2021
3Rs in transition From development to application
VIRTUAL CONGRESS - AUGUST 2021

THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY INTERNATIONAL
UNITED KINGDOM

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

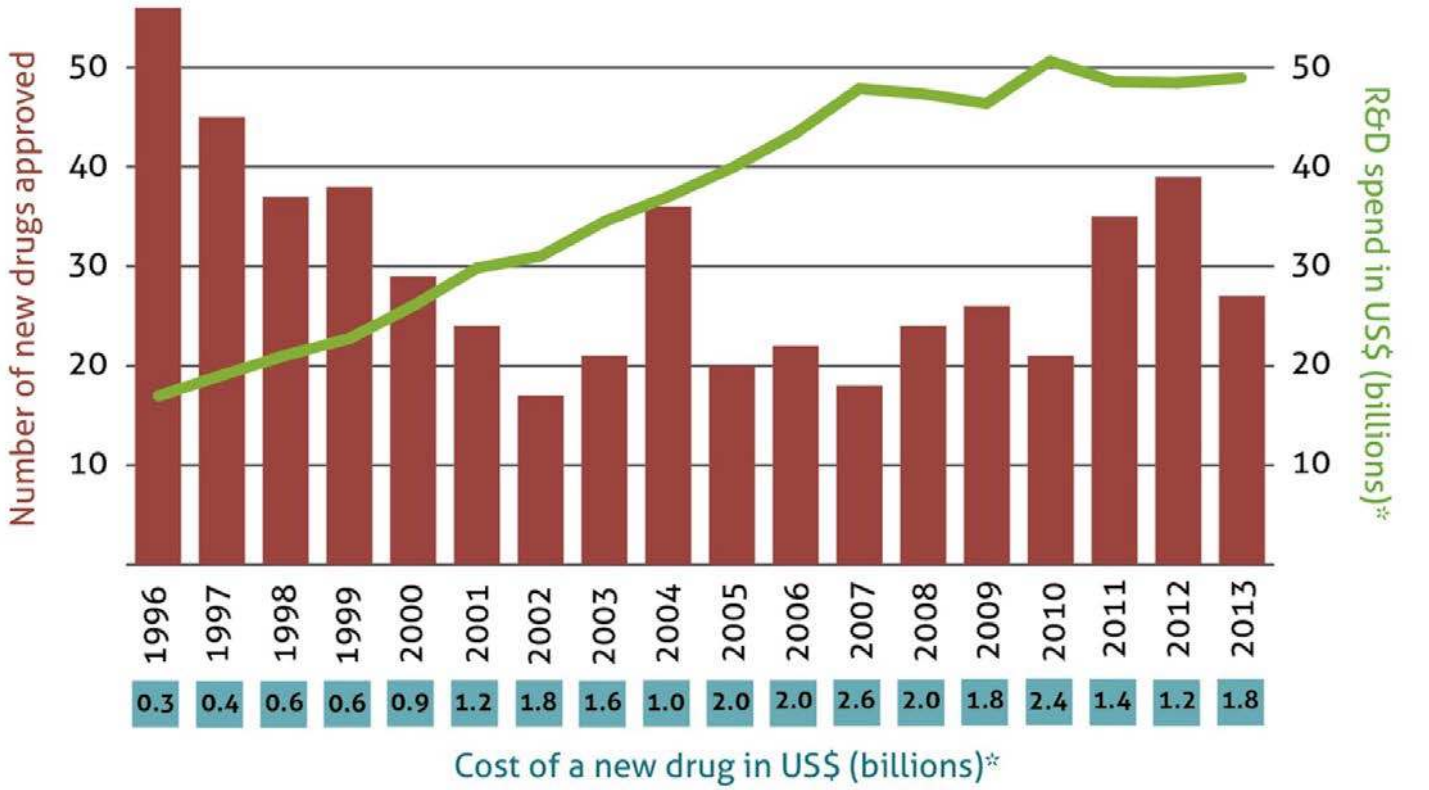
The need for a new approach

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

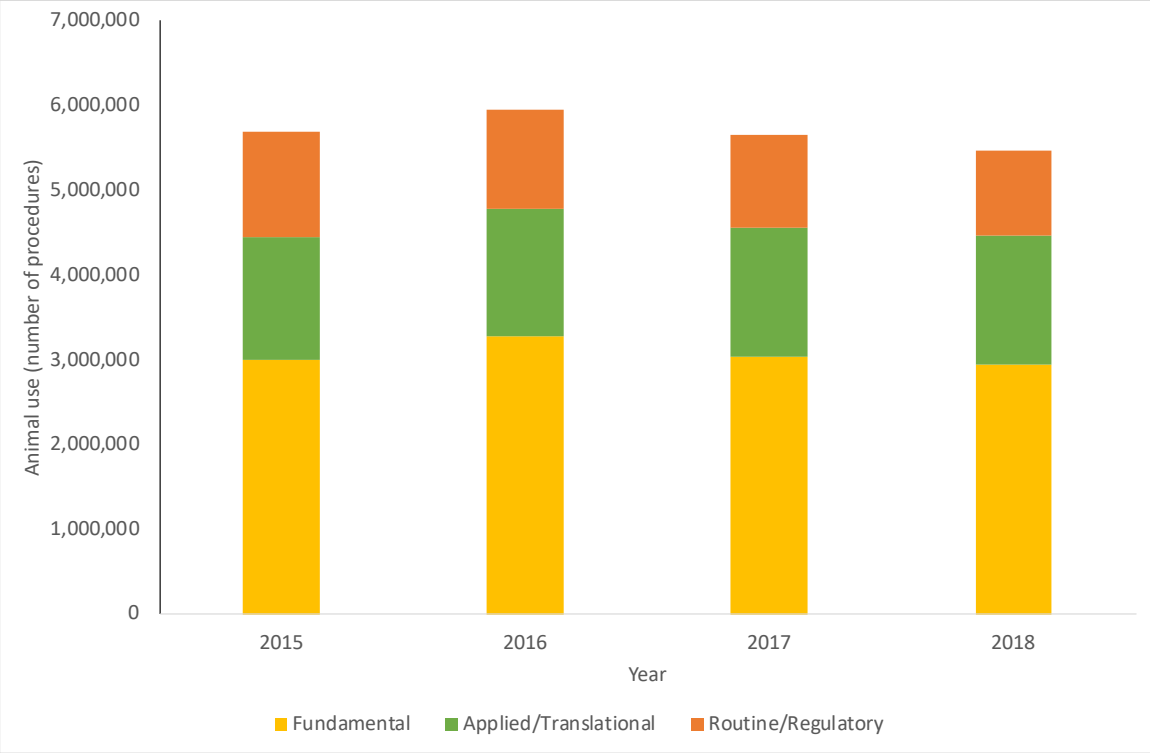


Data: USFDA, PhRMA

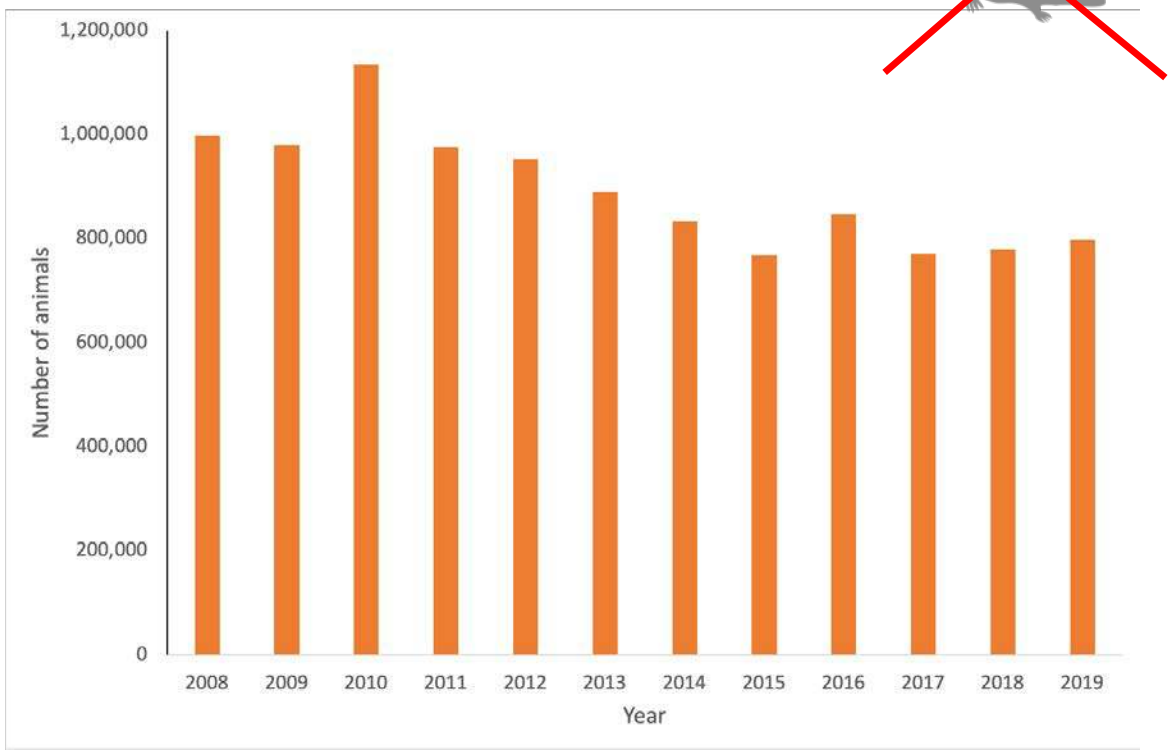
- 95% drugs that appear safe and effective **preclinically** fail in the clinic – unexplained toxicity or lack of efficacy
- Failure associated with the limited predictive value of preclinical models of disease – insurmountable species differences
- People ≠ 70kg 

Animal use is sustained over time

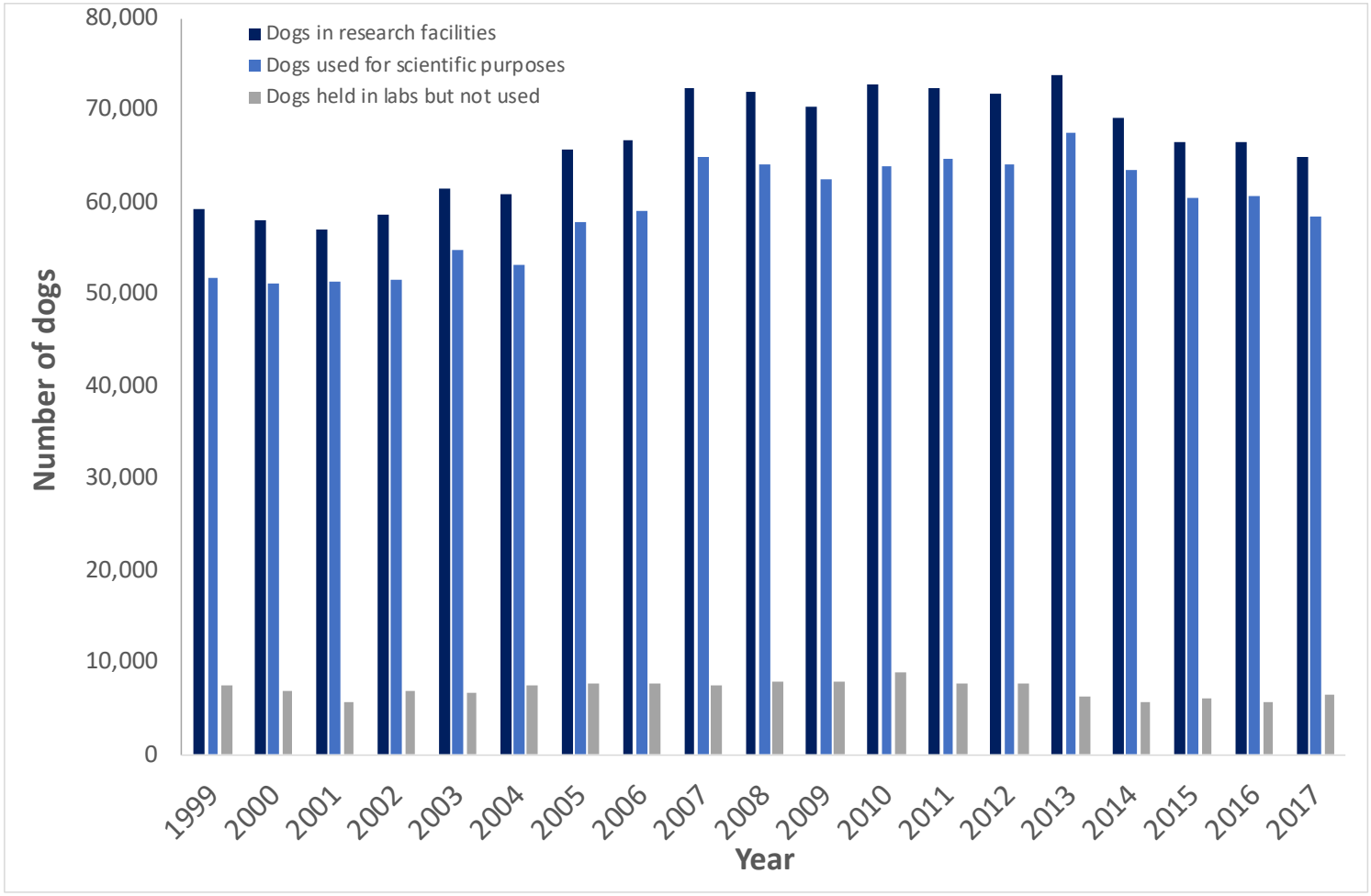
EU

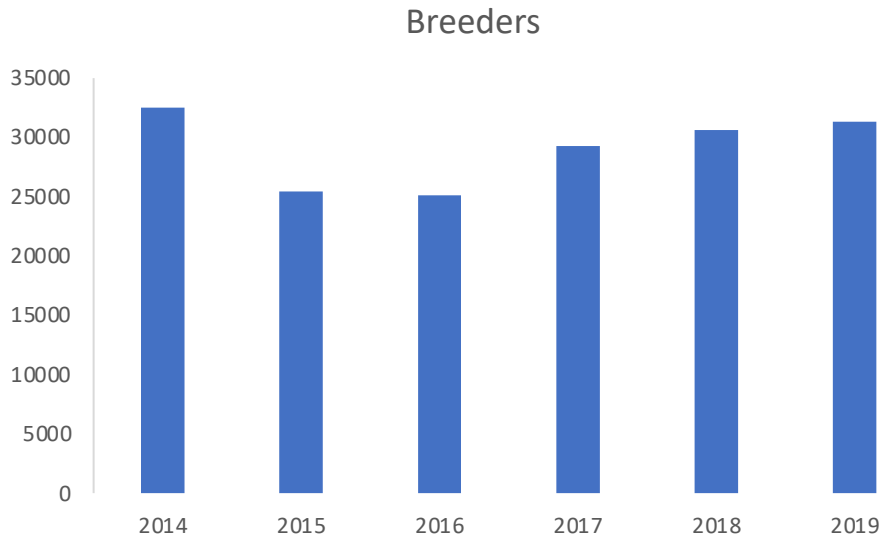


US



Use of dogs across the US





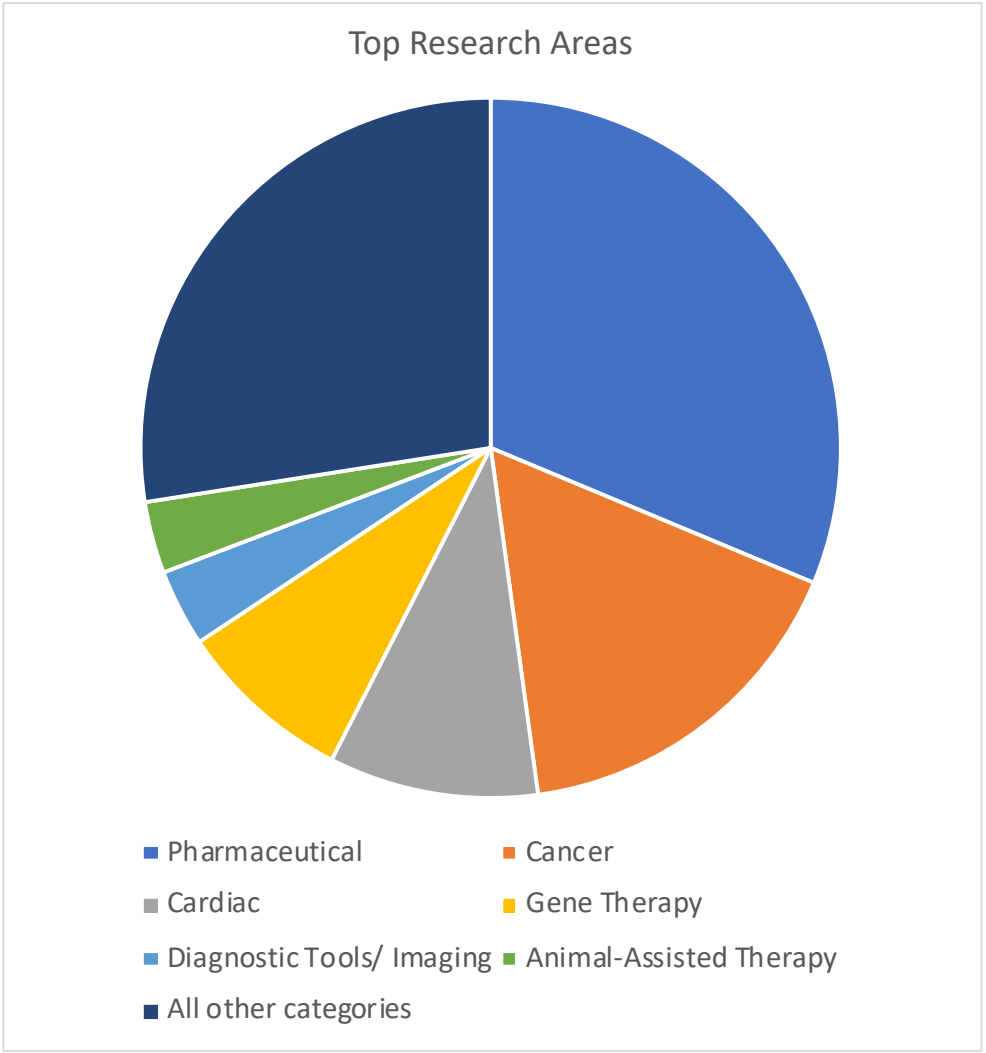
Biomedical research using dogs (US)

NIH-funded research using dogs between 2015-2019

388 grants

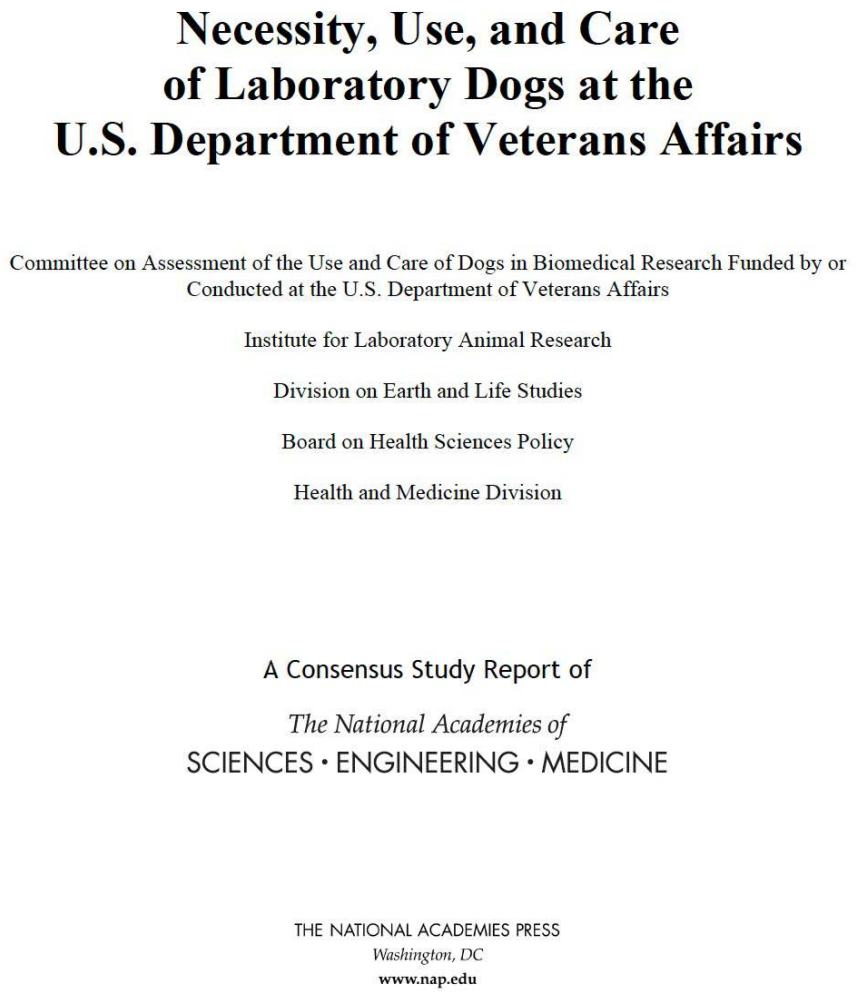
260 million USD total

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)



Necessity, Use, and Care of Laboratory Dogs at the U.S. Department of Veterans Affairs

Committee on Assessment of the Use and Care of Dogs in Biomedical Research Funded by or Conducted at the U.S. Department of Veterans Affairs

Institute for Laboratory Animal Research

Division on Earth and Life Studies

Board on Health Sciences Policy

Health and Medicine Division

A Consensus Study Report of

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

What drives animal use for biomedical research?

ALTEX preprint
published June 22, 2020
doi:10.14573/altex.2003301

Research article

Tradition, Not Science, Is the Basis of Animal Model Selection in Translational and Applied Research

Désirée H. Veening-Griffioen[1], Guilherme S. Ferreira[1], Wouter P.C. Boon[2], Christine C. Gispen-de Wied[3], Huub Schellekens[1], Ellen H.M. Moors[2] and Peter J.K. van Meer[1,4]
[1]Utrecht Institute of Pharmaceutical Sciences, Utrecht, The Netherlands; [2]Copernicus Institute of Sustainable Development, Utrecht, The Netherlands; [3]Gispen4RegulatoryScience: advies en educatie, Bilthoven, The Netherlands; [4]Medicines Evaluation Board, Utrecht, The Netherlands

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

What can we learn from toxicity testing? AdOPting a 21st century approach

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

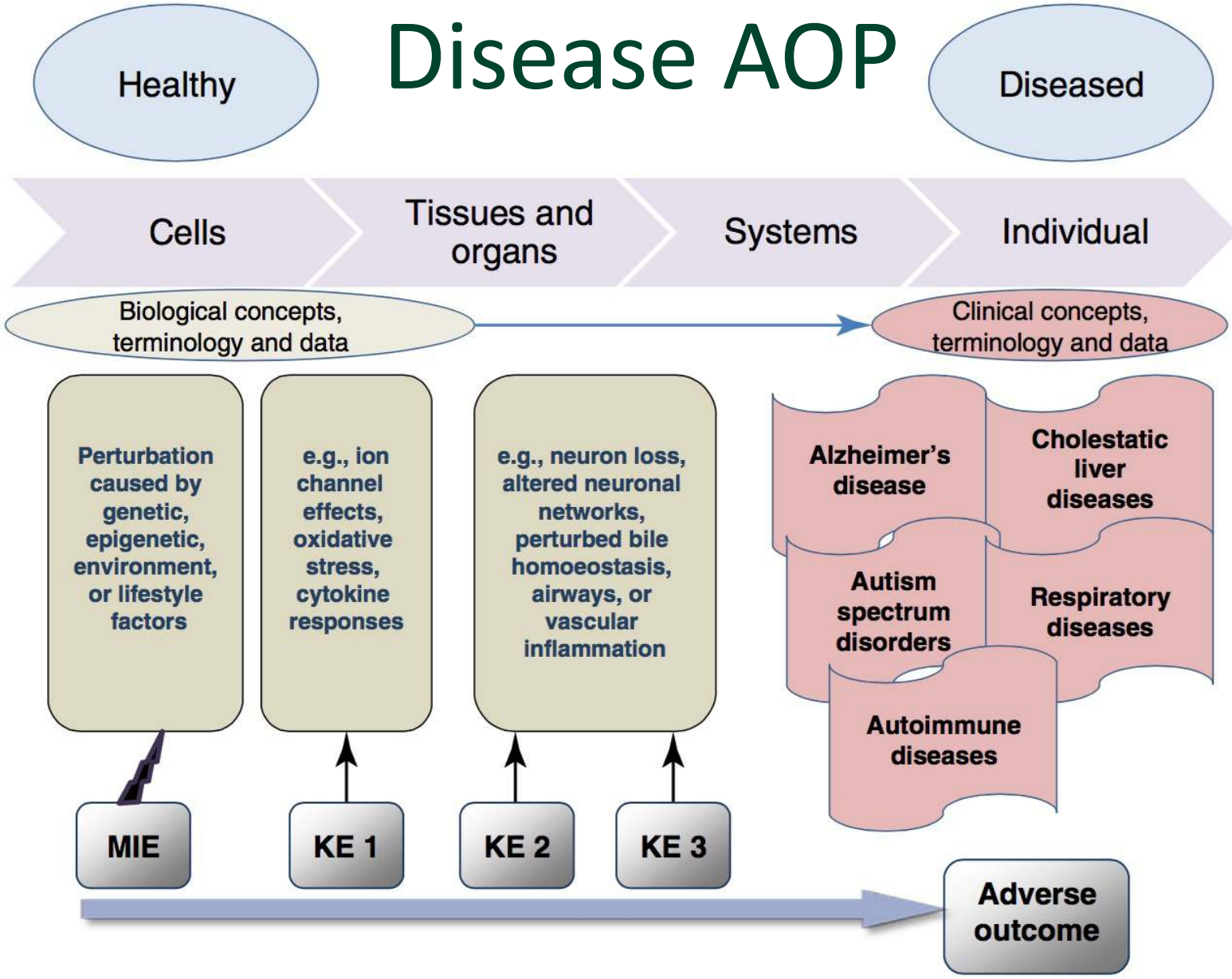
http://dx.doi.org/10.1289/ehp.1510345

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

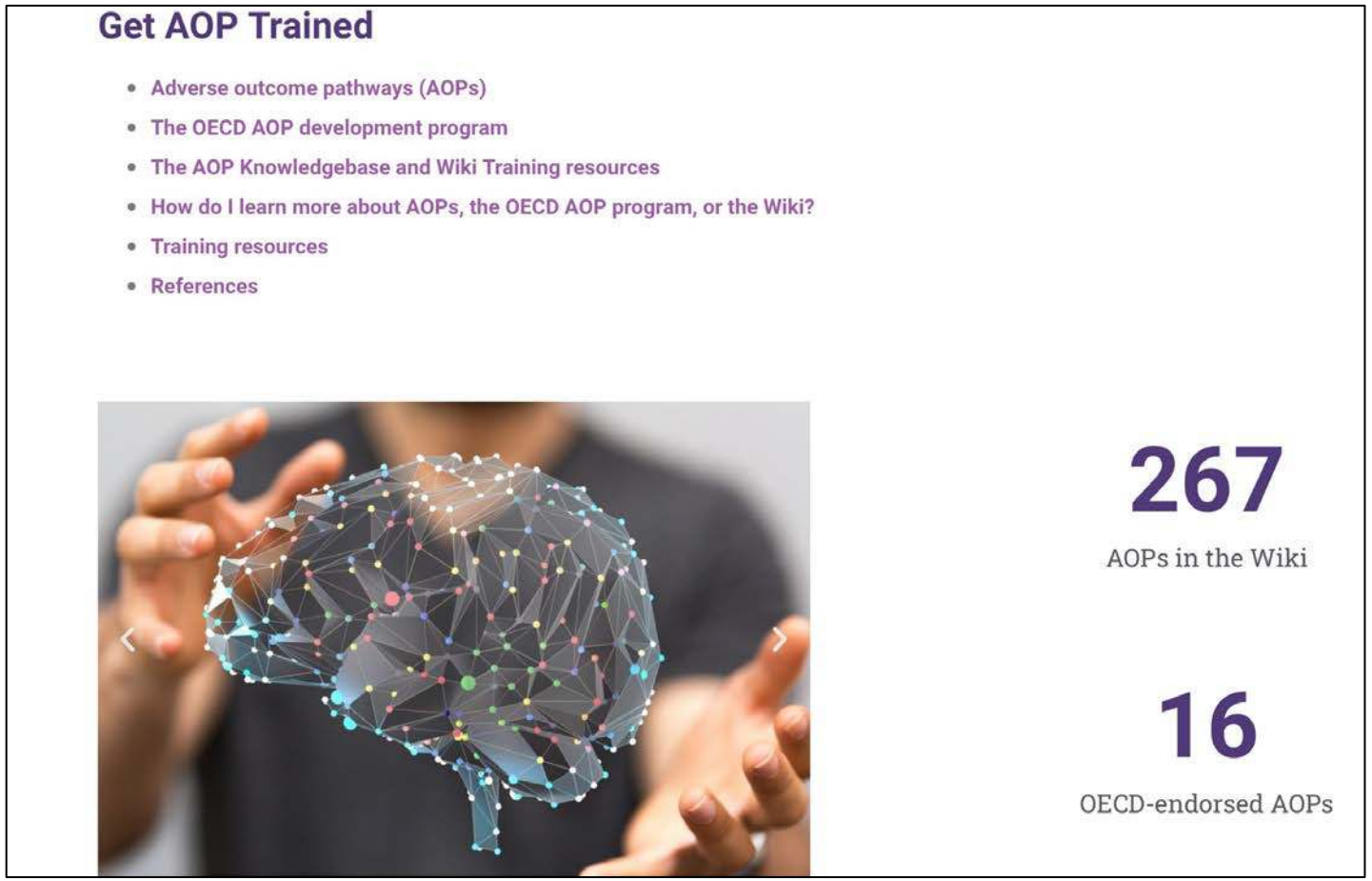
Promoting adverse outcome pathways (AOPs)

"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."

Disease AOP


Healthy
Diseased
Cells
Tissues and organs
Systems
Individual
Biological concepts, terminology and data
Clinical concepts, terminology and data
Perturbation caused by genetic, epigenetic, environment, or lifestyle factors
e.g., ion channel effects, oxidative stress, cytokine responses
e.g., neuron loss, altered neuronal networks, perturbed bile homoeostasis, airways, or vascular inflammation
Alzheimer's disease
Cholestatic liver diseases
Autism spectrum disorders
Respiratory diseases
Autoimmune diseases
MIE
KE 1
KE 2
KE 3
Adverse outcome

AOP training

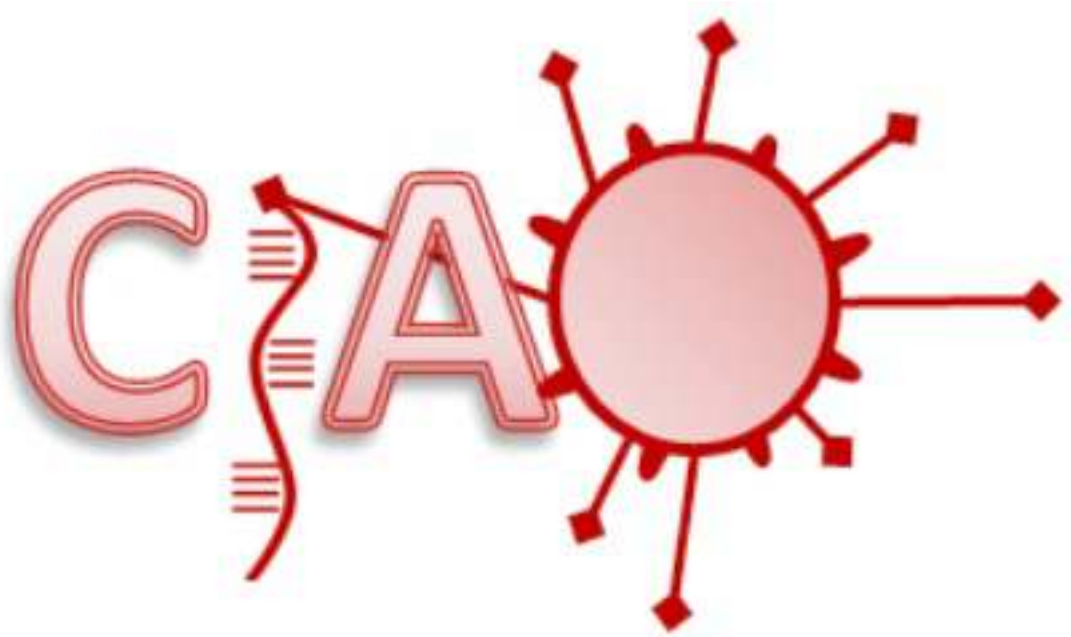


Free online training

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

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

Flavivirus infection (Dengue, Zika)

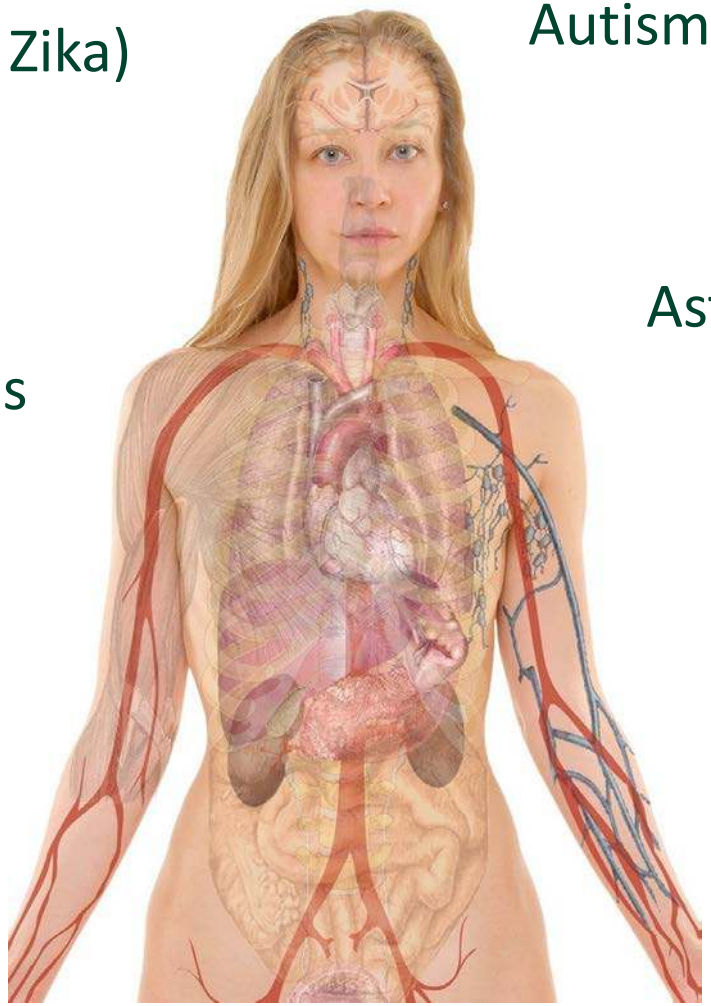
Auto immune disorders

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)

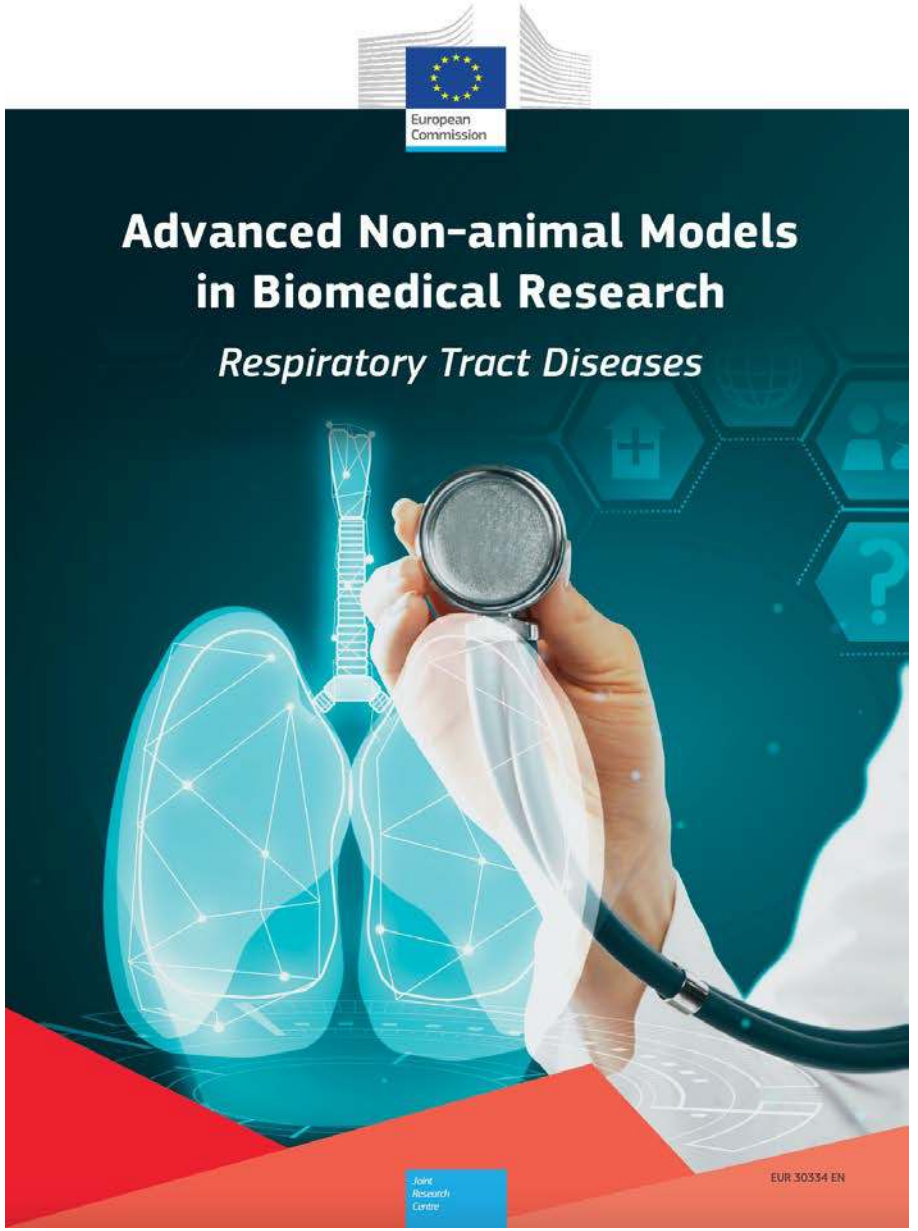
- European Commission Joint Research Centre- Knowledge sources on advanced non-animal models (with EcoMole and Prof Ian Adcock (Imperial College, London)

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:
Report - https://ec.europa.eu/jrc/en/page/respiratory-tract-diseases-183208
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

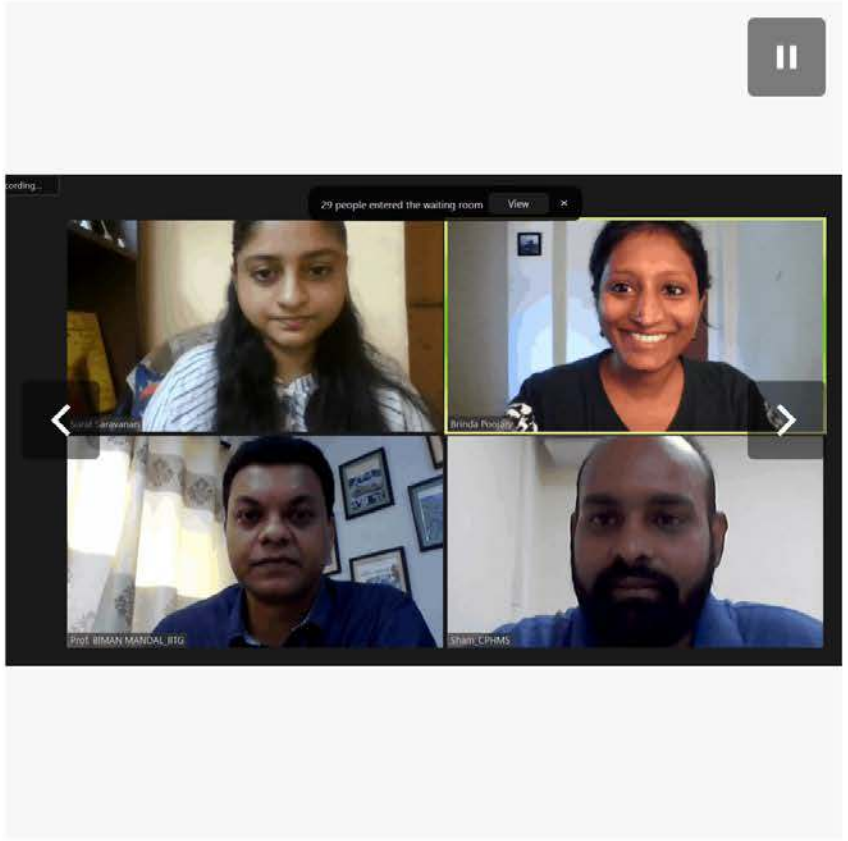
- WC11 session 23 Asia: A place ripe for the development of 21st century science Wednesday 1400 CEST

CPHMS webinar series

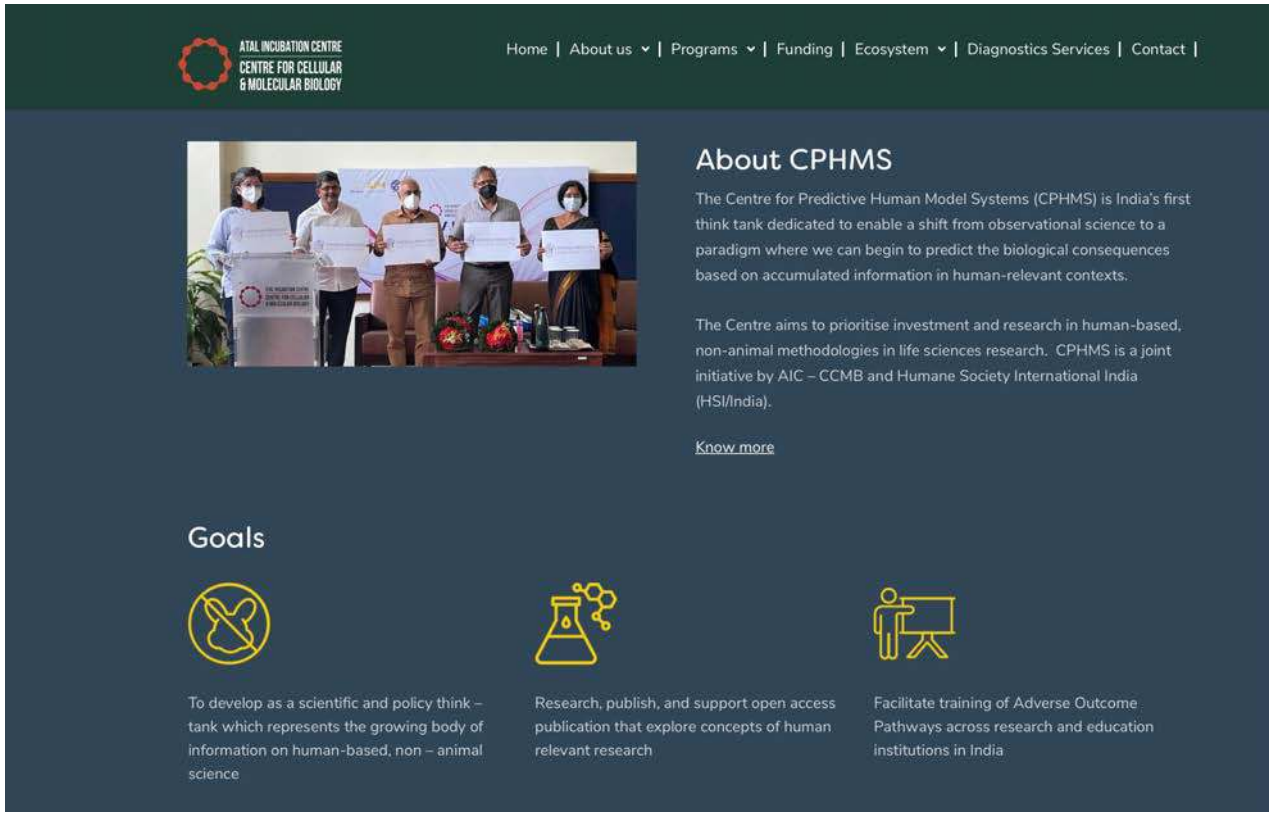
August 2020-June 2021

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**



* Humane Society International, co-founder of the BioMed21 Collaboration, co-organized the webinar series.



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Our projects (so far)

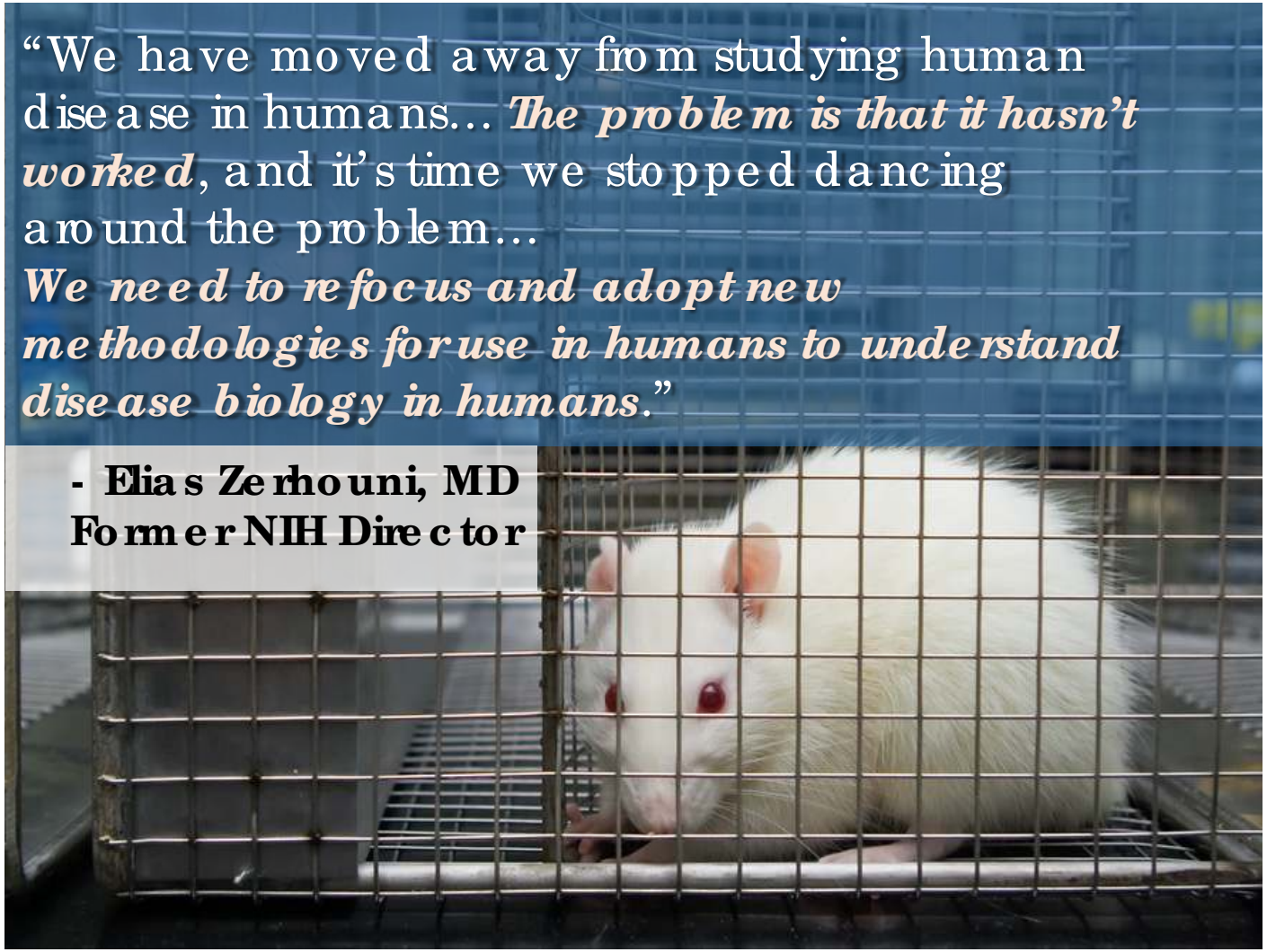
- European Commission Joint Research Centre- Knowledge sources on advanced non-animal models (with EcoMole and Prof Ian Adcock (Imperial College, London)
- Centre for Predictive Human Model Systems – CPHMS - with HSI India and the Atal Incubation Centre for Cellular and Molecular Biology
- PCRM - confronting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



Thank you!

Contact me on - lmarshall@hsi.org