B⊗OMED²¹

A Human Pathways Approach to Disease Research

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WORKSHOP *Flash* REPORT

HUMANE SOCIETY INTERNATIONAL
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Medical researchers and stakeholders call for a comprehensive strategy to improve our mechanistic understanding of human disease and support the development of human-specific models to accelerate the identification and successful translation of new treatments to the clinic.

Leading health scientists, officials representing European institutions, national regulatory and research agencies, science funding organizations and other stakeholders participated in the December 2015 workshop **BioMed²¹: A Human Pathways Approach to Disease Research** in Brussels. The workshop, part of a new global initiative led by Humane Society International,[1] examined five human disease case studies alongside research funding frameworks and regulatory structures in key innovation economies with the aim of identifying actionable consensus recommendations as a first step towards a comprehensive roadmap for 21st century, human biology-based health research and funding.

The workshop reviewed the status of human and animal models in the following disease areas:

Alzheimer's disease

Lead discussants: **Dr Gill Langley**, *Humane Society International;* **Prof James Adjaye**, *Heinrich Heine University;* **Dr Martin Hofmann-Apitius**, *University of Bonn*

There are currently no disease-modifying therapies for Alzheimer's disease despite decades of intensive animal research, and hundreds of interventions reported as effective in animal models have subsequently failed in the clinic.[2] Experts noted that current research paradigms are too dependent on transgenic mice that differ significantly from humans in protein pathways, metabolism and physiology. Human-specific models, such as human induced pluripotent stem cells (hiPSCs) generated from patients with Alzheimer's disease and differentiated into functional neurons, show important pathologies of the disease.

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[1] Langley G, Austin CP, Balapure AK, et al. (2015) Lessons from toxicology: Developing a 21st-century paradigm for medical research. *Environ Health Perspect.* **123**(11):A268-72. doi: 10.1289/ehp.1510345

[2] Langley G (2014) Considering a new paradigm for Alzheimer's disease research. *Drug Discov Today*. **19**(8):1114–24.

Genomics and metabolomics analyses of hiPSC models as well as multi-electrode studies *in vitro* provide important functional data. Powerful tools for analyzing *ex vivo* human tissues are contributing to elucidating Alzheimer's disease pathways and new targets for drug development. Computational systems are key to capturing and displaying diverse data about Alzheimer's disease.

Autism spectrum disorders

Lead discussants: **Prof Alysson Muotri,** *University of California San Diego;* **Prof Anthony Bailey,** *University of British Columbia;* **Prof Hilde van Esch,** *Leuven University*

The lack of live human brain cells for research and the unreliability of animal models has limited progress in understanding the mechanisms underlying autism spectrum disorders, but experts reported novel findings with hiPSC-derived cortical neurons and an 'autism in a dish mini-brain' approach.[3] Research with iPSC-derived neurons from girls with Rett syndrome showed classic pathologies and a reduced frequency of spontaneous postsynaptic currents in 3-dimensional mini-brains *in vitro*. Co-culturing Rett derived neurons with wild type astrocytes achieved neuronal rescue. Thousands of new drugs for autism spectrum disorders are being screened robotically using hiPSC-derived neurons. Experts agreed that more post-mortem tissue from autistic patients is also crucial, as mouse models are overly simplistic.

Cholestatic liver disease

Lead discussants: **Dr Fozia Noor,** *Saarland University;* **Dr Brigitte Landesmann,** *European Commission Joint Research Centre*

Despite many animal models and a large volume of clinical data, translation of knowledge towards developing treatments for cholestatic liver disease, conditions associated with bile flow obstruction, has been disappointingly limited. Animal models fail to adequately mimic human cholestatic liver disease because of major differences in gut and liver physiology and in disease pathogenesis.[4] Experts reported findings with spheroids of human HepaRC cells showing that they express key bile acid transporters. Researchers have used these cells in 2D and 3D models to study the influence of bile acid load and the mechanisms of drug-induced cholestasis, including using cutting-edge

technologies in metabolomics to identify and quantify cellular metabolites. Patients' clinical samples can be a benchmark for assessing new approaches, so biomarkers which span clinical and *in vitro* systems are needed. Human pathways of liver disease should be developed, as they will support the integration of data from a range of research approaches and improve predictive tools.

Asthma and respiratory diseases

Lead discussants: **Prof Ian Adcock,** *Imperial College London;* **Dr Grzegorz Woszczek,** *King's College London;* **Dr Lindsay Marshall,** *Aston University*

Much of the current understanding of asthma has come from animal models but they have largely failed to provide novel therapies that translate into humans, particularly in people with severe asthma.[5] Experts presented results from the U-BIOPRED (Unbiased biomarkers for the prediction of respiratory disease outcomes) program, funded by the Innovative Medicines Initiative, which has used a systems biology approach enabling the investigation of novel pathways associated with the disease. Functional genomics can help clarify the links between genotype and phenotype on a genome-wide scale, but improved bioinformatics programs are needed to handle the data. Human cellular models are also valuable in developing our understanding of respiratory diseases.

Autoimmune disease

Lead discussants: **Dr Anja Van de Stolpe,** *Phillips Research;* **Dr Christoph Giese,** *ProBioBen;* **Dr Elena Csernok,** *Klinikum Bad Bramstedt*

Autoimmune diseases are exquisitely human diseases with complex genetic backgrounds and variable clinical presentation.[6] Current treatment is mainly empirical with limited efficacy and significant side effects. Under development is a human-specific organ-on-chip model of anti-neutrophil cytoplasmic antibody autoimmune vasculitis, consisting of cultured organ-specific vascular tissue that can interact with components of the immune system such as lymph node and thymus tissue. When fully validated, investigational work with this model combined with knowledge-based computational disease modeling carries the promise of filling in currently missing information on disease pathways and pathogenesis in autoimmune disorders.

3   Muotri AR (2015) The human model: changing focus on autism research. *Biol Psych*; doi: 10.1016/j.biopsych.2015.03.012.
4   Noor F (2015). A shift in paradigm towards human biology-based systems for cholestatic-liver diseases. *J Physiol*; **593**(23):5043-55.
5   Buckland GL (2011) Harnessing opportunities in non-animal asthma research for a 21st-century science. *Drug Discov. Today*. **16**:914-27.
6   van de Stolpe A, Kauffmann RH (2015) Innovative human-specific investigational approaches to autoimmune disease. *RSC Adv*. **5**:18451-63; doi: 10.1039/c4ra15794j.

Discussion & Recommendations

A number of the participating researchers reported difficulties in obtaining funding for programs using innovative human-specific approaches and in publishing findings in peer-reviewed journals. These difficulties were considered to be attributable to a conservative approach favouring traditional animal models.

BioMed[21] delegates recommended that an overarching strategic roadmap is essential to build on the progress made with human-specific models so far and to give a clear direction for more effectively incorporating their use into biomedical research over the next decade. They recommended that such roadmap(s) should ideally be developed for the EU, U.S. and other key innovation economies, through a transparent process inclusive of all stakeholders, including academic and pharmaceutical researchers, research funding bodies, European and national regulators, and advocacy organizations, to ensure that recommendations benefit every step of the research and drug development process to enable new treatments to progress 'from the bench to the bedside' more quickly.

Roadmap(s) could be based on human disease pathways-based approaches at multiple biological levels, from molecular to individual, that can identify current gaps in science and target the development and use of new technologies more closely replicating human disease. This human pathways approach is already proving effective in toxicology, where it has been adopted as part of the U.S. EPA *Strategic Plan for Evaluating the Toxicity of Chemicals*[7] and globally as the foundation for the Adverse Outcome Pathway Development Project at the OECD.[8]

The proposed new strategy should also support measures such as: tools and databases to integrate and share information and to support predictive models; encouraging open access publication and data sharing; increased access to diseased and healthy human tissue, appropriate use of patient data, and data from clinical trials.

Participants

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[7] EPA (2009) http://www.epa.gov/osa

[8] OECD (2016) http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm