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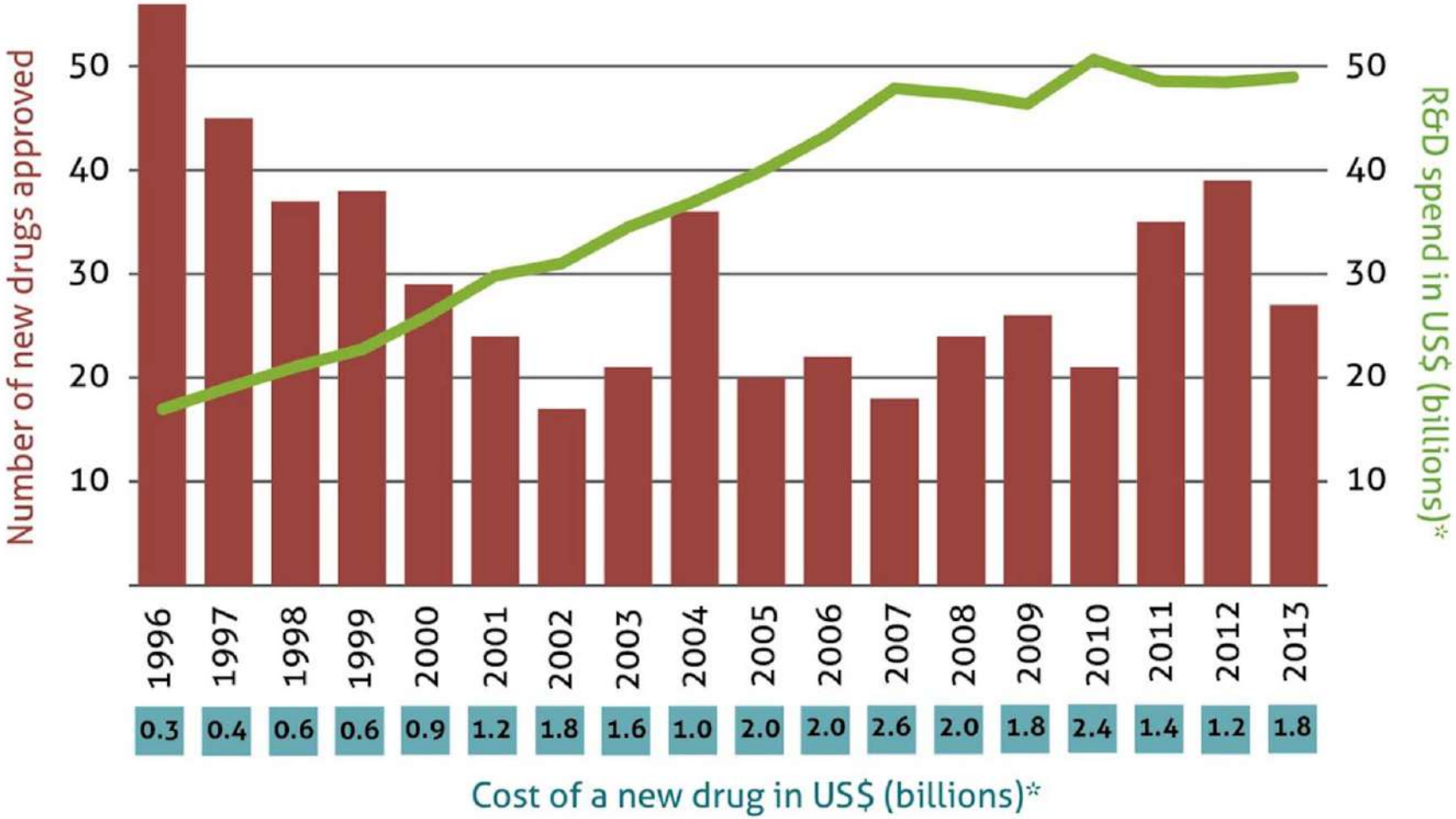
HUMANE SOCIETY INTERNATIONAL

BIOMED 21

Toward a Human-Specific Paradigm for Health Research

95% clinical failure for new drugs that appear safe & effective in animal tests



Data: USFDA, PhRMA

"Most of this failure is due to the ***limited predictive value*** of preclinical models of disease"

(Plenge et al. *Nat Rev Drug Discov.* 2013; **12**: 581-94)

"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***."

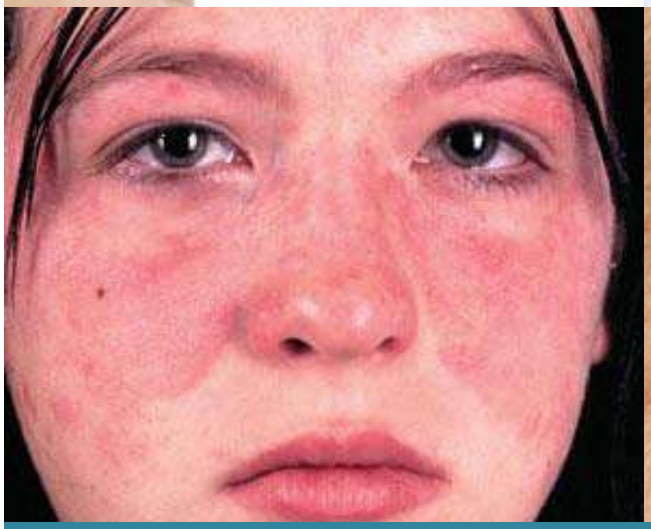
- Elias Zerhouni, MD
Former NIH Director

Reviews of preclinical disease models & roadmaps for human-specific approaches

Asthma (Buckland, 2011)

Alzheimer's Disease (Langley, 2014)

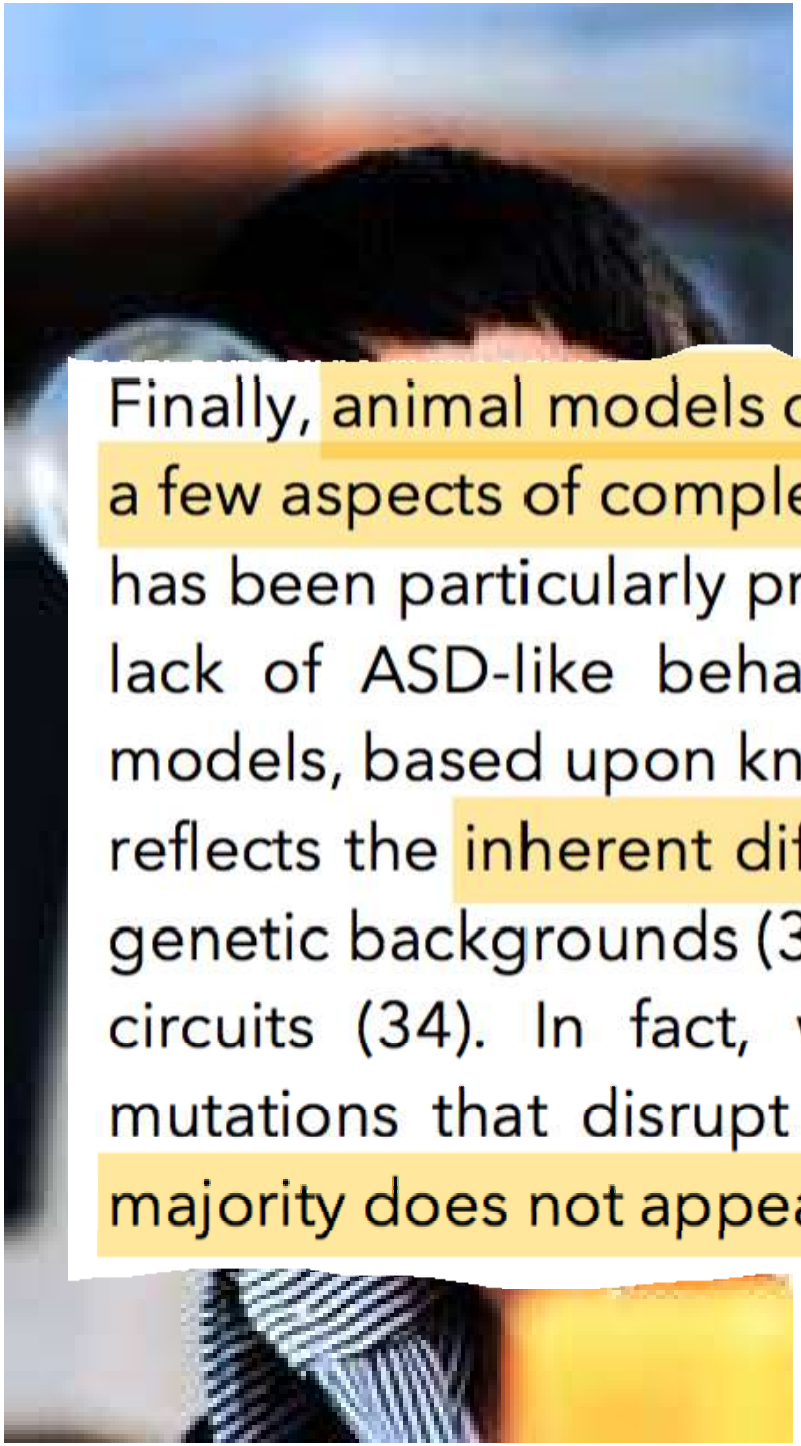
Autism Spectrum Disorders (Muotri, 2015)



Autoimmune Disorders (van de Stolpe & Kauffmann, 2015)

Liver Disease (Noor, 2015)

ALS (Clerc et al, 2016)



Review

Biological Psychiatry

The Human Model: Changing Focus on Autism Research

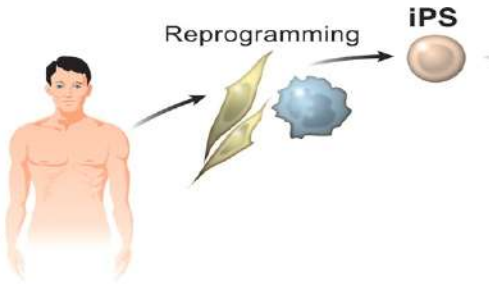
Alysson Renato Muotri

Finally, animal models often do not recapitulate more than a few aspects of complex human diseases, if at all, and this has been particularly problematic in the case of ASDs. The lack of ASD-like behaviors in several knockout mouse models, based upon knowledge of genes related to ASDs, reflects the inherent differences between the two species genetic backgrounds (32), immune system (33) and neural circuits (34). In fact, while there are multiple genetic mutations that disrupt social behavior in mice, the vast majority does not appear to have direct relevance to ASDs.

adhesion pathway in ASD, or the ubiquitin-proteasome system, which regulates synaptic attributes such as neurotransmitter release and synaptic vesicle recycling (9). Other studies have found that genes with rare CNV defects interfere with neurodevelopmental pathways by affecting the maturation and

years. The exact reasons for this increase remain unclear; however, the improvement in and availability of diagnosis and a legitimate increase in the rate of affected newborns may be contributing factors (26,27). According to the Centers for Disease Control and Prevention 2014 Autism and Developmental Disabilities Monitoring Network, approximately 1 in 68

Autism in a dish



Marchetto *et al*, 2010

Drug Discovery Today • Volume 00, Number 00 • July 2011 REVIEWS

The existing framework is overly dependent on often unvalidated animal models, particularly transgenic mice. Translational success remains elusive and costly late-stage drug failure is common. The conventional paradigm tends to overlook species differences and assumes that animal-based findings are generally applicable to humans. Could pathways-based research using advanced human-specific models probed with new tools, including those of systems biology, take centre stage?

Gillian R. Langley

8 Crow Furlong, Hitchin, Hertfordshire, SG5 2HW, UK

Using Alzheimer's disease as a case study, this review argues that it might be time to consider a new paradigm in medical research and drug discovery. The existing framework is overly dependent on often unvalidated animal models, particularly transgenic mice. Translational success remains elusive and costly late-stage drug failure is common. The conventional paradigm tends to overlook species differences and assumes that animal-based findings are generally applicable to humans. Could pathways-based research using advanced human-specific models probed with new tools, including those of systems biology, take centre stage? The current transition in chemical toxicology to a 21st-century paradigm could be a model for health research, with probable medical and economic benefits.

Introduction

Total new drug approvals have continued to fall whereas the costs of producing novel medicines have grown exponentially. Despite increasing investment, 92% of all novel drugs fail in clinical trials, mainly because of unpredicted toxicity or insufficient efficacy in humans [1]. Problems in basic medical research, drug discovery and effective translation from laboratory to clinic are widely recognised. Meanwhile, in chemical toxicology a transformation is already unfolding, following a seminal report from the US National Research Council in 2007 [2]. This recommended a '21st-century paradigm' for safety testing, involving an explicit transition away from a reliance on adverse endpoints in animal tests and towards a novel framework based on understanding toxic perturbations to cellular pathways, mainly using *in silico* tools and human-specific cell and tissue models. The National Research Council's vision is being implemented actively worldwide, including by the US multi-agency Tox21 consortium [3] and the Environmental Protection Agency's multi-million dollar ToxCast programme [4].

A recent refinement in toxicology is the concept of adverse outcome pathways (AOPs), which are intended to provide clear mechanistic representations of critical toxic effects spanning molecular, cellular, organ, individual and population levels. AOPs have a common structure comprising exposure to the first molecular initiating event (*e.g.* a chemical binds to a cell receptor), intermediate steps and key events and an adverse outcome that (in toxicology) could for example be cancer, allergy or liver damage. The first validated AOP (for skin sensitisation) has now been accepted at the Organisation for Economic Cooperation and Development and several further AOPs are in draft form [5].

The transition in toxicology could provide a template for modernising the disease modelling and drug discovery paradigm. Developments in systems biology have enabled studies of human gene pathways and networks linked to disease, and expanding this concept to an AOP approach would have obvious relevance, widening consideration of disease pathways to include environmental factors at the start of the pathway and whole-person or population-level outcomes at the pathway's conclusion. Incorporating advanced scientific tools into a research framework emphasising pathways and networks in human-specific models could offer better progress towards understanding and treating diseases than the current emphasis on animal models.

The animal model paradigm

For many decades, animal models have had key scientific and conceptual roles in health research and drug discovery, because human experimentation was unethical and impractical and *in vitro* models were simplistic and poorly representative of the *in vivo* situation. Within the traditional research paradigm, animal models remain dominant and animal data are used in a 'gate-keeper'

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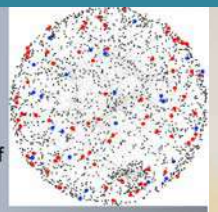
 http://dx.doi.org/10.1016/j.drudis.2014.03.013

Roadmap for 21st century Alzheimer's research

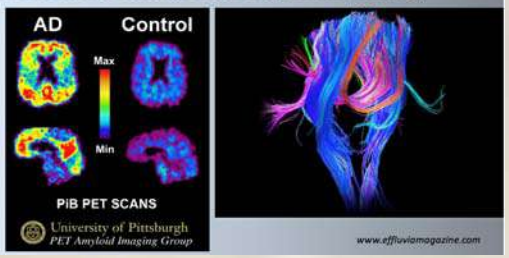
????
Human-specific paradigm

4. Human *ex vivo* tissues



- Next-generation sequencing (all the 'omics, multiplexed fluorescent *in situ* visualisation of DNA, RNA, proteins)
- disease pathways research
- status & dynamics of regulatory gene networks
- drug targets, efficacy & toxicity

5. Advanced clinical studies e.g. neuroimaging

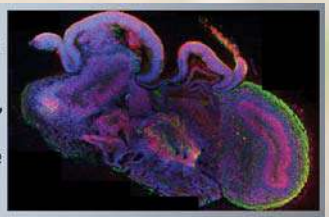


6. Computational modelling & systems biology/systems pharmacology

3. Microfluidics = organs-on-chips:
Rapid, reproducible, sensitive platforms for:

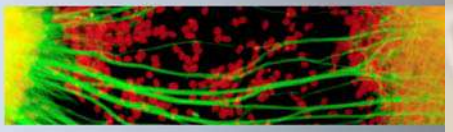
- pathways research
- drug discovery
- testing lead compounds in human 'organs'

2. 3D human cell models:
Robust, controllable, improved viability, retain cellular/tissue properties *in vitro*.



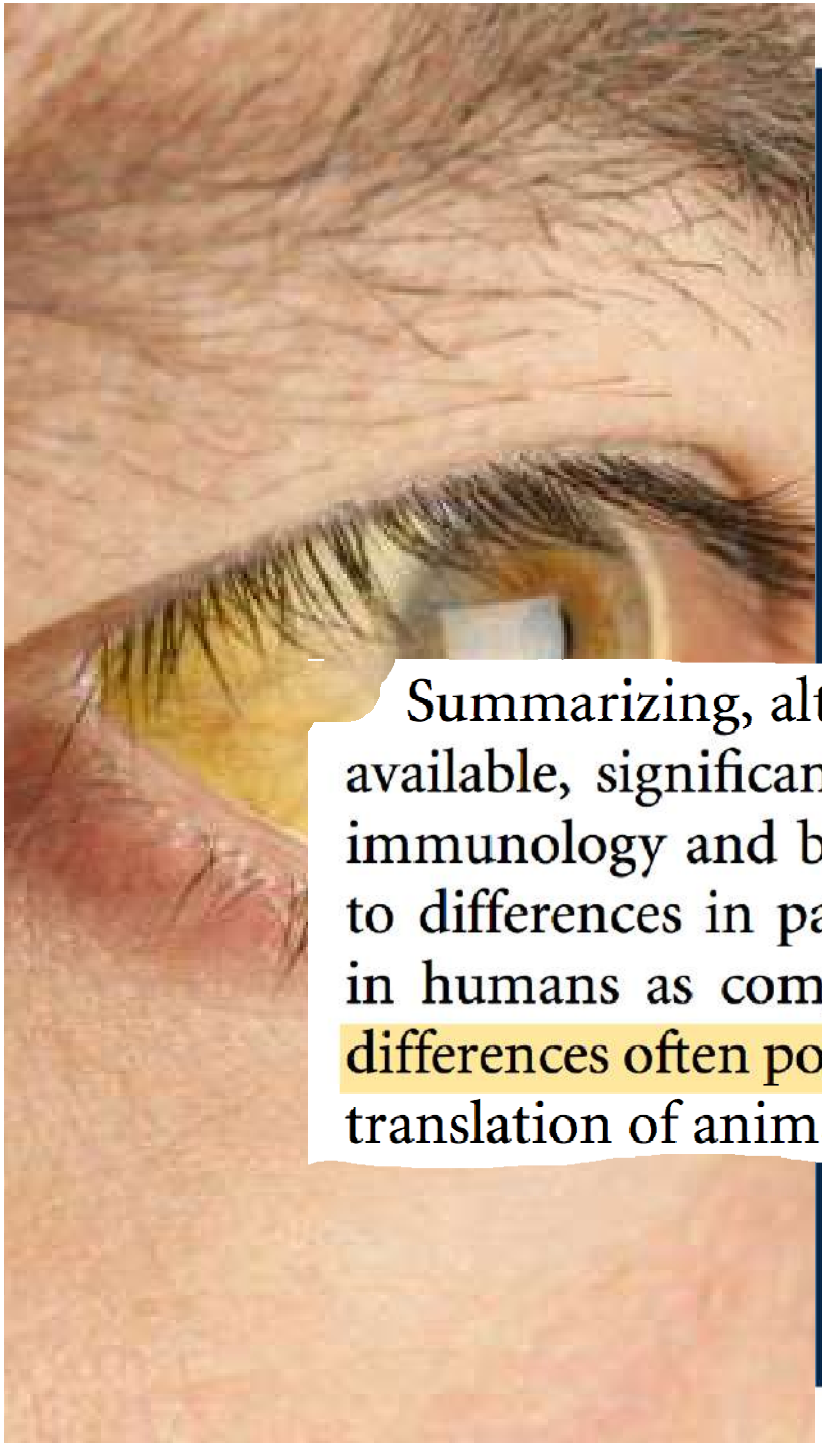
Human pluripotent stem cells developed into cerebral organoids
M.A. Lancaster et al. Nature (2013). doi:10.1038/nature12517

1. Brain cells derived from human induced pluripotent stem cells (normal & patient-specific)



Alysson Muotri, Univ. California, San Diego

2015 Mouse-based paradigm



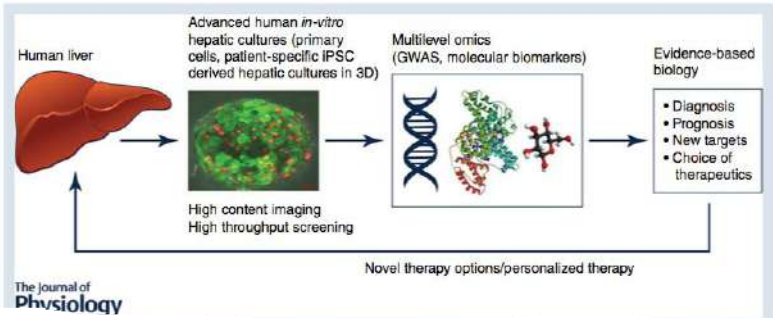
J Physiol 000.00 (2015) pp 1–13

TOPICAL REVIEW

A shift in paradigm towards human biology-based systems for cholestatic-liver diseases

Fozia Noor

Biochemical Engineering Institute, Saarland University, Saarbrücken, Germany

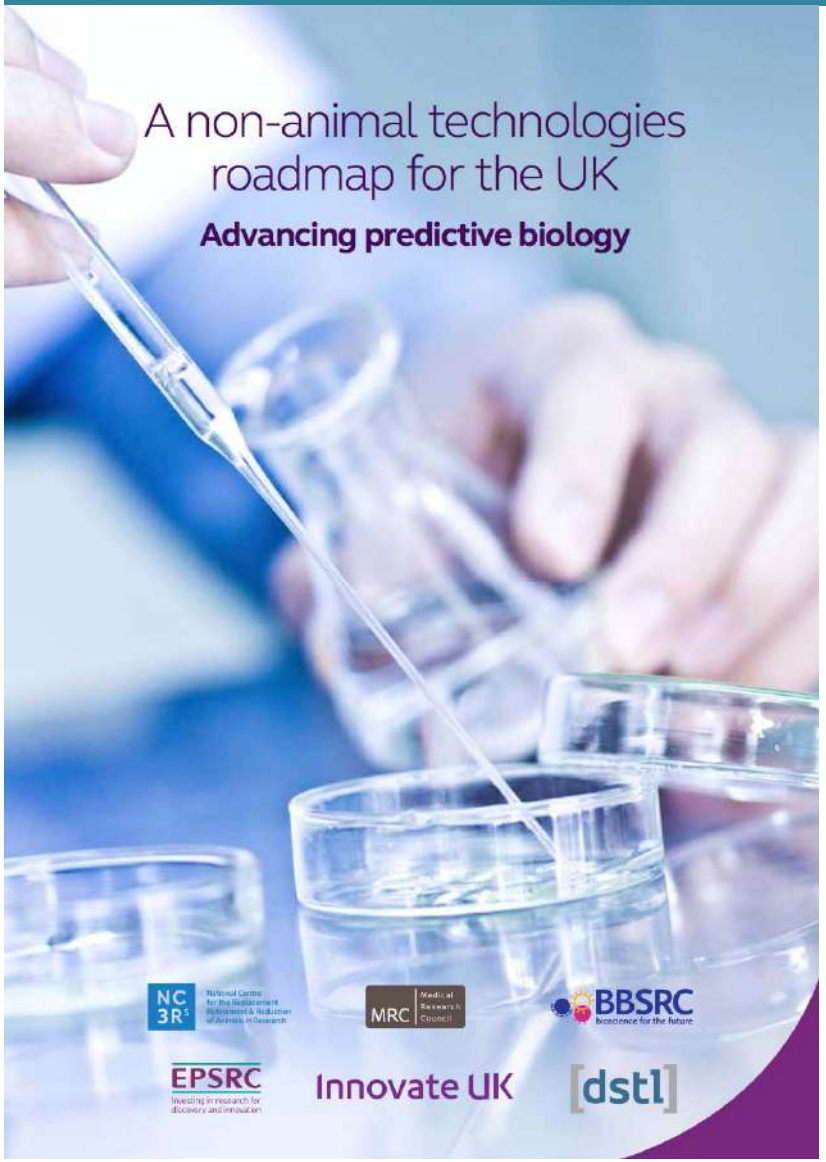


Summarizing, although a variety of animal models are available, significant species–specific differences in liver immunology and biliary physiology exist and these lead to differences in pathogenesis and progression of CLDs in humans as compared with animals. Species–specific differences often pose an insurmountable challenge in the translation of animal results into clinical practice

Fozia Noor graduated *suma cum laude* from Heidelberg University at the Institute of Pharmacy and Molecular Biotechnology obtaining her PhD with Nils Metzler-Nolte. She joined Elmar Heinzle's group at the Biochemical Engineering Institute of Saarland University where she is currently finalizing her Habilitation as a group leader of cell culture and systems toxicology laboratory. Her research focuses on the development and application of *in vitro* methods including 3D cultivation systems of liver and heart for toxicological and mechanistic studies in combination with *in vitro* metabolomics.

DOI: 10.1113/JP271124

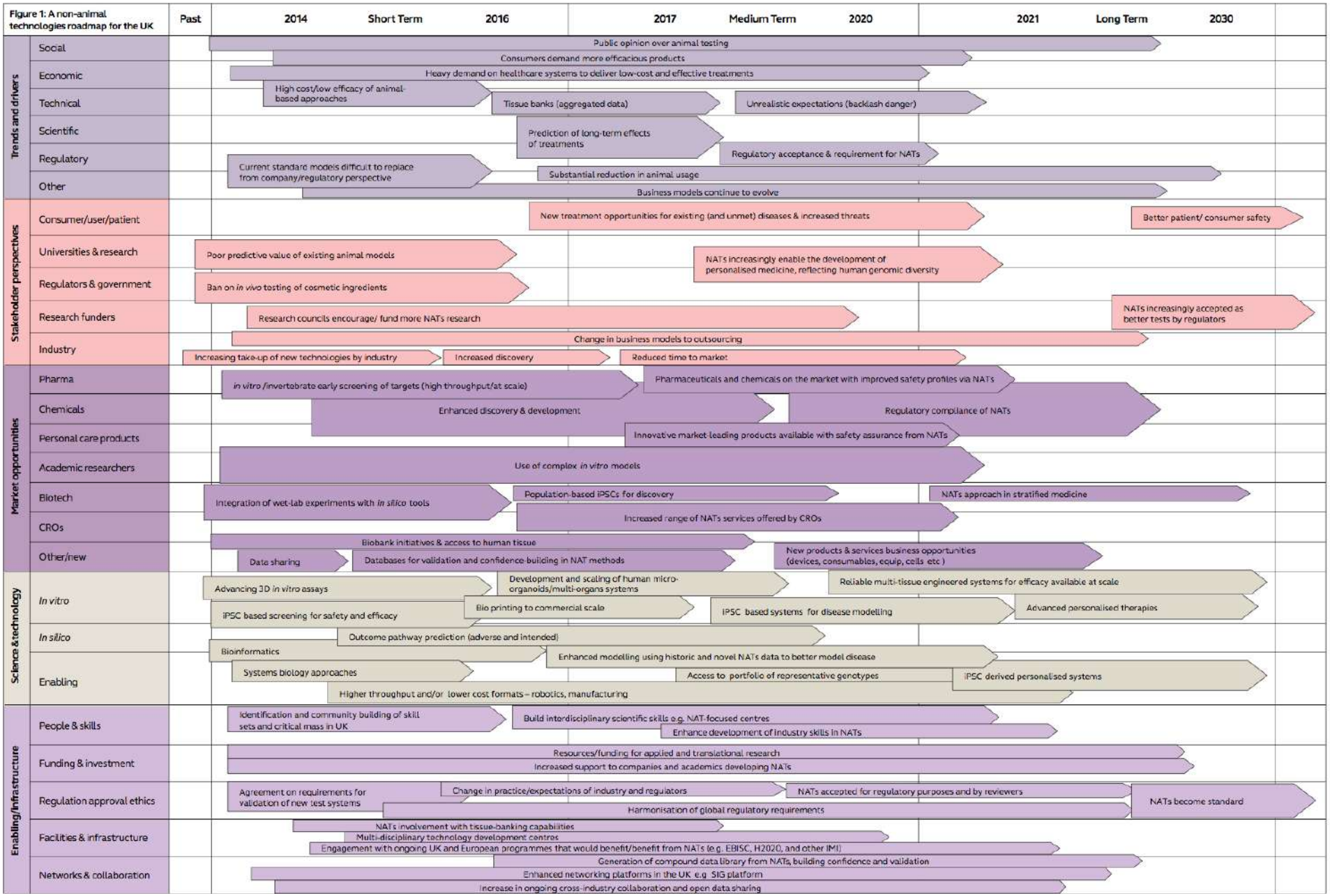
Advances in science are yielding more predictive tools



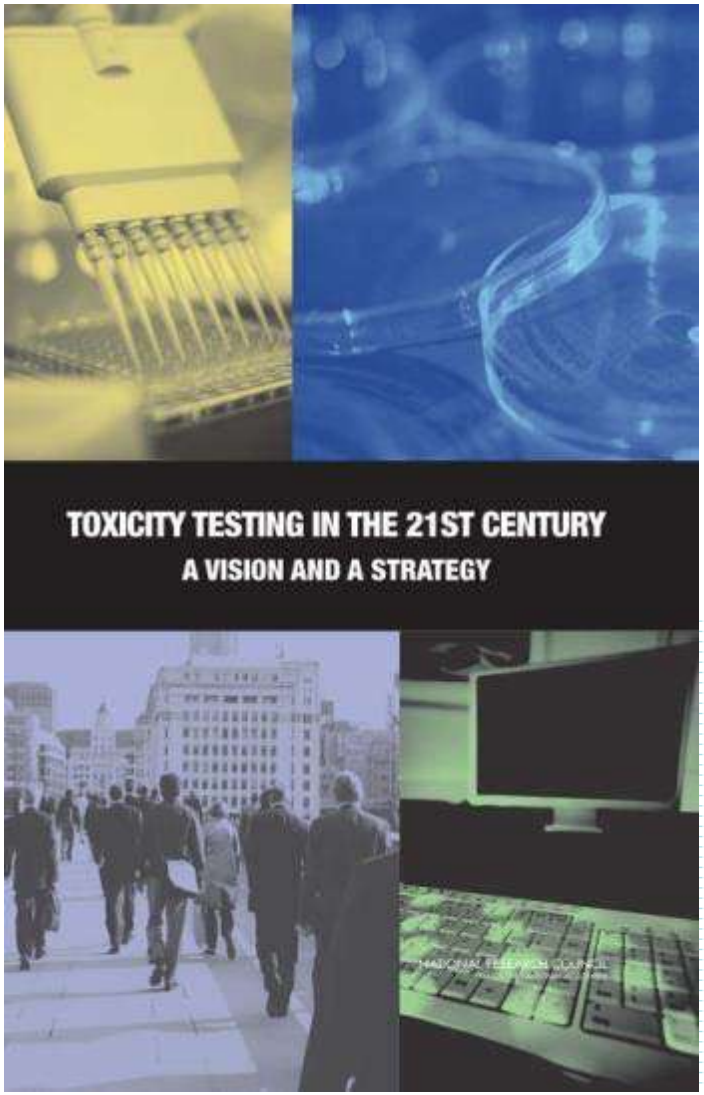
Innovate UK has identified non-animal technologies as one of a series of emerging technologies with the potential to drive future UK economic growth. The UK has world-leading research in this area and companies, large and small, with the ability to take advantage of new commercial opportunities. The market potential is huge. The global market for cell based assays in drug discovery, safety, and toxicology will reach $21.6 billion by 2018. The estimated global market for induced pluripotent stem cells is expected to reach $2.9 billion in 2018, and the 3D cell culture market is expected to grow to about $2.2 billion in 2019.

https://www.gov.uk/government/publications/non-animal-technologies-in-the-uk-a-roadmap-strategy-and-vision

UK ‘non-animal technologies’ roadmap



Advances in science are yielding more predictive tools



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*."

– Francis Collins, MD
Director, NIH

"I predict that 10 years from now, safety testing…will be largely carried out using human biochips that are loaded with cells accurately representing heart, liver, kidney, muscle, brain, and other tissues. This approach…will mostly replace animal testing…giving results that are more accurate, at lower cost and with higher throughput."

Engaging scientists to shape a new 'human-specific' paradigm for medical research

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

European Commission

United States Environmental Protection Agency

SBI The Systems Biology Institute

CDRI

中國科學院 Chinese Academy of Sciences

Russian academy of sciences

Unilever

PHILIPS Philips Innovation Services

UC San Diego

Unifal MG Universidade Federal de Alfenas

Australian National University

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

Engaging scientists to shape a new 'human-specific' paradigm for medical research

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Perspectives | Brief Communication

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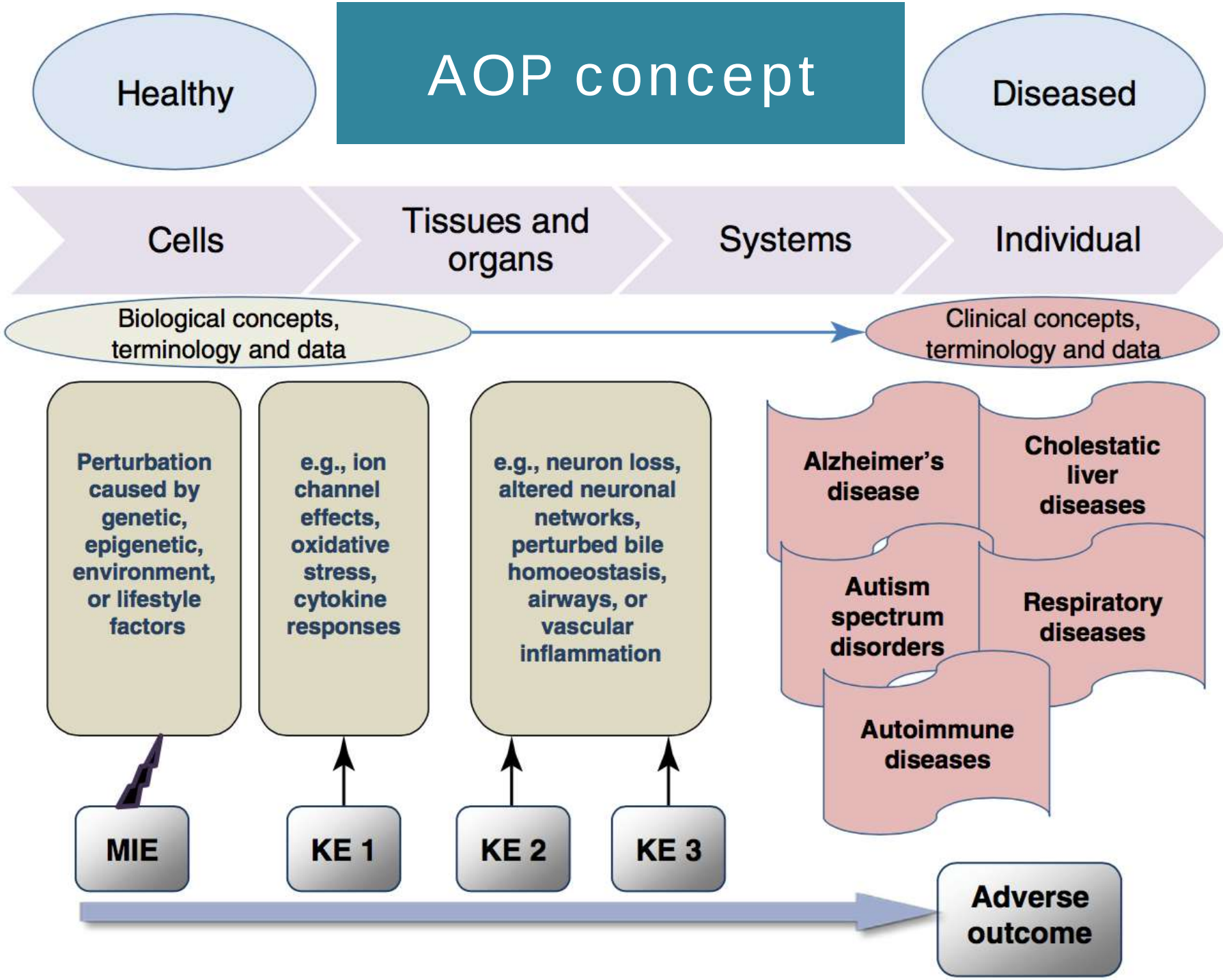
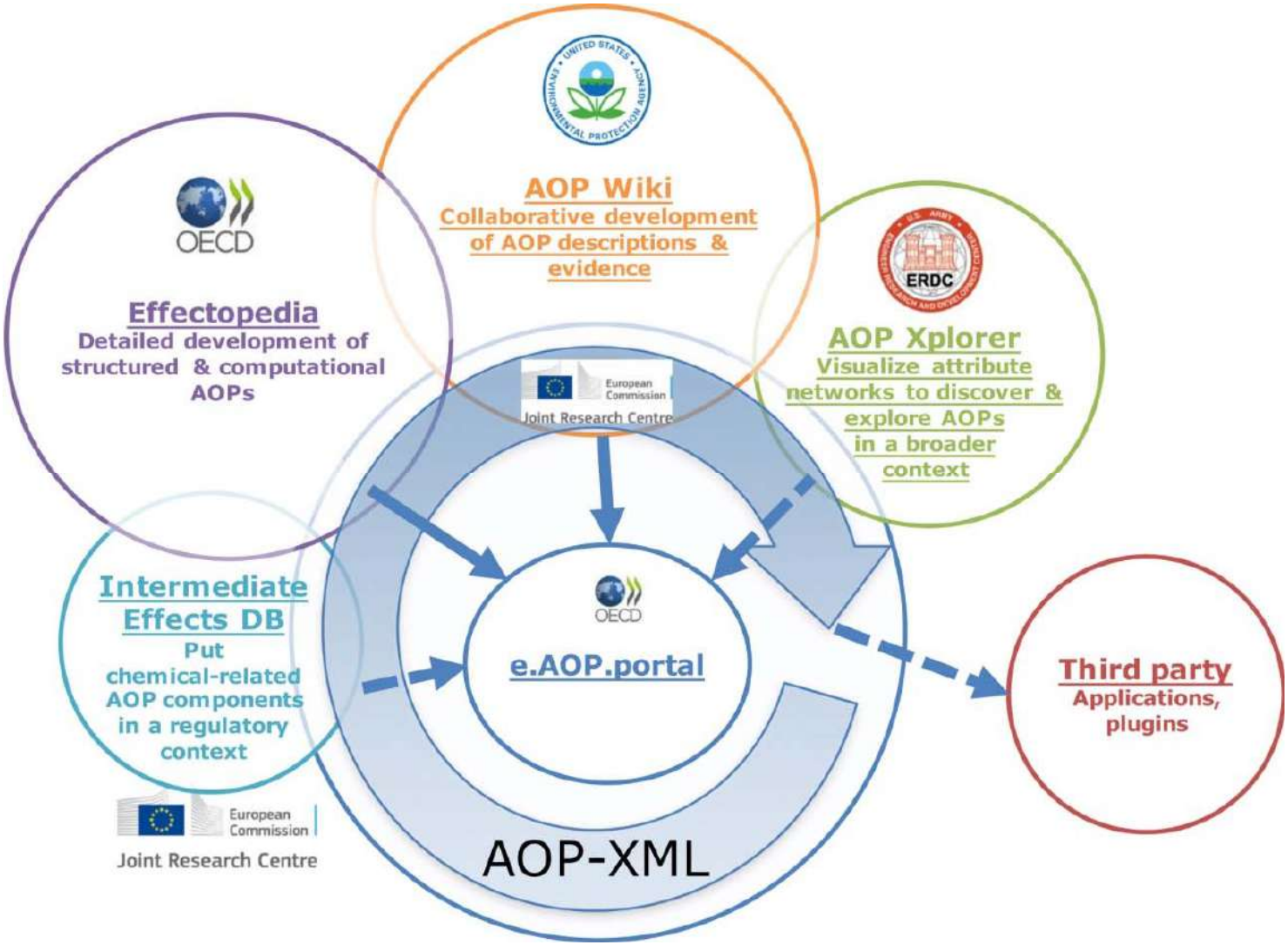
"We suggest a *new conceptual framework* … with research focused on *human-specific models* to understand disease pathways at multiple biological levels that are *analogous to adverse outcome pathways*."

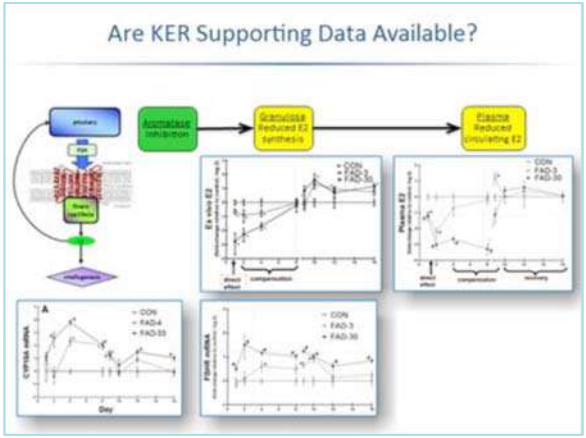

Healthy
AOP concept
Diseased
Cells
Tissues and organs
Systems
Individual
Biological concepts, terminology and data
Clinical concepts, terminology and data
Perturbation caused by genetic, epigenetic, environment, or lifestyle factors
e.g., ion channel effects, oxidative stress, cytokine responses
e.g., neuron loss, altered neuronal networks, perturbed bile homoeostasis, airways, or vascular inflammation
Alzheimer's disease
Cholestatic liver diseases
Autism spectrum disorders
Respiratory diseases
Autoimmune diseases
MIE
KE 1
KE 2
KE 3
Adverse outcome

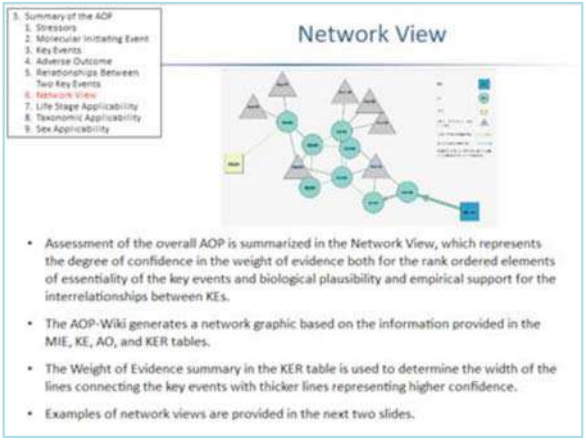
OECD AOP development program & open-access knowledge management tools



AOP online e-learning course

1. Intro and Review of AOPs and AOP-KB
2. Characteristics and Good Practices
   - Assembling information
   - Characteristics of KEs, MIEs, AOs, KERs
3. Introducing the AOP Wiki
4. Development and Review Process
   - OECD AOP development and review process
5. Registering on the AOP-Wiki
   - Access and use of the AOP-Wiki site
6. Entering Information: Step-by-Step Training
7. References





HUMAN TOXICOLOGY PROJECT CONSORTIUM

https://aopwiki.org/training/wiki/

HUMANE SOCIETY INTERNATIONAL SCIENTIFIC SERIES

BOMED 21

A Human-Specific Approach to Disease Research

European Union | North America | South America | Asia-Pacific




BIOMED[21] European Workshop

8-9 December 2015 | Brussels

- Keynote lecture
- Alzheimer's disease
- Asthma & COPD
- Autoimmune disease
- Liver disease
- Research funding programs
- Toward a pathway approach to human disease re search

Financial support for the BioMed[21] European workshop and 3 disease review grants was provided by **World Animal Protection**

Brussels Workshop High-Level Conclusions

Drug Discovery Today • Volume 00, Number 00 • November 2016 REVIEWS

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

Reviews • KEYNOTE REVIEW

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.

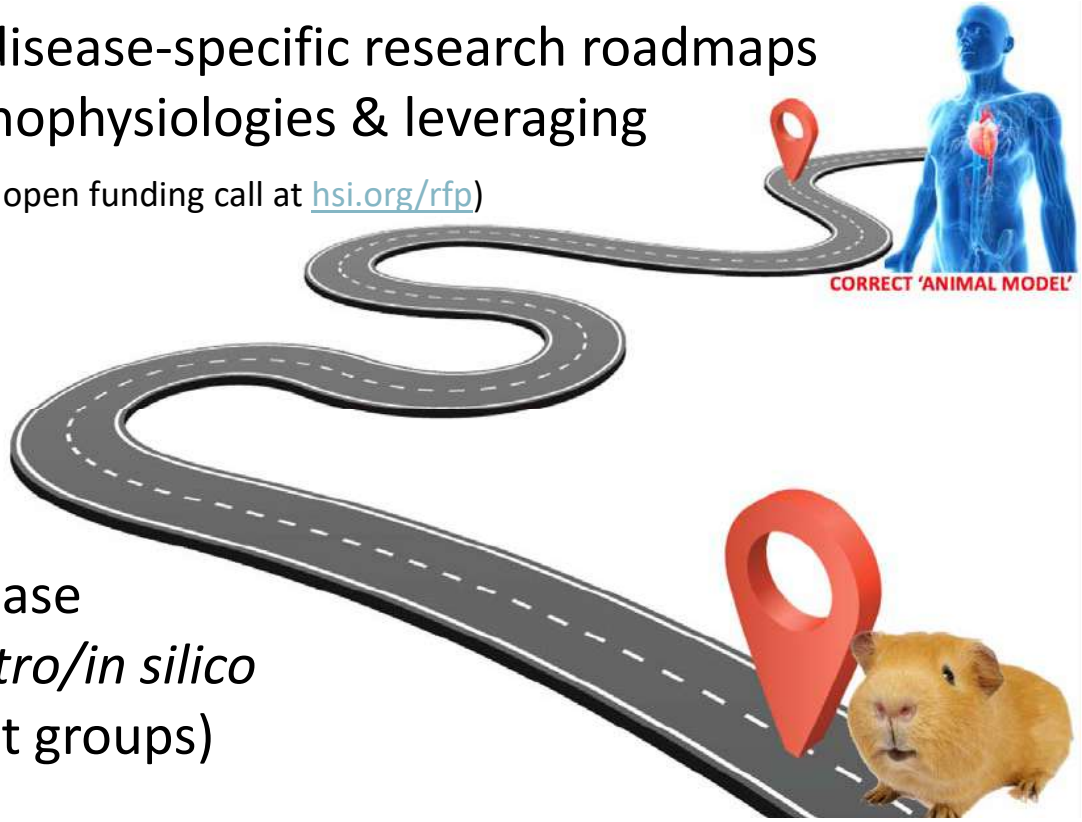
Alysson Muotri is a professor at the University of California San Diego and director of the UCSD Stem Cell Program. His research focuses on human brain development and evolution, and utilises a range of advanced models and molecular tools to study neurological diseases, such as autism spectrum disorders. 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'.

- Continued reliance on animal models unlikely to improve clinical translation
- Adapt the AOP concept to provide a mechanism-based framework for describing human disease patho-physiology for biomedical research

Brussels Workshop High-Level Conclusions

- Need to develop 21st century disease-specific research roadmaps focused on understanding pathophysiologies & leveraging human-specific models (HSI/HSUS open funding call at hsi.org/rfp)



- 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)
- Augmented support for systems biology & bioinformatics tools
- Obligatory open-access publication & data sharing for all publicly funded research, e.g., common global knowledgebase (OECD AOP KB)

Brussels Workshop High-Level Conclusions

- Overarching strategic frameworks are essential to guide science policy & funding to areas that need further development & coordinate related activities
- Funding should be focused on acquiring critical human information & developing/ validating human-specific tools (vs. new or 'improved' animal models)
- Enhanced research coordination among key economies, e.g., US Tox21 model or EU joint programming initiatives
- Challenge conservativism within funding bodies, among journal editors/reviewers & within the 'mainstream' bioscience community generally

BIOMED 21 North American Workshop

26-27 June 2017 | Washington, DC

"A HUMAN PATHWAY-BASED APPROACH TO DISEASE & MEDICINE"

Venue

- National Institutes of Health

Organizing Committee

- Drs Chris Austin & Dan Tagle, NIH/NCATS
- Dr Brian Berridge, GSK
- Dr Warren Casey, NIH/NIEHS
- Dr Suzy Fitzpatrick, FDA
- Dr Robert Kavlock, EPA
- Dr Kate Willett & Troy Seidle, HSI/HSUS

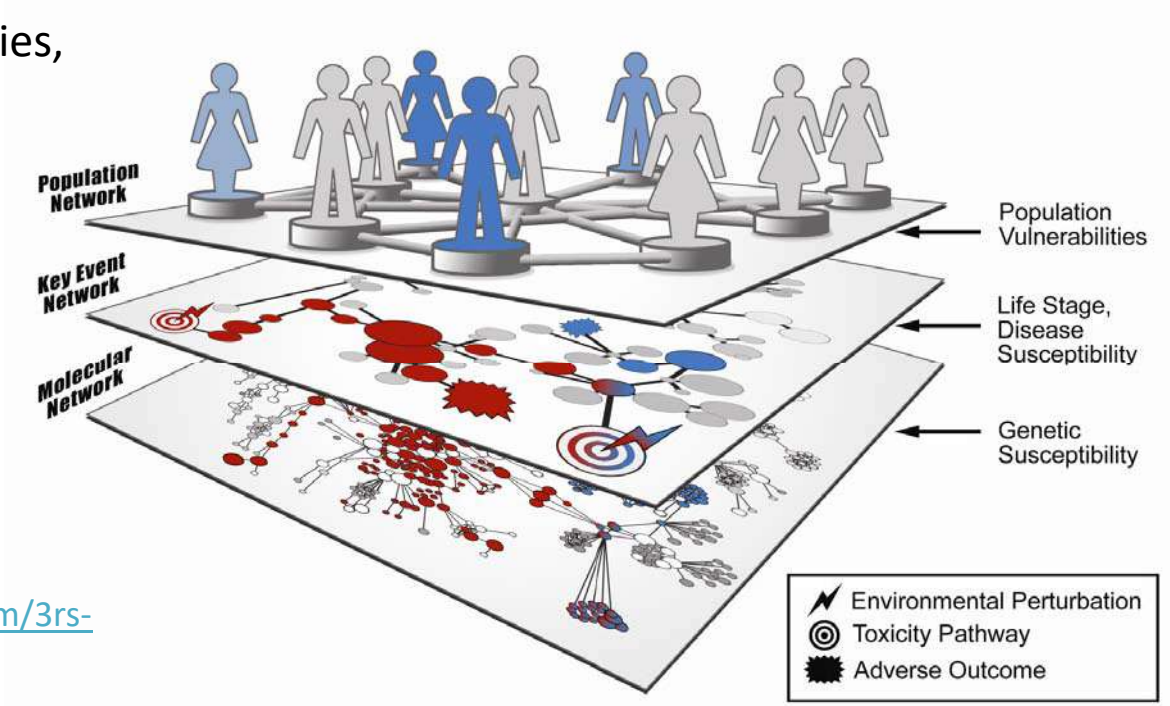
BIOMED[21] North American Workshop

26-27 June 2017 | Washington, DC

"A HUMAN PATHWAY-BASED APPROACH TO DISEASE & MEDICINE"

Agenda

- Issues with disease models & drug pipeline
- Big data: information > knowledge > action
- The present: pathway-based tools & approaches
- The future: role of funding bodies, regulators & pharma
- Round-table discussion



https://ntp.niehs.nih.gov/pubhealth/evalatm/3rs-meetings/biomed21-2017/index.html

BIOMED21 South American Workshop

29-30 May 2017 | Rio de Janeiro

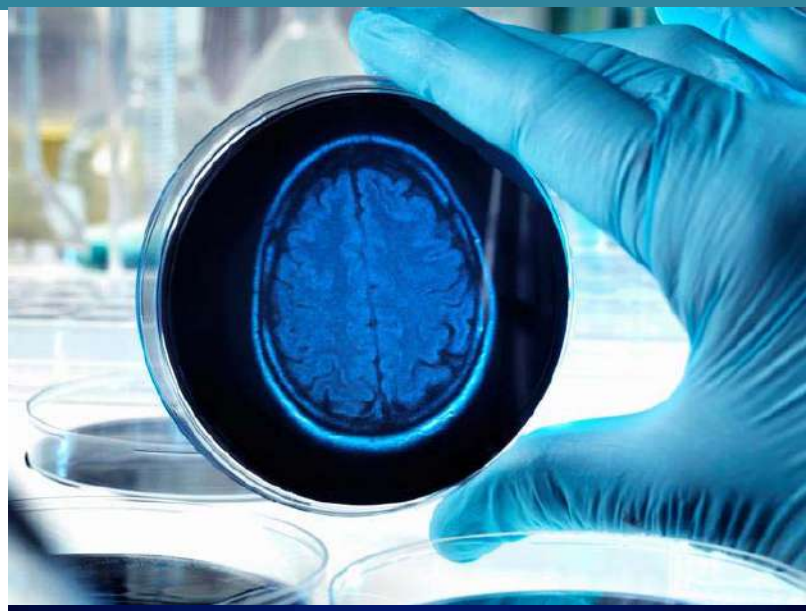
"EMERGING TOOLS FOR PATHWAY-BASED HUMAN BRAIN RESEARCH"

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



BIOMED[21] South American Workshop

29-30 May 2017 | Rio de Janeiro

"EMERGING TOOLS FOR PATHWAY-BASED HUMAN BRAIN RESEARCH"

Workshop outputs

- Flash report for swift dissemination of key discussions and conclusions
- Publication of slides and video clips (with presenters' approval) online
- Preparation of workshop report as manuscript for open-access publication
- Possible oral presentation at 10th World Congress on Alternatives (August in Seattle)
- Ongoing dialogue with Brazilian funding bodies and politicians re. input into future funding calls

Medical researchers and stakeholders call for a comprehensive strategy to improve our mechanistic understanding of human disease and support the development of human-specific models to accelerate the identification and successful translation of new treatments to the clinic.

Leading health scientists, officials representing European institutions, national regulatory and research agencies, science funding organizations and other stakeholders participated in the December 2015 workshop **BioMed[21]: A Human Pathways Approach to Disease Research** in Brussels. The workshop, part of a new global initiative led by Humane Society International,[1] examined five human disease case studies alongside research funding frameworks and regulatory structures in key innovation economies with the aim of identifying actionable consensus recommendations as a first step towards a comprehensive roadmap for 21st century, human biology-based health research and funding.

The workshop reviewed the status of human and animal models in the following disease areas:
*

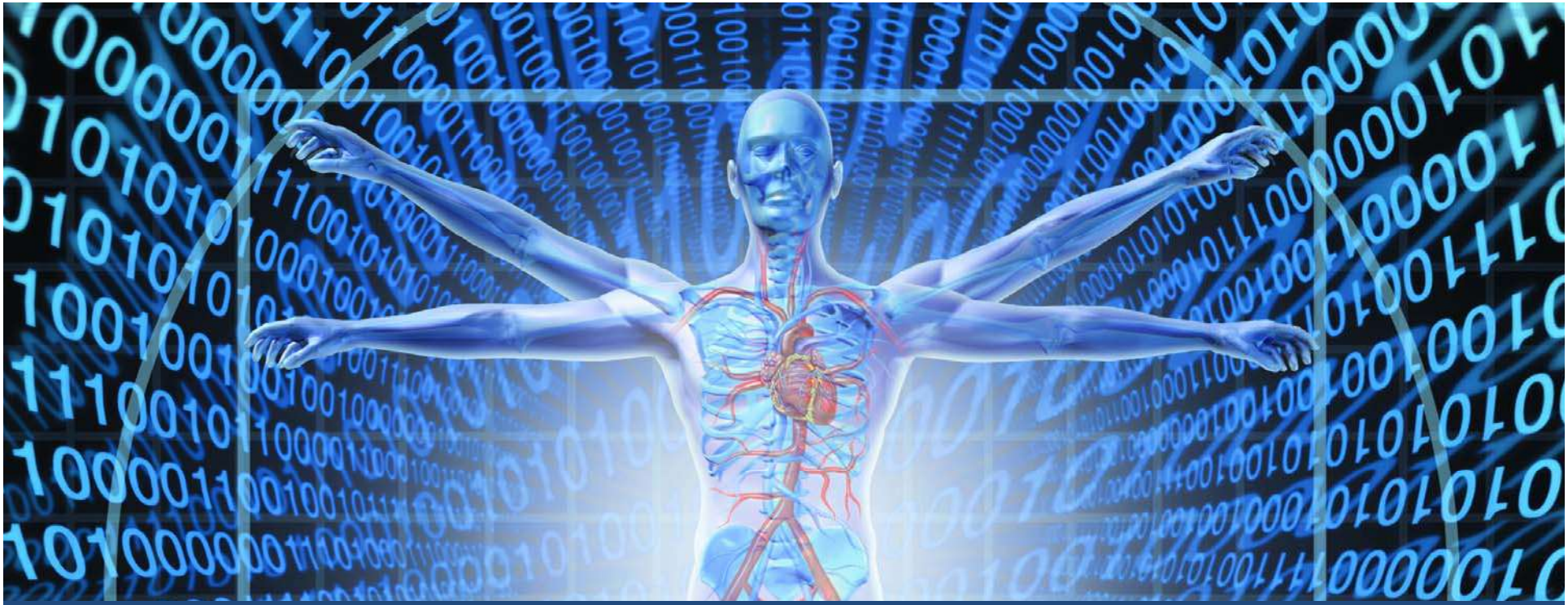
Alzheimer's disease

*Lead discussants: **Dr Gill Langley**, Humane Society International; **Prof James Adjaye**, Heinrich Heine University; **Dr Martin Hofmann-Apitius**, University of Bonn*

There are currently no disease-modifying therapies for Alzheimer's disease despite decades of intensive animal research, and hundreds of interventions reported as effective in animal models have subsequently failed in the clinic.[2] Experts noted that current research paradigms are too dependent on transgenic mice that differ significantly from humans in protein pathways, metabolism and physiology. Human-specific models, such as human induced pluripotent stem cells (hiPSCs) generated from patients with Alzheimer's disease and differentiated into functional neurons, show important pathologies of the disease.

[1] Langley G, Austin CP, Balapure AK, et al. (2015) Lessons from toxicology: Developing a 21st-century paradigm for medical research. *Environ Health Perspect.* **123**(11):A268-72. doi: 10.1289/ehp.1510345

[2] Langley G (2014) Considering a new paradigm for Alzheimer's disease research. *Drug Discov Today*. **19**(8):1114–24.



Let's begin!

25 Years of
Celebrating Animals

HUMANE SOCIETY
INTERNATIONAL