Catherine Willett
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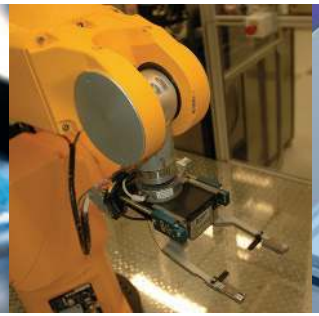
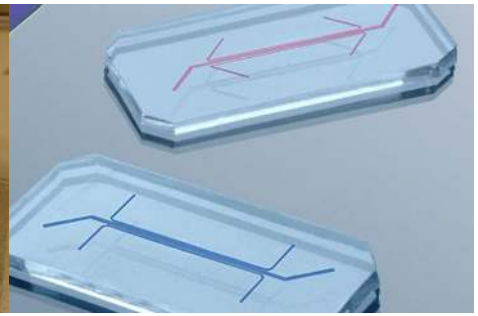
BIOMED 21

Toward a human-specific paradigm for health research: harmonization of global efforts

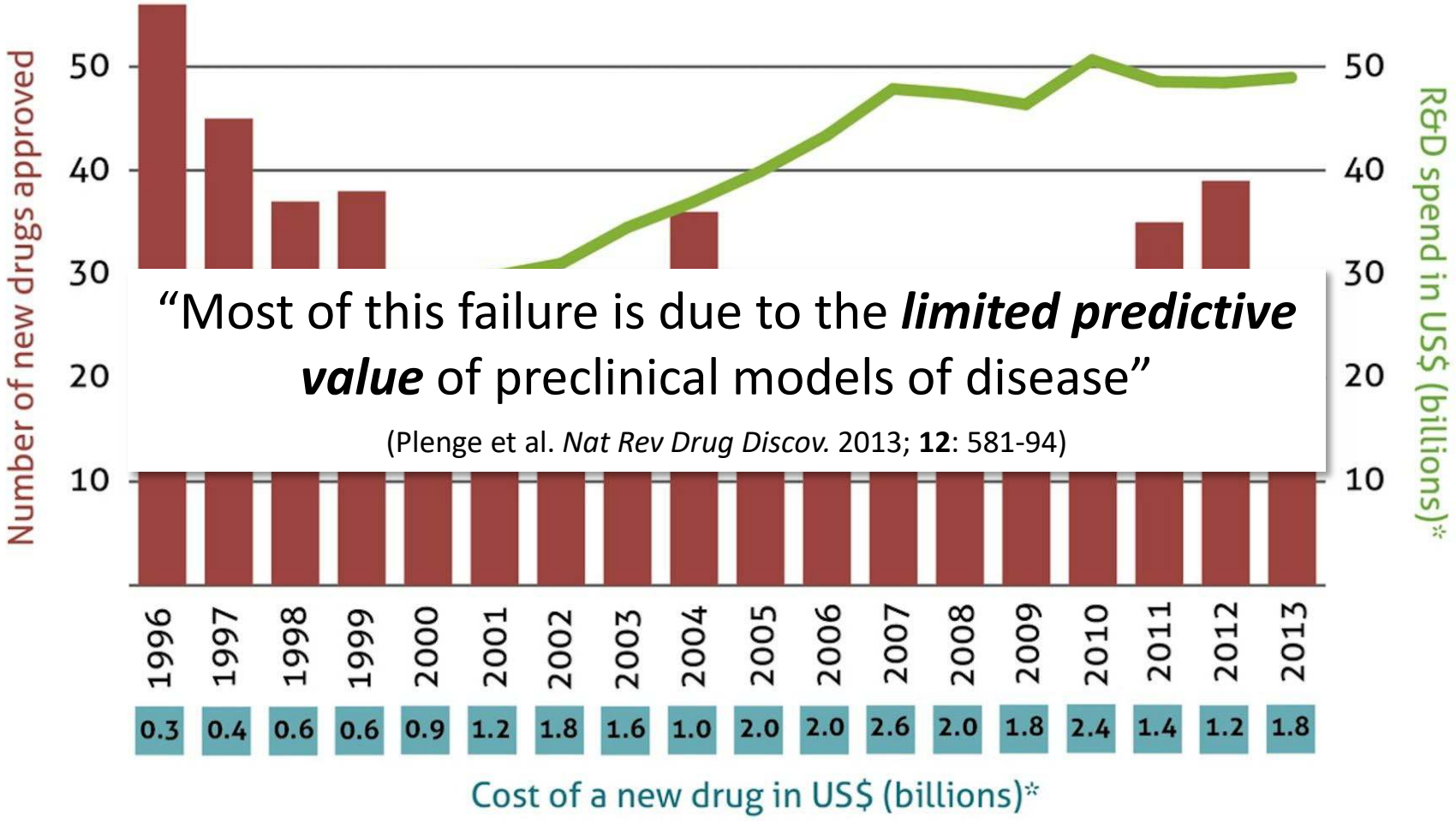
Overview

- The need and desire for a new approach to biomedicine
- Recent work to set the stage
- Survey of global "roadmaps" for a transition to more human-focused research
- Common themes and recommendations for future success



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



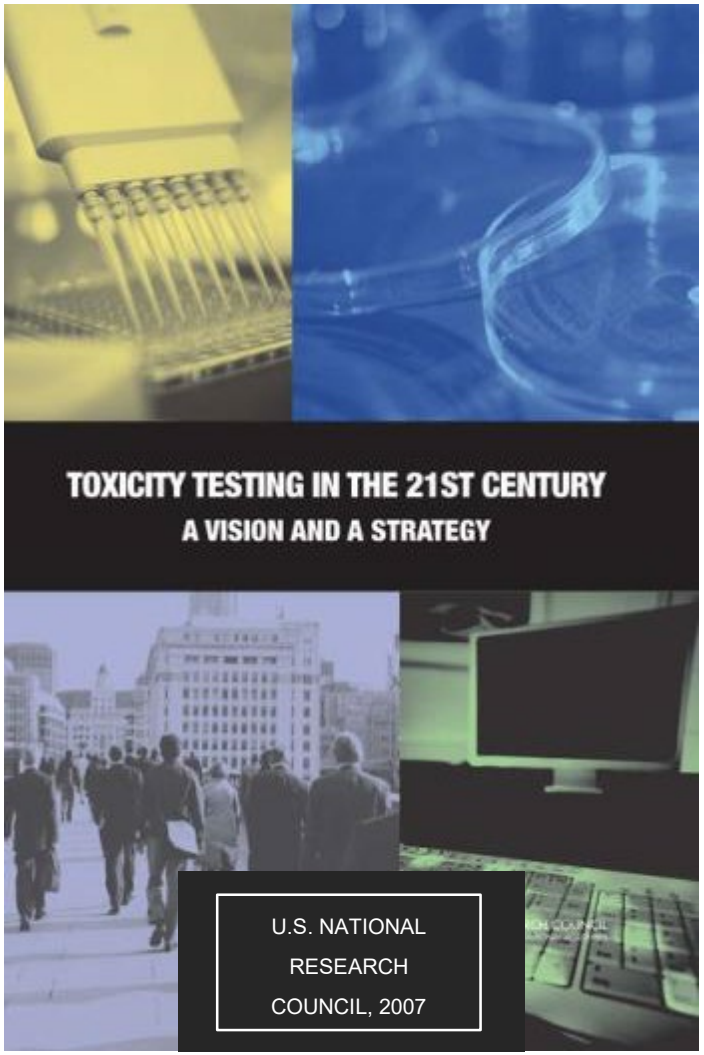
"Most of this failure is due to the ***limited predictive value*** of preclinical models of disease"

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

Rathi, A. (2014) TheConversation.com

Data: USFDA, PhRMA

The need for a shift from empirically measured to predictive toxicology



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*."

"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*…"

"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 U.S. National Institutes of Health
2013

"I predict that 10 years from now, safety testing for newly developed drugs…will be largely carried out using human biochips…This approach…will mostly replace animal testing for drug toxicity and environmental sensing, giving results that are more accurate, at lower cost and with higher throughput."

Francis Collins, MD, PhD
Director U.S. National Institutes of Health
2016

Similar solution to the same problems in biomedicine?

ehp ENVIRONMENTAL HEALTH PERSPECTIVES
Perspectives | Brief Communication

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

Langley et al. 2015. Nov 1;123(11):A268-72.

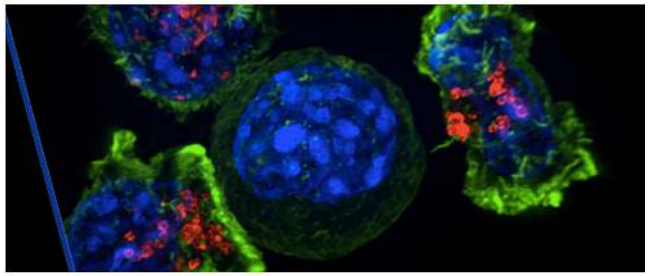
"We suggest a *new conceptual framework* … with research focused on *human-specific models* to understand disease pathways at multiple biological levels that are *analogous to adverse outcome pathways in toxicology*."

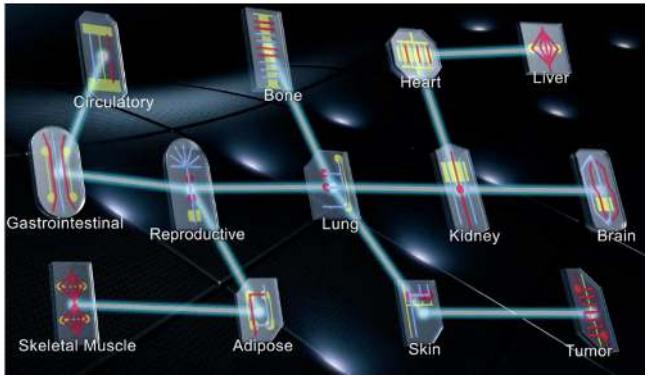
NIH National Center for Advancing Translational Sciences
HUMANE SOCIETY INTERNATIONAL
THE HUMANE SOCIETY OF THE UNITED STATES
FDA
SBI The Systems Biology Institute
European Commission
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NIEHS National Institute of Environmental Health Sciences
UCSanDiego
CDRI
PHILIPS Philips Innovation Services
Russian academy of sciences
中国科学院 CHINESE ACADEMY OF SCIENCES
Australian National University
Unifal-MG Universidade Federal de Alfenas
Unilever

Early steps in the transition: recent reviews of disease models

- **Common themes:**
  - Following extensive investment in animal models, cures are lacking
  - Understanding of human biological mechanisms is critical for improving health outcomes
  - New technologies based on human biology (iPSC, 3-D tissues, microfluidic devices) are critical for improved understanding
  - Improved future outcomes depend on increased investment in these human-relevant approaches

Early steps in the transition: large scale data generation/management/integration systems

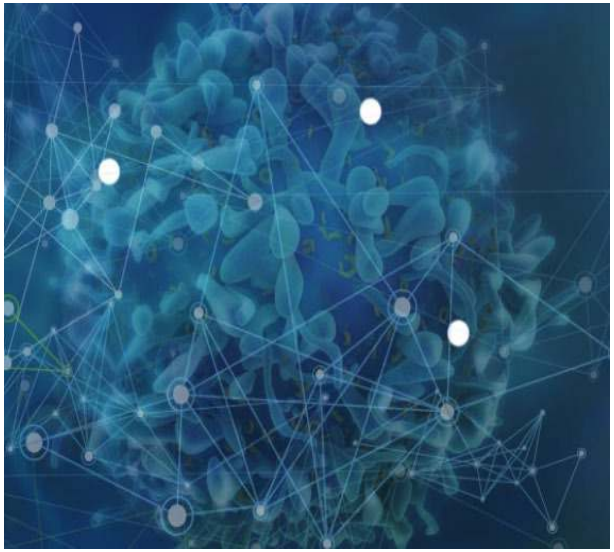




US National Institutes of Health

- **National Center for Advancing Translational Science**
  - facilitates the translation of new findings in basic research into improved diagnostics and therapeutics, through:
    - collaborations across disciplines and organizations
    - effective linking of research on disease mechanisms with clinical outcomes
    - High-throughput screening facility
- **Biomedical Data TRANSLATOR**
  - integrates multiple types of existing data sources.
  - to enable a *shift from the current symptom-based diagnosis* of disease classification to one that is based on *a set of molecular and cellular abnormalities*
- **NIH/DARPA/FDA human-on-a-chip**
  - Tissue Chip Program: (https://ncats.nih.gov/tissuechip)
  - To develop a ten-organ system via grants

Early steps in the transition: large scale data generation/management/integration systems



US National Institutes of Health

- **Big Data to Knowledge (BD2K)**
  - trans-NIH initiative
  - integration of big data and data science into biomedical research
  - "FAIR" principles: Findable, Accessible, Interoperable, and Reusable
- **National Cancer Institute**
  - ***Cancer Systems Biology Consortium***
  - tackling the challenges of complexity in cancer research
  - combining experimental biology and computational modeling, multi-dimensional data analysis, systems engineering
- **National Institute of Mental Health**
  - ***Research Domain Criteria framework project***
  - goal of improving the development of novel targets for therapeutic intervention *by realigning patients* with the *molecular signatures of their underlying disease*

Early steps in the transition: large scale data generation/management/integration systems

SEURAT-1

Towards the Replacement of in vivo Repeated Dose Systemic Toxicity Testing

EUTOXRISK

Europe

- **Innovative Medicines Initiative (IMI)**
  - ***eTOX project (www.etoxproject.eu)***
  - mine pharmaceutical databases, align the data, identify new linkages
  - development of better predictive tools
  - proprietary
- **Framework programs SEURAT-1 and EU ToxRisk**
  - comprehensive mechanistic understanding of cause-consequence relationships of chemical adverse effects (AOPs) of repeat-dose toxicity
  - integrate advancements in cell biology, omics technologies, systems biology and computational modelling
  - Proof-of-concept case studies

A UK roadmap for non-animal technologies

Innovate UK has identified *non-animal technologies* (NATs) as one of a series of emerging technologies with *the potential to drive future UK economic growth*…

The vision is to use NATs to deliver "*improved decision-makingtools* that result in more rapid discovery and development of medicines, agrichemicals, chemicals and consumer products."

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

A UK roadmap for non-animal technologies

Recommendations:

- Support capacity building in multidisciplinary science and technology
- Foster collaborations between industry, the SME sector and academia
- Analyze emerging international trends and activities to identify collaborators…and…avoid duplication
- Establish a strategic advisory board…to provide advice and to help drive forward the roadmap

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

Netherlands government opinion on non-animal research

- Goal is to move to completely non-animal approaches
- Sector-specific goals, timelines, etc.
  - *Regulatory science*
  - *Fundamental research*
  - *applied and translational research,*
  - *Education and training*
- Essential elements
  - *Clear transition objectives*
  - *Transition strategy*
  - *Interdisciplinary, multi-level, international*
  - *Strong management*

https://www.ncadierproevenbeleid.nl/documenten/rapport/2016/12/15/ncad-opinion-transition-to-non-animal-research

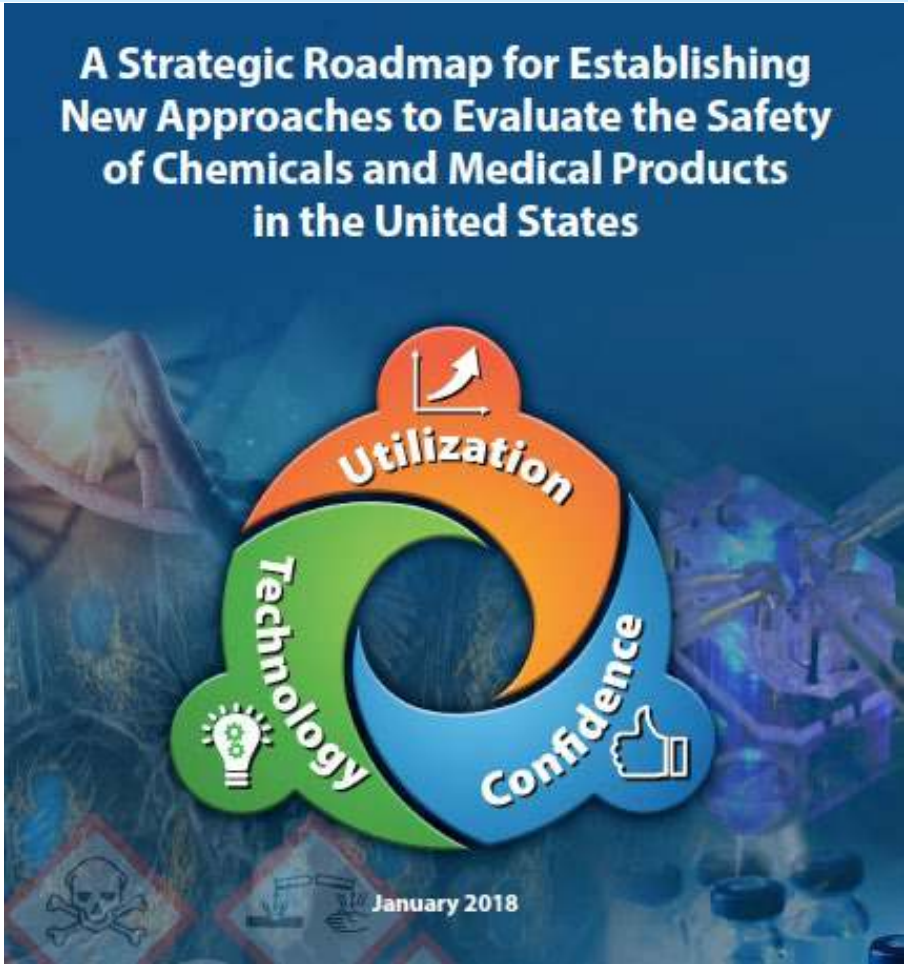
Netherlands roadmap for non-animal research

- "*if we imagine that we have achieved our goal of animal-free safety assessment, looking back from that point, what steps were taken to get there?*"
- Themes
  - *Societal perception of safety*
  - *Implementation in legal framework*
  - *Future safety assessment*
  - *Populate the toolbox*
- Essential conditions
  - *Commitment*
  - *Coordination*
  - *Continuity*
  - *Cooperation*
  - *Communication*
  - *Cost*

https://www.rivm.nl/dsresource?objectid=571f1221-8ada-4488-99ef-2424acd50d30&type=PDF

US ICCVAM strategic roadmap

The Interagency Coordinating Committee on the Validation of Alternative Methods



Developed with input from the 16 US Federal Agencies that use animals in safety testing

Enable development
- *ID information needs*
- *Connect developers with users*

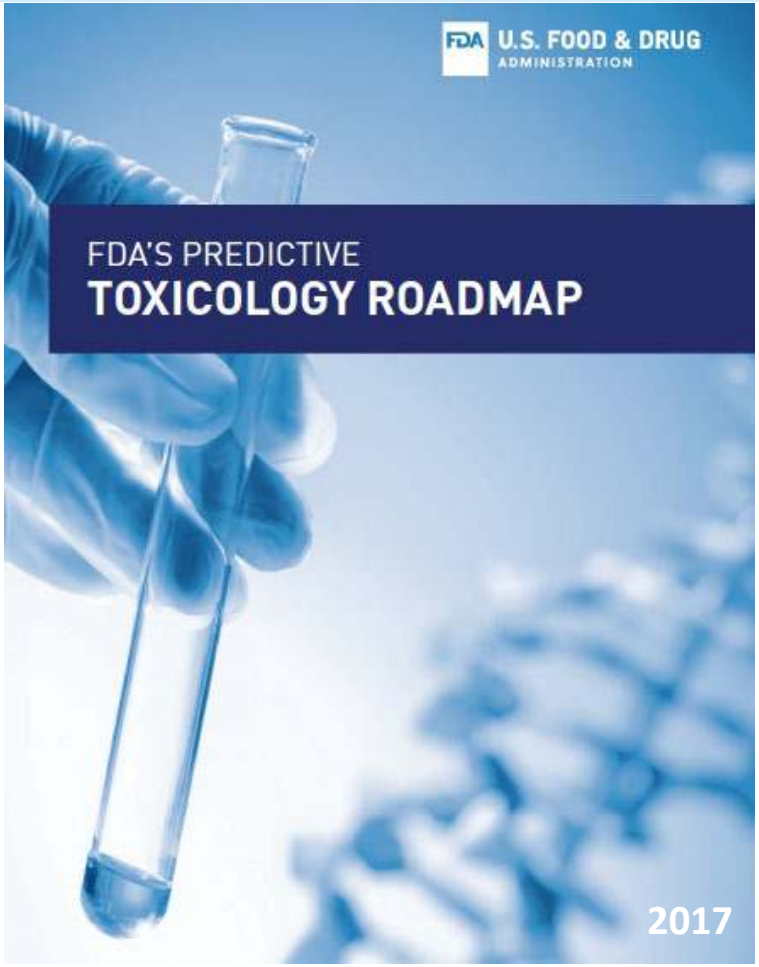
Establish confidence
- *Context of use*
- *Case studies*
- *Collaboration*

Ensure use
- *Agencies provide clear guidance*
- *International collaboration*
- *Incentives*

Plan implementation through working groups and detailed action plans

https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html

FDA Roadmap for predictive toxicology



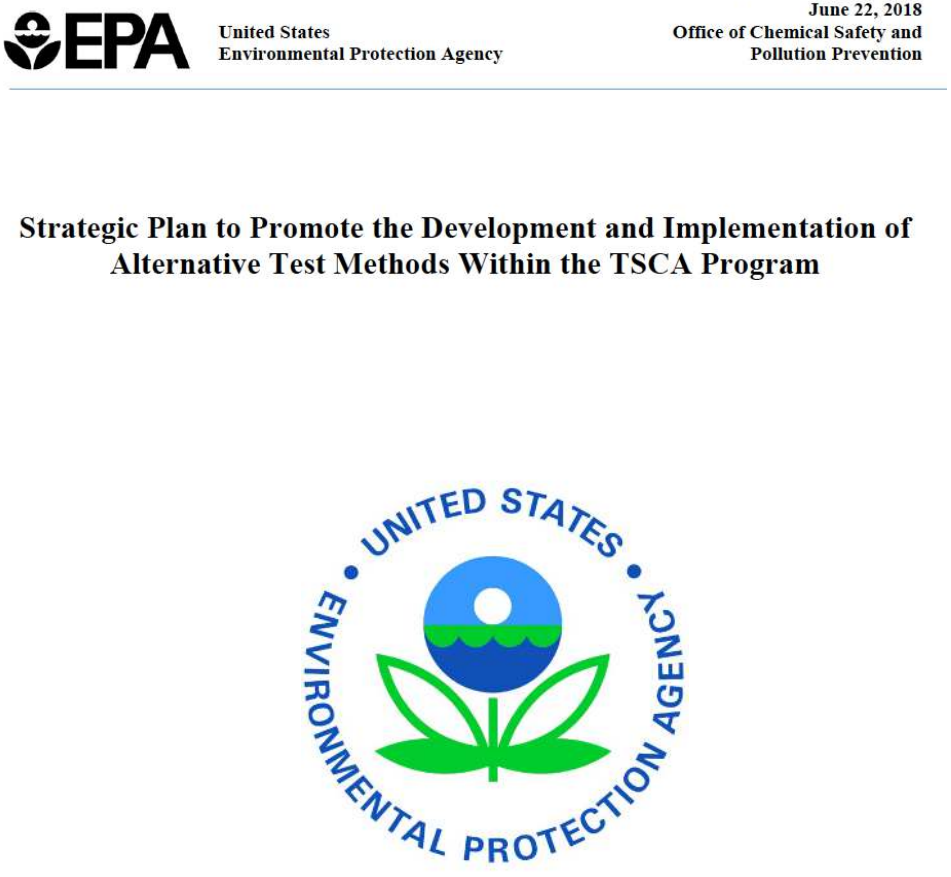
Goal: to expand predictive capabilities and integrate these methods into regulatory review

Framework

- Organizing committee: cross-center working group
  - Reviews ongoing FDA research
  - Develop context of use examples
  - Acceptance of newer technologies
  - Establish confidence
    - Context of use qualification
- Training
- Communication with drug developers
- Collaboration across sectors/disciplines
- Oversight: track progress and report to commissioner annually

https://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/ucm601090.htm

EPA OPPT Strategic Plan to promote NAMs



EPA

United States
Environmental Protection Agency

EPA Document# EPA-740-R1-8004
June 22, 2018
Office of Chemical Safety and
Pollution Prevention

Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf

Principles

- Multi-office collaboration
- public-private partnerships
- Meeting needs of regulators and end-users

Approach

- Identification, development, and Integration
- ID knowledge gaps → research
- Scientific Confidence
  - Relevance: fit for purpose and use
  - Reliability: performance-based criteria (Casati et al. (2017)
- Integration Frameworks
  - AOP, IATA, Defined Approaches

Implementation

- TSCA NAM Team (TNT) oversight
- Communication, Training, Outreach, Collaboration
- Short, medium, long-term actions

BIOMED 21 COLLABORATION

Toward a human-focused paradigm in health research

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

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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[18] Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium
[19] Animal Research Issues, The Humane Society of the United States, Boston, MA, USA
[20] MRC/Asthma UK Centre in Allergic Mechanisms of Asthma, Division of Asthma, Allergy & Lung Biology, King's College London, Guy's Hospital, London, UK

Corresponding author: Langley, G.R. (sciencesources@btinternet.com)

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'.

EU Workshop 2015, Brussels

Conclusions

- Continued reliance on animal models unlikely to improve clinical translation
- Overarching strategic frameworks are essential to guide science policy
- Funding should be focused on acquiring critical human information & developing/ validating human-specific tools
- Enhanced research coordination among key economies,
- Enhanced strategies to collect human biological material & clinical information
- Obligatory open-access publication & data sharing for all publicly funded research

BIOMED 21 COLLABORATION

Toward a human-focused paradigm in health research

Drug Discovery Today • Volume 00, Number 00 • June 2018 REVIEWS

ELSEVIER

Teaser Improved translation of research is needed to inform safe and effective drug development. This will require a broad collaborative effort, open data sharing, and prioritized funding for human-relevant research.

Recommendations toward a human pathway-based approach to disease research

Lindsay J. Marshall[1], Christopher P. Austin[2], Warren Casey[3,4], Suzanne C. Fitzpatrick[5] and Catherine Willett[1]

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[2] Office of the Director, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD 20817, USA
[3] National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, USA
[4] National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709, USA
[5] Center for Food Safety and Applied Nutrition, FDA, Harvey W. Wiley Building, 5100 Paint Branch Parkway, College Park, MD 20740, USA

Failures in the current paradigm for drug development have resulted in soaring research and development costs and reduced numbers of new drug approvals. Over 90% of new drug programs fail, the majority terminated at the level of Phase 2/3 clinical trials, largely because of efficacy failures or unexplained toxicity. A recent workshop brought together members from research institutions, regulatory agencies, industry, academia, and nongovernmental organizations to discuss how existing programs could be better applied to understanding human biology and improving drug discovery. Recommendations include increased emphasis on human relevance, better access and curation of data, and improved interdisciplinary and international collaboration.

Introduction

Despite the investment of billions of dollars, development of new drugs and other potential disease interventions remain elusive and immensely expensive. The average pre-approval cost of research and development for a successful drug is estimated to be US$2.6 billion [1] and the number of new drugs approved per billion US dollars spent has halved approximately every 9 years since 1950 [2]. More than 90% of drug candidates entering clinical trials fail to gain regulatory approval, mainly as a result of insufficient efficacy and/or unacceptable toxicity, because of the limited predictive value of preclinical studies [3]. One analysis of attrition rates between 1991 and 2000, using data from ten big pharma companies in the EU and USA, found Phase 2 and 3 failures of 62% and 45%, respectively [4]. Although there is widespread acknowledgement that the likelihood of success varies with therapeutic area (oncology has particularly low success rates [5]), it is clear that drug candidates are failing between Phase 2 and submission,

Corresponding author: Marshall, L.J. (marshall@hsi.org)

Christopher Austin is the director of the National Center for Advancing Translational Sciences (NCATS) at the US National Institutes of Health (NIH). He leads the Center's work to improve the translation of observations in the laboratory, clinic, and community into interventions that reach and benefit patients, from diagnostics and therapeutics to medical procedures and behavioral changes. Under his direction, NCATS researchers and collaborators are developing new technologies, resources, and collaborative research models demonstrating their usefulness, and disseminating the data, analysis, and methodologies for use by the worldwide research community.

Warren Casey is the director of National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and Executive Director of the US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). These groups work together to facilitate the development, validation, regulatory acceptance, and industry adoption of non-animal test methods. He has been a diplomate of the American Board of Toxicology (DABT) since 2007, received the 2016 Society of Toxicology Animal Welfare Award, currently serves as the vice president of the SOT in vitro and Alternative Methods Specialty Section, and co-chairs the OECD Validation Management Group – Non-Animal.

Catherine Willett is the director of Regulatory Toxicology, Risk Assessment and Alternatives at Humane Society International and the Humane Society of the United States. She coordinates the Human Toxicology Project Consortium, a multistakeholder group focusing on pathway-based toxicology. She is an active member of the OECD Adverse Outcome Pathway (AOP) training group as well as the Society for the Advancement of AOPs. Dr Willett is a member of SOT, serves on the US National Toxicology Program Scientific Advisory Committee on Alternative Toxicological Methods, and is on the Scientific Advisory Board of the Institute of *In vitro* Sciences and Shell's Animal Testing Review Panel.

US Workshop 2017, Bethesda

Participants

- 160 scientists, policy makers from government, industry, academia, NGO, consulting
- US government: 6 NIH institutes, 5 FDA centers, EPA

Recommendations

- International and inter-agency collaboration
- Funding agency focus on human-based biology and open access data
- Collaborative, open-access high-quality databases
- Common reporting formats and common ontologies
- Better cross-sector communication
- Creation of case studies to show applications

In summary

- In biomedicine, a global transition to molecular understanding of disease pathways and human biology-based approaches is urgently needed and is already underway

Roadmaps

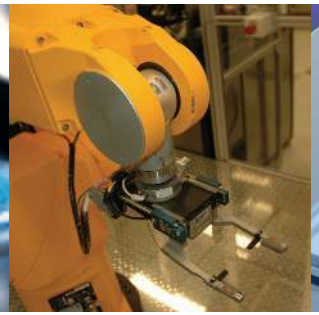
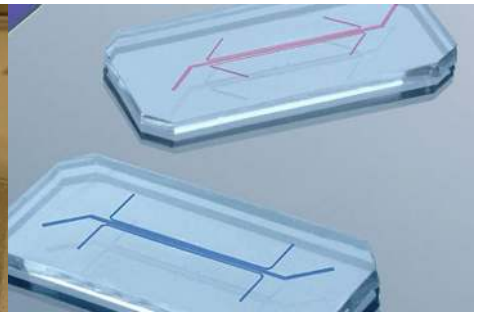
Common themes

- Leadership and oversight
- Collaborative: cross-agency/office/center
- Communication from inception to implementation

Common Approaches

- Identify information needs
- Develop NAMs to meet those needs
- Establish confidence
  - Context and use dependent
  - Performance criteria
- Integration based on AOPs, IATA, DA
- Communication with stakeholders
- Training



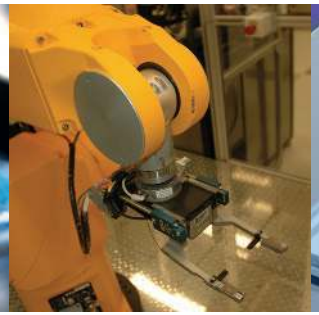
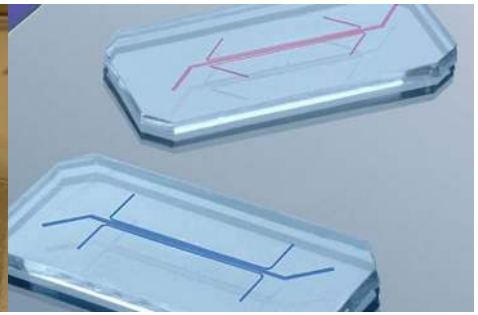



In summary

Common recommendations for success from workshops:

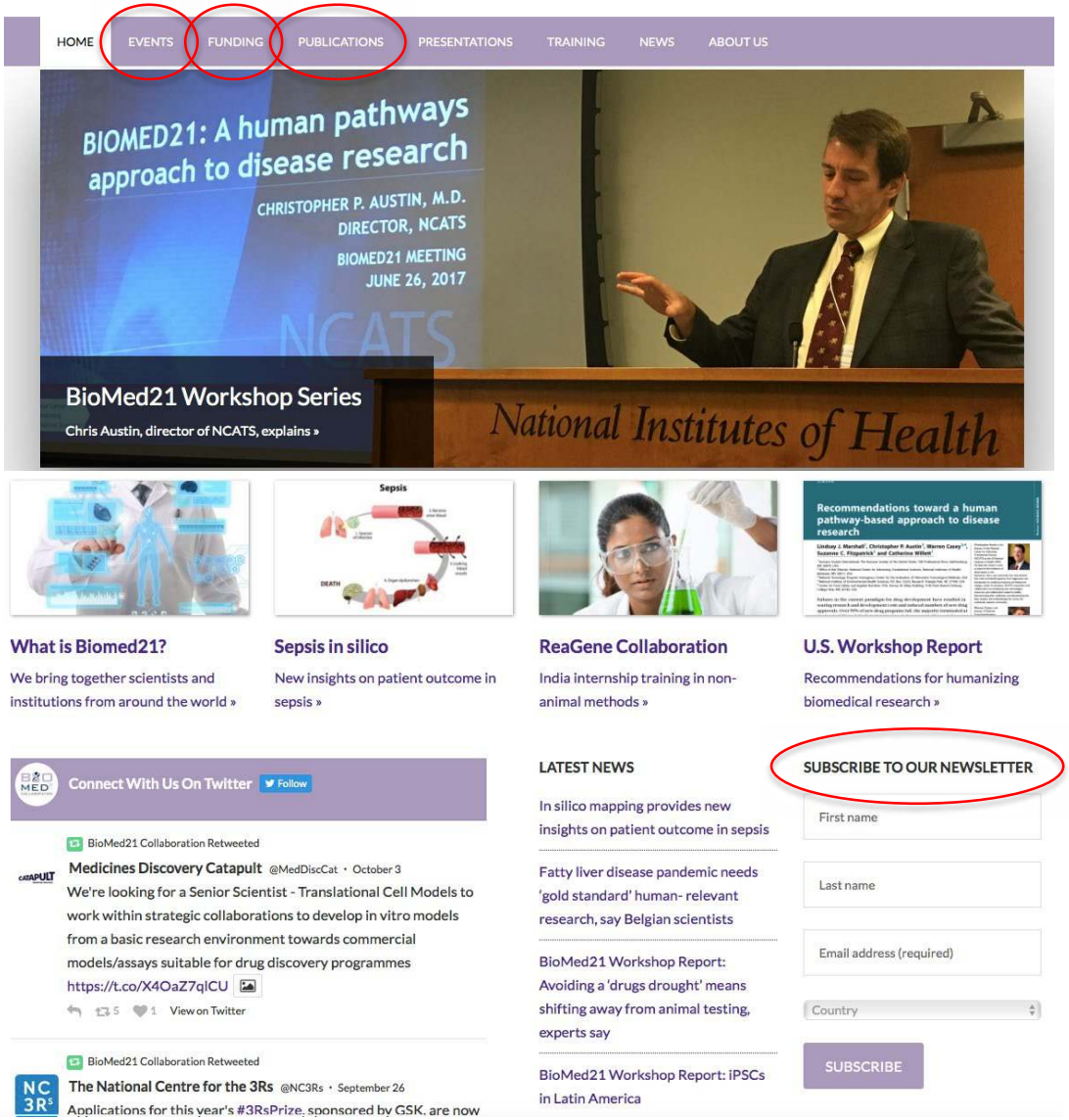
- Inter-agency, interdisciplinary and international collaboration
- Shift in funding to prioritize human biology-based approaches
- Leadership – to provide direction and focus
- Creation of strategic roadmaps to direct public policy
- Open access to high quality research and clinical data
- Creation of case studies to show proof of principle, gain confidence



BIOMED 21 COLLABORATION

Toward a human-focused paradigm in health research



The Biomedical Research for the 21st Century (BioMed21) Collaboration brings together scientists and institutions from across Europe, Asia and the Americas who share a vision of a new, human-focused paradigm in health research. This unique mix of health research stakeholders provides both a broad, global outlook as well as deep ties at regional and national levels. We welcome new collaboration opportunities with like-minded organizations and individuals.

BIOMED 21 COLLABORATION

Toward a human-focused paradigm in health research

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

EcoMole

HUMANE SOCIETY INTERNATIONAL
UNITED KINGDOM

Non-animal models for research on human respiratory tract disease

- EcoMole™, Imperial College London, and Humane Society International/United Kingdom, with support from the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)
- Compile and distribute information about available and emerging non-animal models in respiratory tract disease research

- Building a network of Indian scientists to share information and cooperate in promoting a shift in research focus and funding in India
- Supporting continuing education for Indian authorities to support confidence and accelerated acceptance of non-animal approaches for regulatory use
- Offering continuing education and hands-on training on OECD-validated non-animal technologies for young scientists in India via an internship program

ReaGene BIOSCIENCES
Translational Assays of Alternatives to Animals

HUMANE SOCIETY INTERNATIONAL
INDIA

Thank You!

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