Health Science Inquiry

ASK AN

EXPERT

Dr. Craig Moore is an Assistant Professor and Canada Research Chair (Tier 2) in Neuroscience and Brain Repair within the Division of BioMedical Sciences and cross-appointed in the Discipline of Medicine (Neurology) in the Faculty of Medicine at Memorial University of Newfoundland (MUN). His primary research interests include basic and clinical neuroimmunology, glial cell biology, elucidating pathogenic mechanisms of neurodegenerative diseases, and novel drug and biomarker discovery. Dr. Moore's research has contributed to further our understanding of the interactions between cells of the immune and central nervous system (CNS) and has demonstrated how novel markers of inflammatory injury (e.g. microRNAs) are clinically and pathologically relevant in the injured brain. At MUN, Dr. Moore is a Co-PI with the Health Research Innovation Team in MS (HITMS), a multi-disciplinary team of dedicated MS researchers and clinicians that are collecting prospective and longitudinal data relating to the health, disease symptoms and progression, neuro-immune profiles, and physical and cognitive performance among people with MS in the Province of Newfoundland and Labrador. Dr. Moore's laboratory is currently funded by grants from the Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Council of Canada (NSERC), Multiple Sclerosis Society of Canada, InnovateNL, and the Canada Research Chair Program. Dr. Moore is a native of Saint John, New Brunswick and completed his post-secondary degrees at the University of New Brunswick (BSc) and Dalhousie University (PhD), and postdoctoral training at the University of Connecticut Health Centre and Montreal Neurological Institute at McGill University.

Stephanie N. Blandford, MSc
& Craig S. Moore, PhD
Faculty of Medicine, Division of Biomedical Sciences, Memorial University of Newfoundland

Patient-derived induced pluripotent stem cells — Bridging the gaps between preclinical and clinical effectiveness in brain illness?

At present, patient-derived central nervous system (CNS) tissue is often only available post-mortem. While these tissues can be helpful during autopsy and when confirming a clinical diagnosis, the obvious barriers in accessing primary human CNS tissue in live patients presents an impediment to developing patient-specific personalized approaches in clinical medicine. Furthermore, ideal access to post-mortem tissues is often limited for both clinicians and researchers, and a delayed post-mortem interval can significantly impact tissue and cellular integrity. As a result, animal models of CNS diseases are frequently used in research and are heavily relied upon when studying disease mechanisms and identifying possible treatment strategies. While certain imaging techniques (CT, MRI, PET, etc) can provide valuable clinical information in vivo, their lack of specificity and detailed resolution at the microscopic level is insufficient in providing detailed cellular mechanisms related to pathophysiological mechanisms of neurodegenerative diseases.

The majority of neurological illnesses rarely occur spontaneously in animals. Researchers have therefore developed animal models that function as extremely valuable tools when attempting to model specific pathophysiological mechanisms related to chronic neurological diseases. Unfortunately, most models do not recapitulate the full spectrum of the human condition and have limited translational potential [1]. For example, experimental autoimmune encephalomyelitis (EAE) is a widely used model and a valuable tool for studying multiple sclerosis (MS). EAE is most commonly induced in rodents and has made a significant impact on understanding how the immune system contributes to the neuropathology observed in MS. Furthermore, the majority of disease modifying therapies that are currently prescribed for MS patients were initially tested and validated in the EAE model [2]. Nevertheless, EAE does not model the entirety of the human condition and the majority of drugs that are successful in EAE often fail in human clinical

trials, thus limiting the applicability of the model. Non-human primate models of EAE can better recapitulate human disease and carry increased translational potential; however, these models are expensive and difficult to implement [3]. The limited translational potential of animal models of most neurodegenerative disorders has been widely documented [1, 4]. It is important to mention that similar disadvantages are observed in modeling other CNS diseases, including Parkinson's disease, Alzheimer's disease, stroke, and ALS. While evidence indicates that many of these failures arise from inadequate internal and external study validity [1], it underscores the unmet need for more optimal models that can help bridge the gap between successful preclinical animal studies and human clinical trials.

The relatively recent discovery that terminally differentiated cells can be reprogrammed to pluripotency, generating induced pluripotent stem cells (iPSCs) [5], provides a novel tool to study the etiology, development, and treatment of disease, including most neurological diseases. Patient-derived iPSCs can be reprogrammed from mature adult cells (often fibroblasts) and selectively differentiated into cells of interest. This not only permits the study of genetic associations with neurodegenerative diseases, but it also allows researchers to study the direct pathological and cellular mechanisms *in vitro* using patient-specific CNS cells. Importantly, using patient-derived iPSCs can circumvent ethical debates that have plagued allogeneic stem cell trials, eliminate concerns of immune rejection, and provide a format/model that may help to move novel therapies from preclinical animal studies to successful human clinical trials.

Certain challenges remain when studying diseases that arise from the dysregulation and/or mutation of multiple genes or those that are associated with strong gene-environment interactions. Using cells derived from MS patients, stable iPSC-derived lines have been successfully generated [6], and primary patient-derived iPSCs have been successfully differentiated into neurons and oligodendrocytes [7-9]. While no differences in the intrinsic properties of iPSC-derived neurons in patients with MS have been reported, recent evidence indicates that neural precursor cells (NPCs) derived from individuals with a progressive form of MS (primary progressive MS) have inherent defects in their ability to respond to myelin injury compared to cells derived from healthy controls [10]. A second critical finding of Nicaise and colleagues was that NPCs derived from iPSCs of patients with progressive MS exhibited marked individual differences [10]. This finding underscores the significant heterogeneity associated with this disease, which is most often reflected in patients' clinical trajectories, responsiveness to certain medications and immune cell profiles/activity.

While still in the early stages, the study of patient-derived cell populations has the potential to help us better understand critical pathophysiological mechanisms related to human CNS disorders. For complex and heterogeneous neurodegenerative conditions, like MS, the best hope for appropriate and successful treatment is a personalized approach, where treatment is tailored to the individual. iPSCs may indeed help determine this "best course" of treatment. For example, the genetic predisposition of certain patients might make them unresponsive to certain treatments or even perhaps predispose them to certain risks associated with a particular treatment. Prior screening of potential treatments *in vitro* using patient-derived iPSCs could reduce these risks and possibly guide optimal treatment strategies for individual patients.

References

[1] Jucker, M. (2010) The benefits and limitations of animal models for translational research in neurodegenerative diseases. *Nat Med*, 16(11), 1210-1214.

[2] Gold, R., Linington, C., Lassmann, H. (2006) Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research. *Brain*, 129 (8), 1953-1971.

[3] Haanstra, K. G., *et al.* (2013) Induction of Experimental Autoimmune Encephalomyelitis With Recombinant Human Myelin Oligodendrocyte Glycoprotein in Incomplete Freund's Adjuvant in Three Non-human Primate Species. *Journal of Neuroimmune Pharmacology*, 8 (5), 1251-1264.

[4] Zahs, K. R., Ashe, K. H., (2010) 'Too much good news' - are Alzheimer mouse models trying to tell us how to prevent, not cure, Alzheimer's disease? *Trends Neurosci*, 33 (8), 381-389.

[5] Takahashi, K., Yamanaka, S. (2006) Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell*, 126 (4), 663-676.

[6] Miquel-Serra, L., *et al.* (2017) Generation of six multiple sclerosis patient-derived induced pluripotent stem cell lines. *Stem Cell Res*, 24, 155-159.

[7] Song, B., *et al.* (2012) Neural differentiation of patient specific iPS cells as a novel approach to study the pathophysiology of multiple sclerosis. *Stem Cell Res*, 8 (2), 259-273.

[8] Douvaras, P., *et al.* (2014) Efficient generation of myelinating oligodendrocytes from primary progressive multiple sclerosis patients by induced pluripotent stem cells. *Stem Cell Reports*, 3 (2), 250-259.

[9] Massa, M.G., *et al.* (2016) Multiple Sclerosis Patient-Specific Primary Neurons Differentiated from Urinary Renal Epithelial Cells via Induced Pluripotent Stem Cells. *PLoS One*, 11 (5), p. e0155274.

[10] Nicaise, A. M., *et al.*, (2017) iPS-derived neural progenitor cells from PPMS patients reveal defect in myelin injury response. *Exp Neurol*, 288, 114-121.