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

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• “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

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

No funding
No authority
Vertebrate Animal Use in the EU: ~12 Million

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

- Breeding: 50%
- Research: 37%
- Toxicology: 13%

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

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

Can Animal Models of Disease Reliably Inform Human Studies?

H. Bart van der Worp, David W. Howells, Emily S. Sena, Michelle J. Porritt, Sarah Rewell, Victoria O’Collins, Malcolm R. Macleod

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

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

Peter J.K. van Meer, Marilous Kooijman, Christine C. Gispen-de Wied, Ellen H.M. Moors, Huub Schellekens
Challenges

Institutional resistance

• Existing legislation, policy, and practices.
Challenges

Institutional resistance

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

- Upton Sinclair
Challenges

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
Challenges

Complexity

• Mammalian physiology is complex
Challenges

Complexity

- Mammalian physiology is complex
- Toxicology is predominantly observational (not predictive) and subjective
Parallelogram Approach

*In Vitro to In Vivo Extrapolation (IVIVE)

Rodent In Vitro -> Interspecies Differences -> Human In Vitro

IVIVE*

Rodent In Vivo

Human In Vivo

*In Vitro to In Vivo Extrapolation (IVIVE)
Parallelogram Approach

**In Vitro to In Vivo Extrapolation (IVIVE)**

*Interspecies Differences*

Rodent In Vitro → Human In Vitro

IVIVE* → Human In Vivo

Rodent In Vivo → Human In Vivo

*In Vitro to In Vivo Extrapolation (IVIVE)*
Opportunities

New Technologies

Systems Pharmacology to Predict Drug Toxicity: Integration Across Levels of Biological Organization*
Jane P.F. Bai and Darrell R. Abernethy

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
Opportunities

Acute Toxicity


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
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
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.
Opportunities

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?

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Thank you!

Questions?