Towards a 21st Century Roadmap for Biomedical Research

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Moving from ‘3R’ language to a scientifically articulated vision

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.”

“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.”

Francis Collins, MD
Director, NIH
Declining animal use for testing vs. steady growth in research

*Trends in Purpose of Animal Use 1996-2015*

- Basic
- Medical
- Reg. Testing
- Prod. Dev.
- Education

*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.

Data: USFDA, PhRMA
“Most of this failure is due to the **limited predictive value** of preclinical models of disease”

“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 '21st 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 pathophysiolgies 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.

* The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of their organizations.
“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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Disease AOP (Adverse Outcome Pathway) concept

Healthy → Cells → Tissues and organs → Systems → Individual → Diseased

Cells:
- Perturbation caused by genetic, epigenetic, environmental, or lifestyle factors
- e.g., ion channel effects, oxidative stress, cytokine responses

Tissues and organs:
- e.g., neuron loss, altered neuronal networks, perturbed bile homoeostasis, airways, or vascular inflammation

Systems:
- Clinical concepts, terminology and data

Individual:
- Alzheimer’s disease
- Cholestatic liver diseases
- Autism spectrum disorders
- Respiratory diseases
- Autoimmune diseases

Adverse outcome

MIE → KE 1 → KE 2 → KE 3
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
Experimental study of tuberculosis: From animal models to complex cell systems and organoids

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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.

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.
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

Source: Christian Desaintes, EC/DG R&I
Information

Tender reference number: JRC/IPR/2017/F.3/0050/OC.
Title: Reviews on non-animal methods in use for biomedical research – 4 lots.
Description: 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.
Contract type: Services
Procedure type: Open procedure
Status: Open
Published on TED: 

Lots

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<tr>
<th>Lot number</th>
<th>Title</th>
<th>Description</th>
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<tr>
<td>Lot 1</td>
<td>Reviews on non-animal methods in use for biomedical research in neurodegenerative diseases area</td>
<td>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.</td>
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<td>Lot 2</td>
<td>Reviews on non-animal methods in use for biomedical research in respiratory tract diseases area</td>
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<td>Lot 3</td>
<td>Reviews on non-animal methods in use for biomedical research in cardiovascular diseases area</td>
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<td>Lot 4</td>
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A Human-Specific Approach to Disease Research

European Union | North America | South America | Asia-Pacific
Financial support for the BioMed21 European workshop and 3 disease review grants was provided by World Animal Protection.
“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
“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
Major Recommendations: EU Workshop

- 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 21st-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
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
Major Recommendations: U.S. Workshop

- 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
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

Asia-Pacific Workshop 2018
Acknowledgments

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Thank you!