Friday 24 August 2018

Queensland Brain Institute, The University of Queensland

Spinal cord and brain injuries are hallmarked by long-lasting inflammatory changes, which are thought to negatively interfere with recovery and may also predispose affected individuals to other neurological conditions. This symposium will bring together both emerging and established leaders in the field of neurotrauma research from across the world to discuss the latest insights into (neuro-) inflammation and immune function after spinal cord and brain injury.

Speakers

Prof. Phil Popovich
OHIO STATE UNIVERSITY

Dr. Kylie Alexander
MATER MEDICAL RESEARCH INSTITUTE

Prof. Daniel Anthony
OXFORD UNIVERSITY

A/Prof. Marc Ruitenberg
THE UNIVERSITY OF QUEENSLAND

Dr. Shu Wen Wen
MONASH UNIVERSITY

Prof. David Brown
WESTMEAD HOSPITAL

Prof. Steve Lacroix
LAVAL UNIVERSITY

Dr. Jana Vukovic
THE UNIVERSITY OF QUEENSLAND

Dr. Bridgette Semple
MONASH UNIVERSITY

Dr. Anna Leonard
UNIVERSITY OF ADELAIDE

Prof. Richard Ransohoff
THIRD ROCK VENTURES

Dr. Marta Gómez-Galán
KAROLINSKA INSTITUTE

Dr. Frances Corrigan
UNIVERSITY OF SOUTH AUSTRALIA

Dr. Liviu Bodea
QUEENSLAND BRAIN INSTITUTE, THE UNIVERSITY OF QUEENSLAND

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Frontiers in Spinal Cord Injury Research

Friday 24th August 2018, 8:00am – 5:35pm
QBI Auditorium (Building 79), Queensland Brain Institute, UQ

Program – morning

Registration:	8:00 – 9:00am	Participant Registration - coffee served from 8:15am
Opening:	9:00 – 9:15am	Welcome & Introduction

Session Title:	***The systemic response to SCI and other forms of CNS injury - I -***		
Chair(s):	A/Prof. Marc Ruitenberg & Prof. Perry Bartlett		
Speakers/Topics:			
Time	**Name of Speaker**	**Topic**	**Contact Details**
Keynote #1: 09:15 – 09:50	**Prof. Phil Popovich**	Understanding immune dysfunction after spinal cord injury: implications for infection susceptibility and recovery of function	Phillip.Popovich@osumc.edu
09:50 – 10:15	**Dr. Kylie Alexander**	Macrophages, key effectors of neurogenic heterotopic ossification following spinal cord injuries	kylie.alexander@mater.uq.edu.au
10:15 – 10:45	***Morning tea***		

Session Title:	***The systemic response to SCI and other forms of CNS injury - II -***		
Chair(s):	Prof. Phil Popovich & Dr. Jana Vukovic		
Speakers/Topics:			
Time	**Name of Speaker**	**Topic**	**Contact Details**
Keynote #2: 10:45 – 11:20	**Prof. Daniel Anthony**	Role of extracellular vesicles in the acute phase response, sickness behaviour and outcomes from CNS injury	daniel.anthony@pharm.ox.ac.uk
11:20 – 11:45	**A/Prof Marc Ruitenberg**	Targeting post-traumatic inflammation in acute SCI	m.ruitenberg@uq.edu.au
11:45 – 12:10	**Dr. Shu Wen Wen**	Age-dependent effect of post-stroke infection	shu.wen@monash.edu
12:10 – 12:35	**Prof. David Brown**	MIC-1/GDF15 as a novel target for neuroprotection in SCI	d.brown@amr.org.au
12:35 – 13:30	***Lunch***		

Program – afternoon

Session Title:	***Neuroinflammation and recovery from traumatic brain or spinal cord injury***		
Chairs:	Prof. Dan Anthony & Dr. Frances Corrigan		
Speakers/Topics:			
Time	**Name of Speaker**	**Topic**	**Contact Details**
Keynote #3: 13:30 – 14:05	**Prof. Steve Lacroix**	Understanding how interleukin-1α signalling mediates neuroinflammation and secondary cell death after spinal cord injury	Steve.Lacroix@crchul.ulaval.ca
14:05– 14:30	**Dr. Jana Vukovic**	Microglia regulate spatial learning outcomes following traumatic brain injury	j.vukovic@uq.edu.au
14:30 – 14:55	**Dr. Bridgette Semple**	Traumatic injury to the paediatric brain – how does developmental age influence the inflammatory response?	bridgette.semple@monash.edu
14:55 – 15:20	**Dr Anna Leonard**	The role of neurogenic inflammation following neurotrauma	anna.leonard@adelaide.edu.au
15:20 – 15:45	***Afternoon tea***		

Session Title:	***Co-morbidities, inflammation and cognitive function***		
Chairs:	Prof. David Brown & Dr. Bridgette Semple		
Speakers/Topics:			
Time	**Name of Speaker**	**Topic**	**Contact Details**
Keynote #4: 15:45 – 16:20	**Prof. Richard Ransohoff**	Myeloid cells and post-traumatic neuroinflammation 2018	rransohoff@thirdrockventures.com
16:20 – 16:45	**Dr. Marta Gómez-Galán**	Hippocampal metabolic and synaptic neuro-glial dysfunction after surgery	marta.gomez@ki.se
16:45 – 17:10	**Dr. Frances Corrigan**	Modulating the immune response following mild traumatic brain injury to alter the functional outcome	frances.corrigan@adelaide.edu.au
17:10 – 17:35	**Dr. Liviu Bodea**	TYROBP models to understand microglial involvement in Alzheimer's disease	l.bodea@uq.edu.au
17:35 –	***Closing remarks & BBQ dinner @ QBI terrace***		

0915 – 0950
Keynote 1

Understanding immune dysfunction after spinal cord injury: implications for infection susceptibility and recovery of function

Prof Phillip G Popovich

Center for Brain and Spinal Cord Repair

Department of Neuroscience

The Ohio State University, Wexner Medical Center

Columbus, Ohio

An important but often overlooked feature of traumatic spinal cord injury (SCI) is the permanent damage it causes to the sympathetic nervous system (SNS). Since all sympathetic pre-ganglionic neurons are all located in the spinal cord, SCIs "decentralize" or "unplug" the SNS from brain/brainstem control. A decentralized SNS wreaks havoc on many organ systems including the gastrointestinal (GI) tract and immune system. Consequently, people and animals with SCI have difficulty voiding their bladder and bowel and immunological dysfunction and infectious complications are frequent. These primary and secondary complications of SCI likely predispose individuals to infection and gut "dysbiosis", a state in which beneficial symbiotic bacteria (probionts) in the GI tract become outnumbered by pathological bacteria (pathobionts).

This presentation will introduce the concept of manipulating the SNS or the gut microbiome to restore homeostasis to the spinal cord-gut-immune axis and achieve effective recovery with improved QoL after SCI. Recently published or preliminary data will be presented showing that SCI causes profound aberrant plasticity within the spinal autonomic circuitry that controls immune function and that "silencing" this circuitry using chemogenetics (e.g., DREADDs) can block post-injury immune dysfunction. Additional data will show that SCI also causes gut dysbiosis and that this adversely affects intraspinal inflammation, lesion pathology and recovery of function. Importantly, post-injury delivery of oral probiotics elicits a protective mucosal immune response that is associated with neuroprotection and improved functional recovery. Together, these data highlight a previously unappreciated role for the spinal cord-gut-immune axis in regulating neuropathology and functional recovery after SCI.

Research supported by NIH-NINDS and the Ray W. Poppleton Endowment.

Phillip Popovich is Professor and Chair of Department of Neuroscience, The Ray W. Poppleton Research Designated Chair and Director of the Center for Brain and Spinal Cord Repair at The Ohio State University. Dr. Popovich completed his PhD training in Physiology and Spinal Cord Injury (SCI) at The Ohio State University (OSU) in Columbus, Ohio. As a post-doctoral fellow, also at OSU, he was awarded a Sandoz Research Fellowship that supported his formal training in immunology and CNS autoimmune disease. His unique multi-disciplinary training pedigree allowed him to quickly establish a novel neuroimmunology research program that today, is among the most actively studied research topics in the SCI field. His research program continues to focus on understanding how traumatic SCI affects communication between the nervous and immune systems with a goal for improving neural plasticity and central nervous system repair and for overcoming the chronic immune suppressive complications caused by SCI. He has published more than 125 peer-reviewed articles and invited reviews in top-tier journals. Dr. Popovich is a Fellow of the American Association for the Advancement of Science (AAAS), a Faculty of 1000 member and also is a member of scientific advisory boards for several national and international spinal cord injury research foundations and organizations.

Macrophages, key effectors of neurogenic heterotopic ossification following spinal cord injuries

09:50 – 10:15

Dr Kylie Alexander

Mater Research

University of Queensland

Neurogenic heterotopic ossifications (NHO) are frequent complications of spinal cord (SCI) and traumatic brain injuries, which manifest as abnormal ossifications of muscles. NHO are mostly periarticular and consequently extremely debilitating. The only effective treatment is surgical resection. The mechanisms leading to NHO are unknown, therefore we developed the first NHO mouse model. The combination of SCI and muscular damage/inflammation is required for NHO development, and inflammatory monocytes play a critical role, as their depletion prevents NHO. We confirmed a significant upregulation of the cytokine Oncostatin M (OSM) in mice developing NHO. OSM was expressed by macrophages and osteoblasts around NHO, and OSMR-/- mice had reduced NHO development. OSM was also significantly higher in human patients developing NHO, and conditioned media from macrophages isolated from patients' NHOs promoted mineralisation of patient muscle-derived stromal cells in vitro, and this effect was inhibited by addition of neutralising anti-OSM antibody. A downstream signalling target of OSM is the phosphorylation of STAT3 via JAK1/2 tyrosine kinases. STAT3 phosphorylation was significantly higher in mice developing NHO and treatment with a JAK1/2 inhibitor reduced NHO development. In conclusion, we have identified OSM as a key mediator of NHO pathogenesis and potential therapeutic targets to reduce the development of NHO.

Kylie Alexander is a research officer at Mater Research-UQ where she is currently investigating the pathogenesis of neurogenic heterotopic ossification after spinal cord injury. Kylie obtained her PhD in osteoimmunology at the University of Queensland investigating the role of osteal macrophages in fracture healing. Kylie subsequently worked as a research officer at the Queensland Institute of Medical Research examining the role of macrophages in graft versus host disease.

10:45 – 11:20
Keynote 2

The role of circulating extracellular vesicles in the activation of the acute phase response, sickness behaviour and outcome of CNS injury

Prof Daniel Anthony

Oxford University

UK

CNS injury outcome is modulated by a peripheral immune response, but the signal that initiates this response is poorly understood. We have shown that extracellular vesicles that are released from the brain into circulation are responsible. IL-1 evokes the release of extracellular vesicles from endothelial cells and astrocytes by a mechanism involving the stabilization of nSmase2 into ceramide-rich membrane microdomains. Using an *in vitro* blood brain barrier (BBB)-model with murine brain endothelial cells and GFAP-GFP expressing astrocytes we found that exosomes carrying GFP as cargo readily cross brain endothelial cells with intact tight junctions as revealed by electron microscopy. The particles, once released into the circulation, distribute widely in the periphery and switch on the hepatic acute phase response that, downstream, regulates leukocyte trafficking into the injured CNS through mechanisms dependent on peroxisome proliferator-activated receptor gamma. The introduction of exogenously generated extracellular vesicles from IL-1-stimulated CNS cell populations (ECs and microglia) increases leukocyte recruitment and increases damage to the blood-brain barrier in brain injury models. Furthermore, the adoptive transfer of extracellular vesicles from brain-injured animals to naïve animals is also sufficient to induce sickness behaviours in the recipient animals. Together these data show that that extracellular vesicles released from injury sites in the brain cross the BBB and provide the missing link for the communication of injury signals from brain to the periphery.

Following the completion of his PhD in 1994 at UCL, Daniel joined Professor Hugh Perry, then in Oxford, on a British Biotech Fellowship investigating metalloproteinase expression in the CNS. It was during this period that he became interested in the leukocyte-mediated mechanisms of neurodegeneration. In 1998 he moved to a faculty position at the University of Southampton, where he was a Lecturer in Neurobiology before returning to Oxford in 2004. Professor Anthony is also a Fellow of Somerville College and holds an honorary Professorial position at the University of Southern Denmark. The focus of the work of the laboratory is to identify how inflammation contributes to the outcome of acute and chronic brain injury or infection. We are particularly interested in the role played by circulating extracellular vesicles in the pathogenesis of CNS disease and the way in which that impact on behavior. Professor Anthony has generated over 150 publications on the neurobiology of inflammation that have been generated with the help of long-established connections in Oxford with psychiatry (Phil Burnet) for our behavioural work, with oncology (Nicola Sibson and Len Seymour) for imaging, chemistry (Ben Davis), cardiology (Robin Choudhury), and obstetrics (Ian Sergeant). We also have collaborations with Turku, Finland (TSPO imaging); Odense, Denmark (Imaging stroke); Maastricht , Netherlands (Animal models of Depression), Johns Hopkins, USA (Lipomics); Augusta, USA (isolated perfused vessels); and, of course, Brisbane (Marc Ruitenberg). The laboratory is well equipped for in vivo biology, molecular biology and immunohistochemistry.

Targeting post-traumatic inflammation in acute spinal cord injury: from bench to bedside

11:20 – 11:45

Traumatic spinal cord injury (tSCI) leads to acute inflammatory changes, both at the lesion site itself as well as systemically. In anatomically incomplete tSCI, aspects of this inflammatory response are thought to negatively interfere with neurological recovery, spreading tissue damage into areas of the spinal cord that were spared in the initial accident. Retrospective analysis of patient data from the Princess Alexandria Hospital Trauma Registry (Brisbane, Australia; 2012-2017) indeed supports this premise, as individuals with high circulating neutrophil numbers at the time of admission to hospital, i.e. those with a greater systemic inflammatory response to their injury, were less likely to have a positive conversion in their neurological grading at discharge (American Spinal Injury Association (ASIA) Impairment Scale (AIS); $p<0.01$). This difference remained after taking into account patient age, sex, admission AIS grade, and also 'New Injury Severity Scores' (NISS) as possible confounders through logistic regression analysis (odds ratio (OR) = 5.895; 95% confidence internal (CI) 1.421-24.453; $p<0.05$). Our pre-clinical experiments in mice provided further direct evidence that the extent of neutrophil mobilization and recruitment after tSCI is inversely correlated with recovery and, most importantly, that antibody-mediated depletion of these cells improves outcomes. The process of neutrophil mobilization from the bone marrow in response to tSCI is complex, but critically involves the cytokine CXCL1 as well as other innate immune signaling molecules such as the complement activation product C3a, highlighting these as potential targets for future therapeutic intervention. As part of our ongoing efforts to also facilitate rapid translation of basic research findings to the clinic via the repurposing of existing drugs, we further identified intravenous immunoglobulin (IVIG) therapy as a promising approach to target post-traumatic inflammation in acute experimental tSCI, and are currently exploring both the safety and efficacy of this treatment in human patients (Trial ID: ACTRN12616001385437).

A/Prof Marc Ruitenberg

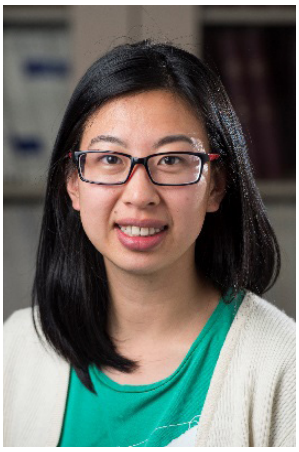
School of Biomedical Sciences

University of Queensland

A/Prof Marc Ruitenberg was awarded his PhD from the VU University Amsterdam, and received his postdoctoral training with the Neurotrauma Research Program (Perth, WA). He is now an Honorary Research Fellow of SpinalCure Australia and Reader in Neuroanatomy at The University of Queensland. A/Prof Ruitenberg's research is aiming to advance our understanding of post-traumatic inflammation and immune function after spinal cord injury. His laboratory is combining pre-clinical research with the study of human SCI, and is directing the world's first clinical trial on the use of intravenous immunoglobulin (IVIG) to target post-traumatic inflammation in acute spinal cord injury.

11:45 – 12:10

Age dependent effect of post-stroke infection



Dr Shu Wen

Neuroinflammation Research Group

Centre for Inflammatory Diseases

Monash University

In Australia, stroke is a leading cause of death, contributing to over 10% of all deaths annually and this is expected to rise with an increasingly aging population. In 2015, there were more than 50,000 new and recurrent strokes – that is one stroke every 10 minutes. Despite its well-recognised primary effects on the brain, a major cause of death after stroke is infection: a post-stroke complication that has received increasing attention for its large clinical implications. While age is a known risk factor for post-stroke infection, the underlying mechanism for exacerbated infection in the elderly remains unclear. We provide evidence that the risk of bacterial infection after stroke is age dependent, and that onset is contributed by impaired innate immune response at the site of infection. Additionally, our results suggests that aging promotes the breakdown of colonic barriers after stroke, allowing for the translocation of commensal bacteria for systemic dissemination, hence a possible route for infection post-stroke.

Shu Wen is an early-career researcher who joined the Neuroinflammation Research Group at the Centre for Inflammatory Diseases, Monash University in 2016. Her current research focuses on understanding what factors render the elderly more susceptible to the development of infection after stroke. Previous to this, Shu Wen trained at QIMR Berghofer Medical Research Institute exploring the role of microvesicles in promoting cancer metastasis.

MIC-1/GDF15 as a novel target for neuroprotection in Spinal Cord Injury

12:10 – 12:35

Spinal cord injury (SCI) has devastating consequences, with limited therapeutic options. The outcome of SCI is contributed to by neuroinflammation, which might therefore be a target to improve recovery and quality of life after injury. MIC-1/GDF15 is a neurotrophic cytokine, which potentially modulates innate immunity and may thus have potential efficacy in SCI. To test this, we examined its effect on contusive SCI in MIC-1/GDF15 overexpressing mice compared to wild-type (WT) and MIC-1/GDF15 knockout mice. Following contusive SCI, MIC-1/GDF15 overexpressing mice had superior locomotor recovery, reduced tissue injury at 28 days and enhanced spinal cord recruitment of inflammatory cells. This inflammatory cellular infiltrate included an increased frequency of various dendritic cell populations (incl. mDCs, pDCs, and CD8α^+ DCs), as well as macrophages, prior to recruitment of CD4$^+$ and CD8$^+$ T cells, and this was associated with elevated expression of MCP-1/CCL2 at the SCI injury site. Our findings suggest elevating the level of MIC-1/GDF15 is associated with beneficial changes in the clinical course of SCI, characterised by altered post-injury inflammation and an improved functional outcome. The MIC-1/GDF15 effects on inflammation are linked to changes in immune cell recruitment and increased MCP-1/CCL2 levels in the spinal cord. Further investigation of MIC-1/GDF15 as a novel therapeutic target for traumatic SCI is therefore warranted.

Prof David Brown

Laboratory of Neuroinflammation

The Westmead Institute for Medical Research

David Brown graduated in Medicine from University of NSW in 1989. He trained in clinical immunology and immunopathology and was awarded an FRACP and FRCPA in 2000. In 2003 he completed a PhD research degree after which he undertook further post-doctoral studies at the the Salk Institute for Biological Sciences, USA in neuroanatomy and neuroinflammation. He returned to Australia in 2006 and has headed his research group investigating CNS immunoregulation and injury. He is Director of Immunopathology at Pathology West, ICPMR and Heads the Laboratory of Neuroinflammation at The Westmead Institute for Medical Research where he continues his research into CNS immunoregulation, injury and the immune contribution to psychiatric disorders. He is past president of Neuroimmunology Australia and is organizing the International Society for Neuroimmunology Congress in Brisbane in 2018. He also serves on the board of The International Society of Neuroimmunology.

13:30 – 14:05
Keynote 3

Understanding how Interleukin-1α mediates neuroinflammation and secondary cell death after spinal cord injury

Prof Steve Lacroix

Axe neurosciences du Centre de recherche du CHU de Québec et Département de médecine moléculaire de l'Université Laval, Québec, QC, Canada.

At the site of spinal cord injury (SCI), damage to cell bodies of neurons and glia results in the release of damage-associated molecular patterns (DAMPs), thus inducing sterile inflammation. This is followed by a second wave of tissue degeneration characterized by a delayed death of oligodendrocytes (OLs) and the demyelination of axons that survived the trauma. We recently demonstrated that damaged microglia at the site of SCI rapidly release the DAMP interleukin (IL)-1α, which in return triggers neuroinflammation and OL cell death. Accordingly, mice lacking the *Il1a* gene exhibit improved locomotor recovery compared to wild-type mice as early as day 1 post-SCI, as well as over time. Here, we further investigated the role of IL-1α in secondary cell death. We found that IL-1α injected intra-cisterna magna (i.c.m.) to C57BL/6 mice induced death of mature OLs at day 1 post-injection. The injection of IL-1α also triggered massive infiltration of neutrophils, as well as caused neuronal activation throughout the entire mouse spinal cord. Taking advantage of an innovative conditional restore mouse line that allows Cre recombinase-inducible restoration of functional IL-1R1/3 expression in mice that otherwise exhibit an IL-1R1/3-knockout phenotype, we discovered that the effect of IL-1α on OLs is indirect. Indeed, restoration of IL-1R1/3 expression in astrocytes, but not in microglia nor OLs and their precursors, restored the *in vivo* effect of IL-1α on OL cell death. Altogether, our data suggest that IL-1α released by damaged microglia after SCI indirectly regulates OL cell death and demyelination through the intermediary of astrocytes.

Steve Lacroix is a Professor in the Department of Molecular Medicine at Université Laval, Québec, Canada. He received his Ph.D. from Université Laval in 1998. He was trained as a Postdoctoral Fellow at the University of California, San Diego, from 1998 to 2001 under the supervision of Dr. Mark H. Tuszynski in the field of spinal cord regeneration. From 2001 to 2003, he completed a second Postdoctoral Training at McGill University, Montréal (Canada), with Dr. Samuel David in the field neuroimmunology. Dr. Lacroix teaches and conducts research in the field of neuroimmunology and regenerative medicine. His recent research has focused on the identification of the endogenous signals initiating neuroinflammation and the role of immune cells in neural damage and repair in the context of spinal cord and peripheral nerve injury and multiple sclerosis.

Microglia regulate spatial learning outcomes following traumatic brain injury

14:05– 14:30

Immune mechanisms contribute to secondary tissue loss after traumatic brain injury (TBI), including in the hippocampus – a brain region that is key for learning and memory but highly vulnerable to insult. Activation of microglia, the brain's resident immune cells, has been implicated in the progressive secondary tissue loss after TBI, and also in the ongoing cognitive dysfunction and decline during the more chronic stages of injury. Much of this has, however, been based on correlative observations rather than direct evidence for a causal pathological role of microglia in these processes. To address this, we are using both genetic and pharmacologic approaches to conditionally deplete microglia from the brain, subsequently studying how absence of these cells influences the outcome from a moderate controlled cortical impact. Our results show that microglia directly contribute to secondary cell and tissue loss after TBI, that these cells negatively interfere with hippocampal neurogenesis, i.e. the birth of new neurons in the post-TBI brain, and also spatial learning abilities after TBI. Our ongoing experiments are now focused on elucidating the cellular and molecular effector mechanisms via which microglia influence the outcome from TBI.

Jana Vukovic

School of Biomedical Sciences

Faculty of Medicine

The University of Queensland

Dr Jana Vukovic received her PhD from the University of Western Australia in 2009. Since 2015, she has been heading the Neuroimmunology and Cognition laboratory at The University of Queensland. Dr Vukovic has demonstrated that microglia can exert a dual and opposing influence over adult neurogenesis (the birth of new neurons) in the hippocampus under different physiological conditions, namely exercise, ageing and following brain injury. The ultimate goal of her research is to link cellular and molecular events to altered behaviour, and to harness the regenerative potential of adult neurogenesis through immunomodulation to stimulate optimal cognitive function and treat conditions associated with learning and memory deficits.

14:30 – 14:55

Traumatic injury to the paediatric brain – how does developmental age influence the inflammatory response?

Dr. Bridgette Semple

Paediatric Neurotrauma Group

Monash University

Despite the general consensus that injuries to the developing brain can have profound long-term behavioural consequences, the biological mechanisms that determine such outcomes remain incompletely understood. This talk will review the current state of the literature regarding our current understanding of how the inflammatory response differs in the juvenile injured brain compared to the adult, with a focus on data generated with an experimental murine model of paediatric traumatic brain injury.

Dr. Bridgette Semple is an NHMRC R.D. Wright Biomedical Career Development Fellow and Head of the Paediatric Neurotrauma Group at Monash University. Her research focuses on the acute and chronic consequences of traumatic injury to the developing brain, with a particular interest in neuroinflammation and behavioural outcomes. After previously obtaining her PhD at Monash University, Dr. Semple completed postdoctoral training at the University of California San Francisco, USA. After returning to Australia to establish a small laboratory team at the University of Melbourne, in 2018 she came full circle back to Monash to join the new Department of Neuroscience in the Central Clinical School, Alfred Hospital.

The role of neurogenic inflammation following neurotrauma: Brain vs Spinal Cord

14:55 – 15:20

Neurogenic inflammation has been shown to play an important role in the development of edema following a range of CNS injuries. Neurogenic inflammation is a response of perivascular nerve fibres to injury or infection and is typically characterized by vasodilation, protein extravasation and edema. The vascular response is facilitated by the release of neuropeptides such as substance P (SP), known to preferentially bind to the tachykinin NK1 receptor. Increased SP immunoreactivity has been associated with increased blood brain barrier (BBB) permeability and edema development following both TBI and stroke, whilst antagonism of the NK1 receptor has been shown to reduce BBB permeability and edema, as well as improve functional outcome. Despite similarities in injury mechanisms, such an effect was not observed following traumatic spinal cord injury (SCI). SP stores within the spinal cord dorsal horns are shown to reduce following SCI, indicative of SP release and induction of neurogenic inflammation. However, NK1 antagonism did not reduce BBB permeability, oedema or functional outcome. This contrasting result may be due to the severe primary damage occurring following traumatic SCI that results in destruction of vasculature and haemorrhage playing a greater role in BSCB disruption, subsequent edema development and associated tissue damage and functional deficits.

Dr Anna Leonard

Adelaide Medical School

University of Adelaide

Dr Anna Leonard, PhD is a research active lecturer within the Adelaide Medical School at the University of Adelaide and leads the Spinal Cord Injury program within the Translational Neuropathology Laboratory. Dr Leonard's research is primarily focused on understanding the acute secondary injury processes that occur following spinal cord injury and how these can be targeted to improve outcome. She actively collaborates across disciplines and with clinical colleagues to improve the translational potential of her work. She received international post-doctoral training at the University of Alabama in Birmingham, where she gained expertise in a large animal model of SCI and subsequently established such a model at The University of Adelaide.

15:45 – 16:20
Keynote 4

Prof Richard M. Ransohoff, MD

Entrepreneur-in-Residence, Third Rock Ventures

Visiting Scientist, Dept of Cell Biology, Harvard Medical School

Myeloid cells and post-traumatic neuroinflammation 2018

The myeloid cell response after central nervous system (CNS) trauma is believed to play a consequential role in its outcome. As a generalization, the reaction after spinal cord injury (SCI) involves two distinct cell populations: resident microglia and infiltrating monocyte-derived macrophages.

Microglia initially enter the developing murine brain around E10.5, before other glia and prior to neuronal differentiation. During development, microglia interact extensively with neurons, helping to establish neuronal populations through influences on survival, apoptosis and corpse-clearance. As neuron-to-neuron contacts are forming, microglia refine neuronal network properties by promoting synapse formation, removing redundant synapses and monitoring and modulating synaptic activity. These activities continue during adult life and, among other functions, support synaptic plasticity as seen during learning. Different to other tissue macrophages, the microglial reaction to physical trauma does not appear to follow a reparative program.

Monocyte-derived macrophages arise from distinct circulating populations, broadly termed inflammatory and infiltrating monocytes. These cells can be loosely distinguished by surface markers including chemokine receptors. Deciphering the varied roles of these different cell populations in the context of SCI should uncover mechanisms that modulate the outcome of injury, and potentially unveil a variety of therapeutic targets and strategies.

Richard M. Ransohoff is Entrepreneur-in-Residence at Third Rock Ventures, Visiting Scientist in the Dept of Cell Biology, Harvard Medical School and Adjunct Professor, Molecular Medicine, Cleveland Clinic Lerner School of Medicine at CWRU and Adjunct Professor, Genetics and Genome Sciences, and of Pathology.

After AB (Literature) from Bard College and MD from CWRU School of Medicine, residencies in Internal Medicine at Mt. Sinai Medical Center (Cleveland) and Neurology (Cleveland Clinic [CCF]), he performed post-doctoral research work (Dept Molecular Biology and Microbiology, CWRU with Dr. Timothy Nilsen).

From 1984-2014 Ransohoff was Staff Member at Cleveland Clinic where he founded and directed the Neuroinflammation Research Center (2005-2014) and served (1984-2014) as Staff Neurologist, Cleveland Clinic Mellen Center for MS Treatment and Research. He lists more than 415 scientific articles and reviews in PubMed (Google Scholars h-index 115 in May 2018), and has trained >70 students and post-docs who now hold positions in academics and industry. He's served as regular member of NIH Study Sections and as Chair, Scientific Review Panel B, National Multiple Sclerosis Society; as Section Editor, J Immunology (through 2005); Advisory Editorial Board, Trends Immunol (2003-present); Highlights Advisory Board, Nature Rev Immunol (through 2011), Associate Editor of Neurology® (through 2014) and founding Editor of Neurology®: Neuroimmunology and Neuroinflammation (2014).

Among other honors, he was awarded a Harry Weaver Neuroscience Scholarship from the National MS Society (1987), the John and Samuel Bard Award in Science or Medicine, Bard College (2002), F.E. Bennet Lectureship of American Neurological Association (2009), Sam and Maria Miller Scientific Achievement Award in Basic Science, Cleveland Clinic (2009) and the John J. Dystel Award for MS Research from the National MS Society and American Academy of Neurology (2012). He was named in the "Best Doctors" compendium from 1996-2014 for his expertise in patient care of individuals with MS and related conditions. He is a member of the Association of American Physicians (2005) and a Fellow of the American Association for the Advancement of Science (2007).

At Biogen, Ransohoff served as Senior Biogen Research Fellow (2014-5); as Head, Neuroimmunology Research Unit (2015-2016); and as Head Neuroimmunology, Pain and Acute Neurology Research and Early Development Unit (2016-2017), which entailed leading a group of >45 scientists and clinicians in finding and prosecuting neuroinflammatory targets for treatment of neurological disease and pain, and bringing those relevant for acute neurology indications through phase II proof of concept (PoC). During this time, he led the transformation of the neuroinflammation portfolio, successfully bringing 5 compounds (internally developed and externally identified) into the clinic as well as directing activities in blood-brain barrier (BBB) function, progressive multifocal leukoencephalopathy (PML) risk mitigation and novel screening technologies for glial targets, in addition to basic neuroinflammation biology.

Ransohoff's main contributions to science have been in the mechanisms of neuroinflammation. He has provided insight into the ontogeny, functions and research methods for microglia; elucidated the mechanism of central nervous system (CNS) immune surveillance by cerebrospinal fluid T cells; pioneered the study of chemokines and chemokine receptors in the CNS; established methods contributed understanding of the blood-brain barrier (BBB) and made substantial discoveries in the pathogenesis of inflammatory demyelinating disease as seen in multiple sclerosis (MS).

At Third Rock, Ransohoff is building a company to apply understanding of neuroinflammation for the prevention and treatment of dementia.

Hippocampal metabolic and synaptic neuro-glial dysfunction after surgery

16:20 – 16:45

Dr Marta Gómez-Galán

Karolinska Institute

University in Solna

Sweden

Long-term cognitive impairment after surgery is a common and serious complication particularly in the elderly population. While there are growing body of evidence suggesting that surgery-induced inflammation play a key role behind this surgical phenotype, the pathogenesis within the central nervous system is not fully understood.

In mice, orthopaedic surgery induces a systemic inflammatory response associated with changes in hippocampal synaptic plasticity and cognitive decline at 72h after surgery (Terrando et al., 2013). In humans, dynamic changes in brain immune system have recently been confirmed (Forsberg et al., 2017). To further understand the temporal pattern of immune activation and simultaneous changes in synaptic transmission within hippocampal neuronal circuits of relevance for cognitive processing, we recently investigated the effect of rodent surgery on neuronal-glial function combining calcium imaging in astrocytes and whole-cell patch clamp in CA1 pyramidal cells with molecular tools.

Accordingly with the notion of a peripheral-brain communication after systemic trauma, we demonstrated that hippocampal neuronal dysfunction related to surgery associates with alterations in different aspects of astrocyte physiology, including decreased expression of proteins involved in the formation of BBB and neurovascular coupling (GFAP and AQP4) and reduced expression and protein levels of transporters and enzymes involved in the precise maintenance of glucose and glutamate homeostasis (Femenía et al., 2018).

All together, our findings confirm an interaction between the peripheral and central immune system and uncover a role for the astrocyte as a mediator between systemic immune and inflammatory events and synaptic neuronal functions and processing, such as cognition.

Marta Gómez-Galán is an assistant professor at Karolinska Institute in Stockholm, Sweden. Marta's research interest focuses on identify the brain cellular and molecular correlates to the cognitive decline associated to systemic immune activation and inflammation and their potential involvement in neurodegeneration. For that she uses a broad range of functional and molecular tools. Marta recently demonstrated that in rodents, orthopaedic surgery orchestrates temporal metabolic adaptations in the hippocampus, including alteration in glucose and glutamate signaling in astrocytes, and reduction in brain lactate availability. As a consequence, the neuro-glial metabolic coupling is compromised as well as the astrocyte and neuronal function suggesting that metabolic alterations in the hippocampus might be related to the cognitive impairment observed acutely after trauma (J Neuroscience, 2018).

16:45 – 17:10

Modulating the immune response following mild traumatic brain injury to alter functional outcome.

Dr. Frances Corrigan

School of Health Sciences

University of South Australia

Mild traumatic brain injury (mTBI), both singular and repeated, can lead to the development of ongoing symptoms including depression, anxiety and cognitive deficits in a proportion of sufferers. What drives the development of these symptoms is not yet known. This study sought to investigate the role of a peripheral inflammatory insult in the development of ongoing behavioural symptoms following both a single and repeated concussive insults. Male Sprague Dawley rats were administered a single or 3 mTBIs spaced 5 days apart using the diffuse impact-acceleration model to generate ~100 G of force. At 1 or 5 days following last injury rats were given either the TLR4 agonist, LPS (0.1mg/kg) or an equal volume of saline. When LPS was given at 5 days post-injury in both smTBI and rmTBI animals it increased levels of inflammatory cytokines at 24hrs post-dose compared to saline treated controls. When behaviour was examined at 3 months post-injury LPS administered animals, had increased time-spent immobile on the forced-swim test, suggestive of depressive like behaviour and impaired cognitive performance on the Barnes Maze. However LPS administration at 1 day post-injury, reduced the immediate inflammatory response in rmTBI animals, with an associated improvement in behavioural symptoms at 3 months when compared to vehicle controls. In contrast LPS at 1D post-injury in smTBI animals had no apparent effect. This suggests that modulation of the immune response following mTBI can have long-lasting consequences and may offer a target for intervention.

Dr. Frances Corrigan is a senior lecturer at the University of South Australia in the School of Health Sciences. She leads the Head Injury laboratory at the University, which investigates mechanisms that drive neurodegeneration following traumatic brain injury, with an interest in the role of the inflammatory response and its links with accumulation of pathological proteins. She was awarded a South Australian Tall Poppy award in 2017 and has received over $1,000,000 in funding for her research.

TYROBP models to understand microglial involvement in Alzheimer's disease

17:10 – 17:35

Dr. Liviu Bodea

Clem Jones Centre for Ageing Dementia Research

Queensland Brain Institute

Alzheimer's disease (AD) is a neurodegenerative disease characterised by the pathological accumulation of amyloid-β (Aβ) and tau, as well as the decrease of neuronal synapses and increase of glial reactivity. One type of glial cells, the microglia, respond to changes in the surrounding environment by alterations of their intracellular pathways, some of them involving immunoreceptor tyrosine-dependent activatory motifs (ITAMs) or immunoreceptor tyrosine-dependent inhibitory motifs (ITIMs). A known AD risk factor, the triggering receptor expressed on myeloid cells 2 (TREM2) is associated with the ITAM pathway by forming a complex with the ITAM-bearing TYROBP molecule to elicit its intracellular functions.

TYROBP is an adaptor molecule which associates with several immune receptors and that was identified by us to be a top causal regulator of AD. To validate these findings, we assessed the effect of TYROBP on the uptake of Aβ using mouse embryonic stem cell derived microglia lines overexpressing full length or truncated TYROBP (missing the ITAM motif), and showed that the internalisation of Aβ as well as several other microglial functions elicited by Aβ are ITAM-dependent.

Currently, we are using CRISPR-based genetic editing to further investigate these results in vivo, by generating Tyrobp animal models for AD.

Dr. Liviu Bodea is the Peter Hilton Early Career Research Fellow at the Clem Jones Centre for Ageing Dementia Research (CJCADR) within Queensland Brain Institute (QBI).

Dr. Bodea earned his degree from the University of Bonn (Germany) in 2014, before being recruited to the laboratory of Prof. Jürgen Götz (CJCADR). Dr. Bodea's research focusses on the involvement of microglial cells in the neurodegenerative process, with studies published in journals such as Cell or J Neurosci.

Currently, Dr. Bodea is working on generating improved models for Alzheimer's disease by using gene editing techniques.

Notes

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Funding research to cure
spinal cord injury

www.spinalcure.org.au