Neuroprotection upon Multiple Sclerosis: there are a lot more to do

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Multiple sclerosis (MS) is a progressive, chronic central nervous system (CNS) demyelinating disease disease. It is the most common cause of neurological disability that affects young Caucasian adults, striking three times more women than men with diagnosis peaking at around 30 years of age, thus affecting people in their most productive years. MS has a lifelong impact and almost any neurological symptom can appear with the disease. A person with MS can suffer almost any neurological symptom or sign, including changes in sensation such as numbness, muscle weakness and fatigue, difficulty in moving, difficulties with coordination and balance, visual and speech problems, acute or chronic pain, and bladder and bowel difficulties. With the progression of the disease, MS can affect cognitive functions such as memory and concentration as well as importantly emotions. A people with MS can experience psychiatric symptoms such as depression and anxiety. Thus, this disease can severely disrupt multiple facets of people's life quality.

The prevalence of MS is increasing steadily over time. In Australia in 2010, the prevalence was estimated to be 21,200 (95.2 per 100,000 persons) with the incidence increasing by 7% each year compounding the pressure for research. 1 in 20 Australian will be touched with MS through a family member, colleague or friend with the disease. The total financial cost annually is close to $2 billion dollars. Investment in research that would delay or ideally prevent the progression could bring substantial rewards in terms of both reducing the financial burden and increasing quality of life.

There is currently no cure for MS. Many people with the disease use complementary and alternative medicine such as medications to modulate or suppress the immune system, which unfortunately usually cause strong side effects. Although some of these treatments can manage the disease course, they are only partially effective, which means that some people's MS will worsen in spite of everything they and their doctors do to try and prevent it. There is currently lack of effective treatments that directly target the nervous system repair.

MS is thought to result from an inflammatory attack against myelin, which is produced by specialized glial cells in the CNS known as oligodendrocytes, and their death are commonly observed elements in MS lesions [1]. As a result, the efficient transmission of neuronal signals is disrupted, causing nervous system dysfunction. An endogenous repair process often follows the death of these glial cells, which is effected by surviving oligodendrocytes in the lesion area and complemented by the recruitment of oligodendrocyte precursor cells. This repair process is variable, but can result in the return to relatively normal CNS function. However over time and following successive demyelinating events, the myelin repair is ultimately insufficient, and becomes less efficient with age and disease progression, invariably leading to irreversible axonal damage and progressive and extensive disability [2-4]. Currently remyelination failure remains a major obstacle to recovery in Multiple Sclerosis. Strategies aimed at improving and enhancing remyelination is critically important to complement the currently available immunomodulatory treatments. One of the most promising therapeutic approaches involves enhancing the innate capacity of the endogenous oligodendrocytes to remyelinate.

The ultimate goal of our research is to promote human health and focus on identifying strategies designed to directly enhance myelination. This is an ambitious goal, and one that I consider can only be realistically achieved by developing a more complete understanding of the signals that control normal myelination during development and applying these to the myelin repair paradigm. One of our current projects focus on investigating the influence that Brain Derived

Neurotrophic Factor (BDNF), a growth factor expressed in the brain, exerts upon remyelination following acute CNS demyelination. These studies will be critical to understand how BDNF signaling might be modulated to maximize myelin repair, thus identifying it as a *bona fide* therapeutic target worthy of further investigation for regenerative therapeutic benefit in Multiple Sclerosis. These studies will contribute significant knowledge to the field of neurobiology, which may ultimately aid the development of novel interventions that lead to improved control of demyelinating diseases that represent a substantial socio-economic burden within Australia and international-wide.

Reference:

1. Barnett, M.H. and J.W. Prineas, Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Ann Neurol, 2004. 55(4): p. 458-68.
2. Kilpatrick, T.J., H. Butzkueven, and A. Grigg, Prospects for stem cell transplantation in multiple sclerosis. J Clin Neurosci, 2002. 9(4): p. 361-7.
3. Franklin, R.J. and C. Ffrench-Constant, Remyelination in the CNS: from biology to therapy. Nat Rev Neurosci, 2008. 9(11): p. 839-55.
4. Franklin, R.J. and M.R. Kotter, The biology of CNS remyelination: the key to therapeutic advances. J Neurol, 2008. 255 Suppl 1: p. 19-25.