A 21ST-CENTURY ROADMAP FOR BIOMEDICAL RESEARCH AND DRUG DISCOVERY: RECOMMENDATIONS

Lindsay Marshall, PhD.
Today’s talk

- The issue with biomedical research today
- What is the BioMed21 collaboration – our projects
- What else do we need?

For more on HSI and HSUS – please visit our virtual booths
The need for a new approach

Biomedical research is often (overly) reliant on animals as surrogates of (healthy or sick) people...

or...

Give me 2,000 mice, a billion dollars and 10 years...
Animals don’t predict human responses

- 95% drugs that appear safe and effective \textbf{preclinically} fail in the clinic – unexplained toxicity or lack of efficacy
- Failure associated with the limited predictive value of preclinical models of disease – insurmountable species differences
- People \( \neq \) 70kg

Data: USFDA, PhRMA
Animal use is sustained over time

EU

US
Use of dogs across the US

![Graph showing the use of dogs across the US over the years.](image)

**Number of dogs**

- Dogs in research facilities
- Dogs used for scientific purposes
- Dogs held in labs but not used

**Year**

- 1999 to 2017

**Breeders**

- 2014 to 2019
Biomedical research using dogs (US)

NIH-funded research using dogs between 2015-2019

388 grants

260 million USD total

See poster 545 for more details 😊
Shifting research away from dogs

- 2019 – NASEM review
  - Determine where there is continued necessity for dog use; make recommendations for how/when dogs should be used for biomedical research relevant to the VA/s mission
  - “Laboratory dogs are no longer the preferred model for studies of diabetes or narcolepsy, for most imaging studies, or for primary pharmacological research.”
- 2021 - California legislation – Bill 252 to prohibit toxicity testing on dogs not required by law passed through California Senate in July– paws crossed for the next steps
- 2021 – Consideration of the “value” of data from dogs in 90 day testing of pesticides (Poster 345)
What drives animal use for biomedical research?

Research article

Désirée H. Veezing-Griffioen¹, Guilherme S. Ferreira¹, Wouter P.C. Boon², Christine C. Gispen-de Wied², Huub Schellens², Ellen H.M. Moors² and Peter J.K. van Meer²,₄

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NASEM report – historic use (of dogs) does not justify continued use...

Funding call (does not specify/prioritise non-animal approaches)

Internal ethical review/grant reviewers are all experienced animal users

PI has established/experience of an animal model

Paper reviewers/editors request additional animal data prior to publication

Education and training use animals as examples

ALTEX preprint
published June 22, 2020
doi:10.14573/altext.2003301
What can we learn from toxicity testing?

AdOPting a 21st century approach

Promoting adverse outcome pathways (AOPs)

“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.”
AOP training

Free online training

Access via
https://www.afsacollaboration.org/tox21/get-trained/

Get AOP Trained
- Adverse outcome pathways (AOPs)
- The OECD AOP development program
- The AOP Knowledgebase and Wiki Training resources
- How do I learn more about AOPs, the OECD AOP program, or the Wiki?
- Training resources
- References

267 AOPs in the Wiki

16 OECD-endorsed AOPs

Take a look, get trained, share!
AOPs for biomedical research

Modelling the pathogenesis of COVID-19 using the adverse outcome pathway framework

JRC-led project
Based on crowd sourcing - multi disciplinary approach
Making sense of the “tsunami” of existing knowledge, collecting, organising, creating networks

https://www.ciao-covid.net/contact
BioMed21 disease case studies

“Roadmaps to Human Biology-Based Disease Research”

To support strategic scientific dialogue around the concept of extending the vision of “21st century toxicology” to the wider biosciences, Humane Society International is offering grants to support the development and open-access publication of in-depth, independent review articles in discrete areas of human disease/biomedicine by health scientists with relevant expertise.

Remit

Each review should:

- Examine the state of the science in a specific area of human biomedicine, including current understanding of the underlying pathophysiological pathways and networks;
- Critically evaluate the human relevance, translational success and limitations of conventional research models;
- Offer concrete recommendations/roadmap for optimizing the funding and use of advanced, human-specific tools and approaches (pathway paradigm as an organizing framework, primary human cells/tissues, iPSC, organoids, bioengineering, computational systems biology modeling, etc.) in the disease area under discussion; and
- Be accepted for publication in a high-visibility, peer-reviewed journal.
BioMed21 disease case studies – the library

- Flaviviruse infection (Dengue, Zika)
- Auto immune disorders
- Diabetes
- Tuberculosis
- NASH
- Parkinson’s disease
- Autism spectrum disorder
- Alzheimer’s disease
- Asthma
- Cardiovascular disease
- Liver disease
- Endometriosis
BioMed21 workshops

- Europe (Brussels), 2015
  A human pathways approach to disease research
- Latin America (Brazil), 2017
  Emerging tools for pathway-based brain research
- North America (Washington DC), 2017
  Human pathway-based approach to disease and medicine
- South Korea (virtual), 2021
  3D Tissue chip and MPS, from development to regulatory adaptation
- India (online) 2020 – ongoing
  Developing Human Relevant Research in India
Our workshop recommendations/themes

• Funding strategies to prioritise non-animal approaches (gradual shift away from animals)

• Human data should be collected in high-quality open-access databases

• Common reporting formats and ontologies should be established

• Case studies to demonstrate applications and benefits of predictive, mechanism-based approaches
Our projects (so far)

- European Commission Joint Research Centre- Knowledge sources on advanced non-animal models (with EcoMole and Prof Ian Adcock (Imperial College, London))
**Our project:**
Non-animal models for respiratory tract diseases
Note that our research was all carried out PC (pre-covid19!)

**Methods:** Literature searches, plus outreach to researchers in the field. Publication years - 2008-2019

**Exclusion criteria:** live animals, drug effects, novel formulations
Separate searches for non-cancer (asthma, COPD, cystic fibrosis) and cancer

**More info:**
Dataset - https://data.jrc.ec.europa.eu/dataset/176d71e6-5082-4b29-8472-b719f6bda323
Respiratory tract models – conclusions

- 264 models from over 700 papers
- Healthy airways models needed/important
  - 69 publications describe “general” models
- Disease models
  - Recapitulate discrete, specific disease features
  - Utility in drug development
- Disconnect between lung models and lung cancer models
- Other models are needed
- Promote/enable more commercial model use eg MucilAir (EPA) and OncocilAir

For more on this and the other knowledge sources - Session 122: Biomed2.0- nonanimal models for biomedical research Monday 1400 CEST
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- European Commission Joint Research Centre- Knowledge sources on advanced non-animal models (with EcoMole and Prof Ian Adcock (Imperial College, London)

- Centre for Predictive Human Model Systems – CPHMS - with HSI India and the Atal Incubation Centre for Cellular and Molecular Biology
Centre for Predictive Human Model Systems

- CPHMS – initiative of HSI India and the Atal Incubation Centre for Cellular and Molecular Biology
- First of its kind in India 🎉
- Think tank dedicated to enable a shift towards human-relevant, predictive science in biomedical research & drug discovery

- WC11 session 23 Asia: A place ripe for the development of 21st century science
  Wednesday 1400 CEST
August 2020-June 2021
Webinar Series: Developing Human Relevant Research in India

- Part 1: Microphysiological Systems
- Part 2: Systems Biology & Pharmacology
- Part 3: Computational Tools & Biological Networks
- Part 4: Understanding Cancer Using Microphysiological Systems
- Part 5: Virtual Demonstration of Organ-on-Chip / Understanding Polycystic Kidney Disease Using Kidney-on-Chip
- Part 6: Use of In-vitro Human Surrogate Models – An Industry Perspective
- Part 7: Use of Human Clinical Samples to build Microphysiological System Models
- Part 8: Tissue Engineering and MPS models
- Part 9: Brain Organoids
- Part 10: In Vitro 3D Osteochondral Model for Drug Screening
- Part 11: In vitro humanized disease models: Focus on 3D bioprinted lung model

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Our projects (so far)

- European Commission Joint Research Centre- Knowledge sources on advanced non-animal models (with EcoMole and Prof Ian Adcock (Imperial College, London)
- Centre for Predictive Human Model Systems – CPHMS - with HSI India and the Atal Incubation Centre for Cellular and Molecular Biology
- PCRM - confronting publication bias

WC11 Session ID 26 - “Proof in animals”: Has journal editorial policy fallen behind advances in human-based approaches? Tuesday 31st 1400 CEST

More on BioMed21 – WC11 session 84: Beyond the 3Rs Expanding the Use of Human-Relevant Replacement Methods in Biomedical Research Monday 1830 CEST
What (else) do we need?

Prioritise funding for NAMs

Incentivise education and training

Enable access to human data

Increase the evidence base - more case studies

Standardise NAMs (for reproducibility, reliability etc)

Animals on chips – bridging/vet medicine

Combined strategies

Rethink our research - make it as complex as you need it to be

“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 NIH Director
Thank you!

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