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PATHWAYS PRECISION MEDICINE

THE SECOND P2M ROUEN INTERNATIONAL SYMPOSIUM
ROUEN SCHOOL OF HEALTH SCIENCES
UFR SANTÉ ROUEN

MARCH 24 | 25 2022
ROUEN NORMANDIE FRANCE

Pathways *to* PRECISION MEDICINE
FROM RARE TO COMMON DISEASES

Prof. Soumeya BEKRI (President)
Dr. Abdellah TEBANI (Chair)

Precision Healthcare. Beyond Medical Data

Jan Schildmann
Institute for History and Ethics of Medicine, Halle/Saale, GERMANY

Precision Medicine has focused on biological data. However, the current discussion as well as developments in precsision medicine miss an important point. This is to include non-biological data to realize the full potential of precision care.There is abundance evidence for the relevance of behavioural, psychological and social factors for health and healthcare. However, while the benefit of information on behaviours, social and further determinants for tailored health interventions has been taken up by scholars more recently, the debate still remains on a theoretical level. In addition, the methods and methodology of precision medicine have gained little attention outside genetics and biological medicine. To be able to realize the full potential of precision care we need empirical health care research to identify and characterise actionable non-biological determinants. Such basic research needs to be complemented by trials to determine the clinical benefits of tailored interventions. In this respect the lessons to be learnt from the last 20 years of precision medicine can inform health care research and pave the way to precise healthcare.

Ethical Shifts in the Digital Medicine Era

Alessandro Blasimme
Eidgenössische Technische Hochschule (ETH), Zürich, SWITZERLAND

Digital technologies are expected to have a transformative impact on biomedicine spanning biomedical research, clinical practice and public health alike. Ubiquitous digital devices and advances in data analytics fuel progress towards the coming of age of personalized medicine. A broad array of stakeholders – including patients – is implicated in the digital transformation of medicine. It is thus not surprising that new ethical and societal challenges accompany the growth of digital health.

In this talk, I will first provide a definition of digital health and illustrate some notable examples of its rapidly expanding scope. Then, I will discuss pressing ethical and governance issues in this field.

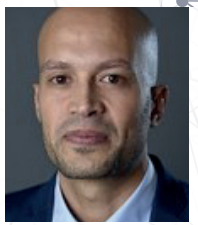
In the second part of the talk, I will focus on a specific domain of digital health, namely the use of artificial intelligence (AI) in medicine. I will illustrate specific ethics challenges linked to biases in existing datasets and challenges in the clinical interpretation of algorithmic outputs.

Awareness regarding ethical and regulatory bottlenecks in digital health and medical AI is key to advance those fields for the benefit of patients.

The End of Medicine as we Know it

Harald Schmidt
Maastricht University, Masstricht, NETHERLANDS

Existing drugs often fail to provide relevant benefit for most patients. The efficacy of the discovery of new drugs is low and in a constant decline predicting that pharma's current approach may by the end of the 20's no longer be financially sustainable. Also, why should we eternally need to discover new drugs. This poor translational success rate of biomedical research is due to lack of study quality and reproducibility and publication focus and bias. The most important reason, however, is our current concept of disease, i.e. mostly by organ or symptom, not by mechanism. Network Medicine will lead to a mechanism-based redefinition of disease, thereby enabling precision diagnosis and therapy. Due to drug repurposing this may eventually eliminate in many cases the need for drug discovery. Successful clinical drug repurposing will in turn also provide the necessary proof-of-concept for network medicine in general. If successful, we will need to reorganization of how we teach, train and practice medicine, moving from current organ-based disciplines, specializations and clinics and moving towards interdisciplinary board like structures. Examples of this new approach to disease include the redefinition of several cancers, immune diseases and a cluster of cerebro-cardio-metabolic phenotypes according their underlying molecular mechanism, including examples for drug repurposing and mechanism-based diagnostics. Importantly, a molecular disease mechanism is not a single protein, as currently often linked to common disease therapeutics, but always a signaling network. We observe however, that these networks in many cases differ from current signaling networks, which are rather mind maps of proteins assumed to function in a similar manner or use similar messengers. With respect to disease modules these networks are often smaller, overlap and thus lead to different drug repurposing decisions. Finally, since these mechanisms are networks, optimal therapy is a combination of drugs targeting several molecules within the same module in a synergistic manner. This allows low dosing and reduce the risk of any potential side effects. Finally, diagnostics are essential, in order to match patients that present both the phenotype and mechanotype and thus make therapies reach numbers needed to treat close to 1, i.e. that work in every patient. Since 80% of all proteins are present in all cells, the likelihood that a necessary pathway can be detected in (rare) circulating blood cells is proving a readily accessible platform to test module dysfunction, which we term the stimulome assay and which can also be considered an ex vivo efficacy test for the drugs to be clinically repurposed.



Advances Towards Precision Psychatry

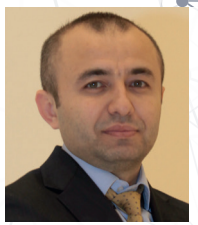
Michael Eriksen Benros
Copenhagen University Hospital, Copenhagen, DENMARK

Currently, choice of treatment for mental disorders is determined by trial and error using a "one-size-fits-all" approach resulting in an unacceptably large proportion of non-responding patients. Previous research has been hampered by a focus on single exposures and single outcomes, not accounting for the complexity of mental disorders, hence not leveraging the wealth of data and novel data analytical approaches now available (computer-intensive methods accounting for non-linear relationships and patterns between risk factors and outcomes). Prof. Benros will, during this talk, discuss how Precision Psychiatry can increase the understanding of biological and behavioral mechanisms of mental disorders, and pave the way for more precise diagnostics, prevention, and new treatment strategies.

Risk Prediction in Alzheimer Disease

Gaël Nicolas
Rouen University Hospital, Rouen, FRANCE

Alzheimer disease (AD) is the leading cause of dementia with no clinically relevant disease-modifying cure. Biomarker, imaging, and neuropsychological data obtained from presymptomatic carriers of rare mutations in exceptional autosomal dominant families suggest that the pathophysiological mechanisms of AD start years, if not decades, before the first symptoms. Accordingly, recent results of clinical trials suggest that AD prevention using antibodies targeting the main triggering factor of AD, i.e. A peptide aggregation, might be efficient if delivered years after the first symptoms. Thus, predicting AD appears necessary to enable personalized AD prevention. Beyond rare autosomal dominant forms, AD is a complex disorder with a high genetic component. Deciphering the genetic determinants of AD etiology is hence necessary to detect individuals with a high risk. Large-scale case-control genetic studies recently identified a number of genes modulating AD risk. Among them, results from so-called rare variants identified in exome and genome sequencing data are associated with the highest levels of risk. I will present the genetic landscape of AD, from common variants to rare variants, and discuss on how we can build novel strategies to gather such heterogeneous information at the individual level, to make AD personalized prevention a reality in the future.



The Role of Systems Biology in the Treatment of Liver Diseases

Adil Mardinoglu
King's College, London, UK and Royal Institute of Technology, Stockholm, SWEDEN

To develop novel strategies for prevention and treatment as well as to gain detailed insights about the underlying molecular mechanisms of liver diseases, it is vital to study the biological functions of liver and its interactions with other tissues and gut microbiota. Biological networks can provide a scaffold for studying biological pathways operating in the liver in connection with disease development in a systematic manner. In my presentation, I will present our recent work where biological networks have been employed to identify the reprogramming in liver physiology in response to NASH/NAFLD. I will further discuss how this mechanistic modelling approach can contribute to the discovery of biomarkers and identification of drug targets which may lead to design of targeted and effective personalized medicine.

Key points of my presentation

– Omics technologies are used in detailed characterization of human liver tissue in health and disease states.

– Biological network models are functional tools for exploring and integration of multiomics data.

– Systems biology uses a holistic and integrative approach for comprehensive analysis of the biological functions in healthy and diseased states

– Systems Biology approaches have been successfully employed in hepatology to identify biomarkers and drug targets.

– These integrative tools can be used for simulation of liver tissue functions and its crosstalk with other tissues for prediction of therapeutic and side effects.

Population Variation of Microbiota

Nele Brusselaers
Universiteit Antwerpen, Antwerpen, BELGIUM
and Karolinska Institutet, Stockholm, SWEDEN

Technical advancements have accelerated microbiome research making it more affordable and feasible to perform large scale studies with thousands, or even hundreds of thousands of samples. Although size matters, proper study design remains crucial since humans and especially their microbiota are more diverse than a litter of new-born rodents or a series of patients. Where do we recruit our study participants? Who are they and how healthy are they? What do they eat, and which medications do they use? Which factors are affecting our microbiome compositions at different anatomical niches including our gastro-intestinal and reproductive tracts?

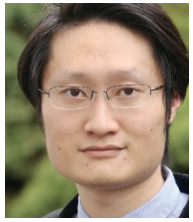
During this talk I will discuss what we already know about our microbiome during the different phases of life, in sickness and in health, and which scientific challenges still lie ahead. As an MD and clinical epidemiologist, I approach the microbiome field from a clinical and public health perspective – and how the microbiome can become useful as a tool in precision medicine, from prevention to diagnosis and treatment.

Genome-scale Metabolic Modeling of the Human Microbiome in the Era of Personalized Medecine

Almut-Katrin Heinken
University of Lorraine, Nancy, FRANCE

The human microbiome plays an important role in human health and disease. Meta-omics methods such as metagenomics, metatranscriptomics, and metabolomics have generated a wealth of publicly available data, yet their interpretation is lagging. Here, I propose genome-scale metabolic modeling as a mechanistic approach to integrate meta-omics data, resulting in testable hypotheses. I will introduce a resource of over 7,000 curated, genome-scale models of human microbes, AGORA2, and its application to interrogating drug-microbiome interactions. I will discuss how, through integration of metagenomic sequencing data, genome-scale models of human microbes can give rise to personalized models that can provide novel insight into metabolic changes in the microbiome in disease states. I will present recent applications of such personalized modeling of the microbiome approaches to multifactorial diseases such as inflammatory bowel disease, Parkinson's Disease, and colorectal cancer. I will also introduce a whole-body model of human metabolism that can be personalized with physiological parameters, dietary information, and metagenomic sequencing data.

Finally, I will outline a workflow for how metabolic modeling could be used to contextualize data and findings from clinical trials. Personalized computational models could be built for each participant and subsequently interrogated through simulations. Simulation results could then be stratified through machine learning methods and correlated with clinical parameters through multivariate statistics. Ultimately, such a modeling framework could propose testable hypotheses that could be validated in prospective trials.



Tissue Engineering and 3D Printing for Regenerative Therapy

Shrike Zhang
Harvard Medical School, Cambridge, USA

Over the last decades, the fabrication of three-dimensional (3D) tissues has become commonplace. However, conventional 3D fabrication techniques are limited in their capacity to produce complex tissue constructs with the required precision and controllability that is needed to replicate biologically relevant tissues. To this end, 3D bioprinting offers great versatility in the fabrication of biomimetic volumetric tissues that are structurally and functionally relevant. It enables precise control of the composition, spatial distribution, and architecture of bioprinted constructs facilitating the recapitulation of the delicate shapes and structures of targeted organs and tissues. This talk will discuss our recent efforts in developing a series of advanced 3D bioprinting strategies along with various cytocompatible bioink formulations. These platform technologies are likely to provide new opportunities in constructing functional tissues to facilitate regeneration and microtissue models for promoting personalized medicine.

Precision Surgery Coming of Age

Ronan Cahill
Mater Misericordiae University Hospital, Dublin, IRELAND

Personalised medicine indicates doing "the right thing in the right place at the right time" for the individual person receiving care. In surgery, such precision most relates to the emerging field of Digital Surgery which is the combination of real-time analytics with technology and the operator own expertise during the act of surgery and so the time-frame for such decision-support needs to be within moments. While of course there is considerable ongoing application of patient triage and categorization methodology around surgery (including preoperative selection and optimization as well as postoperative risk prediction and realization), the key driver of surgical outcomes at this phase of the 21st century will be better surgery through intraoperative analytics. Although image-guidance is widespread now in orthopaedics, neurosurgery and opthalmology, general surgery has lagged behind due to issues with dynamic registration, complexity of decision-tree cascades encounter commonly in major visceral resections and the necessity to embrace video rather static imagery. While robotic systems may represent applicable platforms for such data synthesis and display, currently available robotic system do not provide such capability partly explaining why generally clinical outcomes haven't augmented significantly outside of pelvic urology despite increasingly widespread adoption. Cognitive technologies such as fluorescence-guidance in contrast have the capability to shift curves to the right generally and can be applied, potentially through software, globally everywhere laparoscopic surgeries are performed. Alongside capable existing technologies, large scale randomized controlled trials are nearing completion despite the pressures of the pandemic heralding a near-term step change in intestinal surgery. Further, and perhaps helped by the pandemic, visual support systems have enabled remote proctorship and consensus decision-support during critical intervention. These steps along with the emerging capability to harness the power of operative video at scale indicate how Precision Surgery can soon come of age in parallel with allied medical specialties.

Population Health and the Precision Medicine Ecosystem

Kenneth Mandl
Harvard Medical School, Boston, USA

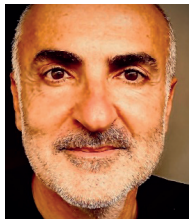
Precision care for the individual requires multilevel insight into the biology, health, outcomes, and trajectories of populations. However, researchers and care delivery systems have faced nearly insurmountable barriers to permissioning and combining data from the care delivery system and research measurements. Mandl will discuss key underpinnings of an interoperable precision health ecosystem, affording access to broad population data. Important features will be parsimonious standards, targeted governmental regulation, and federated models for sharing and collaboration.

SATELLITE EVENT I PERKINELMER

A two-tier approach to the neonatal screening of Lysosomal Storage Disorders (LSD)

Enzo Ranieri
Women's and Children's Hospital, Adelaide, AUSTRALIA

Enzo Ranieri is the Head of Biochemical Genetics within the Directorate of Genetics & Molecular Pathology, SAPathology at the Women's & Children's Hospital in Adelaide, South Australia. He holds an associate academic position at the University of Adelaide within the Faculty of Health & Medical Sciences. He obtained postgraduate higher degrees from Flinders University in the School of Medicine, Department of Neurophysiology and from the Faculty of Health and Medical Sciences at the University of Adelaide.
He has acquired over 25 years experience in Newborn Screening in biochemical genetics with certification in Biochemical Genetics as a Fellow of the Human Genetics Society of Australasia (FHGSA) and was appointed as a Fellow of the Faculty of Science of the Royal College of Pathologists of Australasia (FFScRCPA). He was appointed to the Board of the International Society of Newborn Screening in 2016 and serves on the committee responsible for Asia-Pacific region.
He is a member of the Human Genetics Society of Australasia (HGSA) and Australasian Society of Inborn Errors of Metabolism (ASIEM) and has served as a member on numerous committees and subcommittees for both the HGSA & ASIEM including the American Clinical and Laboratory Standards Institute (CLSI). He has served as a national committee member of the Australasian Newborn Screening and Metabolic Diseases and is currently a member of the standing scientific committee on quality assurance of the International Society of Newborn Screening (ISNS).
He has published numerous articles in leading scientific journals, books and reviews and has been an invited speaker at numerous international and national congresses and meetings as a keynote speaker. He has an international expertise in newborn screening for inborn errors of metabolism (IEM) using tandem mass spectrometry (MSMS) and his laboratory is considered a world leader in the field of neonatal screening being one of the first laboratories in Australia to implement MSMS into routine screening. He was one of the first pioneers and instrumental in the developed the two-tier IRT/DNA screening strategy for Cystic Fibrosis in December 1989. He has a strong interest in teaching and training having had numerous international scientific and clinical trainees spend time in the laboratory to undertake specialised training in all aspects of MSMS newborn screening for IEM. He also has a strong research interest in Metabolomics and the department is a leader in this new emerging field, specifically looking at MSMS to screen, characterise and monitor metabolic diseases.



SATELLITE EVENT | TAKEDA

New approaches for diagnosis & therapeutics in lysosomal disorders

Jérôme AUSSEIL
Toulouse Un iversity Hospital, Toulouse, France

Lysosomal storage disorders (LSDs) constitute a group of almost 60 innate metabolic errors. These diseases are caused by mutations in genes encoding for acid hydrolases, integral membrane proteins, activators and transporter proteins, or other proteins involved in lysosomal function. Deficiencies of these molecules result in substrate accumulation in multiple organs or tissues causing a multitude of clinical symptoms characterized by multisystemic and progressive manifestations, of which neuropathology is the most common. In the brain, the progressive accumulation of the metabolite induces a series of pathological complications in particular neurodegeneration, neuroinflammation, and oxidative stress. Till the end of the 1980s, only support therapies were available for LSD patients. During the past two decades, different therapeutic approaches based on the physiologic mechanisms that regulate lysosomal function have been introduced. Among them, intravenous enzyme replacement therapy (ERT), the most common treatment for LSDs, does not address the neurological problems, as these recombinant enzymes are not able to cross the blood-brain barrier (BBB) due to their high molecular weight. To prevent this problem, other therapeutic options are being studied to treat neurological manifestations such as gene therapy, intracerebroventricular or intrathecal delivery of enzymes, substrate reduction therapy, fusion proteins that cross the BBB or pharmacological chaperones that helps in the refolding of misfolded proteins. Whatever the therapeutic option proposed, the lesson from the past years has highlighted the need for early diagnosis for these pathologies so that the benefit of the treatment is optimal.

SATELLITE EVENT | TAKEDA

Launch of LysoDiag platforms in France for the diagnosis of lysosomal diseases

Soumeya BEKRI
Rouen University Hospital / Rouen Medical School, France

Lysosomal diseases are a group of about 70 inherited diseases caused by deficiencies in lysosomal proteins. These impairments result in a progressive accumulation of compounds in the lysosome. Most are inherited in an autosomal recessive mode, although some are X-linked (Hunter, Fabry, Danon). The biological complexity and phenotypic heterogeneity of lysosomal diseases are frequently the cause of delayed diagnosis and dramatic diagnostic wandering. In order to accelerate diagnosis and better cover the French territory, advanced diagnostic platforms called LysoDiag have been set up in France: the LysoDiagRouen platform (Rouen University Hospital) and the LysoDiagLyon platform (Lyon University Hospital). The LysoDiagRouen platform started its activity in March 2022. The objective of the LysoDiag platforms is to provide DBS kits for the biochemical and molecular diagnosis of Fabry disease, Gaucher disease and mucopolysaccharidosis type 2. At the Rouen University Hospital, biochemical analyses are performed using liquid chromatography-mass spectrometry and an NGS-based approach is applied for the molecular analyses. These platforms allow for high throughput analyses and may eventually allow the internalization of assessments sent abroad.

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