Toward a Human-Focused Paradigm in Health Research

THE BiOMED21 vision

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BioMed21.org
• HSI is active on the ground in 60 countries, including India and Asia-Pacific, Europe and the Americas

• Our Research & Toxicology Department brings together experts in biomedicine, eco/toxicology & regulatory science, public policy, etc.

• Working with research institutes, companies, government regulators, policy-makers and other stakeholders

• OECD expert groups, national government advisory bodies on alternative methods and product safety, etc.
Age-old dilemma in health research & drug discovery

Animal models
Systemic but not human(e)

Static 2D & 3D human cell models
Human but not systemic
High failure rates for drug candidates that appear safe and effective preclinically

Up to $2.5 billion
13.5 years
Thousands of animals

“Most of this failure is due to the **limited predictive value** of preclinical models.”

“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
National Institutes of Health, USA
Transform toxicity testing from a system based on whole animal testing to one founded primarily on *in vitro* methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin.”
Adverse outcome pathways (AOPs) as an organizing framework

Human bio-monitoring, Risk21 tools

High-content (subcellular, in chemico, etc.)

2D/3D in vitro (iPSC, high-throughput, etc.)

3D in vitro (organoids, organs-on-a-chip)

Clinical, human-on-a-chip, in silico

Epidemiology

Cross-disciplinary expertise needed

- Biology (fundamental & applied)
- Chemistry
- Clinical & epidemiology
- Engineering
- Computational modeling
- Etc.
Tox21 vision

» animal-free human risk assessment

Adapted from Dr AH Piersma – Evolution vs Revolution in Innovating Regulatory Toxicity Testing” – June 2018, RIVM, Utrecht

(e.g.)

IMMUNE
DART
CANCER
ENDOCRINE
ETC.
Articulating a scientific vision of ‘21st century’ biomedical research

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 pathophysiology 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 [AOPs].”

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BioMed21 scientific vision

» bridging the disciplinary silos

More multidisciplinary collaboration (clinicians, big data)

Build models around human path/physiology (AOPs)

Describe human physiology in the form of AOPs

Human micro-physiological systems

Computational models for prediction
Funded reviews have identified poorly predictive models & suggested novel roadmaps

- Alzheimer’s disease
- Amyotrophic lateral sclerosis
- Asthma
- Autism spectrum disorder
- Autoimmune disorders
- Cardiovascular disease
- Diabetes type II
- Flaviviruses (Zika)
- Liver disease (cholestatic + NASH)
- Parkinson’s disease
- Tuberculosis

... others in development

International workshop series

- Europe (Brussels, Dec. 2015)
- Latin America (Brazil, May 2017)
  - Triunfol et al. Drug Discov. Today 2018
- North America (Bethesda, June 2017)
  - Participation from 6 NIH institutes, 5 FDA centers, co-sponsored by NIEHS
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

Christian Desaintes, European Commission DG Research
**Take-away thoughts**

- **Human biology as the gold standard** in health research (& prioritize funding based on proof of relevance)

- **Modern, science-based terminology** (e.g. human iPSC-derived cancer models) vs. ‘3R / alternatives’ bioethics lingo from 1959, which can be marginalizing

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"Let's think outside the cage"