a local injection of ACVR2B-Fc-expressing iMSCs and not an intraperitoneal injection improved the treadmill performance, suggesting compound effects of ACVR2B-Fc and iMSCs.

Conclusions: These results offer a new perspective for treating FOP through stem cell therapy.



conditioned medium inhibited SMAD1/5/8 phosphorylation (induced by Activin-A and BMP-9) in FOP-iMSCs. (C) Representative X-ray and μCT images of each group and average of HO volume (right side). Arrowheads indicate HO. Scale bar, 10 mm.

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Major Publications

1. **Pan Gao**; Shan Liu; Xiaoyi Wang; Makoto Ikeya; Dental applications of induced pluripotent stem cells and their derivatives, Japanese Dental Science Review, 2022, 58: 162-171
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Conversion of Tfh cells to Tfr cells through epigenetic modification in systemic lupus erythematosus

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Key words: T follicular helper, T follicular regulatory, systemic lupus erythematosus

[Objective] T follicular helper (Tfh) cells are critical for the B cell help and autoimmunity, whereas T follicular regulatory (Tfr) cells suppress Tfh-mediated antibody responses. In this study, we aimed to identify the molecular mechanisms underlying the plasticity between Tfh cells and Tfr cells in the pathogenesis of systemic lupus erythematosus (SLE).

[Methods] Peripheral blood mononuclear cells from SLE patients and healthy donors (HD) were analyzed by flow cytometry. Naive CD4+ T cells and memory CD4+ T cells were cultured with TCR and various cytokines in vitro. Expression of characteristic markers of T helper subsets were analyzed by flow cytometry and qPCR.

[Results] The proportion of CD4+CXCR5+FoxP3+ Tfr cells was increased (2.455% vs 1.117%, p=0.0021); however, that of CD4+CD45RA-FoxP3hi activated Tfr cells was decreased (5.085% vs 8.909%, p=0.0010) while CD4+CD45RA-FoxP3low non-suppressive Tfr cells was increased (47.64% vs 38.83%, p=0.0285) in SLE patients compare to HD. The percentage of PD-1hi activated Tfh cells was significantly higher in SLE patients than that of HD (12.14% vs 6.119%, p=0.0001). Furthermore, active patients had higher ratio of activated Tfh/Tfr cells compared to inactive patients. In vitro study showed that, IL-2, but not other cytokines such as TGF-β1, IL-12, IL-27 and IL-35, induces the conversion of memory Tfh cells to functional Tfr cells characterized by CXCR5+Bcl-6+Foxp3hipSTAT3+pSTAT5+ cells. The relative level of IL-2 mRNA in CD4+ T cells was significantly lower in SLE patients compared with HD (0.7314 vs 1.208, p=0.0393). Finally, stimulation with IL-2 increased activated Tfr cells in CD4+ T cells isolated from SLE patients.

[Conclusions] Our findings indicated that the regulatory function of Tfr cells is impaired due to low ability of IL-2 production by CD4+ T cells and that IL-2 restores the function of Tfr cells in SLE. Thus, the reinstatement of the balance between Tfh and Tfr cells will provide important therapeutic approaches for SLE.

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Regulation of vessel diameter during blood vessel remodelling

Yan Chen [1,✉], Nuria Taberner Carretero[1], Li-Kun Phng1

Keywords: angiogenesis, vessel constriction, cell shape, actomyosin network, zebrafish

The cardiovascular system consists of blood vessels of different sizes including arteries, veins, and capillaries to transport nutrients and oxygen for all tissues in a living organism. Endothelial cells (ECs) that form the inner layer of the vessel therefore are subjected to molecular signals as well as mechanical forces exerted by the blood flow. **How endothelial cells establish a hierarchically organised vascular tree of optimal vessel size is still unclear.**

In this study, we showed that intersegmental vessels (ISVs) in zebrafish underwent vessel constriction from 3 days post fertilisation (dpf) to 4dpf. By transient labelling of single ECs, we performed in vivo cell shape analysis and found that the decrease in vessel diameter correlated with changes in cell deformation, suggesting that vessel constriction was mediated via changes in cell size and cell shape. Transplantation of ccm1-/- ECs in wildtype zebrafish displayed enlarged cell size and decreased cell aspect ratio, as well as increased lumen diameter, suggesting that Ccm1 regulated cell shape change autonomously. We discovered novel actin organisations (AOs) that exhibited vessel-type and stage-specific differences during vessel remodelling, which were altered at the expense of circumferential actins in transplanted ccm1-/- vessels. Overexpression of zWasp, which is required for actin branch growth, led to increased meshed actin. In addition, the motor protein non-muscle myosin II exhibited dynamic oscillations in the EC cortex. Overexpression of mutant form of Myl9b (myl9bA2A3) in ECs led to increased vessel diameter, suggesting that myosin regulates vessel diameter. **Collectively, our data suggested that actomyosin-mediated cell shape and size changes act as an underlying mechanism for the development of an ordered vasculature with proper sizes.**

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Same Clock Ticks Different Time: Molecular Insights into Temporal Scaling of Neurogenesis

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Abstract

The evolution of the human cerebral cortex, endowed with advanced functions, remains a pivotal subject in neuroscience and evolutionary biology. While the fundamental developmental blueprint of the cortex is consistent across mammals, the duration of neurogenesis exhibits significant variance, ranging from under a week in mice to approximately one month in ferrets and nearly four months in humans[1]. The molecular underpinnings of this temporal scaling, however, remain largely unexplored.

In mammals, the cerebral cortex's neural stem cells (NSCs) sequentially generate deep-layer neurons, upper-layer neurons, and eventually glia. This progression is marked by a temporal patterning in NSC gene expression. Our study aims to elucidate how this gene expression is modulated across species to align with their distinct developmental timelines. While previous research in somite and spinal cord development attributes species-specific differences in protein/mRNA degradation rates as a primary factor in 2-3-fold temporal scaling[2,3], our mathematical models and empirical data indicate limitations to this framework when considering the more extensive 15-fold scaling observed between mice and humans.

Our investigations reveal that gene expression in NSCs is influenced by H3K27me3-mediated epigenetic regulation in mice[4], ferrets, and human brain organoids. Manipulations of H3K27me3 levels have shown to impact the duration of neurogenesis in both mice and ferrets. Consequently, we introduce a novel model incorporating epigenetic regulation to elucidate the mechanisms of temporal scaling in brain development. This presentation will explore the benefits of our model in explaining the intricacies of temporal scaling in brain development.

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Mechanisms of platelet production in intracellular regulatory molecules targeted by AhR antagonist

Xiangji Jiang[1,✉], Sou Nakamura[1], Koji Eto[1,2]

Keywords: iPS Cells, Megakaryocyte, Platelets

The development of ex vivo platelet production using induced pluripotent stem cells (iPS cells) has been advancing. However, the efficiency of differentiation into megakaryocytes in culture has been low, and the production process has been lengthy, posing significant challenges. The study by Eto et al. in 2002[1], which first successfully differentiated mouse embryonic stem (ES) cells into megakaryocytes and platelets, led to the development of differentiation methods from human ES cells and iPS cells, and to the establishment of an immortalized megakaryocyte cell line (imMKCL), forming the basis for mass production of platelets ex vivo[2]. Analysis focusing on the amplification of megakaryocytes revealed that SCF-dependent amplification could be substituted by StemRegenin 1 (SR1), an aryl hydrocarbon receptor (AhR) inhibitor. This finding suggests a potential overlap in the downstream effects of AhR inhibition and the cellular effectors and molecules involved in the SCF response. Subsequently, shear stress and turbulent energy were discovered as environmental factors in the in vivo release and production of platelets from megakaryocytes, leading to the development of a new bioreactor (VerMES). This, in conjunction with the synergistic effects of AhR antagonists in a liquid culture medium, demonstrated the production of platelets in numbers comparable to transfusion products[3]. These advancements enabled the world's first clinical trial of autologous iPS cell-derived platelet products for patients with thrombocytopenia and platelet transfusion refractoriness from 2019 to 2022[4]. However, the molecular mechanisms of action of several drugs that enhance platelet production from imMKCL remain unclear. The aim of this study is to elucidate the platelet production molecular mechanisms by analyzing the action mechanism of the AhR antagonist.

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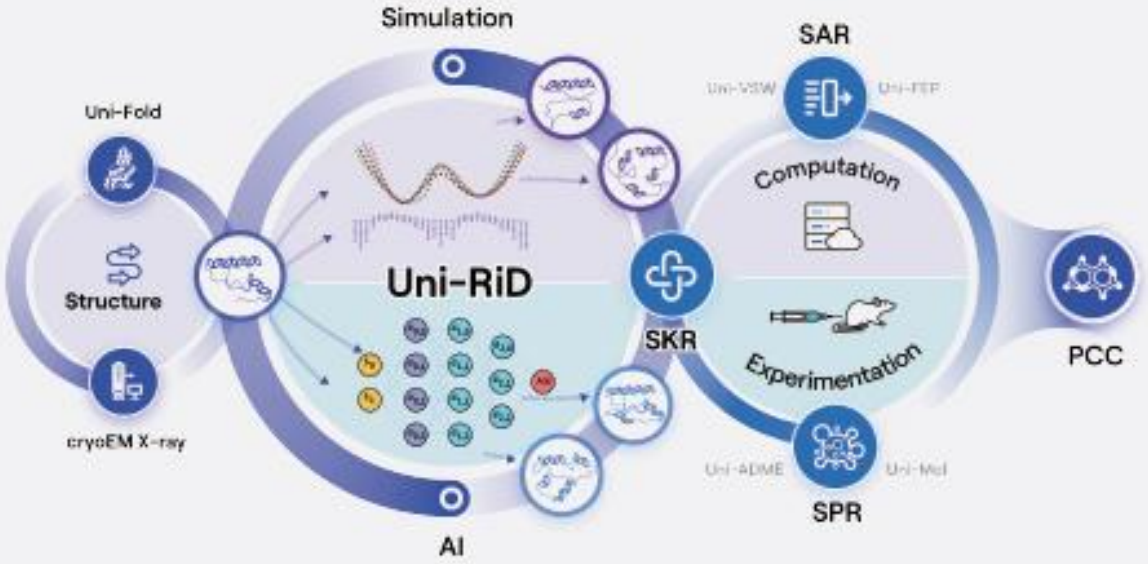

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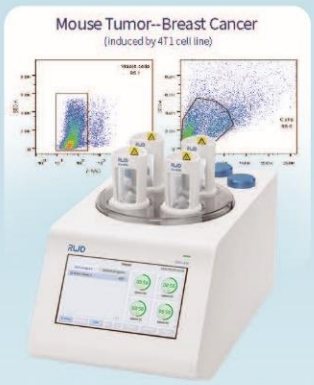

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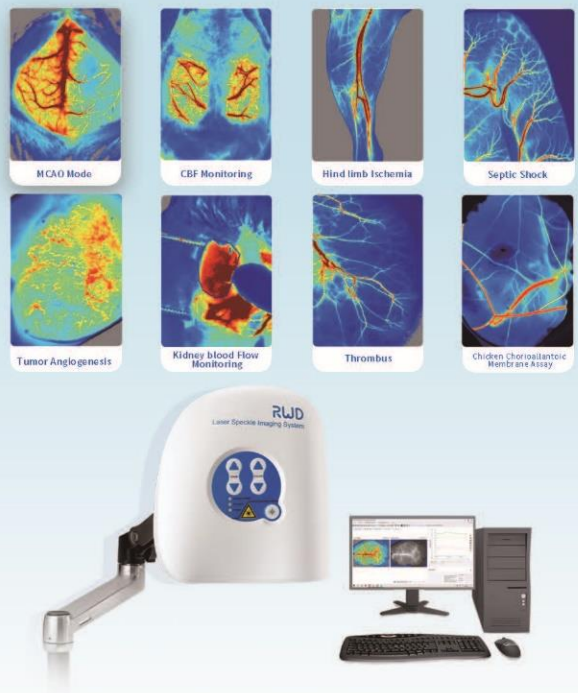

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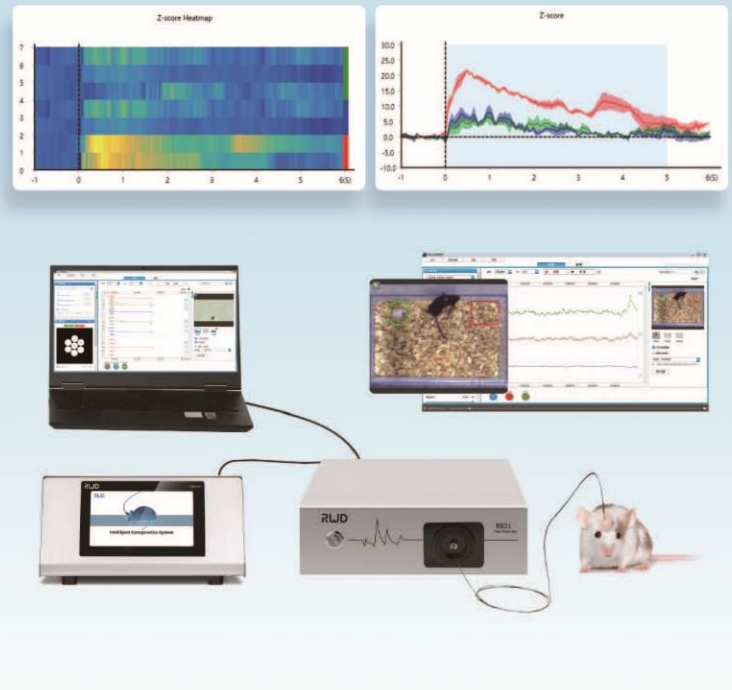

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