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**HUMANE SOCIETY**  
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**B**  **OMED** <sup>21</sup>

# Towards a 21<sup>st</sup> Century Roadmap for Biomedical Research

HUMANE SOCIETY  
THE UNITED STATES

# Moving from '3R' language to a scientifically articulated vision



**TOXICITY TESTING IN THE 21ST CENTURY  
A VISION AND A STRATEGY**



**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.*”

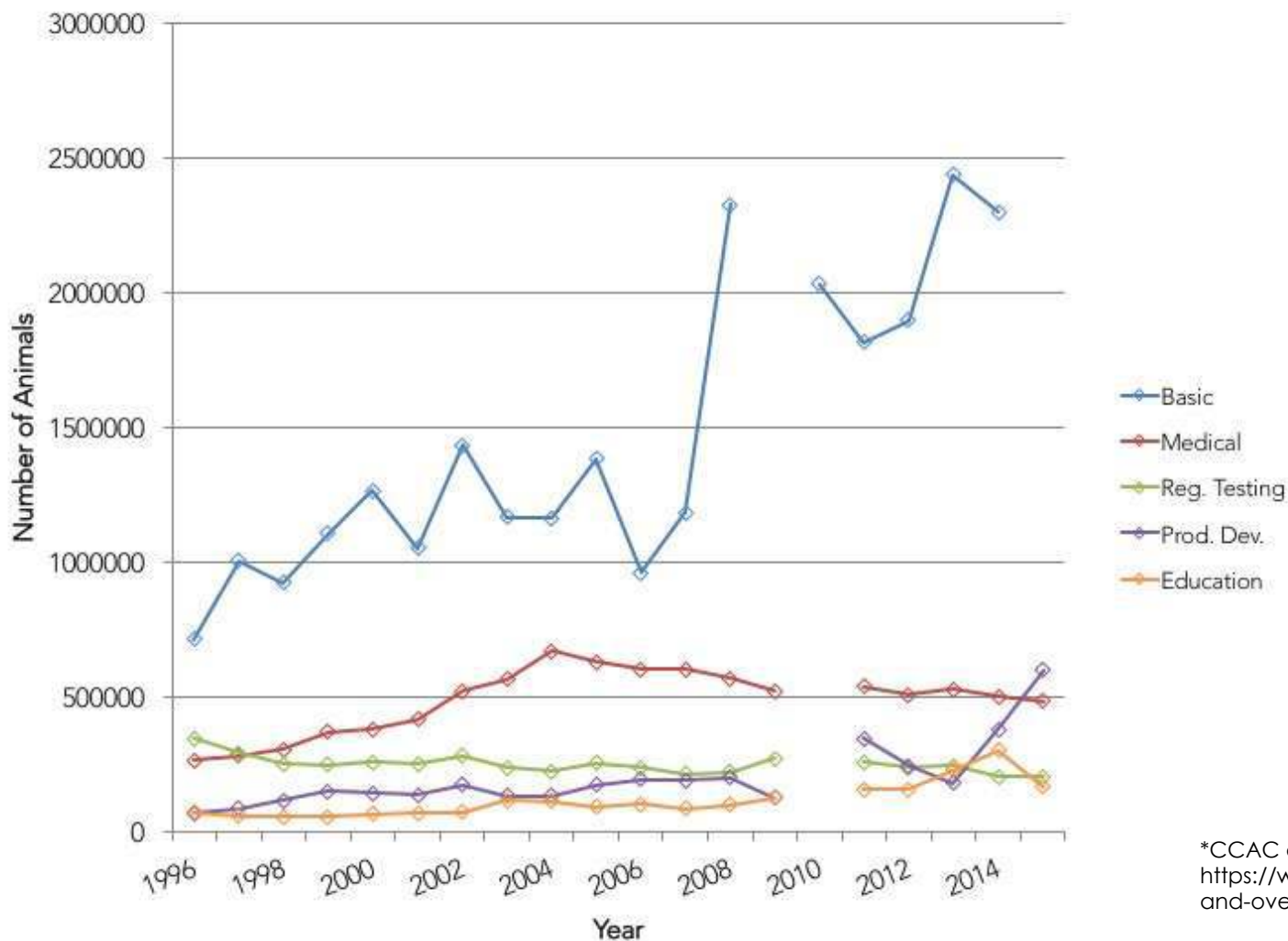
– Francis Collins, MD  
Director, NIH

*“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.”*



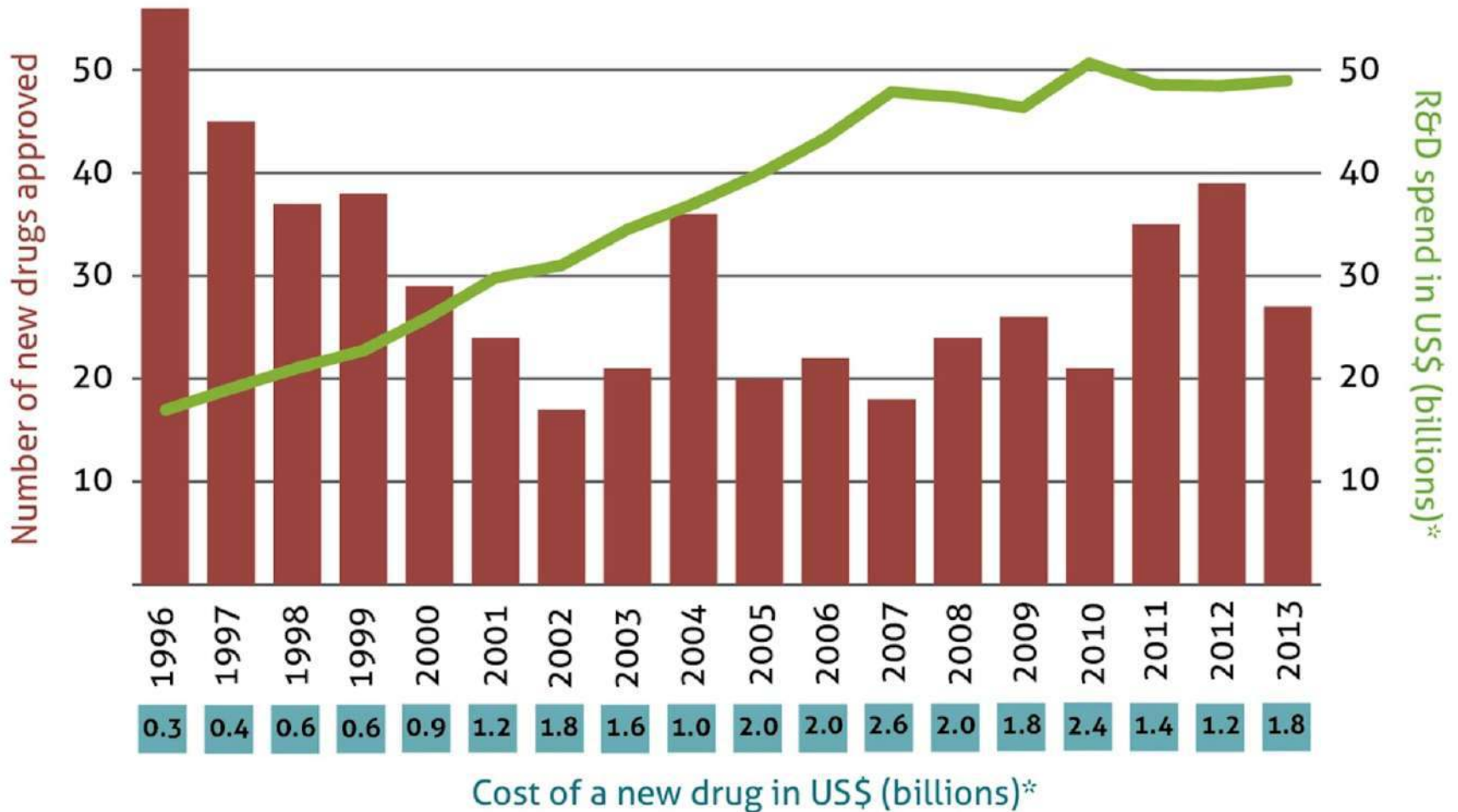
# Declining animal use for testing vs. steady growth in research

Trends in Purpose of Animal Use 1996-2015\*



\*CCAC data for Canada; source: <https://www.animalsinscience.org/policy-and-oversight/facts-and-figures/>

~95% clinical failure for new drugs that appear safe & effective preclinically





“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



# Engaging scientists to articulate a scientific vision for '21<sup>st</sup> century' biomedical 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.



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CHINESE ACADEMY OF SCIENCES



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UC San Diego



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Universidade Federal de Minas Gerais



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 articulate a scientific vision for '21<sup>st</sup> century' biomedical research



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

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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*.”**

Gill Langley,<sup>1</sup> Christopher P. Austin,<sup>2</sup> Anil K. Balapure,<sup>3</sup> Linda S. Birnbaum,<sup>4</sup> John R. Bucher,<sup>5</sup> Julia Fentem,<sup>6</sup> Suzanne C. Fitzpatrick,<sup>7</sup> John R. Fowle III,<sup>8</sup> Robert J. Kavlock,<sup>9</sup> Hiroaki Kitano,<sup>10</sup> Brett A. Lidbury,<sup>11</sup> Alysso R. Muotri,<sup>12</sup> Shuang-Qing Peng,<sup>13</sup> Dmitry Sakharov,<sup>14</sup> Troy Seidle,<sup>15</sup> Thales Trez,<sup>16</sup> Alexander Tonevitsky,<sup>17</sup> Anja van de Stolpe,<sup>18</sup> Maurice Whelan,<sup>19</sup> and Catherine Willett<sup>20</sup>

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# 'Disease AOP' concept

Healthy

Diseased



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**

**Autism spectrum disorders**

**Autoimmune diseases**

**Cholestatic liver diseases**

**Respiratory diseases**

**MIE**

**KE 1**

**KE 2**

**KE 3**

**Adverse outcome**



# What are the opportunities for individual diseases? Ask the experts!



## Call for Proposals

### “Roadmaps to Human Biology-Based Disease Research”

To support strategic scientific dialogue around the concept of extending the vision of “21st century toxicology” to the wider biosciences, Humane Society International is offering grants to support the development and open-access publication of in-depth, independent review articles in discrete areas of human disease/biomedicine by health scientists with relevant expertise.

#### **Remit**

Each review should:

- Examine the state of the science in a specific area of human biomedicine, including current understanding of the underlying pathophysiological pathways and networks;
- Critically evaluate the human relevance, translational success and limitations of conventional research models;
- Offer concrete recommendations/roadmap for optimizing the funding and use of advanced, human-specific tools and approaches (pathway paradigm as an organizing framework, primary human cells/tissues, iPSC, organoids, bioengineering, computational systems biology modeling, etc.) in the disease area under discussion; and



**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

# Experimental study of tuberculosis: From animal models to complex cell systems and organoids

Kaori L. Fonseca<sup>1,2</sup>, Pedro N. S. Rodrigues<sup>1,2,3</sup>, I. Anna S. Olsson<sup>1,2</sup>, Margarida Saraiva<sup>1,2\*</sup>

<sup>1</sup> i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal, <sup>2</sup> IBMC - Instituto de Biologia Molecular e Celular, Universidade do Porto, Porto, Portugal, <sup>3</sup> ICBAS - Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal

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## Abstract

Tuberculosis (TB) is a devastating disease to mankind that has killed more people than any other infectious disease. Despite many efforts and successes from the scientific and health communities, the prospect of TB elimination remains distant. On the one hand, sustainable public health programs with affordable and broad implementation of anti-TB measures are needed. On the other hand, achieving TB elimination requires critical advances in three areas: vaccination, diagnosis, and treatment. It is also well accepted that succeeding in advancing these areas requires a deeper knowledge of host—pathogen interactions during infection, and for that, better experimental models are needed. Here, we review the potential and limitations of different experimental approaches used in TB research, focusing on animal and human-based cell culture models. We highlight the most recent advances in developing in vitro 3D models and introduce the potential of lung organoids as a new tool to study *Mycobacterium tuberculosis* infection.



**OPEN ACCESS**

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## Author summary

Tuberculosis (TB) is the number 1 killer in the world due to a bacterial infection. The study of this disease through clinical and epidemiological data and through the use of different experimental models has provided important knowledge on the role of the immune response generated during infection. This is critical for the development of novel vaccines and therapeutic strategies. However, in spite of the advances made, it is well accepted that better models are needed to study TB. This review discusses the different models used to study TB, highlighting the advantages and disadvantages of the available animal and cellular models and introducing recently developed state-of-the-art approaches based on human-based cell culture systems. These new advances are integrated in a road map for future study of TB, converging for the potential of lung organoids in TB research.

Table 1. Experimental models for the study of tuberculosis (TB).

Tools in TB research		Scientific potential	Limitations	Costs	Infrastructure requirements	Skills
Animal models	Whole animal models (nonhuman primates, rabbits, guinea pig, mouse, zebrafish)	<ul style="list-style-type: none"> <li>Study of the immune response during Mtb infection in a whole organism.</li> <li>Genetic manipulation of key molecules and pathways.</li> <li>Better understanding of host—pathogen interactions.</li> </ul>	<ul style="list-style-type: none"> <li>Anatomical differences, pathogenicity, and virulence of Mtb when compared to the human system.</li> <li>Difficulty to establish LTB1 animal models.</li> <li>Some models limited by the lack of immunological-based tools.</li> <li>Limited housing capacity for larger animal models.</li> <li>Ethical, practical, and economic issues.</li> <li>Poor clinical outcome prediction.</li> </ul>	\$\$\$\$	<ul style="list-style-type: none"> <li>Appropriate animal housing.</li> <li>Animal Biological Safety Level 3 laboratories.</li> <li>Precise training.</li> </ul>	++++
Human-based models	2D model (cell lines)	<ul style="list-style-type: none"> <li>Easily infected by Mtb with production of immune mediators.</li> <li>Lack of confounding factors.</li> </ul>	<ul style="list-style-type: none"> <li>Genetically transformed cells.</li> <li>Lack of tissue-like structure.</li> <li>Lack of tissue-like prediction.</li> </ul>	\$\$	<ul style="list-style-type: none"> <li>Biological Safety Level 3 laboratories.</li> <li>Precise training.</li> </ul>	++
	2D model (primary cells)	<ul style="list-style-type: none"> <li>Study of Mtb cellular invasion and intracellular replication.</li> <li>Cell lines can be bought.</li> </ul>	<ul style="list-style-type: none"> <li>Require samples from patients.</li> <li>Lack of tissue-like structure.</li> <li>Poor clinical outcome prediction.</li> </ul>	\$\$		++
	3D model organoids (pluripotent stem cells)	<ul style="list-style-type: none"> <li>Primary tissue derived.</li> <li>Self-renewal and self-organization capacity.</li> <li>Lack of confounding factors.</li> <li>Tissue-like structure and function.</li> </ul>	<ul style="list-style-type: none"> <li>Lack of the immune system.</li> <li>Absence of local microenvironment.</li> </ul>	\$\$\$		+++

# IMI projects contribute to the 3Rs

## Eliminating poorly predictive models

- Parkinson's Disease
- Diabetes
- Asthma
- Chronic Pain
- Schizophrenia
- Depression
- Autism

## Developing new improved models

- Parkinson's Disease
- Diabetes
- Asthma
- Chronic Pain
- Schizophrenia
- Depression
- Autism

## Replacing animals with better *in vitro* & *in silico* models

- Diabetes
- Cancer
- Schizophrenia
- Chronic pain
- Drug safety
- Parkinson's Disease

## Alternative tools

- Biomarkers
- Novel cell lines
- 2D and 3D cell cultures
- Imaging
- Computation
- Simulation
- Pooling & novel analysis of existing data

## Information

<b>Tender reference number</b>	JRC/IPR/2017/F.3/0050/OC.
<b>Title</b>	Reviews on non-animal methods in use for biomedical research – 4 lots.
<b>Description</b>	A collection of non-animal methods shall be provided in use for basic and applied research concerning the following human disease areas: neurodegenerative diseases, respiratory tract diseases, cardiovascular diseases, breast cancer.
<b>Contract type</b>	Services
<b>Procedure type</b>	Open procedure
<b>Status</b>	Open
<b>Published on TED</b>	✓

## Lots


Lot number	Title	Description
Lot 1	Reviews on non-animal methods in use for biomedical research in neurodegenerative diseases area	The contractor shall provide a collection of novel non-animal models and methods in use for basic and applied research with information on their development status and applications in neurodegenerative diseases area.
Lot 2	Reviews on non-animal methods in use for biomedical research in respiratory tract diseases area	The contractor shall provide a collection of novel non-animal models and methods in use for basic and applied research with information on their development status and applications in respiratory tract diseases area.
Lot 3	Reviews on non-animal methods in use for biomedical research in cardiovascular diseases area	The contractor shall provide a collection of novel non-animal models and methods in use for basic and applied research with information on their development status and applications in cardiovascular diseases area.
Lot 4	Reviews on non-animal methods in use for biomedical research in breast cancer area	The contractor shall provide a collection of novel non-animal models and methods in use for basic and applied research with information on their development status and applications in breast cancer area.



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# A Human-Specific Approach to Disease Research

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



# BOMED<sup>21</sup> European Workshop

8-9 December 2015 | Brussels



- Keynote lecture
- Alzheimer's disease
- Asthma & COPD
- Autoimmune disease
- Liver disease
- Research funding programs
- Roundtable discussion

# BOMED<sup>21</sup> 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<sup>21</sup> North American Workshop

26-27 June 2017 | Washington, DC

“A HUMAN PATHWAY-BASED APPROACH TO DISEASE & MEDICINE”

## Venue

- NIH Conference Center, Bethesda

## Participants

- ~150 in person and online including government (6 NIH institutes, 6 FDA centers, EPA, industry, academia, NGOs)

## 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



[biomed21.org](http://biomed21.org)

# Major Recommendations: EU Workshop

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

REVIEWS



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

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<sup>17</sup> Philips Research (Philips Group Innovation), Eindhoven, The Netherlands

<sup>18</sup> Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium

<sup>19</sup> Animal Research Issues, The Humane Society of the United States, Boston, MA, USA

<sup>20</sup> MRC/Asthma UK Centre in Allergic Mechanisms of Asthma, Division of Asthma, Allergy & Lung Biology, King's College London, Guy's Hospital, London, UK

Gillian Langley is currently a scientific consultant to Humane Society International. Her academic career focused 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'.



REVIEWS • KEYNOTE REVIEW

- 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)
- Need to develop 21<sup>st</sup> century, disease-specific research roadmaps focused on understanding pathophysiology & leveraging human-specific models
- Challenge conservatism within funding bodies, among journal editors/reviewers & within the 'mainstream' bioscience community generally

# Major Recommendations: Brazil Workshop



Latin American scientists and stakeholders call for national strategy and funding boost for human-relevant approaches to health research and safety testing, emphasizing non-animal technology infrastructures such as human stem cells, organoids and organs-on-a-chip.

Leading Brazilian and international health scientists and other stakeholders met in Rio de Janeiro in May 2017 for the workshop *BioMed21: Emerging Technology Toward Pathway-Based Human Brain Research*. The workshop – organized by Humane Society International as part of a global scientific series<sup>1,2,3,4</sup> and hosted by the D'Or Institute for Research and Education – examined the development and application of various human biology-based tools for modeling brain diseases with the aim of identifying actionable, consensus recommendations to guide future funding and developments in this area.

The workshop was inaugurated with a presentation on the historical path that started in 1906 when the first drops of cell culture were examined under the microscope, through the birth of induced pluripotent stem cell (iPSC) technology in the beginning of the 21<sup>st</sup> century. Subsequent presentations illustrated how iPSCs are now

being used to study a variety of brain diseases, including microcephaly-causing Zika virus, Dravet disease, autism, neuropsychiatric disorders, Amyotrophic Lateral Sclerosis and Parkinson Disease, and how these modern, human biology-based tools are being used as an alternative to animal models in labs worldwide. Similarly, human 'mini-brain' organoids and organs-on-a-chip were presented as promising new tools for pre-clinical research and testing for drug safety and efficacy.

Modern, human-based technologies offer the possibility of using patients' cells to study diseases, test new drugs and develop tailor-made treatments according to each patient characteristics. Virtually all presentations included work that has been done using patients' cells. Testing of potential new drugs such as Cannabidiol to treat epilepsy in Dravet Syndrome, Chloroquine to protect from microcephaly-causing Zika virus, or

- Need an overarching, multi-year non-animal technology and biomedical research funding strategy to ensure sufficient and sustained investment in human biology-based research and model development at federal and state levels
- Establishment of a strategic science 'think tank'
- Further examine the role of scientific journals in driving or impeding a paradigm shift in health research
- Address commercial availability and import of human tissues, models and chemical reagents
- Address local industry/CRO capacity, infrastructure and training to perform all available non-animal guideline tests according to OECD GLP standards

<sup>1</sup> Langley G, et al. *Environ Health Perspect*. 2015;11:A268-72.  
<sup>2</sup> Langley G, et al. *Drug Discov Today*. 2016;22:327-39.

<sup>3</sup> <https://ntp.niehs.nih.gov/ga/biomed21>  
<sup>4</sup> <http://www.biomed21.org>



# Major Recommendations: U.S. Workshop



**BIO MED<sup>21</sup>**  
A HUMAN PATHWAYS-  
BASED APPROACH TO  
DISEASE RESEARCH

NIH Conference Center  
Bethesda, 26-27 June 2017

WORKSHOP *Flash* REPORT



ational Institutes of Health

U.S. federal agencies, biomedical scientists and stakeholders examined ongoing efforts to elucidate the molecular underpinnings of human disease and discussed opportunities for enhanced coordination and prioritization of human-relevant approaches with the goal of improved translation of research results from the bench to the clinic.

Despite increasing sophistication in technology as well as in our understanding of biology, the issue of failures in clinical translation of biomedical research still looms large. This is tangibly evident, as the number of new drugs have halved every 9 years since 1950<sup>1</sup>, despite investment of billions of dollars into these efforts and the promise of the new technologies. The global community has been aware of the shortcomings of current approaches to disease models and drug development for some time. To this end, the BioMed21 Initiative and global scientific workshop series<sup>2,3,4,5</sup> was launched by Humane Society International to bring together all stakeholders, with the overall aim of understanding how to leverage existing projects to develop human systems biology-based roadmaps for health research. The U.S. workshop was hosted by the National Institutes of Health (NIH) with organizational

support and backing from the National Institute of Environmental Health Sciences, the Human Toxicology Project Consortium, and The Humane Society of the United States.

## Session 1: Setting the stage

*Keynote lecture: Dr Chris Austin, NIH/NCATS*

*Speakers: Dr Francois Pagnan, Novartis; Dr Warren Casey, NIH/NIEHS; Dr Bruce Cuthbert, NIH/NIMH; Dr Suzanne Fitzpatrick, FDA; Dr Rebecca Clewell ScitoVation; Dr Ian Adcock, Imperial College London; Dr Daniel Levner, Emulate Inc.*

Standardization of data reporting, in line with current Food and Drug Administration (FDA) requirements for clinical trial data, could enable analysis of the dormant

- Formal international and inter-agency collaboration between major organizational and funding bodies should be established
- Funding should be prioritized for researching human-based biology
- Human data should be collected in high-quality open-access databases
- Common reporting formats and ontologies should be established for collecting and collating human biology information, from different 'omics technologies to human clinical data
- Immediate need for the creation of case studies to demonstrate applications and benefits of predictive, mechanism-based approaches

<sup>1</sup> Scannell et al. 2012, Nat Rev Drug Discovery Diagnosing the decline in pharmaceutical R&D efficiency. 11:191-200. doi:10.1038/nrd3681  
<sup>2</sup> Langley G, et al. Environ Health Perspect. 2015;11-A268-72.

<sup>3</sup> Langley G, et al. Drug Discov Today. 2016;22:327-39.  
<sup>4</sup> <https://ntp.niehs.nih.gov/go/biomed21>  
<sup>5</sup> <http://www.biomed21.org>



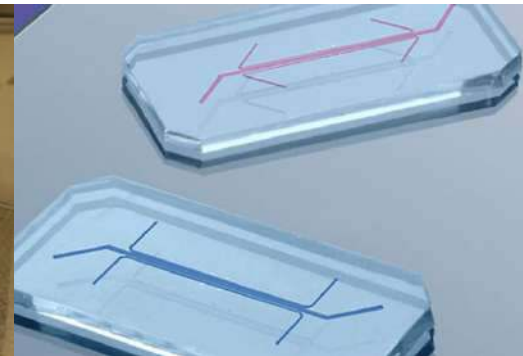
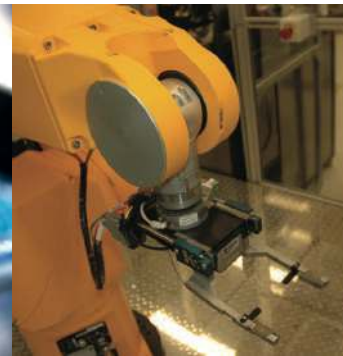
## 5 new disease-specific grants awarded

- Cardiovascular
- Diabetes
- Flavivirus infection
- Non-alcoholic liver disease

## New roadmap funding call for Latin American countries

Online at [biomed21.org](http://biomed21.org)

## Asia-Pacific Workshop 2018



# Acknowledgments

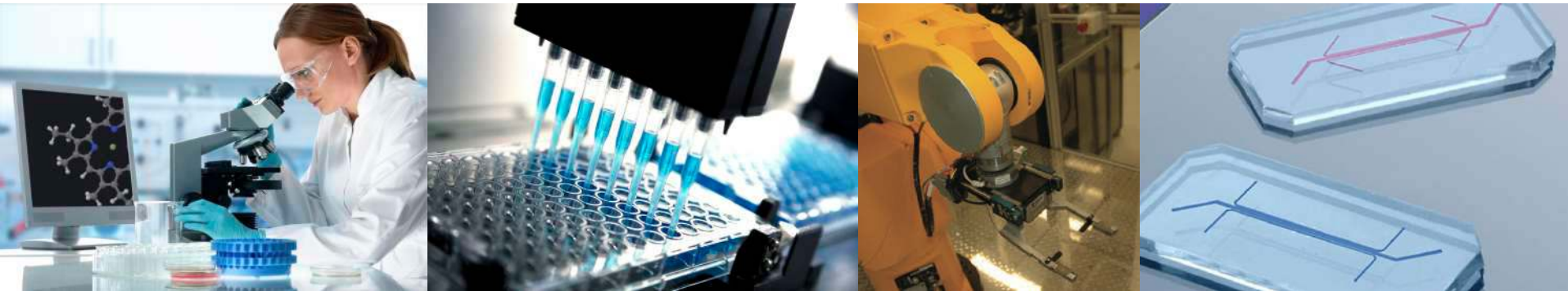
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- Gill Langley, Kate Willett, Marcia Triunfol, Lindsay Marshall, Aviva Vetter (HSI)
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## Sponsors

- NIH/NIEHS
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## Workshop participants & article co-authors





**Thank you!**

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