NTP
National Toxicology Program

Developing a Strategy and Roadmap to Replace the Use of Animals for Toxicity Testing

Warren Casey, PhD, DABT

Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
National Institute of Environmental Health Sciences

H.R. 4281 (106th): ICCVAM Authorization Act of 2000

- "To establish, wherever feasible, guidelines, recommendations, and regulations that promote the **regulatory acceptance** of new and revised toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing (3Rs) animal tests and **ensuring human safety and product effectiveness**."

7 Regulatory Agencies

- Consumer Product Safety Commission
- Department of Agriculture
- Department of the Interior
- Department of Transportation
- Environmental Protection Agency
- Food and Drug Administration
- Occupational Safety and Health Administration

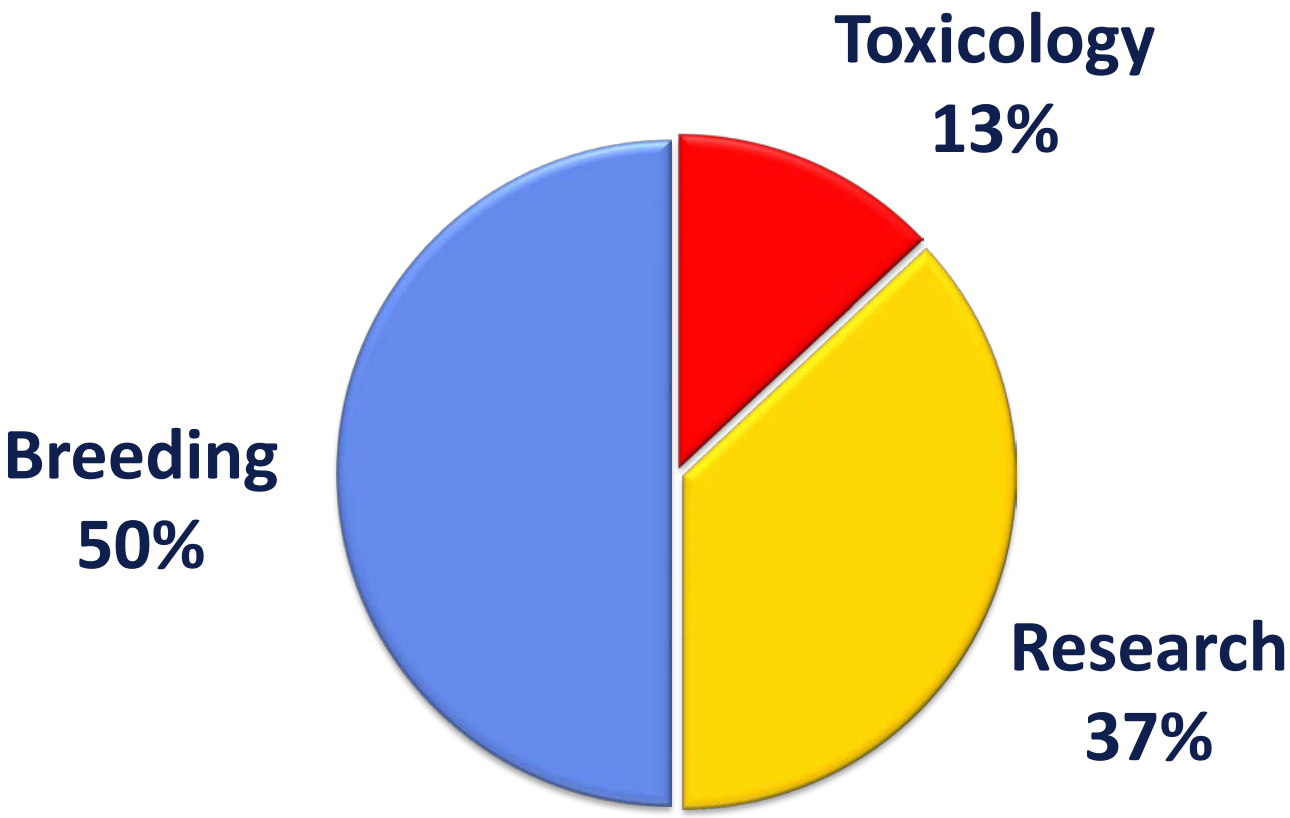
No funding
No authority

8 Research Agencies

- Agency for Toxic Substances and Disease Registry
- National Institute for Occupational Safety and Health-CDC
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Library of Medicine
- National Institutes of Health
- Department of Defense
- Department of Energy

Vertebrate Animal Use in the EU: ~12 Million

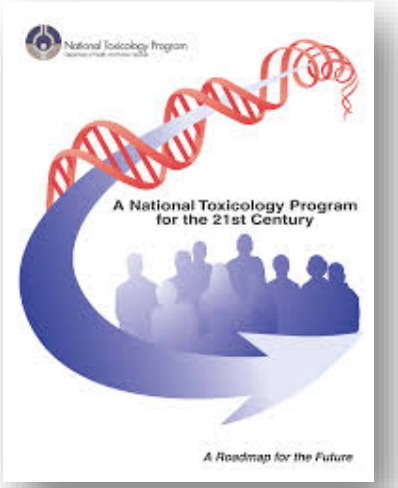
Rodents (rats and mice) account for ~85% of the total

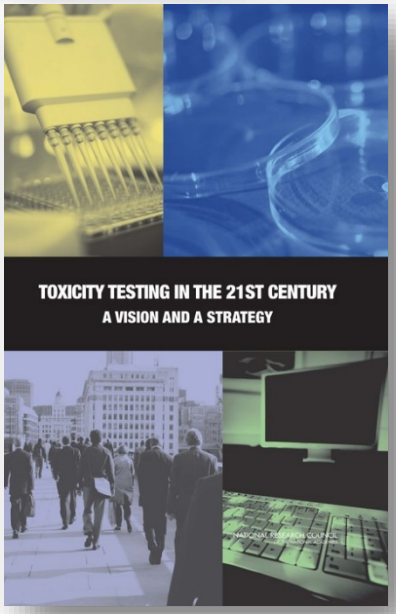


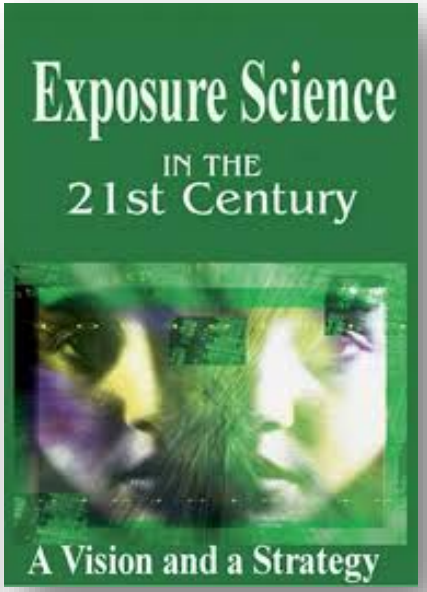
Seventh Report from the Commission to the Council and the European Parliament on the Statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union COM(2013)

Types of Toxicity Tests

- Acute oral toxicity
- Acute dermal toxicity
- Acute inhalation toxicity
- Acute eye irritation
- Acute dermal irritation
- Skin sensitization
- Pyrogenicity
- Repeat Dose Toxicity
- Pharmacokinetics and Metabolism
- Mutagenicity
- Carcinogenicity
- Reproductive and Developmental
- Neurotoxicity







FDA

NIH
National Institutes of Health

Tox21

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

ToxCast™

ehp ENVIRONMENTAL HEALTH PERSPECTIVES

15 Years Out: Reinventing ICCVAM

February 1, 2013 Editorials Comments Off

Linda S. Birnbaum

Director, NIEHS and NTP, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North

NICEATM will expand its scope and concentrate its resources on providing computational toxicology support to Tox21 projects

http://ehp.niehs.nih.gov/2013/02/1206292/

Strategy and Roadmap

“A goal without a plan is just a wish”

- Antoine de Saint-Expery

Strategy and Roadmap

“A goal without a plan is just a wish”

- Antoine de Saint-Expery

- Repeat Dose Toxicity
- Pharmacokinetics and Metabolism
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Neurotoxicity

Why change?

Drivers for change

- **Ethics**

Drivers for change

- **Economics**
  - Efficiency
    - Same result, but cheaper and faster
    - Ability to test 1000's of chemicals
  - International Trade
    - Animal testing bans for cosmetics: EU, India, New Zealand, Norway, Israel, Korea,…..
    - Chemical / product registration
      - REACH (EU, Korea, Japan, Canada,….)
      - Country-specific requirements

Drivers for change

- **Human Relevance / Public Health**

Genomic responses in mouse models poorly mimic human inflammatory diseases

OPEN ACCESS Freely available online

PLoS MEDICINE

Research in Translation

Can Animal Models of Disease Reliably Inform Human Studies?

H. Bart van der Worp[1]*, David W. Howells[2], Emily S. Sena[2,3], Michelle J. Porritt[2], Sarah Rewell[2], Victoria O'Collins[2], Malcolm R. Macleod[3]

1 Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, The Netherlands, 2 National Stroke Research Institute & University of Melbourne Department of Medicine, Austin Health, Melbourne, Australia, 3 Department of Clinical Neurosciences, University of Edinburgh, Edinburgh, United Kingdom

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Regulatory Toxicology and Pharmacology

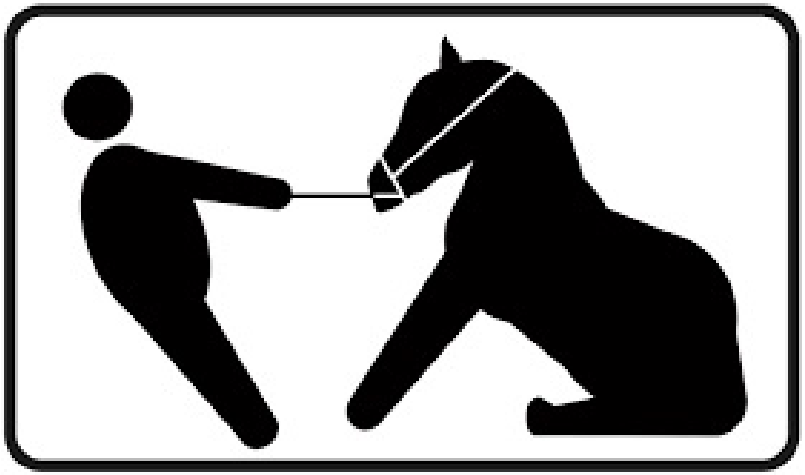
journal homepage: www.elsevier.com/locate/yrtph

The ability of animal studies to detect serious post marketing adverse events is limited

Peter J.K. van Meer [a,*], Marlous Kooijman [b], Christine C. Gispen-de Wied [c], Ellen H.M. Moors [b], Huub Schellekens [a,b]

Institutional resistance

- Existing legislation, policy, and practices.



Institutional resistance

"It is difficult to get a man to understand something, when his salary depends upon his not understanding it.“

- Upton Sinclair

Metrics

- We need a way to measure success quantitatively

International Harmonization

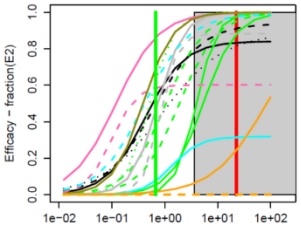
- Trade barriers (i.e., Animal Testing Bans)
- Redundant testing (i.e., China)

Animals as gold standard

- How do you validate “human-based” approaches against animal models that are not predictive of human outcomes?
- Double standards for animal-based tests.
  - Little or no validation
  - Results often reported as point estimates with no estimate of variability

Complexity

- Mammalian physiology is <u>complex</u>



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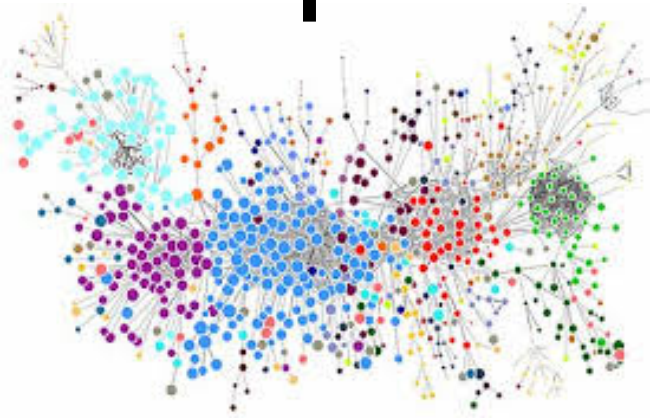

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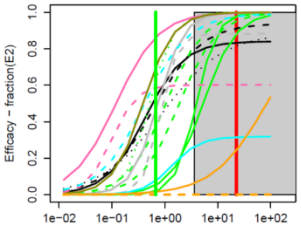
Complexity

- Mammalian physiology is <u>complex</u>
- Toxicology is predominantly observational (not predictive) and <u>subjective</u>



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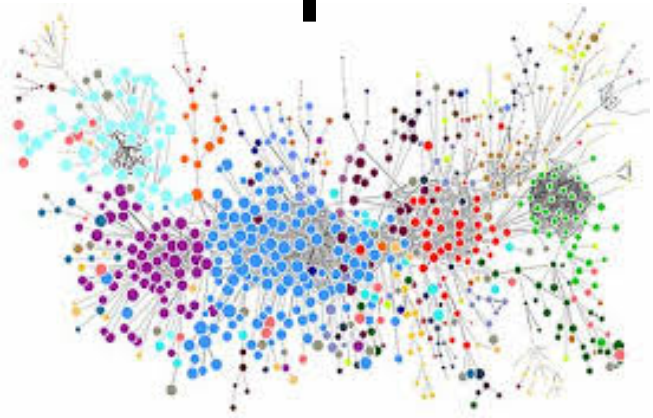

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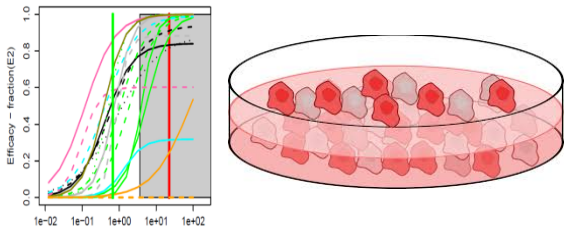
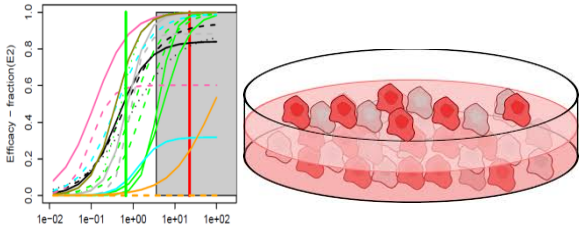
Parallelogram Approach



Rodent In Vitro

Interspecies Differences



Human In Vitro

IVIVE*

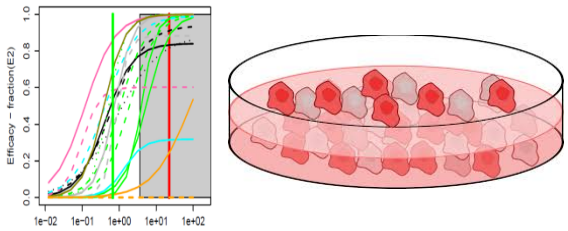
IVIVE*

Rodent In Vivo

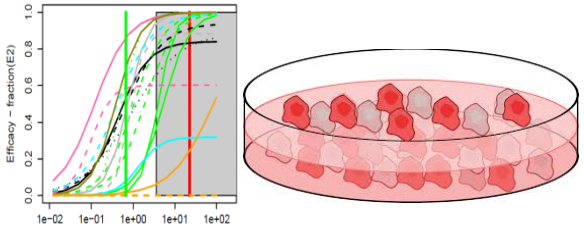
Human In Vivo

*In Vitro to In Vivo Extrapolation (IVIVE)

Parallelogram Approach



Interspecies Differences



Rodent In Vitro

Human In Vitro

IVIVE*

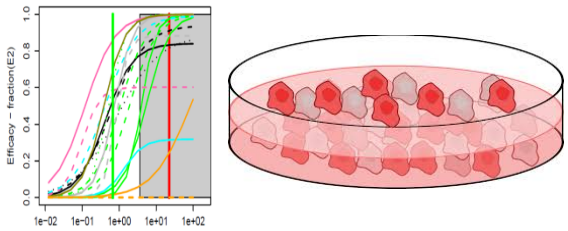
IVIVE*

Human In Vivo

Rodent In Vivo

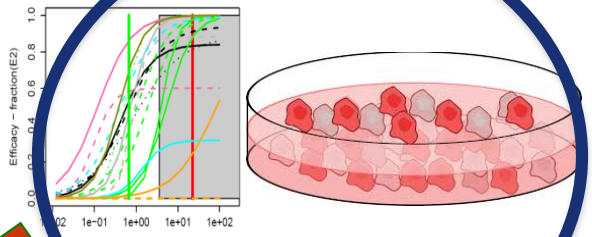
*In Vitro to In Vivo Extrapolation (IVIVE)

Parallelogram Approach



Rodent In Vitro

Interspecies Differences



Human In Vitro

IVIVE*

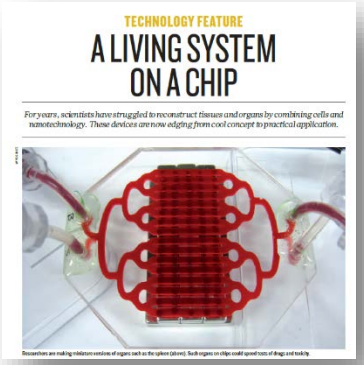
IVIVE*

Rodent In Vivo

Human In Vivo

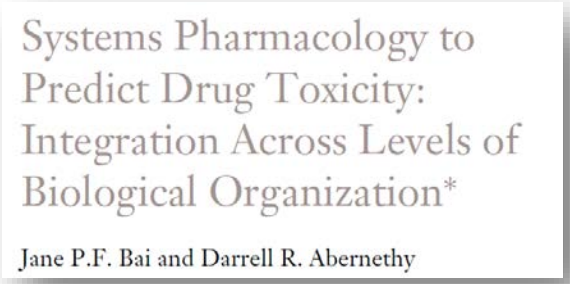
*In Vitro to In Vivo Extrapolation (IVIVE)

New Technologies

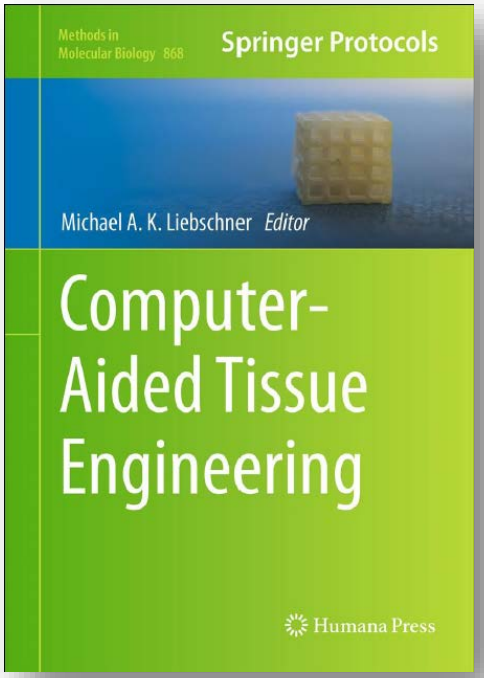

TECHNOLOGY FEATURE

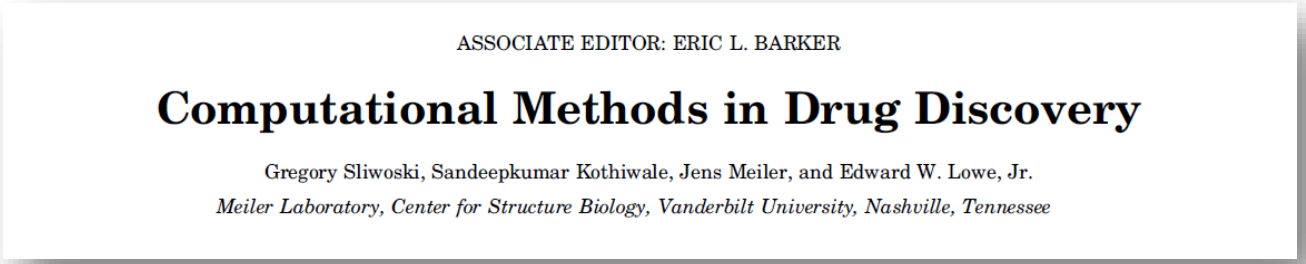
A LIVING SYSTEM ON A CHIP

For years, scientists have struggled to reconstruct tissues and organs by combining cells and nanotechnology. These devices are now edging from cool concept to practical application.


Systems Pharmacology to Predict Drug Toxicity: Integration Across Levels of Biological Organization*

Jane P.F. Bai and Darrell R. Abernethy




ASSOCIATE EDITOR: ERIC L. BARKER

Computational Methods in Drug Discovery

Gregory Sliwoski, Sandeepkumar Kothiwale, Jens Meiler, and Edward W. Lowe, Jr.

Meiler Laboratory, Center for Structure Biology, Vanderbilt University, Nashville, Tennessee

Acute Toxicity

New EPA Guidance for Testing Pesticides Will Reduce Animal Testing

For Release: March 17, 2016

Today, in an open letter to stakeholders EPA is announcing progress on its goal to significantly reduce the use of animals in acute effects testing, and is releasing two guidance documents in support of this goal. Rapid advancements in science and new technologies allow us to evaluate more pesticides across a broader range of potential effects in less time, using fewer animals and reducing costs for everyone. EPA is adopting alternative approaches to more traditional toxicity testing and using Integrated Approaches to Testing and Assessment (IATA) to enhance the quality of its risk assessments and risk management decisions.

Opportunities

Replacing the use of animals for:

- ✔ Acute oral toxicity
- ✔ Acute dermal toxicity
- ✔ Acute inhalation toxicity
- ✔ Acute eye irritation
- ✔ Acute dermal irritation
- ✔ Skin sensitization
- ✔ Pyrogenicity

- Repeat Dose Toxicity
- Pharmacokinetics and Metabolism
- Mutagenicity
- Carcinogenicity
- Reproductive and Developmental Tox
- Neurotoxicity

~2 years

Opportunities

Francis Collins' recent testimony to the congressional subcommittee with NIH budget oversight responsibility, 7 April 2016

http://www.appropriations.senate.gov/hearings/hearing-on-fy2017-national-institutes-of-health-budget-request

United States Senate Committee on
APPROPRIATIONS

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Subcommittee Hearing

Hearing on FY2017 National Institutes of Health Budget Request

Labor, Health and Human Services, Education, and Related Agencies
Date: Thursday, April 7, 2016
Time: 10:00 AM
Location: Dirksen Senate Office Building 138

In Francis Collins' recent testimony to the congressional subcommittee with NIH budget oversight responsibility, he offered that :

- Animal safety testing for environmental chemicals and drugs will largely be replaced by tissue chips and iPS cells in 10 years.

- This approach will mostly replace animal testing for drug toxicity and environmental sensing, giving results that are more accurate, at lower cost and higher throughput.

http://www.appropriations.senate.gov/hearings/hearing-on-fy2017-national-institutes-of-health-budget-request

Strategy and Roadmap

Developing a US Strategy and Roadmap to be the topic of discussion at the upcoming Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) September 27-28, 2016.

Strategy and Roadmap: Questions

- *Given the diversity of political, social, and scientific efforts needed to address refinement vs replacement and reduction, should the US roadmap focus only on replacement and reduction? If so, how should refinement be addressed?*

warren.casey@nih.gov

Thank you!

Questions?