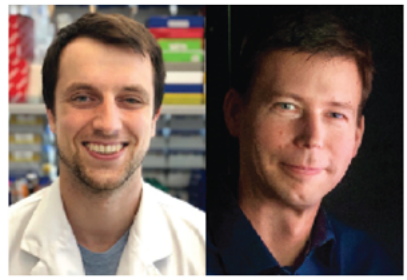
Health Science Inquiry

ASK AN



EXPERT

The Kieffer lab has the capacity to address questions from molecular to cellular to whole organism, using model cell lines, differentiated stem cells, zebrafish and genetically engineered rodents. We utilize tissue-specific knockdown or reintroduction of genes, cell transplant and surgical manipulations to address the role of hormone actions in a site-specific manner. We assess the effects of environment on metabolic function with dietary manipulations, from neonates to adults. We have advanced equipment for high-throughput analyses of cellular function and pathways, for whole animal imaging, and for metabolic phenotyping. Through strong networks of collaborators including basic scientists and clinicians, we have assembled and led multidisciplinary teams and effectively engaged researchers across Canada and around the world to support our research enterprise. We actively collaborate with industry, including large pharmaceutical companies, as we strive to translate our findings to the clinical setting.

Mitchell J.S. Braam[1] **& Timothy J. Kieffer**[1,2]
[1]Department of Cellular and Physiological Sciences, Life Sciences Institute, University of British Columbia
[2]Department of Surgery, University of British Columbia

How do primary/patient-derived cell models compare to mouse models in the study of chronic disease? Do either of these models carry increased translational potential?

The study of chronic disease has long used animal models to elucidate mechanisms, investigate physiology, and test potential therapies. Among the various animal models, the mouse is one of the most widely used. Genetically, humans and mice share sizeable DNA sequence homology, with many of the disease-related genes being near-identical [1,2]. The ability to create transgenic, knockout, and knockin mice in whole-body or tissue specific manners allows for powerful in vivo studies and research on isolated tissues providing valuable insight into complex physiological and disease processes. However, experimental interventions developed using mouse models do not always translate well into humans. A well-known example of this trend is the TGN1412 anti-CD28 monoclonal antibody developed by TeGenero for the treatment of multiple sclerosis, rheumatoid arthritis, and certain cancers [3]. Toxicity studies performed on mice and non-human primates demonstrated safety at doses hundreds of times higher than what would be introduced into humans. However, the first human clinical trials of this drug at sub-clinical doses caused a cytokine storm and devastating organ failure in all the participating patients, all of whom were fortunately rescued with intervention [4]. Indeed, the majority of drugs that enter clinical trials never reach the marketplace and the limitations of animal models used in drug testing are an important contributing factor [5]. Moreover, mouse models that were created to recapitulate human genetic diseases have frequently had phenotypes that differ from their human counterparts [6] and models that do work use genetically identical or near-identical animals that lack the genomic diversity that is the reality of a human population.

Recent progress in the stem cell field has established a variety of techniques that can be utilized to generate cultures enriched for mature cell populations or tissue-specific organoids from human pluripotent stem cells (hPSCs) and adult

stem cells [7,8]. These unique *in vitro* cellular model systems offer several advantages. Because they have a human genome, they are the most appropriate model for studying human disease-relevant genetic variations. hPSCs can also be maintained in culture for many passages while retaining a healthy genome. This is beneficial for studies that require the generation of cellular materials at a large scale, such as those involving high-throughput drug screening. Under defined culture conditions, hPSCs can be directed to differentiate into a variety of mature cell types. These *in vitro* differentiation processes often align with normal developmental pathways, providing the opportunity to probe deeper into developmental and degenerative processes9.

Patient-derived induced pluripotent stem cells (iPSCs) provide the opportunity to model disease development, uncover unique mechanisms, and test potential therapeutics in a personalized approach. Successful modeling using this method incorporates personalized disease information and the recapitulation of disease development at the molecular, cellular and organ levels. Combined with new state-of-the-art genome editing tools, such as CRISPR/Cas9, hiPSCs can be specifically engineered to remove disease-relevant genetic mutations while retaining the global genomic status of the individual [10]. The inverse is also possible; engineering healthy hPSCs to express individual mutations. These new methods are enabling rapid expansion of sophisticated *in vitro* disease models, offering new platforms to perform biomedical research.

Overall disease modelling using mice or human derived cells each have their own benefits, however the translational value of experiments would be most enhanced by a combination of the two approaches. Studies in mice enable researchers to test hypotheses in a live animal, while the use of stem cells allows for more specific disease modelling and drug screening. Moving forward, researchers should design experiments and interpret results with appropriate consideration of the similarities and differences between these approaches in discovery research.

References

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