BIOMED 21

A Human Pathways-Based Approach to Disease Research

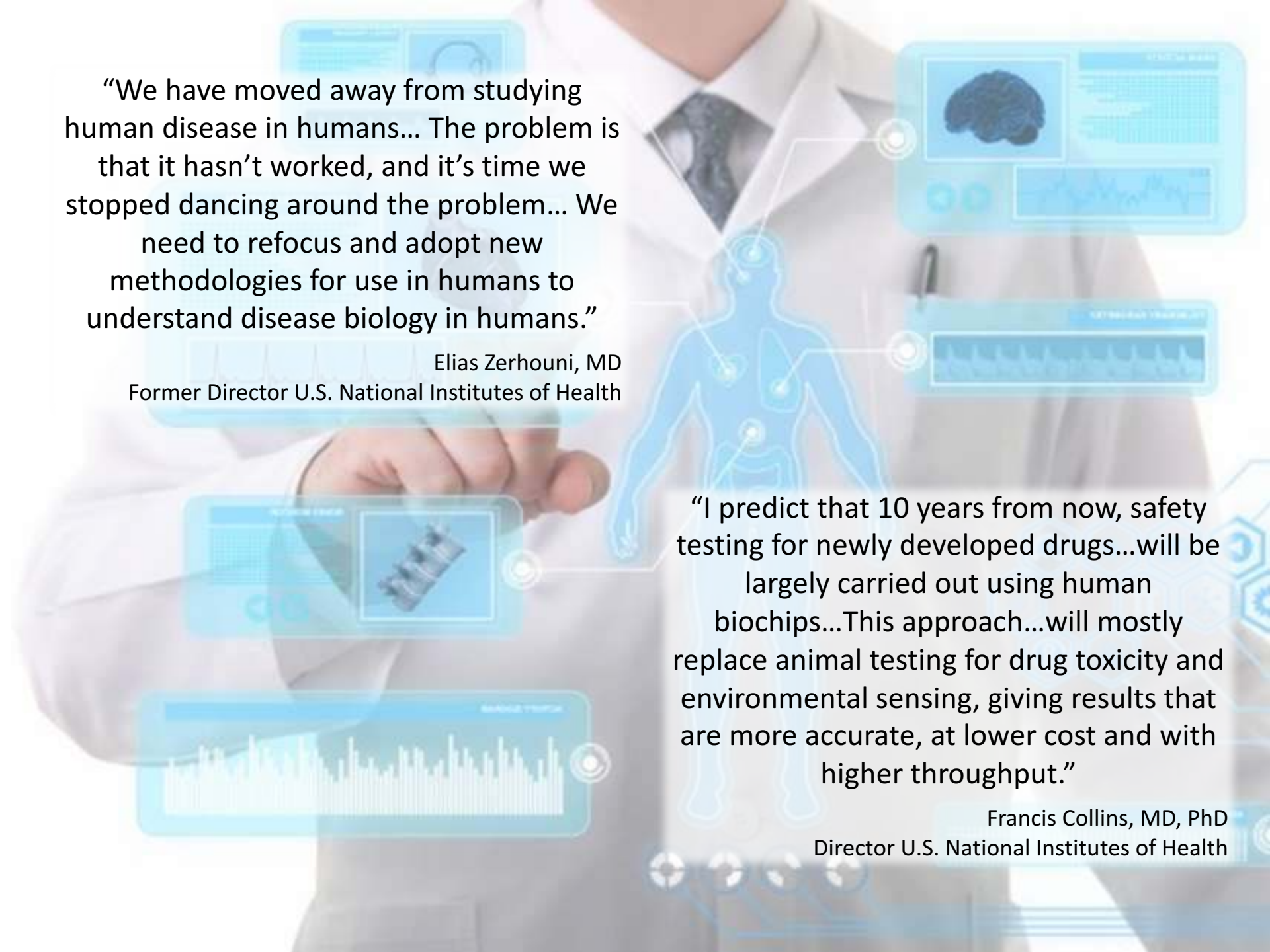
26 – 27 June 2017

NIH Fishers Lane Conference Center

Bethesda, MD

NIH National Institute of Environmental Health Sciences

HUMAN TOXICOLOGY PROJECT CONSORTIUM

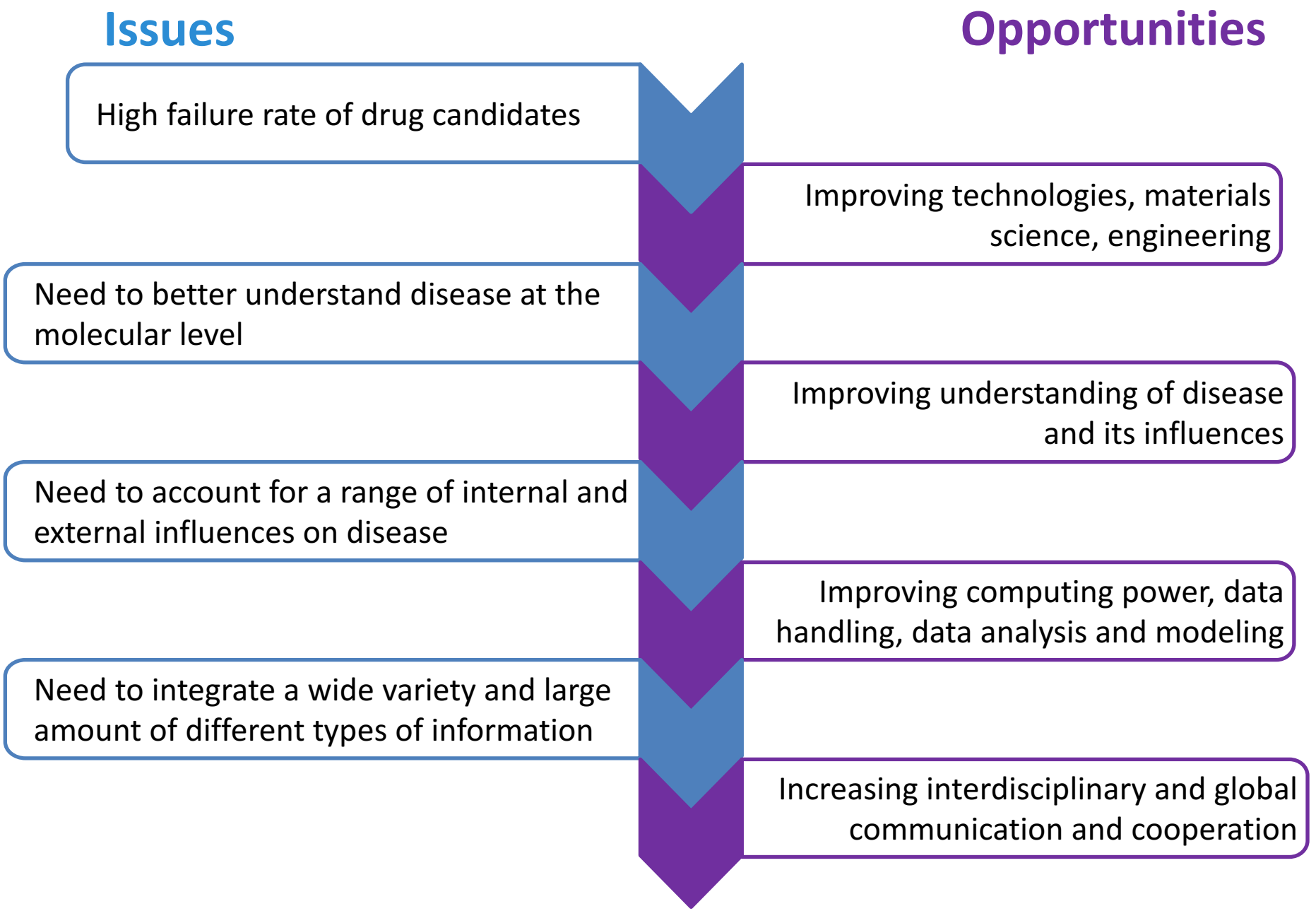


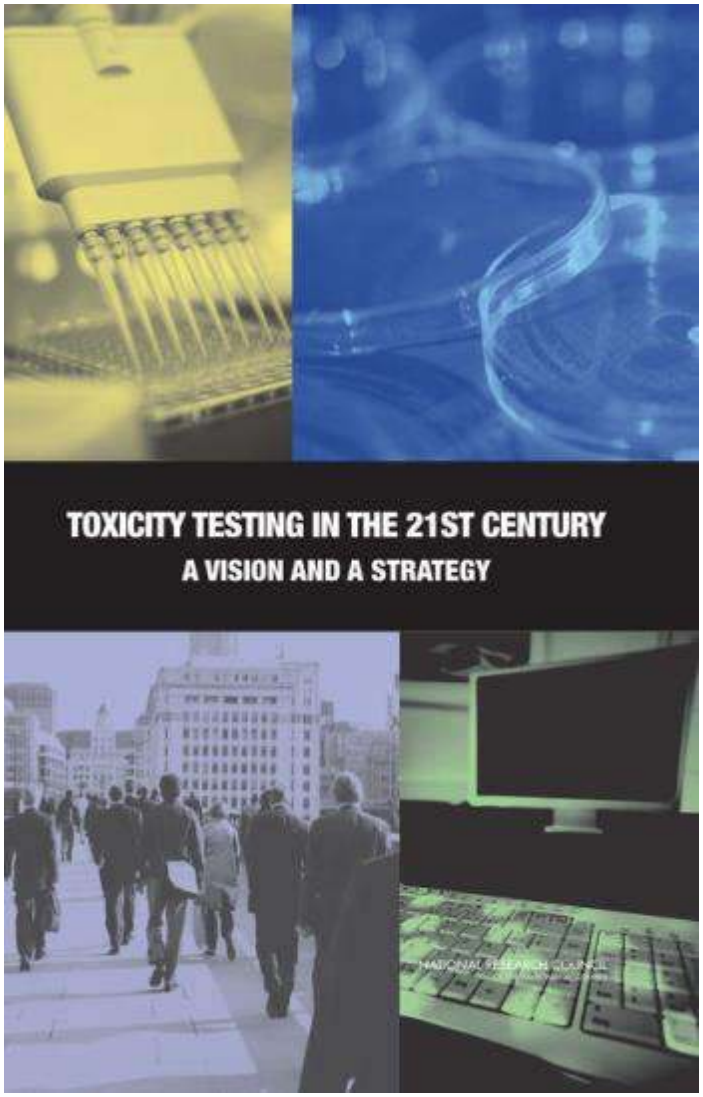
"We have moved away from studying human disease in humans… The problem is that it hasn't worked, and it's time we stopped dancing around the problem… We need to refocus and adopt new methodologies for use in humans to understand disease biology in humans."

Elias Zerhouni, MD
Former Director U.S. National Institutes of Health

"I predict that 10 years from now, safety testing for newly developed drugs…will be largely carried out using human biochips…This approach…will mostly replace animal testing for drug toxicity and environmental sensing, giving results that are more accurate, at lower cost and with higher throughput."

Francis Collins, MD, PhD
Director U.S. National Institutes of Health


Issues
Opportunities
High failure rate of drug candidates
Improving technologies, materials science, engineering
Need to better understand disease at the molecular level
Improving understanding of disease and its influences
Need to account for a range of internal and external influences on disease
Improving computing power, data handling, data analysis and modeling
Need to integrate a wide variety and large amount of different types of information
Increasing interdisciplinary and global communication and cooperation



U.S. National Research Council (2007) "envisions a *new toxicity testing system* that evaluates biologically significant perturbations in key toxicity pathways *using new methods* in computational biology and a comprehensive array of in vitro tests *based on human biology*."

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Lessons from Toxicology: Developing a 21st-Century Paradigm for Medical Research

http://dx.doi.org/10.1289/ehp.1510345

SUMMARY: Biomedical developments in the 21st century provide an unprecedented opportunity to gain a dynamic systems-level and human-specific understanding of the causes and pathophysiologies of disease. This understanding is a vital need, in view of continuing failures in health research, drug discovery, and clinical translation. The full potential of advanced approaches may not be achieved within a 20th-century conceptual framework dominated by animal models. Novel technologies are being integrated into environmental health research and are also applicable to disease research, but these advances need a new medical research and drug discovery paradigm to gain maximal benefits. We suggest a new conceptual framework that repurposes the 21st-century transition underway in toxicology. Human disease should be conceived as resulting from integrated extrinsic and intrinsic causes, with research focused on modern human-specific models to understand disease pathways at multiple biological levels that are analogous to adverse outcome pathways in toxicology. Systems biology tools should be used to integrate and interpret data about disease causation and pathophysiology. Such an approach promises progress in overcoming the current roadblocks to understanding human disease and successful drug discovery and translation. A discourse should begin now to identify and consider the many challenges and questions that need to be solved.

HUMANE SOCIETY INTERNATIONAL

THE HUMANE SOCIETY OF THE UNITED STATES

NIH National Center for Advancing Translational Sciences

FDA

NIEHS National Institute of Environmental Health Sciences

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

European Commission

SBI The Systems Biology Institute

CDRI

Unilever

中国科学院 CHINESE ACADEMY OF SCIENCES

Russian academy of sciences

PHILIPS Philips Innovation Services

UC San Diego

Australian National University

Unifal MG Universidade Federal de Alfenas

* The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of their organizations.

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"We suggest a *new conceptual framework* … with research focused on *human-specific models* to understand disease pathways at multiple biological levels that are *analogous to adverse outcome pathways*."

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1 Humane Society International; 2 National Center for Advancing Translational Sciences, National Institutes of Health (NIH); 3 CSIR–Central Drug Research Institute; 4 National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP), NIH; 5 Division of NTP, NIEHS, NIH; 6 Unilever R&D, Safety and Environmental Assurance Centre (SEAC); 7 Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration; 8 Science to Inform LLC; 9 U.S. Environmental Protection Agency; 10 Systems Biology Institute; 11 Australian National University; 12 University of California, San Diego; 13 Academy of Military Medical Sciences, Beijing, China; 14 Scientific Research Centre Bioclinicum; 15 Humane Society International; 6 Federal University of Alfenas; 17National Center of Medical Radiological Research; 18 Philips Research; 19 Institute for Health and Consumer Protection, European Commission Joint Research Centre; 20 Humane Society of the United States.

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EU Workshop
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ELSEVIER

Teaser To discover and develop new therapies, we need 21st-century roadmaps for biomedical research based on multiscale human disease pathways, and supported by policy and funding strategies that prioritise human relevance.

Towards a 21st-century roadmap for biomedical research and drug discovery: consensus report and recommendations

Gillian R. Langley[1], Ian M. Adcock[2], François Busquet[3], Kevin M. Crofton[4], Elena Csernok[5], Christoph Giese[6], Tuula Heinonen[7], Kathrin Herrmann[8], Martin Hofmann-Apitius[9], Brigitte Landesmann[10], Lindsay J. Marshall[11], Emily McIvor[12], Alysson R. Muotri[13], Fozia Noor[14], Katrin Schutte[15], Troy Seidle[16], Anja van de Stolpe[17], Hilde Van Esch[18], Catherine Willett[19] and Grzegorz Woszczek[20]

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Gillian Langley is currently a scientific consultant to Humane Society International. Her academic career focussed on neurochemistry at Cambridge University, while at Nottingham University, she specialised in studying signalling pathways in human neural cells *in vitro*. Subsequently, she led science programmes at the Dr Hadwen Trust for Humane Research, a medical charity developing human-specific disease models and research techniques. Gill has been a member of the British Government's advisory committee on animal experiments, and was an adviser on non-animal safety tests during the development of the European chemicals legislation (REACH) and a member of European Commission expert subgroups on non-animal testing.

Alysson Muotri is a professor at the University of California San Diego and director of the UCSD Stem Cell Program. His research focuses on human brain development and evolution, and utilises a range of advanced models and molecular tools to study neurological diseases, such as autism spectrum disorders. Using human induced pluripotent stem cells, Alysson's team has developed several techniques to culture human neurons and glia for basic research and drug screening. He is a recipient of numerous awards, including the NIH Director's New Innovator Award.

Martin Hofmann-Apitius is head of Department of Bioinformatics at the Fraunhofer Institute for Algorithms and Scientific Computing, and professor of Applied Life Science Informatics at Bonn–Aachen International Center for Information Technology. Martin's current research focuses on automated methods for extracting relevant information from unstructured information sources, such as journal publications, patents, and web-based sources, as well as knowledge-based, mechanistic modelling of neurodegenerative diseases (including the first comprehensive, computable model of Alzheimer's disease), and mining in real-world data (social networks, patient fora, and electronic patient records). He is the initiator and academic co-ordinator of the Innovative Medicines Initiative project 'AETIONOMY'.

Conclusions, examples:

- Overarching strategic frameworks are essential to guide science policy
- Funding should be focused on acquiring critical human information & developing/ validating human-specific tools
- Enhanced research coordination among key economies, e.g., US Tox21 model or EU joint programming
- Enhanced strategies to collect human biological material & clinical information from large patient cohorts to increase understanding of disease
  & assist validation of new *in vitro/in silico* models (involvement of patient groups)
- Obligatory open-access publication & data sharing for all publicly funded research, e.g., common global knowledgebase (e.g. OECD AOP KB)

South American Workshop
29 – 30 May, 2017
Rio de Janeiro

‘‘EMERGING TOOLS FOR PATHWAY-BASED HUMAN BRAIN RESEARCH”

Venue

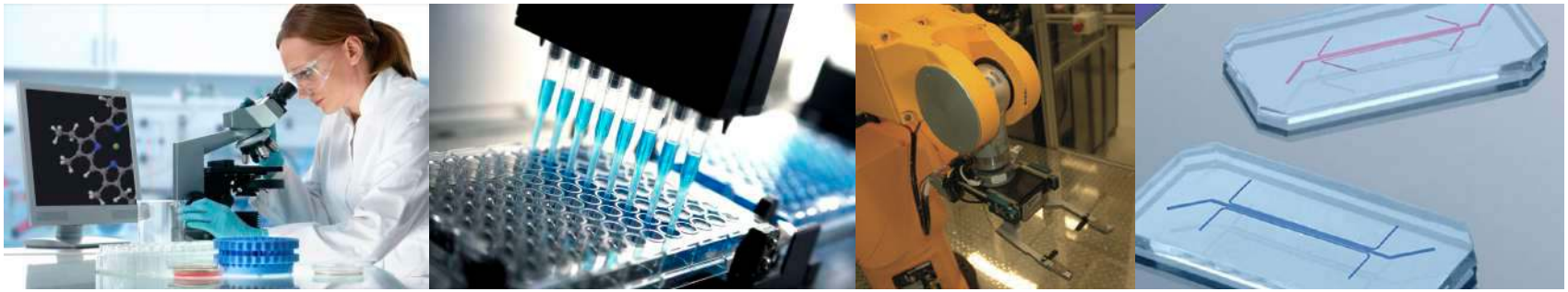
- D’Or Institute for Research and Education

Draft Agenda

- BioMed21 overview
- Organoid/mini-brain models
- Human iPS-derived models
- Microphysiological models
- ‘Omic tools
- Round table discussion: toward a strategic science agenda for human-specific brain research and infrastructures

Objectives of this workshop:

- to explore existing systems biology projects and approaches and how these projects might be better coordinated to optimally improve disease understanding and interventions
- by bringing together experts from several of these projects with stakeholders to identify barriers and opportunities and make recommendations regarding what is needed to achieve the goal of fully implementing a human systems-biology platform for understanding disease and improving interventions.



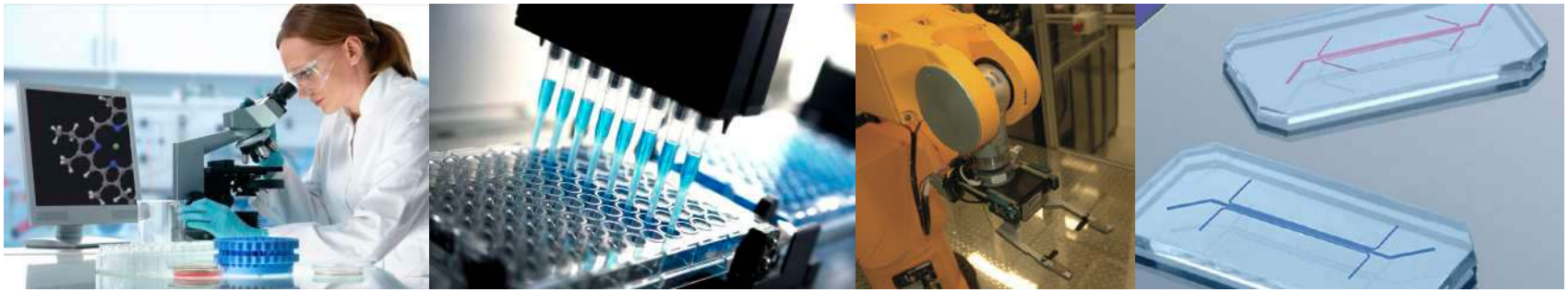
Work products:

General

- ✓ White paper outlining issues and existing related programs/infrastructure
- Workshop report outlining major needs and making recommendations for the way forward

Specific

- Recommendations for primary infrastructure needs
- Recommendations for sustainability



MONDAY JUNE 26

0845 KEYNOTE LECTURE: A CALL TO ACTION Chris Austin, NCATS

0930 SESSION 1 – SETTING THE STAGE: WHAT IS NEEDED AND WHY?

0935 Challenges and needs to use existing data in drug development
François Pognan, Novartis

0955 A strategic roadmap to the implementation of alternatives Warren Casey, NIEHS

1020 Clinical Point of view: current practices, challenges and needs Bruce Cuthbert, NIMH

1100 FDA collaborations for addressing practical applications Suzanne Fitzpatrick, FDA

1120 Case studies in 21st Century disease models

A tiered approach to in vitro-based compound testing Rebecca Clewell, ScitoVation

Using organoids to define key pathways in COPD pathogenesis
Ian Adcock, Imperial College London

Organs-on-Chips: A Platform for Advancing Drug Development and Disease Modeling
Daniel Levner, Emulate, Inc

1345 BREAKOUT GROUP DISCUSSION SESSION 1

The global community has been aware of the shortcomings of current approaches to disease models and drug development for some time, including a lack of understanding of human biology ("normal" and diseased), a heavy reliance on animal studies that modestly translate to human biology, heavy expense and extended timelines. What is needed to solve the problem?

- What data are currently available and who can access these data?
- What is the role and impact of precompetitive data sharing ?
- What additional types of information and processes are needed for acquiring human data in the future?
- What are the major barriers to the pursuit of a human biology-based approach in health research, e.g., funding opportunities, journal or reviewer conservatism/bias, etc.?

MONDAY JUNE 26

1500 SESSION 2: BIG DATA; INFORMATION INTO KNOWLEDGE INTO ACTION

Chair: Ajay Pillai

1510	Overview of NIH Big data projects, LINCS in particular	Ajay Pillai, NIH LINCS
1530	Biomedical Data Translator – What's it going to take?	Christine Colvis, NIH Translator
1550	Translator and Fanconi Anemia	Christopher Chute

1630 BREAKOUT GROUP DISCUSSION SESSION 2

There are several large-scale initiatives underway to mine existing data from the literature, create ontologies for curation and retrieval of this information, and to use this information to improve predictive modeling. At the same time, there is increasing awareness that much of the data is of questionable quality or relevance.

- Is the right information being captured? And how is quality of data captured or assessed?
- How best to link the output from big data projects to human information from large-scale sequencing, 'omics projects and other large data sources?
- How do we integrate new data types, such as single-cell sequencing and/or imaging, with existing data at different scales?
- Who are the users and how can the data be most effectively presented for use?
- What are we missing?

1740 RECAP DAY1

TUESDAY JUNE 27

0830 **SESSION 3: CURRENT TOOLS TO SUPPORT PATHWAY-BASED DECISIONS**
Chair: Suzy Fitzpatrick

0830 Tox21 and beyond for pharma and biomed — Anton Simeonov, NCATS
0850 Organs on a chip: applications for testing and research — Lucie Low, NCATS
0910 Primary Cell-Based Phenotypic Profiling for Building Human Outcome Pathways — Ellen Berg, DiscoveRx Corporation
0930 Systems Biology Approach to Cancer — Shannon Hughes, NCI
1000 How might a "pathway-based" approach help (e.g. AOPs)? — C. Willett, HSUS/HSI
1020 A network based approach to understanding drug toxicity and its application to human liver disease — Jeff Sutherland, Indiana Biosciences Research Institute Consultant
1040 Systems Pharmacology (PredicTox) — Darrell Abernethy, FDA

1115 BREAKOUT GROUP DISCUSSION SESSION 3

How can these advanced technologies be best leveraged to improving human health?

- What is the best method for incorporating human-based 'omics data into a collective knowledge-base for improved understanding of disease and better predictions for drug safety and efficacy?
- What are the pros and cons of combining medical data with the toxicological data in a platform like the OECD AOP Wiki?
- How do you integrate clinical systems biology/disease pathway knowledge into novel predictive modelling platforms?
- How can we broaden stakeholder participation (esp. to basic biological researchers)?
- What are the three main challenges for implementing systems biology understanding as a tool find practical solutions for human disease?

TUESDAY JUNE 27

1445 SESSION 4: COORDINATION AND SUPPORT: HOW TO MAKE IT WORK

Chairs, Troy Seidle

Panel discussion

Role of funding agencies:	Chris Austin, NCATS
Role of pharma	François Pognan, Novartis
Role of academia/SMEs	Daniel Levner, Emulate
Role of regulatory agencies:	Frank Weichold, FDA

1600 GROUP DISCUSSION SESSION 4

Adequate funding and coordination of projects are critical for success of any large-scale endeavor. In this case:

- At what level(s) should this coordination occur? And who should be the "organizing body"?
- What can be done to redirect research efforts toward human biology-based approaches?
- What would incentivize industry to contribute [81] data to populate AOP/pathway knowledge bases, etc.? How do we promote collaboration in the private sector and between the private sector and government?
- In light of emerging technologies and conceptual thinking, should there be an overarching strategic review of health research and funding frameworks and roadmap for incorporating new approaches most effectively?

1650 WRAP-UP: SUMMARY OF DISCUSSION QUESTIONS

Chairs, Kate Willett and Warren Casey

1700 ADJOURN

Breakout Sessions

3 Breakout groups for each session:

#1: room 508 #2 Room 509 #3 Room 510

- Each group will answer the same questions
- Chairs are responsible for keeping on time and addressing all questions
- Rapporteurs will take notes and summarize responses

For people watching the webinar – you will not be able to participate in discussions; however, you may provide input by submitting your answers to the discussion questions by e-mail to:

kwillett@humanesociety.org

After the workshop:

Publication of meeting report and recommendations

Recommendations will be used to feed into:

- The strategic roadmap to implementation of alternatives
- Stakeholder efforts to support programs and infrastructure development based on recommendations

Your participation and ideas are critical

Let’s get going!