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Neuroimmunology Australia is a body that was formed in 2010, with the aim of providing a forum for discussion of immune-mediated diseases of the brain, spinal cord, peripheral and autonomic nerves, the neuromuscular junction and muscles. The members of Neuroimmunology Australia come from the fields of clinical immunology, basic immunology, neurology and neurosciences, and from hospitals, diagnostic laboratories and universities. The intention is to provide a meeting where there can be true inter-disciplinary interaction.

The first meeting was held in Brisbane in 2010, on the topic of “Antibody-mediated Neurological Disease”. The range of diseases that were discussed was wide - ranging from myasthenia gravis to schizophrenia. Subsequent meetings have also been held in Brisbane and Sydney in April 2011, August 2012, July 2014, July 2015, August 2016, and now in July 2017.

The Proceedings of Neuroimmunology Australia is published to provide a permanent record of the work presented at the meetings of Neuroimmunology Australia. The proceedings have been published since the second year of the Neuroimmunology Australia annual scientific meeting.

David A Brown
President,
Neuroimmunology Australia
NIA 2017 Plenary Speakers (alphabetical order)

Professor David Brown, Westmead Medical Research Institute
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 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. 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 and the immune basis for Psychiatric disorders. He is 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.

Professor Iain L. Campbell, University of Sydney
Iain Campbell obtained his doctoral degree from the University of Sydney. After short postdoctoral periods in Britain and Sweden, he returned to the Royal Melbourne Hospital in 1982 as the inaugural D.W. Keir research fellow working with Professor Len Harrison in the Endocrine laboratory. In 1985, he moved to the Burnet Clinical Research Unit of the Walter and Eliza Hall Institute. He left Australia in 1989 to do a sabbatical at the Scripps Research Institute in La Jolla, San Diego, USA and that is where he remained for over 14 years as a NIH-funded biomedical research scientist and a Professor in the Department of Neuropharmacology. Iain returned to Australia in 2004 to take on the role as Chair of Molecular Biology in the School of Molecular Bioscience at the University of Sydney. From 2011-2016 he was the Head of the School of Molecular Bioscience. The overall goal of Iain’s research is to understand the molecular and cellular mechanisms underpinning host defence and immunoinflammatory processes that contribute to disease in the central nervous system. He is author/co-author to over 250 publications and has a current h-index of 64.

Professor Georges Grau, University of Sydney
Immunopathology of microvascular lesions, particularly of cerebral and pulmonary complications of infectious and auto-immune diseases, especially in cerebral malaria, septic shock and multiple sclerosis. Analysis of the cellular and molecular mechanisms of the interactions between microvascular endothelial cells and cells of the immune system. Experience in various in vivo and in vitro experimental systems as well as in clinical studies. More recently, focus on the neurovascular lesion of murine and human cerebral malaria, using co-culture model systems involving brain endothelium, P. falciparum-infected erythrocytes, as well as circulating cells, particularly platelets and monocytes.
Professor Georges Grau obtained a MD from the University of Liège and a Privat-Docent from the University of Genève. He has been the Chair of Vascular Immunology at the University of Sydney since 2006. Since 1979, his research has focused on immunopathological mechanisms of infectious diseases, notably in
cerebral malaria, multiple sclerosis and septic shock, with particular emphasis on cytokines and the microvascular endothelium.

His in vivo intervention studies in murine models contributed to the elucidation of cytokine interactions leading to tissue injury, with particular attention to tumour necrosis factor (TNF), which had important implications for cell adhesion molecules in various models of pathology. In multi-compartment co-culture systems involving human endothelial cells, his group found that platelets can act as effectors of cytokine-induced microvascular damage. His team also demonstrated that membrane microparticles, released by several cell types, profoundly alter endothelial integrity and thereby can be crucial elements in immunopathology.

His 359 papers (264 peer-reviewed) have been cited over 27,000 times and his h-index is 83.

**Associate Professor Judith Greer, University of Queensland**

The main focus of Judith Greer’s lab is diseases affecting the nervous system, particularly those in which the immune system plays (or may play) a role, particularly multiple sclerosis (MS) and schizophrenia. Her MS research is directed particularly towards trying to identify brain components that are targeted by the immune system in people MS, in determining how immune responses within the nervous system relate to the symptoms experienced by people with MS, and in developing new ways to specifically turn off the damaging immune responses in the brain. Her work on schizophrenia investigates whether autoantibodies specific for muscarinic receptors play functional roles in the disease.

**Professor Gilles Guillemin, Macquarie University**

Prof Guillemin has been working in the field of Neuroinflammation for more than 24 years and in the field of tryptophan metabolism for 20 years. He has been studying the involvement of the tryptophan catabolism (via the kynurenine pathway) in human neurodegenerative diseases. He demonstrated the importance of the kynurenine pathway in multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis, which opens numerous very promising research opportunities and has important therapeutic potential. He also extended his research to other diseases such as depression, autism, breast and brain tumours. Prof Guillemin h-index is 50 and current Researchgate score 46.61 (top 2.5% scientist worldwide) is growing every month with presently more than 300 profile view per week.

**Dr Emily Mathey, Brain and Mind Centre, University of Sydney**

Dr Emily Mathey is a research scientist in the Neuroinflammation Laboratory at the Brain & Mind Centre at the University of Sydney. Dr Mathey did her PhD at the University of Sydney followed by Postdoctoral Fellowships at the Max Planck Institute for Neurobiology, Martinsried, and University of Aberdeen, UK where she identified novel autoantibody responses to neurofascin in patients with multiple sclerosis and tested the pathogenicity of auto-antibodies responses to neurofascin and contactin 2 in animal models of MS. Dr Mathey’s research continues to focus on identifying novel autoantibody responses in patients with inflammatory neuropathies, developing assays to routinely test for these antibodies in patient sera and examining the pathogenicity of these responses in animal models.
**Professor Pamela McCombe, University of Queensland**

Dr McCombe is a neurologist at Royal Brisbane and Women's Hospital and Professor at the University of Queensland Centre for Clinical Research. She works in the field of neuroimmunology. Current interests include gender and pregnancy in multiple sclerosis and immune aspects of motor neurone disease and stroke.

**Dr Gila Moalem-Taylor, University of New South Wales**

Dr. Moalem-Taylor graduated with a PhD from the Weizmann Institute of Science, Israel in 2001. She was then awarded a Rothschild Postdoctoral Fellowship and moved to The University of Cincinnati Medical Centre in the USA where she worked for 2 years and developed an interest in the area of neuropathic pain. She then moved to the School of Medical Sciences at the University of New South Wales (UNSW) in Australia, where she was awarded the UNSW Vice-Chancellor’s Postdoctoral Fellowship (2004-2007), followed by the NSW OSMR Career Development Fellowship under the NSW Spinal Cord Injury and Related Neurological Conditions Research Grants Program (2010-2013). In 2014, she was appointed as a Senior Lecturer in the Department of Physiology, Translational Neuroscience Facility, School of Medical Sciences, UNSW. Since her PhD, Moalem-Taylor has worked primarily in the area of neuroimmunology. Her current research focuses on the role of immune cells and their mediators in neurodegeneration and neuropathic pain caused by peripheral nerve injury, autoimmune diseases of the nervous system and spinal cord injury.

**Dr Marc Ruitenberg, University of Queensland**

Dr. Marc Ruitenber is the current SpinalCure Australia Research Fellow and a Senior Lecturer in Biomedical Sciences at The University of Queensland. Marc was awarded his PhD from the VU University Amsterdam in 2003, after having completed his doctoral research at The Netherlands Institute for Neuroscience. He relocated to Perth (Western Australia) that same year to do his post-doctoral training with the WA Neurotrauma Research Program. He was recruited to The University of Queensland in 2009 where he is now the Head of the Laboratory for Neural Injury & Repair. A key focus of his research is to better understand the role of inflammation in acquired central nervous system injury, in particular traumatic spinal cord injury. Marc's laboratory is also engaged with the development of advanced magnetic resonance-based imaging techniques to better diagnose and treat spinal cord injury. The ultimate goal of his research is to develop new and effective immune-modulatory treatments to improve outcomes for neurotrauma patients.
Immune mediated peripheral neuropathies may be associated with the presence of autoantibodies that react to gangliosides. Although the diagnosis of autoimmune neuropathies is based primarily on clinical evaluation and electrophysiological studies, detection of ganglioside antibodies may provide useful additional information to support the diagnosis. The reported frequency of some of these antibodies ranges from a detectable IgM GM1 antibody in 30-40% of patients with multifocal motor neuropathy to very small numbers (2 positive cases in the literature only) for GM4 antibodies.

Clinical samples from 229 consecutive patients with a first request for ganglioside antibodies were tested on the Generic Assays (GA; Germany) immunoblot. The GA assay covers a broad range of ganglioside antibodies of both IgG and IgM classes: GD1a, GD1b, GD2, GD3, GM1-4, GQ1b, GT1a, GT1b. Requests came from similar numbers of males and females (M:F 120:109). The mean age of males and females were 58 and 53 years respectively (SD=18 for both groups). Ganglioside antibodies were detected in 23% (n=51) of the patients. A single ganglioside antibody was detected in n=21, 2 antibodies in n=18, 3 antibodies in n=4, 4 antibodies in n=4 and >4 antibodies in n=4 cases. Of the 4 cases with >4 antibodies detected, 3 had a clinical diagnosis of Miller Fisher Syndrome with both IgG GT1a and GQ1b detected. Of the 18 that had a positive IgG GT1a, 14 had a concurrent positive IgG GQ1b antibody. Of these, 12 had a clinical diagnosis of Miller Fisher Syndrome.

Anti-gangliosides may be seen in a significant proportion of patients referred for testing for autoimmune neuropathy. Multiple antibody positivity was seen in 59% of positive patients with some patients having a large number of positive antibodies. The concurrent detection of IgG GQ1b and GT1a antibodies is consistent with the reported cross reactivity between these two gangliosides. In our cohort, IgG GD2 and GD3 were only detected in associated with other specificities (in all cases IgG GT1a and GQ1b). Further studies of larger cohorts of well-defined autoimmune neuropathy patients are needed to determine the diagnostic accuracies of these antibodies.
Helminths (parasitic worms) can exert protective effects on autoimmune diseases by modulating the type of immune response, and deliberate infection with helminths is being explored as a potential therapeutic strategy for autoimmunity. However, the use of live helminths as therapeutic agents for autoimmune disease has a number of drawbacks, and it would be preferable to identify and use the immunomodulatory components of the helminths. Previously it has been shown that the immunomodulatory activity of the liver fluke Fasciola hepatica resides in its excretory-secretory products (FhES), and further analysis of FhES has identified 3 major components: an 68 amino acid alpha helical cathelicidin-like peptide (FhHDM1), a cathepsin L-cysteine protease (FhCL1), and peroxiredoxin (FhPrx). We have found that FhHDM1 is the most effective at preventing development of the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS). In the current study, we have investigated the therapeutic effects of FhHDM1 when it is given after the first attack of disease in a relapsing-remitting EAE model. FhHDM1 significantly (p<0.0001) reduced the overall severity of the disease and the number of relapses compared to mice treated with vehicle alone. The effects were long-lasting, with mice continuing to show benefits for up to 70 days following a single course of FhHDM1 treatment. Preliminary investigation of the mechanism of action of FhHDM1 suggests that it is not affecting the adaptive arm of the immune response, but is exerting significant effects by modulation of innate pro-inflammatory immune responses and by limiting egress of immune cells across the glia limitans. The data suggest that this parasite-derived peptide has potential as a novel treatment for patients with MS.
CAN AUTOIMMUNE THYROID DISEASE CAUSE AUTOIMMUNE ATTACK IN THE CNS (AND VICE-VERSA)?

Judith M Greer1, Simon Broadley2,3, Michael P Pender4,5

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Several lines of evidence suggest a definite and unique link between CNS demyelinating diseases and autoimmune thyroid diseases (AITD). Some molecules targeted by the immune system in AITD have related family members expressed in the CNS. One example is the thyroid-stimulating hormone receptor (TSHR), present in the thyroid, and the related molecule leucine-rich repeat-containing G-protein coupled receptor 4 (LGR4), which is expressed in the brainstem and spinal cord. In the current study we investigated immunoreactivity directed against TSHR and LGR4, HLA type and other features of disease in 44 patients with co-existing CNS demyelinating disease and AITD (28 hypothyroid and 16 hyperthyroid patients), compared to patients with multiple sclerosis alone or healthy individuals.

Patients with co-existing AITD and CNS demyelinating disease were almost exclusively female (43/44) and had prominent spinal cord involvement as the main neurological finding. Patients with hyperthyroid disease were more likely to have had AITD prior to the onset of CNS disease than were patients with hypothyroidism (67% vs 32%). Blood and DNA were collected and tested for HLA type, and for the response of T cells and antibodies to TSHR, LGR4 and myelin proteolipid protein (PLP). The HLA molecules carried by individuals with CNS demyelinating disease and AITD differed from both other MS patients and healthy individuals, with the most different group being patients with co-existing autoimmune hyperthyroidism preceding the onset of CNS demyelinating disease. Patients with co-existing CNS disease and AITD showed less T cell reactivity than patients with MS alone to myelin proteolipid protein (PLP). Furthermore, patients with co-existing CNS disease and hyperthyroidism showed elevated levels of antibody and T cell reactivity to LGR4 and TSHR compared to other groups.

We suggest that autoreactive immune cells cross-reactive against related antigens present in the thyroid and the spinal cord underlie the pattern of lesion development in the CNS in patients with co-existing AITD and MS. Furthermore, in patients with hyperthyroidism, CNS disease may be a direct consequence of spreading of disease from the thyroid to the CNS, due to immune cross-reactivity targeting TSHR and LGR4. There may be similar links between other antigens that are expressed in the thyroid and CNS.
VALIDATING A MOG-ANTIGEN TETRAMER FOR DETECTING MOG-SPECIFIC MEMORY B CELLS IN PATIENTS WITH CNS DEMYELINATING DISORDERS

Joseph Angelo Lopez1, Fiona Tea1, Deepti Pilli1, Joseph Angelo Lopez1, Alicia Zou1, Sudarshini Ramanathan1, Vera Harb1, Fiona Lee1, Russell Dale1, Fabienne Brilot1

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Autoantibodies against myelin oligodendrocyte glycoprotein (MOG) are found in a subset of patients with demyelinating disorders of the central nervous system (CNS) and are instrumental in distinguishing MOG antibody-associated demyelination from other demyelinating disorders such as multiple sclerosis. Recent literature has highlighted the importance of the protein conformation of MOG in anti-MOG antibody detection and has demonstrated that pathogenic anti-MOG antibodies only recognise MOG in its native conformation. The detection and characterisation of MOG-specific memory B cells in demyelinating patients remains unexplored.

Firstly, we aimed to detect anti-MOG antibodies in the serum of patients with CNS demyelination. Secondly, we aimed to investigate the binding of patient anti-MOG antibodies to the StrepTactin-tagged extracellular Ig-like domain of human MOG (hMOG1-117).

Anti-MOG antibody detection in serum samples was performed on a prospective cohort of 71 adult patients with demyelinating disorders using a live cell-based flow cytometry assay. 4/71 (6.3%) adult patients were seropositive for anti-MOG antibodies, whereas all controls were seronegative (0/24, 0%). Next, a hMOG1-117-coated enzyme-linked immunoabsorbent assay (ELISA) was performed to investigate anti-MOG antibody binding to hMOG1-117. We tested 12 adult controls, 12 anti-MOG antibody negative patients (n=12 from prospective cohort) and 12 anti-MOG antibody positive patients (n=4 from prospective cohort; n=8 biobank-stored serum samples tested previously). Preliminary findings demonstrated that anti-MOG antibodies from 4/12 (33.3%) seropositive patients were able to bind hMOG1-117, while 2/12 (16.7%) seronegative patients and 0/12 (0%) controls bound. A duplicate ELISA was performed on a StrepTactin-coated plate to investigate intermolecular effects of the ELISA plate on hMOG1-117 conformation. 6/12 (50%) seropositive patients were able to bind hMOG1-117 on a StrepTactin-coated plate, while 1/12 (8.3%) seronegative patients and none of the controls (0/12, 0%) bound, suggesting that intermolecular interactions between the ELISA plate and hMOG1-117 may have an effect on its conformation which could decrease the sensitivity of the antibody binding assay. Deciphering the importance of conformation in anti-MOG antibody binding will assist optimization of patient diagnosis and treatment.
AUTOANTIBODY RESPONSES TO NODAL AND PARANODAL ANTIGENS IN CHRONIC INFLAMMATORY NEUROPATHIES

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Autoantibodies to nodal/paranodal proteins have previously been reported in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN). However, the prevalence and significance of nodal and paranodal antibodies in some groups of patients with immune-mediated neuropathies remains unclear. In this study we screened CIDP and MMN patients for antibodies to full length, human neurofascin-155 (NF155), contactin-1 (CNTN1), neurofascin-186 (NF186) and gliomedin proteins using standard ELISA. 7% (3/44) of CIDP patients exhibited anti-NF155 antibodies and 7% (3/44) of CIDP patients exhibited anti-CNTN1 antibodies. In contrast, neither NF155 nor CNTN1 antibodies were found in MMN (N=15), anti-myelin associated glycoprotein positive patients (N=9), other neuropathies (N=37) or healthy controls (N=28). The predominant IgG subclass of NF155 and CNTN1 antibodies was IgG4. Positive results were confirmed using cell-based assays and indirect immunofluorescence on teased nerve fibres. We did not detect IgG autoantibodies against these nodal/paranodal antigens in MMN patients. ELISA assays using commercially available, full length human proteins are useful for the initial screening of patients for IgG reactivity to NF155 and CNTN1. IgG subclass can then be determined and reactivity confirmed using cell-based assays or binding to teased nerve fibres. CIDP patients positive for antibodies NF155 or CNTN1 make an important subgroup of patients and a standardized ELISA to screen for these responses is a useful diagnostic tool. Moreover, early detection of anti-paranodal antibodies in CIDP patients is a key step in defining disease subtypes and will guide the most effective treatment strategies to prevent disruption of the axo-glial junction and axonal degeneration.
Numerous neuroinflammatory conditions such as multiple sclerosis, and autoimmune encephalitis show enhanced expression of the purinergic P2X7 receptor (P2X7R) in the neuroinflammatory foci, where increased microglial activation is a co-existing feature. We have reported that simple P2X7R-overexpression is sufficient in driving microglial activation and proliferation. Once activated, microglia are known to release a number of bio-active substances that include the proinflammatory cytokine interleukin 1beta (IL-1beta). Previous studies have linked P2X7R stimulation to the processing and release of IL-1beta, but whether P2X7 channel or P2X7R pore is the predominant entity driving that release is unknown. Using primary hippocampal cultures, we reveal that the release of IL-1beta to be P2X7R pore dependent. In addition, we found the trophic effects of P2X7R pore (in particular microglial activation and proliferation) to be mediated by IL-1beta. Inhibition of IL-1beta production and inhibition of its function, resulted in a significant decrease in P2X7R pore-induced microglial activation and proliferation. Our results indicate that P2X7R stimulation is important in induction of microgliosis and inflammation and that impairment of IL-1beta release due to blockade of P2X7R pore may be of significant therapeutic benefit in neuroinflammatory and neurodegenerative conditions where excessive IL-1beta is evident.
T CELL ACTIVATION BY THE DOPAMINE-2 RECEPTOR IN CHILDREN WITH MOVEMENT & PSYCHIATRIC DISORDERS

Deepti Pilli¹, Nese Sinmaz¹, Sudarshini Ramanathan¹, Fiona Tea¹, Anthony D Kelleher², Tina.K Nguyen¹, Vera Merheb¹, Alicia Zou¹, Joseph A Lopez¹, Russell C Dale¹, Fabienne Brilot¹

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Introduction & aim: In a subset of children with movement and psychiatric disorders, the dopamine-2 receptor (D2R) is targeted by autoantibodies, reinforcing the current autoimmune hypothesis of these brain diseases. Secretion of antibodies is dependent on an interplay between antibody-secreting B cells and CD4+ T cells, both specific for the same antigen. However, as these D2R-specific T cells remain unexplored, we aim to identify and characterise them in children with movement and psychiatric disorders.

Methods: Rare activated D2R-specific CD4+ T cells were detected via a sensitive whole blood assay that assessed the co-expression of CD25 and CD134 following stimulation with a library of human D2R peptides and positive stimulant controls, PHA, SEB, and tetanus toxoid (TT). Presence of D2R-specific T cells was confirmed in children (n=19) and controls (n=18) if the frequency of CD4+CD25+CD134+ T cells was more than 4 standard deviations over the control mean. To detect anti-D2R antibodies in patient sera, a flow cytometry live cell-based assay was used determine antibody binding to transfected HEK293 cells expressing D2R. When a delta mean fluorescence intensity (MFI) of a patient was 3 standard deviations above the control mean, they were classified as anti-D2R antibody seropositive.

Results: There was a subgroup of patients who had a higher frequency of activated CD4+CD25+CD134+ T cells in response to D2R peptides aa51-75(1/19), aa156-195(2/19), aa206-265(1/18), aa306-365(1/19) and aa381-443(2/19). No differences in T cell activation against PHA, SEB, and TT were observed between the cohorts (p<0.05). Of the 19 patients, 3 were seropositive for anti-D2R antibodies.

Conclusion: Activation of D2R-specific CD4+ T cells is notable in a subset of children with movement and psychiatric disorders. Except for one patient, a large proportion of these responders are negative for anti-D2R antibodies. This suggests a potential role for autoreactive T cells that is independent of antibodies in these autoimmune-associated disorders, thereby offering wider options for treatment.
THE CLINICAL COURSE, THERAPEUTIC RESPONSES, AND OUTCOMES IN RELAPSING MOG ANTIBODY-ASSOCIATED DEMYELENIATION

Sudarshini Ramanathan¹, Mohammad S¹, Tantsis E¹, Nguyen T¹, Merheb V¹, Fung², White O³, Broadley S⁴, Lechner-Scott J⁶, Vucic S⁷, Henderson A⁷, Barnett M⁸, Reddel S⁸, Brilot F¹*, Dale RC¹* on behalf of the Australasian and New Zealand MOG Study Group
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Objective: We characterised the clinical course, treatment, and outcomes in 59 patients with relapsing myelin oligodendrocyte glycoprotein (MOG) antibody-associated demyelination.

Methods: We evaluated clinical phenotypes, annualised relapse rates (ARR) prior and on immunotherapy, and expanded disability status scales (EDSS), in 216 demyelinating episodes from 33 pediatric and 26 adult patients.

Results: The most common initial presentation was optic neuritis (ON) in 54% [bilateral (BON) 32%, unilateral (UON) 22%] in both children and adults, followed by acute disseminated encephalomyelitis (20%) which occurred exclusively in children. ON was the dominant phenotype (BON 19% UON 34%) of all clinical episodes. 107/224 (48%) MRIs had no brain lesions. Patients were steroid responsive but 70% of episodes treated with oral prednisone relapsed, especially at doses <10 mg daily, within 2 months of cessation, and in association with a taper duration less than six weeks. Immunotherapy, including maintenance prednisone (P=0.0004), intravenous immunoglobulin (IVIg), rituximab, and mycophenolate, all reduced median ARRs on-treatment. Treatment failure rates were lowest with maintenance prednisone (6%). Switching therapy in those who failed the first immunosuppressive agent reduced on-treatment ARR (P=0.03). 59% of patients experienced residual disability (average follow-up 60 months, visual loss in 25%). Three or more demyelinating episodes were associated with a follow-up EDSS of ≥2 (OR 4.0, P=0.019).

Conclusions: Relapsing MOG antibody-associated demyelination is strongly associated with ON, is steroid responsive but vulnerable to relapse on withdrawal, and responsive to maintenance corticosteroids, IVIg, or immunosuppression. Increasing relapses lead to sustained disability.
MANAGING MYASTHENIA GRAVIS WITH LOW-DOSE RITUXIMAB: A CASE SERIES AND REVIEW OF THE LITERATURE

Andrew Swayne¹, Baumann F¹, Pamela McCombe¹, Stefan Blum¹

¹ Centre for Clinical Research, University of Queensland

Background: B-Cell depletion therapy has a growing role in the management of neurological diseases which are caused by a pathological immune response. Myasthenia gravis is one such disorder where antibodies are targeted against proteins required for the function of the neuromuscular junction. Rituximab (RTX), a monoclonal antibody against CD20 which depletes B cells, has been used in the management of a growing number of patients with myasthenia gravis.

Methods: A retrospective cohort study was undertaken of patients who had been treated with RTX in Brisbane with either acetylcholine receptor (AChR) or muscle specific kinase antibody (MuSK) positive myasthenia gravis. In total 37 patients were included. In most of these RTX was administered in 2 divided doses of 500mg with a total of 1 gram. Monitoring was conducted via serial clinical assessments, antibody testing and flow cytometry of peripheral blood B lymphocytes.

Results: Across the cohort low dose RTX therapy was associated with peripheral blood B lymphocyte depletion, significant clinical improvement and reduction of immunosuppressive medications. The re-emergence of peripheral blood B lymphocyte markers was linked to worsening of myasthenia gravis symptoms.

Conclusion: The use of RTX at a dose of 1 gram in the management of patients with severe myasthenia gravis appears to be beneficial. Using serial analysis of peripheral blood B lymphocytes appears useful in guiding the need for further RTX therapy.
KYNURENINE PATHWAY METABOLITES AS PROGRESSION MARKERS FOR MND

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A lack of suitable biomarkers for amyotrophic lateral sclerosis (ALS) hampers monitoring of disease progression, furthermore, limits assessment of therapy efficiency during clinical trials. In a pilot study of 66 ALS patients from a clinical trial, we use biochemical chromatography analyses to longitudinally characterize patient serum Kynurenine Pathway (KP) profiles to determine if the KP is a suitable candidate as an objective biomarker or prognostic indicator of ALS. To. The KP is activated by inflammation, and has been shown to be dysregulated in ALS [1], [2]. We show that together with clinical outcomes, ALS Functional Rating Scale (ALSFRS) and Manual Muscle Testing (MMT), KP metabolite 3hydroxyanthranilic acid is increased over time (-1.20, -3.74, and -0.46 units over time). Tryptophan and Kynurenine are both positively associated with ALSFRS; and Kynurenic Acid and Quinaldic Acid are associated with MMT, indicating that they are good candidates as biomarkers for ALS. Lastly, we show that neopterin is a significant prognostic marker for disease progression, with an increased neopterin level being associated with slower disease progression. These findings suggest that the KP may be a useful marker of disease progression and prognosis in ALS, and that further research to integrate the KP with other known biomarkers, and larger datasets may produce a clinically relevant and specific biomarker for ALS.

The KP shows potential for tracking of disease development in ALS. This will allow for a biochemical technique that will allow definitive monitoring of progression. This data has also allowed an in depth analysis of the KP changes through the course of disease. The role of immune modulating KP may be applied towards therapeutic considerations by using KP altering drugs that may lead to new therapeutic options for alleviating the clinical effects of MND.

Autoimmune attack to the myelin sheath of neurons in central nervous system (CNS) demyelinating diseases has piloted extensive study into autoantibodies targeting brain myelin proteins. Recently, autoantibodies which recognise the conformational myelin oligodendrocyte glycoprotein (MOG) have been clinically associated with subsets of CNS demyelinating diseases, such as bilateral optic neuritis. We examined whether the major epitope recognised by MOG autoantibodies from our adult (n=25) and paediatric (n=46) CNS demyelinating cohorts would be similar to that previously described in children. We subcloned and stably expressed in HEK293 cells a human MOG mutant, MOG P42S, where the Proline at position 42 was mutated to Serine. After confirming surface expression of MOG P42S by flow cytometry and confocal microscopy, we assessed sera MOG autoantibody binding using a flow cytometry live cell-based assay. Compared to MOG wild-type, 80% (20/25) of adult, and 76% (35/46) of paediatric MOG autoantibody-positive patients had a reduced binding (<65%) to the P42S MOG mutant. Longitudinal analysis of three paediatric and six adult patients indicated stable epitope recognition overtime. Taken together, the Proline at position 42 of human MOG is a major conformational epitope in human MOG autoantibodies, and this binding remains stable overtime. Furthermore, as rodent MOG contains a Serine at position 42, our results support the assertion that human MOG autoantibodies fail to bind rodent MOG. This species-specific epitope has major implications in future MOG autoantibody studies in rodent models. Greater characterisation of MOG autoantibodies will drive development of novel antibody therapies to improve patient management and treatment.
INTRAVENOUS IMMUNOGLOBULIN (IVIG) AS AN IMMUNOMODULATORY THERAPY FOR ACUTE SPINAL CORD INJURY

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Traumatic spinal cord injury (SCI) elicits immediate neural cell death, axonal damage and disruption of the blood-spinal cord barrier, allowing circulating immune cells and blood proteins into the spinal parenchyma. The acute inflammatory response to SCI involves robust activation of the complement system, which contributes to secondary injury and impairs neurological recovery. This study aimed to determine whether intravenous immunoglobulin (IVIg), an FDA-approved immunomodulatory treatment, can attenuate complement activation products and improve recovery from SCI. We addressed these questions by using functional testing, non-invasive imaging, and detailed post-mortem analysis to assess IVIg’s therapeutic efficacy in a mouse model of severe contusive SCI. Our results show that IVIg therapy at clinically relevant doses of 0.5-2 g/kg significantly improves functional and histopathological outcomes from SCI, conferring protection against lesion enlargement, demyelination, and axonal degeneration. The benefits of IVIg were also detectable through non-invasive diffusion tensor imaging (DTI), with IVIg treatment counteracting the progressive SCI-induced increase in radial diffusivity (RD) in white matter. Diffusion indices significantly correlated with the functional performance of individual mice and accurately predicted the degree of myelin preservation. Further experiments revealed that IVIg therapy reduced complement activation and presence of phagocytically active macrophages at the lesion site, providing insight into its likely mechanisms of action. Our findings highlight the potential of using IVIg as an immunomodulatory treatment for SCI, and the value of DTI to assess tissue damage and screen for the efficacy of candidate intervention strategies in preclinical models of SCI, both quantitatively and non-invasively.
**TH17 CELLS ARE DYSREGULATED IN THE ABSENCE OF DOCK8-POSTER**

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Dedicator of Cytokinesis 8 (DOCK8) is a guanine exchange factor highly expressed in the immune system and connected to cell polarisation, proliferation and migration. Multiple mouse models of DOCK8 deficiency show elevated numbers of inflammatory Th17 cells opening the opportunity to investigate potential intrinsic effects of DOCK8 deficiency in Th17 cells. All DOCK8 deficient mouse models tested showed elevated CD4+ IL-17a producing cells, however no elevation of cytokines produced by other T cell subsets were altered indicting a Th17 cell specific effect. In vitro T helper cell differentiation confirmed that the elevated Th17 cell population was not based on a T helper cell intrinsic differentiation defect or altered apoptosis. Th17 cells expressed normal levels of the Th17 cell specific CCR6 and were able to migrate towards chemokine gradients in in vitro transwell migration assays. We next investigated if the increase in Th17 cells led to an increased pathology in the Th17 cell mediated disease experimental autoimmune encephalomyelitis (EAE), a mouse model of autoimmune aspects of Multiple Sclerosis. Interestingly, homozygous Dock8 mutant mice were found to have ameliorated disease despite increased percentages of Th17 cells in the blood in the steady state. Adoptive transfers of Th1 and Th17 cells in EAE mice pointed towards a Th17 cell specific migration defect in the absence of functional DOCK8. We are currently investigating the molecular mechanisms underlying this effect.
INVESTIGATING THE DIVERSITY AND IMMUNOREACTIVITY OF RECOMBINANT ANTI-MOG ANTIBODIES ASSOCIATED WITH CENTRAL NERVOUS SYSTEM DEMYELINATING DISEASES

Alicia Zou1, Fiona Tea1, Deepti Pilli1, Joseph Angelo Lopez1, Sudarshini Ramanathan1, Vera Harb1, Fiona Lee1, Russell Dale1, Fabienne Brilot1

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Background: Certain disorders of central nervous system (CNS) neuromyelitis optica spectrum disorder (NMOSD), such as bilateral or relapsing optic neuritis, have been associated with the presence of autoantibodies against myelin oligodendrocyte glycoprotein (MOG). The current understanding that a single major immunoreactivity exists in antibody-associated CNS disorders has been challenged by new findings of double autoantibody positivity in patients. As it stands, the diversity of the antibody repertoire in patients with CNS demyelinating diseases and how it evolves with disease is unknown.

Methods: To characterise the autoantibody repertoire in anti-MOG antibody-positive patients, paired heavy and light chain variable regions will be amplified from single B cells to be subcloned into expression vectors and transfected into mammalian cells to produce recombinant monoclonal antibodies (rAbs), which can then be analysed for their binding to a panel of antigenic targets.

Results: Flow cytometric analysis revealed that plasmablasts were more frequent than plasma cells (0.65 ± 0.4% vs 0.00 ± 0.0, respectively) in the peripheral blood of healthy controls, and were subsequently selected for single cell analysis. Amplification of variable heavy and light chains from single plasmablasts using one-step RT-PCR revealed the low efficiency of this process. Based on gel visualisation, the variable Igλ chain was amplified from 4 of 18 (22%) single plasmablasts, which was 4 times more frequent than the amplification of the Igκ chain (1/18; 5.56%). The variable IgH chain was not able to be visualised from any single-sorted plasmablast. A two-step RT-PCR, reported in the literature to be more sensitive than a one-step RT-PCR for limiting concentrations of RNA, was selected to improve the efficacy of immunoglobulin chain amplification, and is currently undergoing optimisation.

Conclusion: The production of rAbs will allow the characterisation of MOG-specific antibody response in patients with CNS demyelinating disorders. Furthermore, the generation of abundant rAbs can be used to model functional pathogenic effects in in vitro cellular models.
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