iPSC technology and 3D tissue technologies as viable, safe, powerful and cost-effective alternatives to failing animal models for brain disease research

Marcia Triunfol, PhD

Humane Society International | mtriunfol@hsi.org | biomed21.org

HUMANE SOCIETY INTERNATIONAL

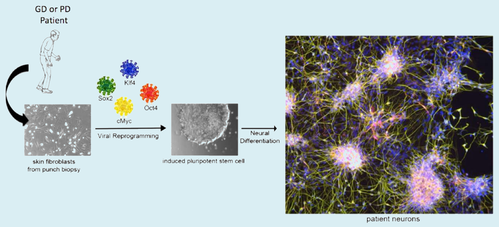
Introduction

The first clear understanding that Zika virus was indeed the main player associated with the high incidence of microcephaly in Brazil was presented in a paper published in *Science* magazine in May 2016, in which a group of researchers at the Institute of Biomedical Sciences at the Federal University of Rio de Janeiro and the D'Or Institute for Research and Education (IDOR) investigated the effects of Zika infection in human neural stem cells cultured as neurospheres and brain organoids.[1] The group was able to show, using innovative *in vitro* technology only, that Zika targets human brain cells and reduces their viability and growth, indicating that infection during pregnancy disturbs neurogenesis during human brain development. The study was recognized by the World Health Organization as the final word on the Zika virus association with the high incidence of congenital microcephaly and other a abnormalities of the CNS in fetuses and newborn babies of mothers who were infected by the virus during pregnancy.

Baby born with Zika-related microcephaly. Photo: Felipe Dana/AP

IDOR researchers have used a sandai virus-based reprogramming method to create iPSCs from urine-derived epithelial cells and fibroblasts from patients with obsessive-compulsive disorder, deficit hyperactive disorder (HDHD) and schizophrenia, while a Biobank Initiative containing 150 cell lines from 17 diseases has been launched in the country. Testing of potential new drugs such as Cannabidiol to treat epilepsy in Dravet Syndrome, Chloroquine to protect from microcephaly-causing Zika virus, or Sofosbuvir to inhibit Zika replication was presented during the meeting. As for psychiatric diseases specifically, in no other area is personalized medicine more necessary.

Improved Disease Models Through the Development of Induced Pluripotent Stem Cell Models of PD and GD



Skin fibroblasts are taken from patients with Parkinsons Disease and reprogramed by retroviral infection to generate induced pluripotent stem cells can then undergo neural differentiation to become patient neurons. Reprinted with permission: Joseph Mazzulli, Northwestern University.

References

1. Garcez PP, Loiola EC, Madeiro da Costa R, Higa LM, Trindade P, Delvecchio R,Nascimento JM, Brindeiro R, Tanuri A, Rehen SK. Zika virus impairs growth inhuman neurospheres and brain organoids. Science. 2016 May 13;352(6287):816-8.
2. EPA (2009) http://www.epa.gov/osa
3. OECD (2016) www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

BIOMED 21

Discussion

Workshop on emerging technology toward pathway-based human brain research

The established community of researchers using human biology-based approaches to study brain diseases offered fertile ground to discuss the potential of 3D tissue and iPSC technology as viable, safe, powerful and cost-effective alternatives to failing animal models. Thus, leading health scientists in the region, representing scientific institutions in Brazil and in Argentina, the Brazilian national research agency CNPq, and other stakeholders participated in the May 2017 workshop, BioMed21: Emerging Technology Toward Pathway-Based Human Brain Research, in Rio de Janeiro. Organized by Humane Society International as part of a global scientific series and hosted by IDOR, the workshop examined the development and application of iPSC technology for studying a number of brain diseases, 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.

Photos: Heloisa Machado/HSI

BIOMED 21

EMERGING TECHNOLOGY TOWARD PATHWAY-BASED HUMAN BRAIN RESEARCH

29-30 May 2017 | D'Or Institute for Research and Education, Rio de Janeiro

Program

Toward a human pathway paradigm in health research
Troy Seidle, HSI Senior Director of Research & Toxicology

Organoids: A historical perspective of thinking in three dimensions
Marina Simian, Instituto de Nanosistemas, Universidad Nacional de San Martín, Argentina

New insights about the biology of zika virus infection using iPS cells
Stevens Rehen, D'Or Institute for Research and Education and Federal University of Rio de Janeiro, Brazil

Mini-brains to study Dravet disease
Fabio Klamt, Universidade Federal do Rio Grande do Sul, Brazil

A human brain microphysiological system derived from iPSC to study neurological diseases, toxicity and infection diseases
David Pamies, Johns Hopkins University, USA

Modeling autism spectrum disorders with human neurons
Patricia Beltrão-Braga, University of São Paulo, Brazil

The promises and challenges of human brain organoids as models of neuropsychiatric diseases
Georgia Quadrato, Harvard Stem Cell Institute, USA

Human iPS-derived motor neurons for Amyotrophic Lateral Sclerosis
Gerson Chadi, University of São Paulo, Brazil

Combining neuroproteomics and mini-brains to understand psychiatric disorders
Daniel Martins-de-Souza, University of Campinas, Brazil

Understanding Parkinson and Alzheimer diseases using patient neurons derived from induced pluripotent stem cells (iPSC) coupled with analytic biochemical techniques
Joseph R Mazzulli, Northwestern University Feinberg School of Medicine, USA

Application of iPSCs in the study of brain disease

Workshop presentations showed how iPSCs are now being used to study a number of brain diseases, including microcephaly-causing ZIKV, Dravet Disease, autism, neuropsychiatric diseases, Amyotropic Lateral Sclerosis, and Parkinson Disease and how IPSCs are being used as an alternative to animal models in labs worldwide. iPSCs can be generated from different types of somatic cells that can be differentiated to all cell types of an organism's body and have great potential in many fields besides beyond medicine and biomedical research as iPSC can also be used in agriculture and biotechnology. While the concept of using animal models for human diseases has been challenged by the fact that study findings obtained with a species cannot be translated into another species, and that include humans, the iPSC technology offers the possibility of working with models that are actually bona fide representations of the species of interest. Additionally, it allows that patients' own cells are used to study diseases, test new drugs and develop tailor-made treatments according to each patient's characteristics. Virtually all presentations included work that has been done using patients' cells.

Conclusions & recommendations

1 / The need for an overarching, multi-year non-animal technology and biomedical research funding strategy to ensure sufficient and sustained investment in human biology-based research and model development at federal and state levels

The manner in which public funding for health research is prioritized and allocated was called into question by a number of presenters, who identified animal models considered to be of dubious to no predictive relevance to humans, while at the same time reporting difficulties in obtaining sufficient funding for programs using human-specific approaches. Sustained, multi-year investment came up repeatedly as a major unmet need. It was recommended that Brazil should develop a multi-year non-animal technology and health research roadmap and funding strategy to guide and coordinate future investments in biomedical and toxicological research by federal and state funding bodies in Brazil.

2 / Establishment of a strategic science 'think-tank'

In view of the complex and often polarized nature of discussions regarding the replacement of animal use in the life sciences, participants recommended that a think-tank inclusive of Brazilian scientific, corporate and civil society stakeholders should be established to help build consensus around challenging topics. Improved stakeholder communication and collaboration through an entity of this nature could contribute for an environment that is more receptive for innovative ideas. Such a group could also be used to connect research groups across Brazil and South America using non-animal technologies for sharing knowledge and resources. Further, coordinated applications for grants as a group could potentially be facilitated by such a group.

3 / Commercial availability/import of human tissues, models and reagents

Legal and practical barriers to the commercialization and import of human skin and other tissues in Brazil continue to impede the replacement of obsolete *in vivo* toxicological models with valid and internationally recognized non-animal approaches. Similar difficulties exist in relation to the import of reagents and other scientific equipment into Brazil and other parts of South America. Participants stressed the urgent need for Brazil to modernize its laws and customs regulations to create a more receptive environment for innovation.

4 / Domestic industry/CRO capacity, infrastructure and training to perform all available non-animal guideline tests according to OECD GLP standards

It was noted that despite investments by the Brazilian 3R coordination network RENAMA, it remained unclear whether local testing capacity and infrastructures were sufficiently developed to fully implement the available— and ever-growing range of—validated non-animal test guidelines and integrated approaches to testing and assessment (IATA) published each year by the OECD and others. A mapping of Brazilian contract testing capacity against OECD non-animal guideline methods was suggested as an initial gap analysis and basis for evaluating the need for a more pro-active strategy by RENAMA going forward.

5 / The role of scientific journals in driving or impeding a paradigm shift in human health research

Scientific journal editors and peer reviewers were identified as either a positive force that could contribute to the advancement of human-specific approaches in biomedical research or as a negative force that many times requires that *in vitro* results are also demonstrated *in vivo*. Some participants noted that reliance on non-animal-based research findings or statements critical of the current paradigm remain a deal-breaker in terms of publication in some peer-reviewed journals due to reviewer conservatism or overt bias. A suggestion was made that an inventory could be created of animal models have not generated useful results as a reference for research funding bodies and institutional ethics committees.