

Toward a Human- Focused Paradigm in Health Research



THE **B** **OMED**²¹ VISION

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BioMed21.org



**HUMANE SOCIETY
INTERNATIONAL**



HUMANE SOCIETY
INTERNATIONAL

- 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.

*Advancing
human-
predictive
approaches
in regulatory
testing &
health
research
worldwide*

Age-old dilemma in health research & drug discovery



Animal models

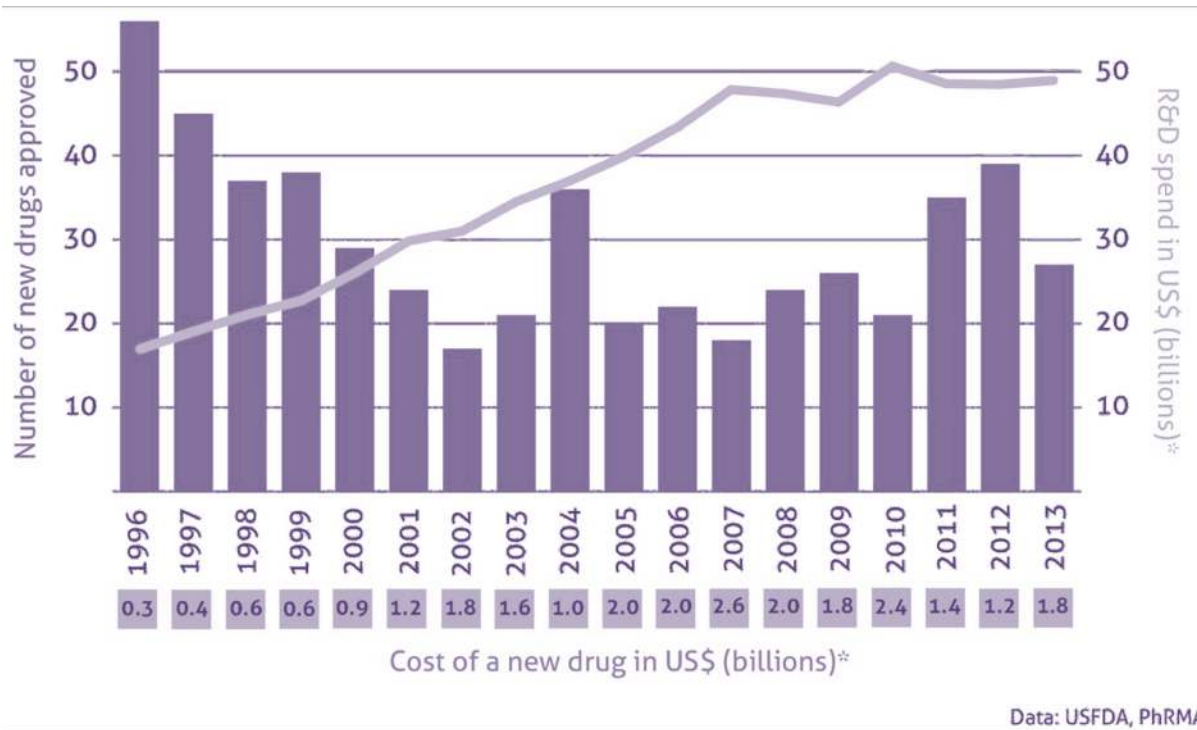
Systemic but not human(e)



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.”

Plenge et al. Nat Rev Drug Discov. 2013; 12: 581-94; Kola & Landis. Nat Rev Drug Discov. 2004; 3: 711-15

“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.”

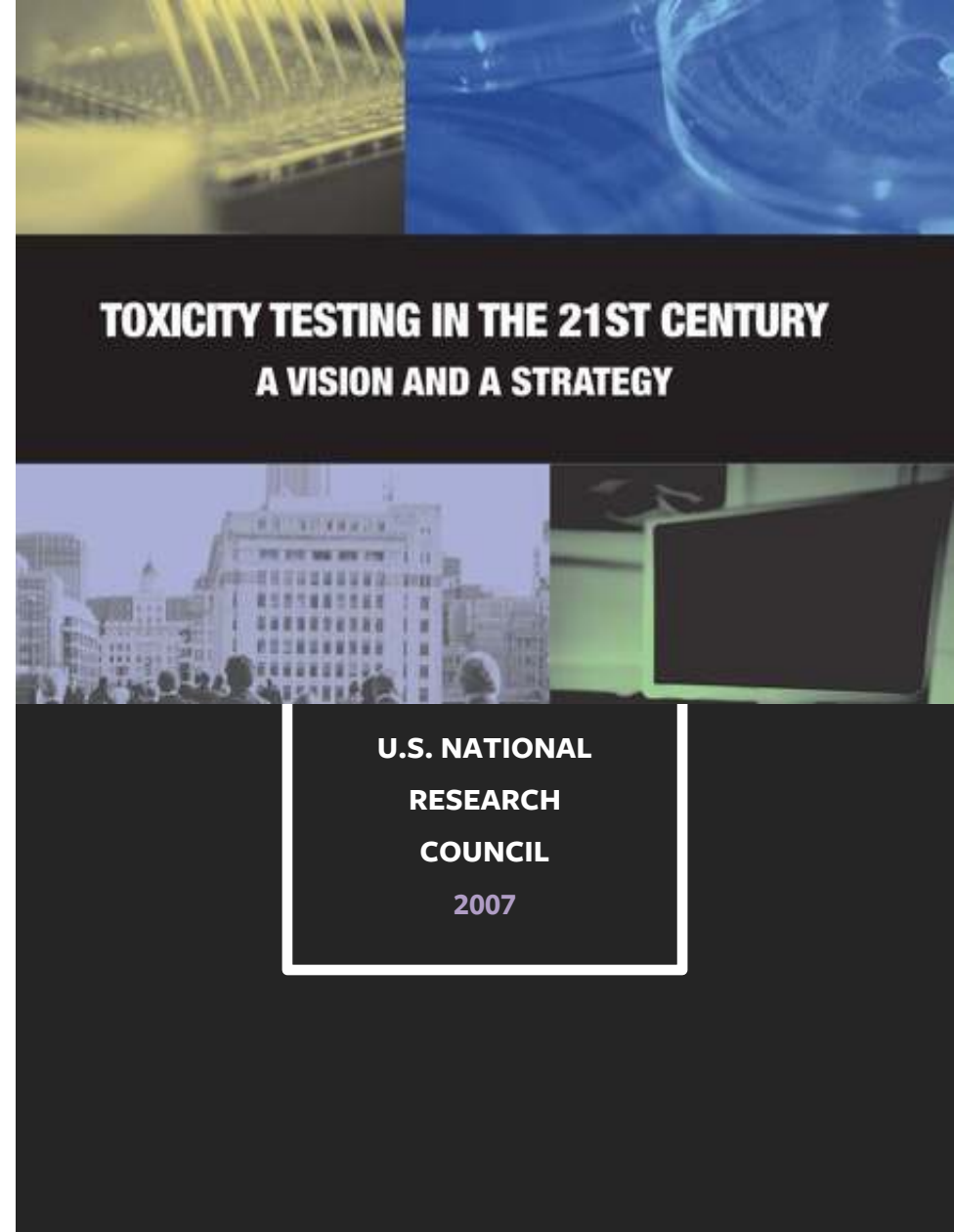
-Elias Zerhouni, MD

Former Director
National Institutes
of Health, USA

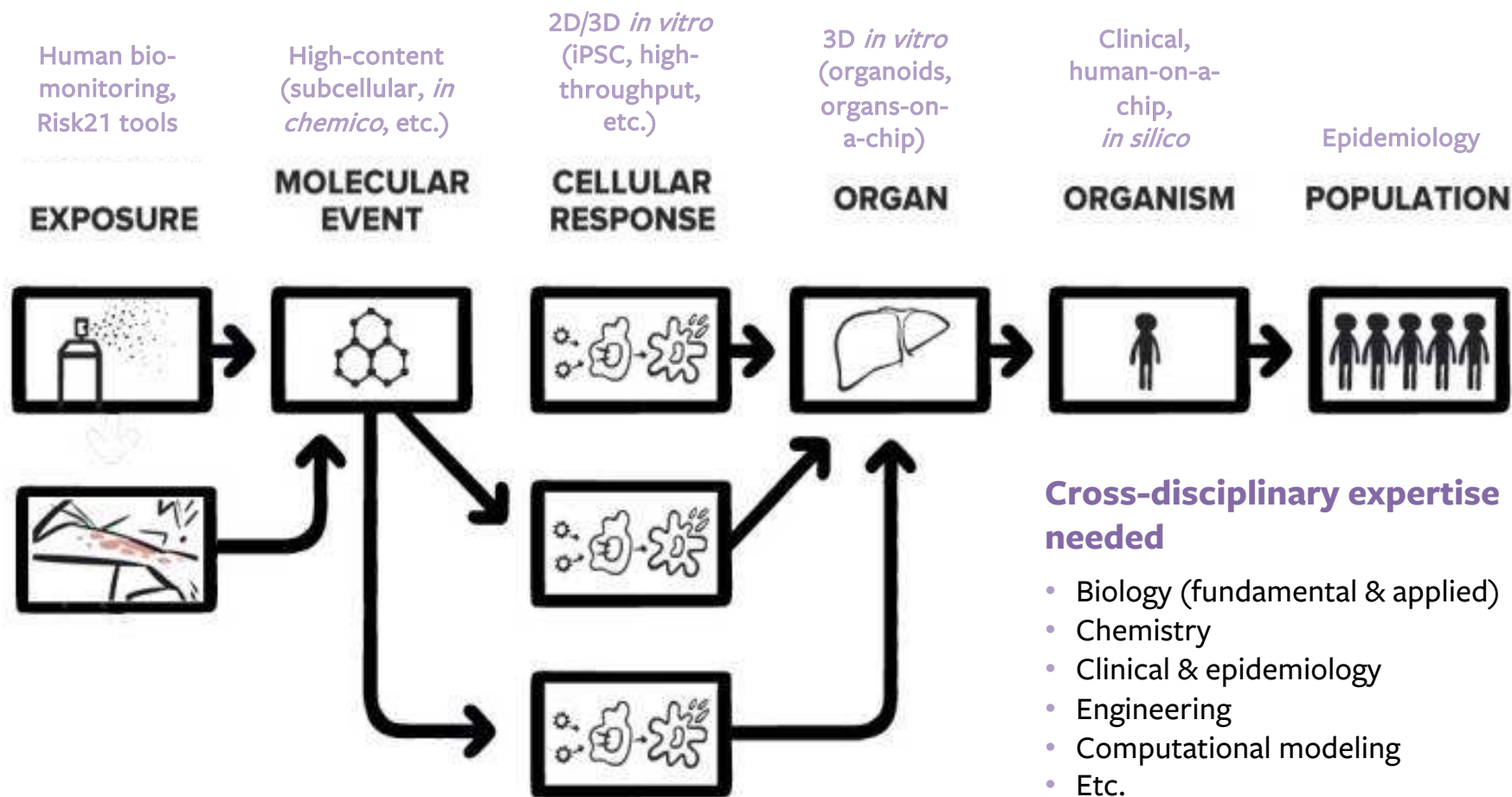


Tox21 vision

“ 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.”

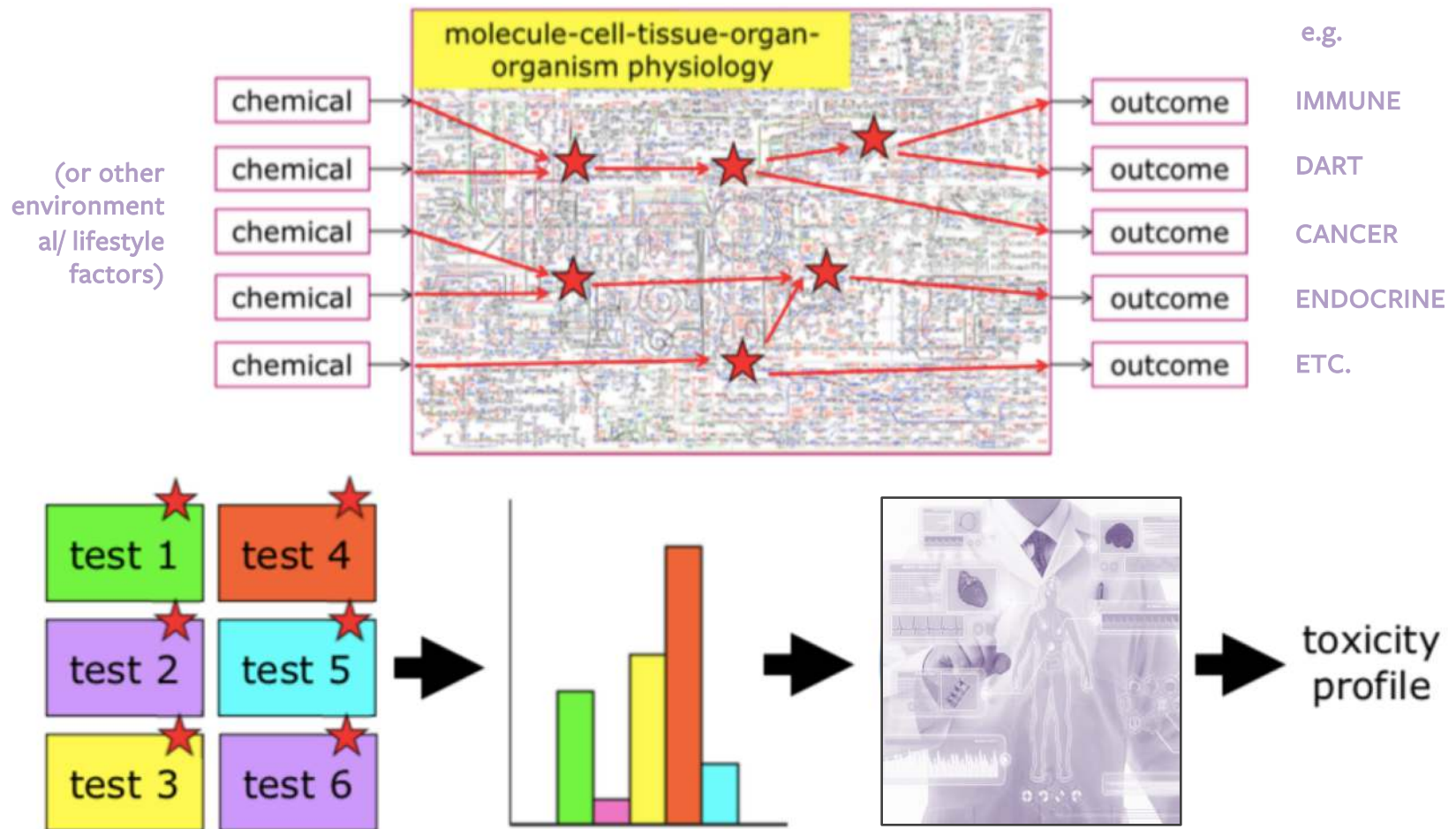


Adverse outcome pathways (AOPs) as an organizing framework



Tox21 vision

>> animal-free human risk assessment



Articulating a **scientific vision** of '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 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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Environmental Health Sciences



**European
Commission**



SBI

The
Systems
Biology
Institute



中国科学院
CHINESE ACADEMY OF SCIENCES



**Russian academy
of sciences**



PHILIPS

Philips Innovation Services

UC San Diego



**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.

BioMed21 scientific vision

>> human biology as the ‘gold standard’



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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 [AOPs].**”

Gill Langley,¹ Christopher P. Austin,² Anil K. Balapure,³ Linda S. Birnbaum,⁴ John R. Bucher,⁵ Julia Fentem,⁶ Suzanne C. Fitzpatrick,⁷ John R. Fowle III,⁸ Robert J. Kavlock,⁹ Hiroaki Kitano,¹⁰ Brett A. Lidbury,¹¹ Alysson R. Muotri,¹² Shuang-Qing Peng,¹³ Dmitry Sakharov,¹⁴ Troy Seidle,¹⁵ Thales Trez,¹⁶ Alexander Tonevitsky,¹⁷ Anja van de Stolpe,¹⁸ Maurice Whelan,¹⁹ and Catherine Willett²⁰

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BioMed21 scientific vision

>> bridging the disciplinary silos

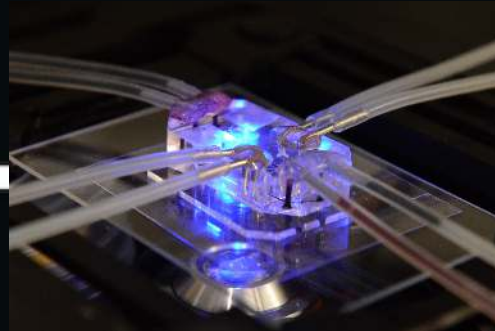
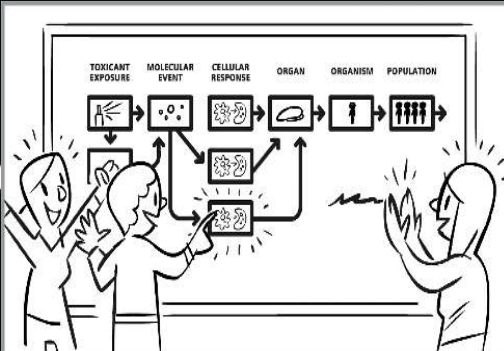
More multidisciplinary
collaboration
(clinicians,
big data)

Build models around
human patho/
physiology
(AOPs)

**Describe human
physiology in the
from of AOPs**

**Human micro-
physiological
systems**

**Computational
models for
prediction**



BioMed21 Collaboration

>> critical reviews & consensus-building



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)
 - Langley et al. Drug Discov. Today 2017
- 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
 - Marshall et al. Drug Discov. Today 2018



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

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
- » Visit **BioMed21.org/subscribe** for news on funding opportunities, events, publications and more

"Let's think outside the cage"

