高精度の予測に基づく予防医療の実現に向けた
疾患ビッグデータ主導型イノベーションハブ

第一回国際シンポジウム
「生命科学のパラダイム転換による新たなヘルスケアの創出」

1st International Symposium on Hub for Predictive and Preventive Precision Medicine Driven by Big Data

“Life Science Paradigm Shift Leading to Innovative Healthcare”

February 7 (Tue), 2017

Ito Hall, Ito International Research Center

RIKEN Medical Sciences Innovation Hub Program
Japan Science and Technology Agency

RIKEN Since 1917 MIHub JST Japan Science and Technology Agency iHub

TIMETABLE

SESSION I

10:00 Opening remarks **Shigeo Koyasu, Executive Director RIKEN, Program Director MIH**

10:05 Opening remarks **Ministry of Education, Culture, Sports, Science and Technology (MEXT) (TBD)**

10:10 Opening remarks **Yoshiaki Ando, Senior Executive Director, Japan Science and Technology Agency (JST)**

KEYNOTE

10:15 **Kazuhiro Sakurada, Depty Program Director, MIH**
『High sensitive compact device for contributing to diagnostic data platform』

10:40 **Kazuyuki Aihara, Professor, Laboratories for Mathematics, Lifesciences, and Informatics, Institute of Industrial Science, University of Tokyo**
『Data-Driven Life Science by Mathematical Approach』

11:05 **Leroy Hood, President & Co-Founder, Institute for Systems Biology; Senior Vice President & Chief Science Officer, Providence Health & Services (USA)**
『Systems Medicine and Proactive P4 Medicine: Transforming Healthcare with Scientific Wellness』

12:05 **Ryozo Nagai, President, Jichi Medical University**
『Medical Research in the Era of Big Data』

12:30 Lunch

SESSION II

SCIENCE DISCUSSION

14:00 **Rudi Balling, Director, Luxembourg Centre for Systems Biomedicine (Luxembourg)**
『Systems approaches to PD: translation into clinic as well as industry』

14:30 **Nisar P. Malek, Director, Internal Medicine, University Hospital Tübingen (Germany)**
『Implementing personalized medicine in a university hospital』

15:00 **Yasuyoshi Watanabe, Compass to Healthy Life Research Complex Program, RIKEN CLST**
『Precision health: maximization of individual health』

15:20 **Kazuhiro Kakimi, Department of Immunotherapeutics, The University of Tokyo Hospital**
『An immunogram for the cancer-immunity cycle: towards personalized immunotherapy』

15:40 Break

16:00 **Haruhiko Koseki, Group Director, RIKEN MIH**
『Towards understanding underlying mechanisms of inflammatory diseases in human: Modeling skin homeostasis』

16:20 **Eiryo Kawakami, Senior Scientist, MIH**
『Discovery of combinatorial biomarkers for personalized medicine based on machine learning』

16:40 **Shinji Nakaoka, JST PRESTO**
『Computational functional association mining of dysbiotic microbial community』

17:00 **Hideo Yokota, Image Processing Research Team, Extreme Photonics Research Group, Center for Advanced Photonics, RIKEN**
『Towards advanced quantitative science using image processing techniques』

17:20 **Kazuyoshi Horii, Research Manager, Technology Development, Sysmex Corporation**
『High sensitive compact device for contributing to diagnostic data platform』

SOCIAL GATHERING

17:40 – 19:00 Foyer, Ito hall

タイムテーブル

第１部

10:00　主催者挨拶 **小安 重夫**　医科学イノベーションハブ推進プログラム　プログラムディレクター、
理化学研究所　理事

10:05　来賓ご挨拶　**文部科学省（予定）**

10:10　来賓ご挨拶　**安藤 慶明**　科学技術振興機構　総括担当理事

基調講演

10:15　**桜田 一洋**　『医科学イノベーションハブ推進プログラムの紹介』
医科学イノベーションハブ推進プログラム　副プログラムディレクター

10:40　**合原 一幸**　『数理的アプローチによるデータ駆動生命科学』
東京大学 生産技術研究所、東京大学大学院 情報理工学系研究科 数理情報学専攻　教授

11:05　**Leroy Hood**　『Systems Medicine and Proactive P4 Medicine:
Transforming Healthcare with Scientific Wellness』
President & Co-Founder, Institute for Systems Biology; Senior Vice President & Chief Science Officer,
Providence Health & Services (USA)

12:05　**永井 良三**　『ビッグデータ時代の臨床医学研究』
自治医科大学学長

12:30　休憩

第２部　（英語：　同時通訳はございません）

一般講演

14:00　**Rudi Balling**　『Systems approaches to PD: translation into clinic as well as industry』
Director, Luxembourg Centre for Systems Biomedicine (Luxembourg)

14:30　**Nisar P. Malek**　『Implementing personalized medicine in a university hospital』
Director, Internal Medicine, University Hospital Tübingen (Germany)

15:00　**渡邊 恭良**　『Precision health: maximization of individual health』
理化学研究所　健康生き活き羅針盤リサーチコンプレックス推進プログラム　副プログラムディレクター、
ライフサイエンス技術基盤研究センター（CLST）センター長

15:20　**垣見 和宏**　『An immunogram for the cancer-immunity cycle: towards personalized immunotherapy』
東京大学大学院医学系研究科　免疫細胞治療学講座　特任教授

15:40　休憩

16:00　**古関 明彦**　『Towards understanding underlying mechanisms of inflammatory diseases in human』
理化学研究所　MIH　グループディレクター、統合生命医科学研究センター　副センター長

16:20　**川上 英良**　『Discovery of combinatorial biomarkers for
personalized medicine based on machine learning』
医科学イノベーションハブ推進プログラム　上級研究員

16:40　**中岡 慎治**　『Computational functional association mining of dysbiotic microbial community』
さきがけ専任研究者

17:00　**横田 秀夫**　『Towards advanced quantitative science using image processing techniques』
理化学研究所　光量子工学学研究領域　エクストリームフォトニクス研究グループ　画像情報処理研究チーム　チームリーダー

17:20　**堀井 和由**　『診断データプラットフォームに貢献する高感度コンパクトデバイス』
シスメックス株式会社 技術開発本部 リサーチマネジャー

懇談会

17:40 – 19:00　伊藤謝恩ホール　ホワイエ

Abstracts

医科学イノベーションハブ推進プログラムの紹介

Introduction of Medical Sciences Innovation Hub Program (MIH)

桜田一洋　(Kazuhiro Sakurada)

理化学研究所　医科学イノベーションハブ推進プログラム 副プログラムディレクター
(RIKEN MIH, Deputy Program Director)
ソニーコンピュータサイエンス研究所　シニアリサーチ―
(Sony Computer Science Laboratories, Senior Researcher)

計算機や計測技術の飛躍的な進歩とは裏腹に臨床上の問題に代表される生命現象の表現や予測の技術開発は停滞している。生物学や医学の論文は生物の様々な形質とその原因に関する因果の仮説である。2015 年に PubMed に新たに掲載された論文の数は 360 万報に及ぶが、その全体像とは因果仮説の集合である。1940 年代に確立した「現代の総合」という生命科学の枠組みは、生命現象を分析し説明するための方法で、遺伝子情報によって説明する部分（遺伝）と、物理や化学の法則によって説明する部分（形質）に分け、さらに遺伝子決定論と還元論に基づき遺伝と形質を部分に分解し、それが 1 対 1 で対応するという枠組みを与えた（図１ A）。

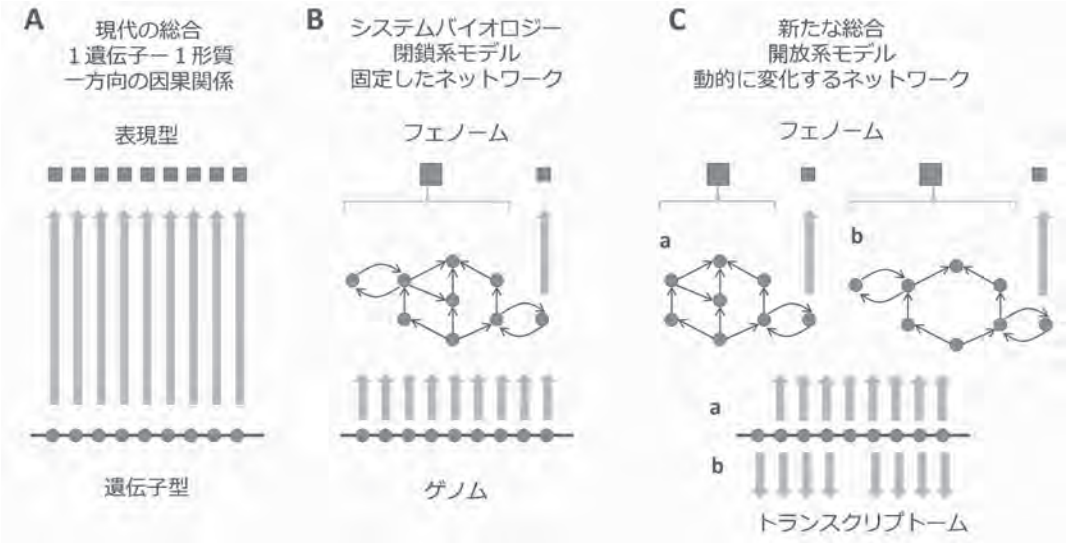

図１　遺伝情報と形質の関係

しかし遺伝子と形質の間に線形の因果関係が観察されるのは一部であり、表現型の可塑性、遺伝的同化、遺伝的順化の現象が発見され「現代の総合」の枠組みに変則性があることが明らかになった。

システムバイオロジーは遺伝と形質の関係をネットワークによって理解するというパラダイムの転換を行い、ネットワークに主眼を置いた Network Biology を生み出した（図１Ｂ）。しかし生物のネットワークは機械の回路とは異なり、ネットワークの構造をダイナミックに変化させる（図１Ｃ）。そのために特定の条件で計測されたネットワークを分析する研究だけでは、実世界の問題に迫ることができない。

ネットワークのダイナミズムは細胞で遺伝子がいつ、どこで、どれだけ発現しているかに依存するので、トランスクリプトーム、プロテオーム、メタボロームなどの解析が進められてきた。しかし、人体は 60 兆個の細胞からなり、一つひとつの細胞には 10 億の分子が発現していることから、実世界の個々の生命現象をネットワークで表現することはできない。

臨床解析の枠組みは独立変数、多変量解析から成り立っており、「現代の総合」の枠組みを継承している。この方法では変数が独立して疾患形質と関係していない場合には解析対象から除かれてしまう。また介入の効果は集合平均によって分析されるため、多様性を有する疾患に対して「標準治療」を押し付けることになる。しかし多因子疾患では「標準治療」が効果のない患者が多数存在するため、生活習慣病の治療に潜在する問題は現時点でも解決していない。

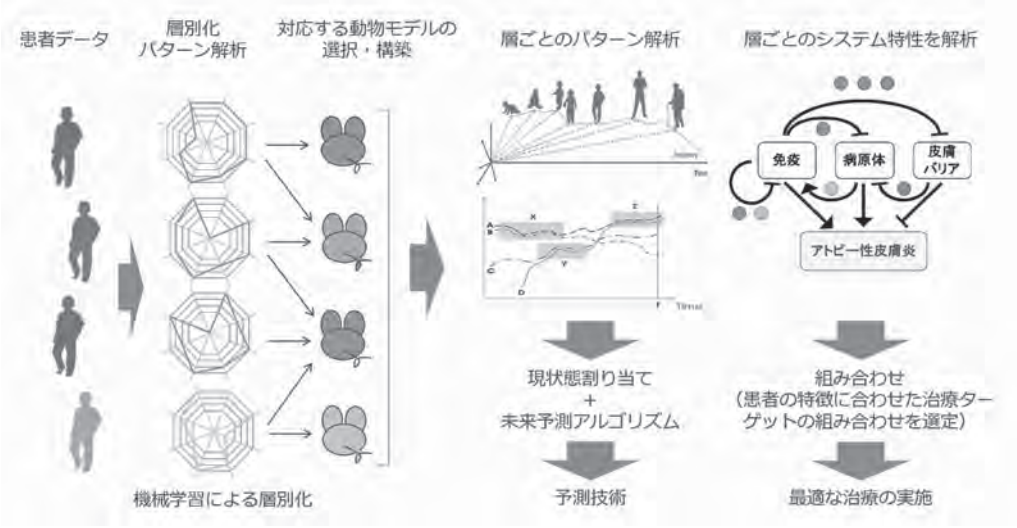

図２　予測技術と新たな治療法の開発

理化学研究所医科学イノベーションハブでは生物学、医学の根本問題に遡り、従来のパラダイムを転換することで医療上の問題を解決することを目指している。それは（１）仮説主導型からデータ主導型の問題解決へ転換、（２）言語的・関数的解析から画像的・幾何学的解析への転換、（３）機械論から有機体論への転換から成り立っている（参考文献参照）。

具体的には大学病院と連携し、個々の免疫疾患に関して多様な患者様をリクルートし、経時的にマルチオミックス解析を実施する。得られたデータを多次元データとして整理したデータベースを構築する。多次元データは様々な方法で次元圧縮を行い人工知能の機械学習を実施する。これら一連の研究から多因子疾患の「現状態割り振り技術」と「未来予測アルゴリズム」を開発し高度個別化医療の枠組みを開発する（図２）。

本プロジェクトの成果を、高度個別化医療及び予防医療の実現に繋げるために、臨床現場で少量のサンプルから高感度で再現性よくサンプルを解析できる検査デバイスの開発（図３）ならびに、患者様から発見された層別化に基づき、動物実験を組み立て新たな治療介入法の同定を実施する（図２）。

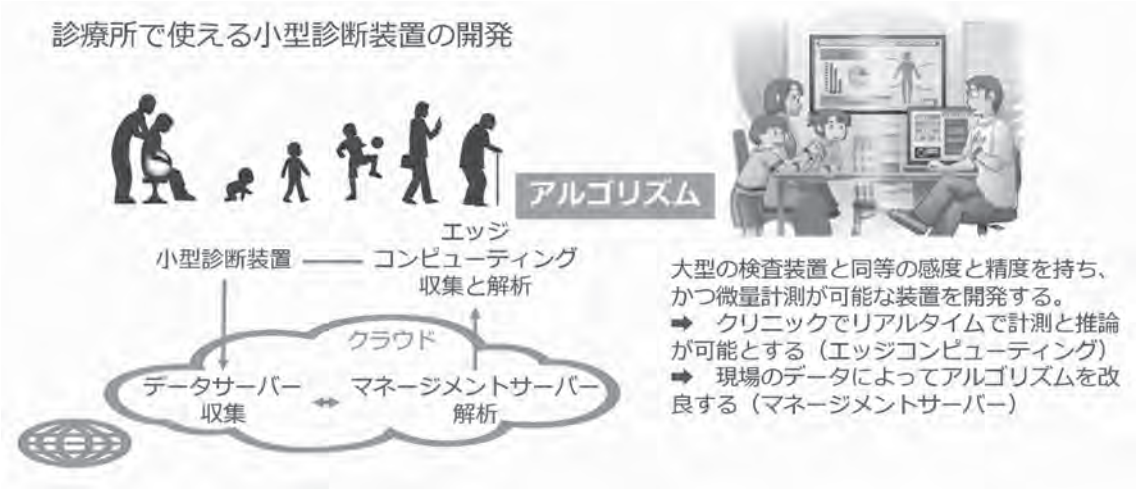

図３　高度個別化医療の実現

本プロジェクトで開発されるデータベースと一連の研究開発により、本医科学イノベーションハブ推進プログラムから生活習慣病に代表される多因子疾患の高度個別化医療ならびに予防医療を実現する。

参考文献

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略歴

1988 年大阪大学大学院理学研究科修士課程修了。同年協和発酵工業（株）入社。東京研究所で創薬研究に従事。その間、京都大学医学部、Salk 研究所で客員研究員。2000 年に協和発酵東京研究所で再生医療グループを立ち上げ主任研究員に就任。

2004 年ドイツ Schering 社により神戸に新設されたリサーチセンターのセンター長として移籍し、Schering 本社コポレート研究幹部会メンバー(Corporate Research Management Team Member, Senior Vice President class)、日本研究部門統括、ならびに日本シエーリング社の執行役員を務めた。Bayer 社と Schering 社が合併に伴い、Bayer Schering Pharma(BSP)の日本研究部門統括、再生医療本部長、グローバル研究幹部会メンバー(Global Research Senior Vice President class)ならびにバイエル薬品の執行役員リサーチセンター長の役職を務めた。

2007 年 12 月末に会社合併に伴う戦略の変更によりリサーチセンターを閉鎖。2008 年 1 月から米国 KPCB(Kleiner Perkins Caufield & Byers)の支援を受けてベンチャー企業 iZumi Bio 社を設立、最高科学執行責任者(CSO)を務め、バイエル薬品で開発したヒト iPS 細胞技術の移管を実施。

2008 年 9 月よりソニーコンピュータサイエンス研究所シニアリサーチャー。個別医療を実現するために医療データを人工知能によって解析する方法を開発。2011 年から理化学研究所政策審議委員（特別顧問）、2016 年 4 月より理化学研究所　医科学イノベーションハブ推進プログラム　副プログラムディレクターを兼務。

1993 年に大阪大学から理学博士を授与。

数理的アプローチによるデータ駆動生命科学

Data-Driven Life Science by Mathematical Approach

合原一幸 (Kazuyuki Aihara)

東京大学　生産技術研究所 (IIS UTokyo)

ビッグデータの蓄積と人工知能の発展は、生命科学の研究を変えようとしている。本基調講演では、数理的アプローチによるデータ駆動生命科学の可能性を論じる。

特に、我々が提案した動的ネットワークバイオマーカー（DNB: Dynamical Network Biomarkers）を具体例にして（1-5）、複雑生命システムから観測されるビッグデータの数理解析により、よりターゲットファクターを絞った生命科学研究が可能になること、そして DNB により、先制・未病医療への道が拓かれることを説明する。また、データ駆動生命科学に関連して、今後の人工知能研究における量子ニューラルネットワーク（6,7）等のハードウエア研究開発の重要性を論じる。

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略歴

1982 年 東京大学 大学院工学系研究科 電子工学専攻 博士課程修了
1993 年 東京大学 工学部 計数工学科 助教授
1998 年 東京大学 大学院工学系研究科 計数工学専攻教授
1999 年 東京大学 大学院新領域創成科学研究科 複雑理工学専攻 教授
2003 年 東京大学 生産技術研究所教授
東京大学 生産技術研究所 最先端数理モデル連携研究センター長 (兼任)
東京大学 大学院情報理工学系研究科 数理情報工学専攻 教授 (兼任)
東京大学 大学院工学系研究科 電気系工学専攻 教授 (兼任)

Systems Medicine and Proactive P4 Medicine: Transforming Healthcare through Scientific Wellness—A Personal View

Leroy Hood

Institute of Systems Biology and Providence Health and Services, Seattle, WA (USA)

Systems medicine, the application of systems approaches to disease, places medicine at a fascinating tipping point—promising a revolution in the practice of medicine. I will discuss some of the new systems-driven technologies and strategies that have catalyzed this tipping point. Moreover, four converging thrusts—systems medicine, big/digital data (and its analytics), the digitalization of personal measurements and patient-activated social networks—are leading to a proactive medicine that is predictive, personalized, preventive and participatory (P4). I will contrast P4 medicine with contemporary evidence-based medicine and discuss its societal implications for healthcare. P4 medicine has two central thrusts—quantifying wellness and demystifying disease.

I will discuss our successful effort to introduce P4 medicine into the current healthcare system with a P4 pilot program—a longitudinal, high-dimensional data cloud study on each of 108 well patients over 2014. The preliminary results both with regard to data analyses and patient responses from these studies are striking. They point to the emerging discipline of scientific wellness—and the fact that it will catalyze several new thrusts in healthcare: 1) optimizing wellness, 2) identifying the earliest disease transitions for all common diseases and 3) employing the dense, dynamic, personal data cloud approach to study diseases (e.g. cancer, Alzheimer's, diabetes) and their responses to therapy. We started Arivale, a company focused on scientific wellness for the consumer, in 2015 and already have 1200 individuals enrolled. I will also discuss preliminary results from the Arivale studies.

My institute, the Institute for Systems Biology (ISB), has recently affiliated with Providence St. Joseph Health to become its research arm. Providence is the largest non-profit healthcare system in the US—and ISB/Providence will be initiating a series of "translational pillars" moving applications of systems (P4) medicine from the bench to the bedside. These pillars include scientific wellness, bringing scientific wellness to cancer survivors, making Alzheimer's a reversible and preventive disease, rather than a relentlessly progressive disease, taking a systems approach to type 2 diabetes and exploring how the deep, dynamic, personal data clouds can be used to gain a deep understanding of glioblastoma and provide new diagnostic and therapeutic approaches.

Scientific wellness will catalyze a transformation in contemporary healthcare and it will provide tens of thousands of dense, dynamic, personal data clouds that will present striking new opportunities for pharma, biotech, nutrition and diagnostic companies. As the cost of the assays for the dense, dynamic, personal data clouds decline, scientific wellness can be brought to the developing world leading to a democratization of healthcare unimaginable in a few years ago.

Biography

Dr. Leroy E. Hood graduated from the Johns Hopkins University School of Medicine in 1964 with an MD and from Caltech with a PhD in biochemistry in 1968. After three years

as a Senior Investigator at NIH, his academic career began at Caltech, where he and his colleagues developed the DNA gene sequencer and synthesizer, and the protein synthesizer and sequencer–four instruments that paved the way for the successful mapping and understanding of the human genome. A pillar in the biotechnology field, Dr. Hood has played a role in founding fifteen biotechnology companies including Amgen, Applied Biosystems, Integrated Diagnostics and Arivale. He is a member of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. Of the more than 6,000 scientists world-wide who belong to one or more of these academies, Dr. Hood

is one of only fifteen people nominated to all three. Dr. Hood has co-authored numerous textbooks in biochemistry, immunology, molecular biology and genetics, as well as a popular book on the human genome project, The Code of Codes and he is just finishing up a text on systems biology. He is the recipient of numerous national and international awards, including the Lasker Award for Studies of Immune Diversity (1987), the Kyoto Prize in advanced technology (2002), the Heinz Award for pioneering work in Systems Biology (2006), and the coveted NAE 2011 Fritz J. and Delores H. Russ Prize for developing automated DNA sequencing. In addition to having received 17 honorary degrees from prestigious universities in the U.S. and abroad, Dr. Hood has published over 750 peer reviewed articles and currently holds 36 patents. In 2013, he received the National Medal of Science from President Obama. Hood has been named by The Best Schools as one of the 50 Most Influential Scientists in the World Today (2014) http://isb.io/top50.

Scientific American has named Hood as one of the top 6 in their selection of 100 biotech visionaries world-wide (2015) http://isb.io/visionary.

Area of Expertise

Adaptive immunity, genomics, biotechnology, systems biology and medicine, technology development, personalized medicine, cancer neurodegeneration, clinical assays

John Aitchison, PhD

Professor and founding faculty member, Institute for Systems Biology

Dr. John Aitchison is a Professor and founding faculty member at the Institute for Systems Biology. He also holds an appointment at Center for Infectious Disease Research (CIDResearch) as Professor and Chief Scientific Officer. As a student, he studied biochemistry, specializing in biotechnology and genetic engineering at McMaster University in Ontario, Canada. There, in the laboratory of Dr. Richard Rachubinski, he investigated the molecular mechanisms responsible for sorting proteins into peroxisomes. After receiving his PhD, Dr. Aitchison performed his postdoctoral work in the laboratory of Nobel Laureate Dr. Günter Blobel at Rockefeller University. In Dr. Blobel's lab, Dr. Aitchison applied classic cell biology techniques and yeast genetics to the study of protein import into the nucleus. During this time, he began to apply large-scale proteomics to the problem, which he continued as an Assistant Professor in the Faculty of Medicine and Dentistry at the University of Alberta until joining the ISB in 2000. Dr. Aitchison also holds affiliate appointments at the University of Washington, University of Alberta, and University of British Columbia and Rockefeller University. He is a member of the Molecular and Cellular Biology and Biomolecular Structural Design Graduate Programs at the University of Washington. Since joining ISB in 2000, his laboratory has been exploiting systems-based assays and analyses to reveal and understand complex biological phenomena. Over the past ten years, his lab has focused on yeast as a model for developing systems biology approaches. At CIDResearch, his lab is focused on enhancing our collective exposure to, and education in research of infectious diseases. With his position and lab at ISB, he will remain at the cutting-edge of systems biology while bringing new developments to infectious disease research at CIDResearch.

https://www.systemsbiology.org/bio/john-aitchison-phd/

ビッグデータ時代の臨床医学研究

Medical Research in the Era of Big Data

永井良三（Ryozo Nagai）

自治医科大学　学長（Jichi Medical University）

ICT の進歩により、基礎生命科学においてはビッグデータ解析が活用されるようになった。臨床医学の分野でも、8K テレビモニターの医療応用、心臓シミュレーター（UT-Heart）による小児先天性心疾患のバーチャル手術や不整脈の解析、医療情報の統合による薬剤副作用情報の早期検出システム、臨床研究用の標準化システムの開発などが始まった。

ビッグデータの利用は少子高齢化が進む我が国の医療政策を考える上でも重要である。30 年後の日本では、一人の現役世代が一人の高齢者を支える時代になる。一方で国内の経済成長は鈍化しているため、有効な医療を効率的に提供するための体制作りが、すでに社会的課題となった。とくに日本の医療提供体制は市場原理でもなく、行政指導だけで改革できるわけでもない。このため、医療のステークホルダーがデータに基づいて協議を重ねる必要がある。

臨床情報にゲノム情報、環境情報などの様々なデータを統合することにより、個別に臨床経過を予測し先手を打つべき医療を推測することができる。これは Precision Medicine あるいは 4P Medicine として世界的に注目されている。しかしながらいかにして標準化したデータを収集して分析するか、また推論の有効性をいかに検証するかなど課題も多い。講演ではこれからの医学と医療において、ICT に期待される役割と留意点について紹介する。

略歴

昭和 49 年 9 月	東京大学医学部医学科卒業
昭和 50 年 1 月–51 年 12 月	東京大学医学部附属病院内科研修医

昭和 52 年 1 月–52 年 7 月	東京女子医大付属心臓血圧研究所研修生
昭和 52 年 8 月–58 年 6 月	東京大学医学部附属病院第三内科医員
昭和 58 年 7 月–62 年 12 月	University of Vermont, Department of Physiology and Biophysics (Professor Norman Alpert), Visiting Assistant Professor
昭和 63 年 7 月–平成 3 年 4 月	東京大学医学部附属病院検査部講師
平成 5 年 3 月–7 年 3 月	東京大学医学部第三内科助教授
平成 7 年 4 月–11 年 10 月	群馬大学医学部第二内科教授
平成 11 年 5 月-24 年 3 月	東京大学大学院医学系研究科内科学専攻 循環器内科教授
平成 13 年 4 月-15 年 3 月	東京大学医学部附属病院副院長
平成 15 年 4 月–19 年 3 月	東京大学医学部附属病院長
平成 21 年 7 月－24 年 3 月	東京大学トランスレーショナルリサーチ機構長
平成 24 年 4 月－現在	自治医科大学学長
平成 24 年 4 月－現在	科学技術振興機構　戦略的創造研究推進事業CREST「生体恒常性維持・変容・破綻機構のネットワーク的理解に基づく最適医療実現のための技術創出」研究総括
平成 26 年 10 月－現在	科学技術振興機構上席フェロー

学会

平成 19 年 9 月–22 年 9 月	日本心臓病学会理事長
平成 19 年 4 月–22 年 4 月	日本内科理事長
平成 23 年 6 月–25 年 6 月	日本循環器学会理事長

受賞

昭和 57 年 3 月	日本心臓財団　佐藤賞
平成 10 年 11 月	ベルツ賞
平成 12 年 10 月	持田記念学術賞
平成 14 年 7 月	日本動脈硬化学会賞
平成 18 年 11 月	日本医師会医学賞
平成 21 年 5 月	紫綬褒章
平成 22 年 3 月	日本心血管内分泌代謝学会　高峰譲吉賞
平成 24 年 8 月	European Society of Cardiology (ESC)　Gold Medal
平成 25 年 10 月	大島国際賞

Systems approaches to PD: translation into clinic as well as industry

Rudi Balling

Professor, Luxembourg Centre for Systems Biomedicine (Luxembourg)

At the Luxembourg Centre for Systems Biomedicine, an interdisciplinary programme has been developed with the main goal to understand the mechanisms of pathogenesis of Parkinson's disease, as well as trying to develop new strategies for early diagnostic and stratification. A longitudinal Parkinson's disease cohort is under development which serves as an anchor point for basic biomedical research questions as well as a validation tool for new prevention and therapeutic strategies. We are trying to develop this cohort and the biomedical eco-system around the LCSB as an attractor for industrial collaborations. Opportunities are seen in the application and further development of smart devices for in-depth patient phenotyping and for the development of Luxembourg as an international data hub for biomedical and clinical data.

Biography

Rudi Balling is Director of the Luxembourg Centre for Systems Biomedicine in Luxembourg (LCSB). He is a developmental biologist and geneticist. He studied nutrition at the Universities of Bonn and Washington State University, USA and received his PhD in Human Nutrition from the University of Aachen, Germany. After completing research posts at the Samuel Lunenfeld Research Institute in Toronto and the Max Planck Institutes in Göttingen and Freiburg, he became director of the Institute of Mammalian Genetics at the GSF in Munich in 1993. From 2001 - 2009 he was scientific director of the Helmholtz Centre of Infection Research in Braunschweig. Rudi Balling coordinated the German Human Genome Project (1996-2000), the European Project EATRIS (European Advanced Translational Medicine Research Infrastructure) (2008-2010) and the

Bill & Melinda Gates Grand Challenges Consortium on the development of Vaccine Animal Models (2005-2009). In 2009, he became founding director of the Luxembourg Centre for Systems Biomedicine, an interdisciplinary Research Centre at the University of Luxembourg. The LCSB is dedicated to the analysis of neurodegenerative diseases through computational and system biology oriented approaches. Rudi Balling is member of several Scientific Advisory Boards, among others the RIKEN Center for Integrative Medical Sciences Advisory Council in Tokyo, the Center for Integrated Oncology in Cologne, the Excellence Cluster at the University of Kiel and the Institute of Molecular Genetics of the Academy of Sciences of the Czech Republic. He is a member of the Berlin-Brandenburg Academy of Sciences.

Implementing personalized medicine in a university hospital

Nisar P. Malek

Hepatology, Gastroenterology, Infektiology, Department Internal Medicine I, University Hospital Tübingen (Germany)

In recent years the concept of personalized medicine has primarily been driven by the enormous advances in high throughput sequencing technology, functional imaging and molecular targeted therapies. However, most patients are still treated in a "non-personalized" way. This is due to several factors: namely, a lack of evidence in most areas of clinical medicine which would support a personalized approach, difficulties in generating, storing, analyzing and interpreting patient derived data and insufficient means to translate it into therapeutic measures. Transforming clinical medicine into personalized medicine is therefore a task which involves a number of changes in the IT structure, biobanking, data analysis and decision making processes of hospitals and their partners. We have started this transformation process and I will present the current status of this endeavour to demonstrate the problems but also opportunities connected to it. Specifically, I will show how this approach has been used to better understand and treat patients with hepato-biliary cancers for whom we are currently conducting a clinical trial which involves all aspects of personalized and systems medicine.

Biography

Prof. Malek studied medicine at Hanover Medical University between 1989 and 1996, completing his doctorate in molecular biology. He is a board certified

Internist with specialisation in gastroenterology and hepatology. From 1998 to 2001 Prof. Malek conducted his postdoctoral research at the Fred Hutchinson Cancer Center in Seattle, USA, where he studied the molecular control of cell division with respect to tumor formation. After returning to Hanover Medical University, he worked as a clinician scientist in internal medicine/gastroenterology and as a group leader at the Institute for Molecular Biology working in basic and translational cancer research. He obtained a professorship in cell division control in 2006 within the framework of the REBIRTH excellence cluster of the DFG. Prof. Malek has been the Medical Director of the Department of Internal Medicine (Gastroenterology, Hepatology and Infectious Diseases) at the Tübingen University Clinical Centre since 2011. His clinical work mainly involves the treatment of malignant diseases of the gastrointestinal tract and liver along with therapy for patients with chronic liver diseases. The focus of his scientific work is decoding cell division mechanisms, with the goal of developing new therapies for patients with gastrointestinal cancers using basic and translational medicine approaches including molecular biology, innovative mouse models, high-throughput drug screening and early clinical trials. With the establishment of the Center for Personalised Medicine Tübingen in 2014, directed by Prof. Malek, he started to implement a precision medicine program within the university hospital and the state of Baden Württemberg.

Precision health: maximization of individual health

Yasuyoshi Watanabe

Director, RIKEN Center for Life Science Technologies (CLST)

An immunogram for the cancer-immunity cycle: towards personalized immunotherapy

Kazuhiro Kakimi

Project Professor, Department of Immunotherapeutics, The University of Tokyo Hospital

Since the anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab were approved for the treatment of NSCLC, robust and durable responses have been observed, but only 20~30% of patients responded to the therapy. Although the expression of PD-L1 or the number of tumor neoantigens was reported to correlate with treatment outcome, better predictive biomarkers for distinguishing between those patients who will respond to therapy and those who should be offered alternative treatments is warranted.

Anti-cancer immunity is a dynamic process described as a Cancer-Immunity Cycle; different steps in the cycle by which tumors escape immunosurveillance are likely to be different patient by patient. Therefore, we propose to construct an immunogram for each patient to better understand the individual patient´s immunological status and to clarify the steps where the anti-cancer response is blocked.

Recently, we defined the “Immunogram for the Cancer-Immunity Cycle” using NGS data and could visualize the status of potential anti-tumor immune responses within the tumor. Three immunogram patterns were observed in lung cancer patients: T-cell-rich, T-cell-poor and intermediate. The T-cell-rich pattern was characterized by gene signatures of abundant T cells, Tregs and MDSCs, checkpoint molecules and immune-inhibitory molecules in the tumor, suggesting the presence of anti-tumor immunity dampened by an immunosuppressive microenvironment. The T-cell-poor phenotype reflected lack of anti-tumor immunity, inadequate DC activation, and insufficient antigen

presentation in the tumor. Immunogram for both the adenocarcinoma patients and the non-adenocarcinoma patients included both T cell-rich and T cell-poor phenotypes, suggesting that histology does not necessarily reflect the cancer-immunity status of the tumor.

Future immunotherapy needs to be personalized in terms of the identification of immunosuppressive mechanisms as well as target antigens and integrated with immune regulatory strategies. The patient-specific landscape of the tumor microenvironment can be appreciated using immunogram as integrated biomarkers, which may thus become a valuable resource for optimal personalized immunotherapy.

Towards understanding underlying mechanisms of inflammatory diseases in human: Modeling skin homeostasis

Haruhiko Koseki

Group Director, RIKEN MIH, Group Director, Laboratory for Developmental Genetics, RIKEN Center for Integrative Medical Sciences

Skin is a complex and highly dynamic organ where there are continuous processes of proliferation, differentiation, migration, and death of cells, in addition to a constantly surveying immune system. Various physiological factors such as pH, external stimuli, moisture, and temperature etc., also play a crucial role in proper skin functioning. A delicate balance between these components maintains homeostasis, and disruption of some of these key phenomena can cause diseases such as Atopic Dermatitis (AD). Several studies have been conducted investigating the different genetic, physiological, microbial and immune-related factors that coordinate in complex yet coherent ways to the progression of AD. However, the exact mechanism and the key components involved in the development of AD are poorly understood. This is mainly due to the extensive complexity of the etiology and pathogenetic process underlying AD. To tackle such complexity, we have launched a center-wide project (hereafter termed the AD project) in which multiple research groups work interactively and synergistically to understand, predict, and cure AD,. This project requires highly integrative efforts from basic research to clinical applications and also needs thoroughly considered project planning with specific milestones. Our primary goal in the AD project, and hence the initial milestone, is to investigate the molecular interaction network leading to the onset of AD, its underlying dynamics and how they play a role in the progression of skin dysfunction in AD by using a combined computational and experimental approaches. The second milestone is to identify important biomarkers, potential drug targets, and to understand key disease mechanisms in AD. The third milestone will be to develop a systems oriented drug design pipeline for effective treatment of AD.

This report summarizes our strategy to reach the first milestone. Briefly, firstly we will perform a time-course study of animal models that mimic human AD. This will be done at molecular, cellular and tissue levels and the information obtained will be used to generate an integrated model describing the progressive transition of these interactions from normal homeostasis to pathogenesis. The second phase of the study will be designed to “humanize” this model. To replace molecular, cellular and tissue interactions in mice with those in human, we need to clarify similarities and differences between mouse and human by combining experimental and computational approaches.

Discovery of combinatorial biomarkers for personalized medicine based on machine learning

Eiryo Kawakami

Senior Research Scientist, RIKEN MIH

Computational functional association mining of dysbiotic microbial community

Shinji Nakaoka

JST PRESTO (Precursory Research for Embryonic Science and Technology), Project Research Associate, Laboratories for Mathematics, Lifesciences, and Informatics, Institute of Industrial Science, The University of Tokyo

Reduced species diversity of microbiota, referred to as dysbiosis, has been reported during the progression of several inflammatory diseases. For instance, association between reduced species diversity of skin microbiota and progression of atopic dermatitis is reported. Enrichment of some particular type of bacterial species such as enterobacteria as a result of dysbiosis has been implicated in inflammatory bowel disease, breast cancer, and HIV infection. This implies that enrichment of a particular species can be a useful indicator of pathogenesis for some disease progression. On the other hand, high degree of heterogeneity in species composition of microbiota exists among individuals. Hence it is hard to characterize the onset of disease by microbial species composition sorely.

Functional redundancy rather than species redundancy can be a feasible alternative indicator of dysbiosis. In some ecological community, functional redundancy is implicated as a better indicator of community stability. Use of functional redundancy as an indicator of dysbiosis instead of species richness will be therefore useful to characterize the onset and progression of several diseases. However, functional interrelationships among species are generically context-dependent and dynamics as exemplified by the process of biofilm formation during which the order of settlement can crucially determine successful organization. Moreover, functional diversity is not directly measured by conventional sequencing analysis. Hence computational challenge needs to be developed to infer functional association.

In this talk, I would like to introduce my current ongoing research on computational functional association mining for microbial ecological communities. Mining of functional association requires preparation of large datasets including microbiome and metabolome data. Several association rule mining methods are applied to infer functional association in a microbial community. Based on functional association rule mining, we discuss role of core functional modules during dysbiotic change.

Towards advanced quantitative science using image processing Techniques

Hideo Yokota

Team Leader, Image Processing Research Team, RIKEN Center for Advanced Photonics

High sensitive compact device for contributing to diagnostic data platform

Kazuyoshi Horii, Ph.D.

Research Manager, Technology Development, Sysmex Corporation

With the maturation of society and the progress of IT technology and the spread of mobile devices including wearable device in recent years, people have actively changed into awareness concerning their own health. In addition, from the viewpoint of medical economic rationality, there is a strong demand for community-based health care role for stretching health age, such as care that delays the severity of chronic diseases, pre-disease care that does not fall into disease .

Under such circumstances, introducing high-sensitivity device that can be used in any location satisfies the social demands. Effective utilization of such a high-sensitive devise that has capable of measurement much lower concentration parameters than ever brings advanced care management for chronic patients and pre-disease prevention.

We have been developing large machines for our business but this time we've developed very compact and high sensitivity immunoassay device. Despite still it is under development phase, we can show you its features and performance because we achieved our primary target.

The device has 3 major features, high sensitivity, IT capability and minimizing blood volume required. Especially for achieving high sensitivity, we adopt CLEIA (ChemLuminescence Enzyme ImmunoAssay) method used in our large flagship device, HISCL. The CLEIA brings us very high sensitive immunology testing. However, it requires so complex procedure that becomes difficult to realize in CD-size microfluidic system.

In my presentation, I introduce concrete examples achieved high sensitivity cited evaluation results of prostate cancer and thyroid biomarker.

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