20th NSW Stem Cell Network Workshop
- in collaboration with MS Research Australia

Stem Cells in Multiple Sclerosis and Neurological Disease

Darlington Centre
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Wednesday, May 28, 2014

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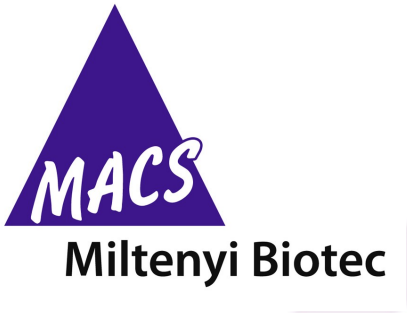

MS Research Australia and the NSW Stem Cell Network gratefully acknowledge the support of the NSW Office of Health and Medical Research.

MS Research Australia and the NSW Stem Cell Network also gratefully acknowledge the Australian Government Department of Health and Ageing and the Australian Diabetes Council for operational support.

WELCOME

Dear Colleagues

MS Research Australia and the NSW Stem Cell Network would like to welcome you to the 20th Workshop of the NSW Stem Cell Network, organised in collaboration with MS Research Australia.

Thank you for giving your time to be here today to share your research findings and your expertise.

This workshop brings together researchers with an interest in the use of stem cell therapies for the treatment of multiple sclerosis and other diseases. Today is an opportunity for researchers and clinicians from a wide range of fields to share their latest findings and engage in an active and open discussion of the barriers and opportunities for translating stem cell research to benefit patients with neurological disease.

We hope today to stimulate and promote cross-disciplinary and innovative research in the field of stem cells and MS; to forge new collaborations; and to accelerate the efficiency of translation of stem cell research.

We very much look forward to an open and extensive discussion of the current state of stem cell research for neurological disease and through our deliberations today, we hope to find avenues for learning and progress that exploit Australia-wide strengths in stem cell and neurological research that cross the boundaries between research disciplines and work towards translating this knowledge to the clinic.

We are most grateful to all of you for your valuable contribution to this workshop.

Dr Juliana Lamoury
Manager
NSW Stem Cell Network

Professor Bernie Tuch
Director
NSW Stem Cell Network

Dr Lisa Melton
Research Development Manager
MS Research Australia

Professor William Carroll
Director
MS Research Australia

Program

9:00am	Registration opens
9:30am	**Welcome -** Professor Bernie Tuch, Director NSW Stem Cell Network **Opening address**: Professor William Carroll, MS Research Australia & Western Australian Neuroscience Research Institute
Session 1:	**Overview of MS, including stem cells and clinical trials** **CHAIR: Professor William Carroll, MS Research Australia**
9:45am	**Professor Claude Bernard,** Monash University *The prospect of stem cells as multi-faceted purveyors of immune modulation, repair and regeneration in multiple sclerosis*
10:30 am	**Professor Trevor Kilpatrick,** Melbourne Neuroscience Institute *The promise of stem cells — what's beyond the horizon*
11:15am	Morning tea
Session 2:	**Stem Cells and Neurological Disorders** **CHAIR: Professor Matthew Kiernan, Brain and Mind Research Institute**
11:30 am	**Professor Carolyn Sue,** Kolling Institute of Medical Research *Use of stem cells to investigate Parkinson's disease*
11:50 am	**Dr Bryce Vissel,** Garvan Institute of Medical Research *Regulation of neurogenesis following neurodegeneration*
12.10 am	**Dr Karlea Kremer,** University of Adelaide *Human adult dental pulp stem cell therapy for treatment of stroke*
12.30 am	**Clinical Professor Richard Herrmann,** Cell and Tissue Therapies WA *Clinical trials of mesenchymal stromal cells in autoimmune diseases in Australia*

Program

12:50 pm	Lunch
Session 3:	**Clinical and Experimental Research in MS** **CHAIR: Professor Trevor Kilpatrick , Melbourne Neuroscience Institute**
1:50 pm	**Dr John Moore,** St Vincent's Hospital *Hematopoietic stem cell transplantation (HSCT) for autoimmune diseases – gold standard for some diseases, emerging evidence in MS*
2:10 pm	**Dr Marzena Pedrini,** Western Australian Neuroscience Research Institute *Hematopoietic stem cell transplantation in multiple sclerosis in a Western Australian cohort*
2.30 pm	**Professor Bruce Brew,** St Vincent's Hospital *The kynurenine pathway and stem cells*
2.50 pm	**Dr Toby Merson,** The Florey Institute of Neuroscience and Mental Health *Neural precursor cells outcompete oligodendrocyte progenitor cells to remyelinate broad regions of the rostral corpus callosum*
3:10pm	Afternoon tea
Session 4:	**Group Panel Discussion – How can we expedite stem cell research for multiple sclerosis towards translational research and clinical trials?** **CHAIR: Professor William Carroll, MS Research Australia**
3:25 pm	***Lead discussants:*** **Professor Claude Bernard,** Monash University **Professor Trevor Kilpatrick,** Melbourne Neuroscience Institute ***With:*** **Mr Mike Hemingway,** person with MS **Associate Professor Megan Munsie,** Stem Cells Australia
4:25pm	**End of workshop**

Speaker: Professor Claude Bernard, Monash University

Claude C. A. Bernard *was born in Paris, France. He graduated from the Sorbonne, Paris in 1968 and received an MSc (1970) and a PhD (1973) from the University of Montreal and a DSc from the University Louis Pasteur, Strasbourg (1978). Professor Bernard was a Research Fellow in the Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research in Melbourne from 1973 to 1976 and then become a Member of the Basel Institute of Immunology. In 1979, he established the Neuroimmunology Laboratory at La Trobe University, Melbourne. In 1990, he was appointed as the first Personal Chair to be made at La Trobe University and the Director of the Brain Behaviour Research Institute. Professor Bernard was recruited by Monash University in 2005, as the Deputy Director of the Monash Immunology and Stem Cell Laboratories. He is currently a Senior Staff Member of the Australian Regenerative Medicine Institute, where he is Head of the Multiple Sclerosis Research Group. He has published over 220 scientific papers and has written many book chapters dealing with various aspects of autoimmunity and MS research. He is on the Editorial Board of a number of scientific journals and is a frequently Invited Professor in the Departments of Neurology at both Stanford University and the University of California in San Francisco, collaborating on MS research. Currently, he is a guest Professor of the Bayi Brain Hospital Affiliated to the General Hospital of Beijing Military Command and the Kunming Medical University. In 1993, he was awarded the Shinshu Medical School Medal, from Shinshu University, Matsumoto City, Japan. He was made a Fellow of the International Behavioural Neuroscience Society in 1995 and in 1998 was recipient of a Fullbright Scholar Award. He was awarded the Bethlehem Griffiths Research Foundation Medal for his contribution to the field of Neurosciences and multiple sclerosis in 2004 and received the ST Huang Chan Memorial Award from the University of Hong Kong in 2010.*

The Prospect of Stem Cells as Multi-faceted Purveyors of Immune Modulation, Repair and Regeneration in Multiple Sclerosis

Given that stem cell transplantation has long been considered a promising regenerative therapy for a number of CNS diseases, we have assessed the therapeutic potential of neural (precursor) cells (NCs) derived from mouse ES cells and mesenchymal stem cells (MSCs) isolated from different tissues in EAE. Intravenous and intraperitoneal injections of GFP+ NCs and MSCs from the onset of the disease lead to a significant clinical improvement of this MS-like disease as compared to untreated EAE mice and those receiving autologous BM cells and/or fibroblasts, used as control cell populations. The mechanism by which this suppressive effect is produced appears to be the result of immunoregulation and/ or immunosuppression occurring in peripheral lymphoid organs, rather than a direct effect on autoreactive cells present in the CNS. Apart from their broad immunomodulatory properties, stem cells are capable of homing to sites of inflammation and therefore represent promising tools for the delivery of therapeutic molecules. We therefore studied the effect of human mesenchymal stem cells engineered to overexpress anti-inflammatory cytokines in mice with chronic progressive EAE. Transplantation studies revealed that IL10-MSCs could prevent or significantly delay the development of EAE when administered during the priming phase of disease, reducing T-cell proliferative responses and pro-inflammatory cytokine secretion. Co-culture studies demonstrated that Ad-IL10-MSCs could inhibit dendritic cell function, suggesting that the mechanism of action may involve inhibition of antigen presentation and T-cell activation. Collectively, these findings further add to the armamentarium of non-toxic cell and gene-based strategies for the treatment of debilitating diseases such as MS.

Contributing authors: Natalie Payne, Guizhi Sun, Aude Silvain, Courtney Mc Donald, Chuanyu Wei, Daniella Herszfeld, Christopher Siatskas and ***Claude C A Bernard.***
Multiple Sclerosis Research Laboratory, Australian Regenerative Medicine Institute, Monash University, Wellington Road, Clayton, Victoria, 3800 Australia.

Speaker: Professor Trevor Kilpatrick, Melbourne Neuroscience Institute

Trevor Kilpatrick *is a Professor of Neurology and Director of the Melbourne Neuroscience Institute at The University of Melbourne; he is the leader of the MS Division at the Florey Institute of Neuroscience and Mental Health and is a neurologist and Head of the MS Unit at the Royal Melbourne Hospital. Professor Kilpatrick graduated with a Bachelor of Medicine, Bachelor of Surgery from the University of Melbourne in 1982 and then went on to specialise in neurology. He undertook graduate studies at The University of Melbourne and gained a Doctor of Philosophy in 1993. Appointments at The Salk Institute for Biological Studies (La Jolla, USA), Institute of Neurology (London, UK) and The National Hospital and Moorfields Eye Hospital (London, UK) followed. He returned to Melbourne as the Viertel Senior Medical Research Fellow at the Walter & Eliza Hall Institute for Medical Research and as the Head of the Melbourne Multiple Sclerosis Research Unit at the Royal Melbourne Hospital. Professor Kilpatrick has been the recipient of the Sunderland Award (1994), AMRAD Postdoctoral Award (1995), inaugural Leonard Cox Award (2000), Bethlehem Griffiths Research Foundation Award for Medical Research (2004), the Australian Museum's Jamie Callachor Eureka Prize for Medical Research (2008), the Stephen C. Reingold Research Award by the US MS National Multiple Sclerosis Society (2010) and most recently, (2013), Professor Kilpatrick was awarded the Bethlehem Griffiths Research Foundation Medal for outstanding leadership in medical research. Professor Kilpatrick has published widely including publications in Nature, Nature genetics and Nature Medicine. His research interests include the neurobiology of multiple sclerosis, neural precursor cell biology and the study of genetic and environmental factors that contribute to MS as well as the translation of basic research discoveries to the clinic.*

Carolyn Sue *is an internationally recognised expert on Parkinson's disease, working as a clinician-scientist at the Kolling Institute for Medical Research, University of Sydney. She is the first neurologist at Royal North Shore Hospital, to be appointed as Professor at the University of Sydney. Dr Sue is also the Director of Neurogenetics at the Kolling Institute and Royal North Shore Hospital and the Director of the National Centre for Adult Stem Cell Research (Sydney node). She has dual research interests, mirroring her clinical interests in the diagnosis and management of mitochondrial disease and movement disorders. Her research studies investigate the role that mitochondria play in neurodegeneration.*

Dr Sue is currently Treasurer Elect for the Asian Oceanic section of the International Movement Disorder Society, NSW Clinical and Research Trials Representative for the Movement Disorder Society of Australia, is on the Scientific Advisory Board of the NSW Parkinson's Disease Association and a member of the taskforce on Genetic Nomenclature for the International Movement Disorder Society.

Use of Stem Cells to Investigate Parkinson's disease

Recent advances in use of stem cell models to create neuronal models have provided investigators the opportunity to understand disease mechanisms that contribute to neurological disease. One important example includes Parkinson's disease, a neurodegenerative disorder caused by degeneration of dopaminergic (DA) neurons in the substantia nigra. Human skin fibroblasts, reprogrammed to create human iPS cells (induced pluripotent stem cells) can be successfully differentiated into neurons and dopaminergic neurons. By reprogramming fibroblasts derived from patients with genetic forms of parkinson's disease, we have created iPS cells with endogenous levels of mutant proteins that can be differentiated into dopaminergic neurons to investigate the pathophysiological processes that contribute to the cause of Parkinson's disease. Similarly, olfactory neurosphere lines established from olfactory mucosal biopsies can be cultured from patients with monogenic forms of PD to develop similar types of specific disease cell models. Use of both olfactory and iPS cells differentiated into neurons have allowed the identification of multiple aberrant pathways that may lead to the development of Parkinson's disease.

Speaker: Dr Bryce Vissel, Garvan Institute of Medical Research

Dr Vissel *completed his PhD at University of Melbourne and then spent 10 years at the Salk Institute in the USA, working as a senior scientist at the world's leading neuroscience laboratory (based on worldwide scientific rankings).*

Dr Vissel was recruited to Australia from the Salk Institute in the USA to establish and lead research for brain and spinal cord repair, with the assistance of the State Government of NSW. His work gained international recognition and he received a number of awards, including the prestigious Fulbright award, a Liebermann award and a BIOFIRST award. He has a record of leadership and team building.

Dr Vissel is on the Advisory Boards of Alzheimer's Australia, Parkinson's NSW and SpinalCure Australia. He was a founder of Spinal Cord Injury Network. He has strong links to cancer researchers. Dr Vissel also regularly appears in the media and has advised State and Federal Goverrnment, committees, ministers and advisors as well as industry. He has strong international links and strong links to leading clinicians.

Regulation of Neurogenesis Following Neurodegeneration

It has long been proposed that excitotoxicity contributes to nerve cell death in neurodegenerative diseases. Activin A, a member of the transforming growth factor-beta superfamily, is expressed by neurons following excitotoxicity. We show for the first time that this activin Aexpression is essential for neurogenesis to proceed following neurodegeneration. We found that intraventricular infusion of activin A increased the number of newborn neurons in the dentate gyrus, CA3, and CA1 layers of the normal adult hippocampus and also, following lipopolysaccharide administration, had a potent inhibitory effect on gliosis in vivo and on microglial proliferation in vivo and in vitro. Consistent with the role of activin A in regulating central nervous system inflammation and neurogenesis, intraventricular infusion of follistatin, an activin A antagonist, profoundly impaired neurogenesis and increased the number of microglia and reactive astrocytes following onset of kainic acid-induced neurodegeneration. These results show that inhibiting endogenous activin A is permissive for a potent underlying inflammatory response to neurodegeneration. We demonstrate that the anti-inflammatory actions of activin A account for its neurogenic effects following neurodegeneration because co-administration of nonsteroidal anti-inflammatory drugs reversed follistatin's inhibitory effects on neurogenesis in vivo. Our work indicates that activin A, perhaps working in conjunction with other transforming growth factor-beta superfamily molecules, is essential for neurogenesis in the adult central nervous system following excitotoxic neurodegeneration and suggests that neurons can regulate regeneration by suppressing the inflammatory response, a finding with implications for understanding and treating acute and chronic neurodegenerative diseases.

Karlea Kremer *is an early career researcher and the inaugural Peter Couche Foundation Post-Doctoral Research Fellow at the University of Adelaide. After completing a PhD in Gene Therapy for Cystic Fibrosis, Karlea moved to the Stroke Research Programme at the University of Adelaide to help undertake pilot studies to investigate the use of human adult dental pulp stem cells in a rodent model of stroke. Following the completion of this study, Karlea has been involved in further animal studies to move the use of dental pulp stem cells for stroke brain repair forward to eventually be used as a clinically acceptable therapy.*

Human Adult Dental Pulp Stem Cell Therapy for Treatment of Stroke

A major challenge for stroke medicine is how to repair the damaged brain following cerebral ischemia. Cell-based therapy is a potential strategy to address this problem and could improve stroke outcomes by direct cell replacement, immunomodulation, neuroprotection, angiogenesis and/or neuroplasticity. In the last decade there have been 192 preclinical studies utilising 2704 animals that demonstrated an overall improvement in function of 40.6%. We have used a novel adult human stem cell therapy from molar teeth, dental pulp stem cells (DPSC). DPSC are ectomesodermal in ontology, are multipotent, have high proliferative capacity, and are capable of differentiating into neurons both *in vitro* and *in vivo*. Recently, we published in a rodent model of ischemic stroke that 24 hours following stroke when DPSC were intracerebral injected this resulted in a significant improvement in function in the forepaw one month post-stroke. $6x10^5$ human DPSC were transplanted into the peri-infarct region, into the cortex and the striatum. Four weeks post-transplant an average of 2.3% of the original DPSC survived in the rodent brain and expressed the astrocytic marker GFAP (glial fibriliary acidic protein) and the mature neuronal marker, NeuN.

We suggest the next step is to translate to a Phase I clinical study as human DPSC are easily accessible and may be sourced autologously. The TOOTH (**T**he **O**pen study **o**f dental pulp stem cell **T**herapy in **H**umans) stroke study, will aim to determine whether intra-cerebral injection of DPSC into chronically disabled stroke survivors is safe and feasible.

Speaker: Clinical Professor Richard Herrmann, Cell and Tissue Therapies W.A.

Richard Herrmann *obtained his medical degree at Sydney University, undertaking postgraduate work in Sydney, Perth and London. He is a lifetime fellow of the Royal Australasian College of Physicians and a fellow of the Royal College of Pathologists of Australasia.*

He has been active in clinical and applied laboratory research all his professional life and has published many papers and coauthored a haematology text book. Research interests currently include mesenchymal (adult) stem cell research, adult stem cell clinical trials and assisting junior scientific and medical staff in their research projects in a variety of blood disorders. He continues in clinical practice.

Richard became director of Cell and Tissue Therapies, W.A. in 2007, a WA Department of Health Facility at Royal Perth Hospital involved in research and manufacture of human adult stem cells. He is a Clinical Professor, School of Pathology and Laboratory Medicine, University of Western Australia.

Clinical Trials of Mesenchymal Stromal Cells in Autoimmune Diseases in Australia

Mesenchymal stromal or stem cells (MSC) are adult stem cells capable of differentiating down multiple pathways. They can be found in many tissues, typically bone marrow or fat or even umbilical cord, amniotic fluid, dental pulp, liver and spleen, lung and skin.

Human MSC are not immunogenic and do not possess histocompatibility antigens so there is very low expression of HLA class I and no expression of class II activity. This means they escape recognition by foreign or alloreactive T lymphocytes and natural killer cells. It also means that they do not need to be matched between the donor and the recipient. Most work is focused on MSC derived from the bone marrow.

Importantly for therapeutic use they have immunosuppressive and immunoregulatory as well as healing properties. Because of these properties MSC were initially trialled in the immunological disease of graft-versus-host-disease after bone marrow transplantation where the donated immune system (T lymphocytes) attacks the recipient's epithelial tissues. This immunomodulatory activity reacts at multiple levels and involves many factors. MSC have been utilised by our group in collaboration with clinicians in successful trials in graft versus host disease and in an Australian multicentre phase 2 trial in biologically refractory Crohn's disease.

The tissue repair capabilities are being investigated by us in trials for bone repair and in renal transplant graft rejection.

The cells are manufactured by us in the Cell and Tissue Therapies WA facility at Royal Perth Hospital. They are manufactured under good manufacturing conditions in a TGA-licensed laboratory. To date, no significant safety issues have arisen with the use of these cells one but safety studies are ongoing and there may be long-term side effects as yet unknown.

Speaker: Dr John Moore, St Vincent's Hospital

John Moore *graduated from Sydney University in 1989 and completed his residency and Haematology Advanced training at Royal North Shore Hospital. He was awarded Fellowship of the College of Physicians and Pathologists in 1997. He continued his training at the Westmead Children's Hospital and subsequently became the Bone Marrow Transplant Coordinator at the Royal Free Hospital, London from 1997-1998. He returned to Australia in 1998 and completed a Doctorate of Medicine at St. Vincents Hospital whilst researching the role of Haematopoietic Stem cell Transplantation for Severe Rheumatoid Arthritis. He is currently a Senior Staff Specialist in the Haematology Department at St.Vincents Hospital and a Visiting Medical Officer at St. Vincents Private Hospital. He was the Chair of the Bone Marrow Transplant Committee of the Australian Leukaemia and Lymphoma Group (ALLG) from 2004-2006. He has been a member of the Executive of the ALLG from 2002-2006, Secretary from 2002-2004 and on the Safety and Data Monitoring Board from 2002-2006. He has been on the Medical Advisory Committee of the Leukaemia Foundation from 2002-2004. Dr Moore has been involved in clinical trials for the past ten years and is presently a Chief Investigator at St. Vincents Hospital in numerous clinical trials. His research interests include thymic differentiation of haematopoietic stem cells and clinical studies of haematopoietic stem cell transplant. He is a conjoint Senior Lecturer in Medicine at the University of New South Wales.*

HSCT for Auto-Immune Diseases—Gold Standard for Some Diseases, Emerging Evidence in MS

Autologous stem cell transplantation (HSCT) is a procedure that is usually used to give high doses of chemotherapy to patients with blood cancers followed by stem cell infusion so that a new blood and immune system can reconstitute. Over the last 15 years, HSCT has become much safer. At the same time, numerous lines of evidence converged to suggest that a small number of patients with very severe auto-immune conditions could also be treated by HSCT. The evidence came from patients who had chemotherapy for co-existant blood tumours and had an auto-immune disease (AID), animal studies and since 1996 Phase II studies. It is possible to select patients with a high standardised mortality for more intensive therapy with HSCT and aim to provide them with a lasting remission. In this situation it could be argued that the small risk of mortality associated with HSCT is justified by the potential poor morbidity and mortality associated with resistant auto-immune conditions. Beyond its immunosuppressive potential, HSCT may replace a defective immune system with stem cells which reconstitute a tolerant immune system.

More than 38% of all HSCT procedures registered with the European Bone Marrow Transplant registry are for severe MS, usually relapsing remitting or secondary progressive disease. Although interferon-b, nataluzimab andf other agents have been shown to delay the time to progression of disease based on EDSS (Expanded Disablity Status Scale) scores, there are still numerous patients for whom there are no other therapeutic options. Given MS has an auto-immune pathophysiology and the consequences of failed therapy are devastating for the patient and family it is reasonable to attempt HSCT in this disorder in prospective, ethically approved Phase II trials in patients who have failed conventional therapies

The data in our own Australian and international studies of HSCT for MS have demonstrated that a majority of patients experience stabilisation of disease and in 30%, an actual improvement of their function. Clearly randomised trials are now required to assess the role of HSCT in the clinical management of MS patients.

Speaker: Dr Marzena Pedrini, Western Australian Neuroscience Institute

Dr Pedrini *received her PhD in Animal Science (with specialization in animal physiology and biochemistry) at University of Life Sciences, Poznan, Poland. During her PhD program she was exploring the influence of neurohormons on insulin secretion and she was teaching physiology and biochemistry in undergraduate programs. Shorthly after graduation, she started her postdoctoral training in the Department of Immunology and later Department of Cancer Biology at Thomas Jefferson University, Philadelphia, PA, USA.*

Dr Pedrini was involved in many projects such as: 1) Blood-brain barrier permeability changes and inflammatory response during experimental allergic encephalomyelitis, an animal model of multiple sclerosis, 2) Intervention against secondary neuronal injury in mouse model of spinal cord injury by the inactivation of peroxynitrite-dependent radicals. The results of her studies are published in peer-reviewed journals such as PNAS, J Immunol, Neurosience, J Pharmacol Exp Ther and others. She was a member of Jefferson Postdoctoral Association where she served as a Treasurer and Vice President. After completing her postdoctoral experience she became a junior faculty at the same university. In 2012 Dr Pedrini moved to Perth, Australia and joined the group of Profs. Allan Kermode and Bill Carroll at WANRI. Her responsibilities are focused on many projects including benign MS, NMO studies, influence of Helicobacter pylori on MS risk and others. Dr Pedrini is also working on the Australian MS HSCT Registry.

Hematopoietic Stem Cell Transplantation in Multiple Sclerosis in a Western Australian Cohort

Background: There is a subset of multiple sclerosis (MS) patients who have continued disease activity and progression, responding poorly to existing treatments with rapidly accumulating clinical disability. In the last 2 decades, intensive immunosuppression followed by autologous hematopoietic stem cell transplantation (HSCT) has been proposed as a possible strategy for treatment of severe immune-mediated disorders, including MS.

Objective: To examine MS patients from Western Australian cohort with progressive disease who continued to deteriorate despite treatment and underwent stem cell therapy.

Methods: Fifteen patients with demyelinating disease with median age of 44 (22-60) years were included in the study. The clinical diagnoses were primary and secondary progressive MS, and one neuromyelitis optica (NMO) phenotype. Prior to transplant, expanded disability status scale (EDSS) scores ranged between 6.0 and 8.5. Disease duration varied from 3 to 30 years and patients had received at least 2 prior immunomodulatory treatments. Peripheral blood HSC were mobilized with cyclophosphamide followed by G-CSF starting at day 5. The conditioning regimen was cyclophosphamide and rabbit antithymocyte globulin.

Results: The therapy was well tolerated by 5 patients, whilst 10 patients experienced febrile neutropaenia, fever, urinary retention, bladder infection or severe constipation. In the first 2-years after HSCT following intensive physiotherapy some patients noticed minor improvement in walking distance or bladder function. However, most patients remained stable with neither improvement nor deterioration and some patients reported worsening of the disease over a minimum 2-year interval. Longest follow-up has been 6 years. Follow up MRIs showed no evidence of Gd-enhancing lesion, but two patients nevertheless developed new cerebral lesions on T2 weighted imaging.

Conclusions: HSCT can halt MRI progression in most patients but clinical progression still occurred. There was no incidence for significant improvement in clinical status in this cohort as a result of HSCT.

Contributing authors: Marzena J Pedrini[1], Gavin Cull[2], Bradley M Augustson[2], Jason Burton[1,3], William M Carroll[1,3], Allan G Kermode [1,3,4]

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Prof Bruce Brew *is head of the department of neurology at St Vincent's Hospital and Director of the Applied Neurosciences Program and Peter Duncan Neurosciences Unit in St Vincent's Centre for Applied Medical Research. He has approximately 320 publications (H index 48 Web of Science, 55 Google Scholar), written three books and has been invited to give 168 national and international lectures in the last decade. He has been active in adult stem cells for approximately 10 years. He has been an invited participant in educational courses for the American Academy of Neurology and the World Congress of Neurology for several years. He has received research funding from governmental bodies in Australia (NHMRC) USA (NIH) as well as industry. He sits on the editorial board of four journals.*

The Kynurenine Pathway and Stem Cells

The kynurenine pathway (KP) is known to play a pathogenetic role in a variety of neurological diseases. We have shown that human and mouse mesenchymal and neural stem cells (MSCs and NSCs) express the complete KP, and that the KP can be modulated by various drugs with an impact on MSC and NSC proliferation and differentiation. Further data point to this being relevant to oligodendrocyte progenitor cell differentiation. We are now expanding this work to optimise NSC and OPC proliferation and differentiation using cell culture systems and animal models including the EAE and cuprizone models. How the KP is expressed and modulated in iPS cells and how the KP interacts with other pathways known to be important in stem cell biology such as the Nogo pathway are areas for collaboration.

Speaker: Dr Tobias Merson, Florey Institute of neuroscience and Mental Health

Dr Tobias Merson *heads a laboratory within the Florey Institute of Neuroscience and Mental Health investigating the life cycle of the oligodendrocyte, the cell type responsible for myelination within the central nervous system (CNS). His research examines how oligodendrocytes are generated during development, how they are regenerated after injury and their role in supporting the function of axons. In particular, current interests are to elucidate how oligodendrocytes support neuronal health beyond the provision of myelin, studying the regulation of neural stem and progenitor cell proliferation, differentiation and recruitment after demyelination and analysing mechanisms of oligodendrocyte turnover and remyelination.*

Dr Merson completed his PhD at the Walter & Eliza Hall Institute for Medical Research in 2006, demonstrating the critical role of epigenetics in the regulation of neural stem cell function and adult neurogenesis. He then took up a postdoctoral position within the Multiple Sclerosis Group at the Howard Florey Institute and was awarded a Betty Cuthbert Training Fellowship (2007-2010) jointly funded by the NHMRC and Multiple Sclerosis Research Australia. During this period he developed expertise in diverse in vitro and in vivo metholologies to study the biology of NPCs and oligodendrocyte progenitor cells. In 2011, he established his own laboratory within the Multiple Sclerosis Division at the Florey Institute and was awarded a Melbourne Neuroscience Institute Fellowship in 2013.

Neural Precursor Cells Outcompete Oligodendrocyte Progenitor Cells to Remyelinate Broad Regions of the Rostral Corpus Callosum

Remyelination of the central nervous system (CNS) is believed to occur primarily via the generation of new oligodendrocytes derived from oligodendrocyte progenitor cells (OPCs) that reside throughout the CNS parenchyma. Recent studies suggest that neural precursor cells (NPCs) residing within the adult subventricular zone (SVZ) can also contribute to oligodendrogenesis following experimental demyelination. However the relative importance of NPCs versus OPCs during remyelination remains largely unexplored. To address this issue, we adopted a genetic fate-mapping approach to independently trace the progeny of NPC and OPC lineages during the course of CNS remyelination. Utilising the cuprizone model of CNS demyelination, we demonstrate substantial recruitment of NPC lineage cells into the demyelinated corpus callosum, and subsequent differentiation into mature oligodendrocytes. Oligodendrogenesis of NPC lineage cells was particularly prominent in the rostral forebrain adjacent to the SVZ. Within this region NPC-derived oligodendrocytes outnumbered those generated from OPCs 4.6-fold, indicating that NPCs exhibit a significant competitive advantage over OPCs in this area. Examination of the remyelination capacity of NPC-derived oligodendrocytes revealed that 62% of all nodes of Ranvier adjacent to the SVZ were flanked by at least one myelin paranode generated from an NPC-derived oligodendrocyte. Ultrastructural analysis at recovery also demonstrated that compared to unchallenged controls, g-ratios of myelinated fibers in regions of the corpus callosum dominated by NPC-mediated remyelination were normal, whereas areas dominated by OPC-mediated remyelination had significantly higher values, suggesting that myelin produced by NPCs is thicker than that generated by OPCs. Collectively, our data reveal that NPCs are major contributors to oligodendrogenesis and remyelination of the rostral corpus callosum and reinforces the notion that enhancing the reparative potential of NPCs could constitute a cogent strategy for the treatment of demyelinating diseases.

Contributing authors: YL Xing[1], PT Roth[1], JAS Stratton[1], SL Ellis[3], BHA Chuang[1], SW Ng[1], TJ Kilpatrick[1,2] and ***TD Merson[1,2]***
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CHAIR: **Professor William Carroll**, MS Research Australia

'How can we expedite stem cell research for multiple sclerosis towards translational research and clinical trials?'

LEAD DISCUSSANTS:

Professor Claude Bernard, Monash University

Professor Trevor Kilpatrick, Melbourne Neuroscience Institute

WITH:

Mr. Mike Hemingway, person with MS

Associate Professor Megan Munsie, Stem Cells Australia

Mike Hemingway

Mike began life with a great interest in scientific research, especially genetics. With a BSc from Sydney University, he worked in the field for a short time with Biotechnology Australia under Dr Rob Forage. However, economic realities (and a fear of hard work) saw Mike change career direction and join the world of banking. Mike worked primarily in financial markets for nearly 30 years and in Sydney, New York and London. He earned a MBA from UTS in 2002. Mike stayed as part of the markets team in NAB until 2013 when his MS forced him to retire.

Mike has been active in Foundation 5 Million, the community fundraising initiative of MSRA, since its creation in concept in 2004 and its fundraising birth in 2005. He and his wife, Katrina, have been involved in many fundraising activities but the three most significant have been Katrina's conquest of the legendary Kokoda Track in 2008 (raising $35,000), the Mudgee2Sydney MS Walk in 2010 (raising $150,000) and in 2014 they will do Wainwright's Coast2Coast MS Walk across England and are aiming to raise $150,000 again. Mike has been Chair of F5m for around 4 years.

Since Mike's diagnosis with MS in 2003, his main interest has been in research. He strongly believes that this as the only way we will find a cure. From the outset, Mike could see no better way to help this happen than to support MS Research Australia through the late Ian Ballard's community fundraising vision. Mike has said that he won't stop until we have a cure.

Associate Professor Megan Munsie

Associate Professor Megan Munsie is a stem cell scientist who combines her extensive technical expertise with an interest and understanding of the complex ethical, social and regulatory issues associated with stem cell science. Megan heads the Education, Ethics, Law & Community Awareness Unit at the Australian Research Council funded Stem Cells Australia initiative and is based at The University of Melbourne.

She is a member of an international research team that is exploring community expectation in relation to stem cell science, and in particular 'stem cell tourism'. Over the last decade, Megan has contributed to the development of stem cell related policy and co-authored educational resources for the public and health professionals. She is an advisor to several international and national organisations.

Megan has a Bachelor of Applied Science from QUT, a Masters in Reproductive Sciences and a PhD from Monash University.

Be a Member of the NSW Stem Cell Network

The NSW Stem Cell Network has around 500 members . Our all inclusive, free membership makes this network unique in consisting not only of researchers and practitioners but members of the public, industry and governmental bodies. Our aim is to ensure effective communications between diverse sectors for the advancement of stem cell research. As a member you will receive invitations to upcoming network and external stem cell related events as well as the latest stem cell news. Sign up at:

www.stemcellnetwork.org.au

Careers

To advertise positions related to the field of stem cells, please email;

stemcellinfo@stemcellnetwork.org.au with a full description of the job on offer.

Contact Details

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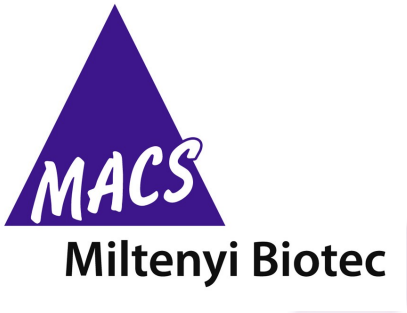

MS Research Australia and the NSW Stem Cell Network gratefully acknowledge the support of the NSW Office of Health and Medical Research.

MS Research Australia and the NSW Stem Cell Network also gratefully acknowledge the Australian Government Department of Health and Ageing and the Australian Diabetes Council for operational support.