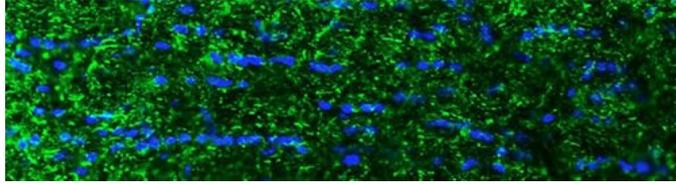


Multiple Sclerosis Research Group



Group Leader Dr Zubair Ahmed

(<http://www.bhamtest1.bham.ac.uk/staff/profiles/cem/NN/Ahmed-Zubair.aspx>)

Overview

Multiple Sclerosis (MS) is a neurological condition that leads to damage of the protective coating around nerve fibres and causes a wide range of symptoms including visual disturbances, problems with balance and spasticity. The condition affects around 100,000 individuals in the UK, is prevalent in women and typically affects

young adults between the ages of 20-40. Currently, there is no cure for MS but symptoms are managed by disease modifying drugs, which often reduce the frequency of relapses. Both genetic and environmental factors are thought to contribute to the disease.

Our research group

Recent research into MS has clearly shown that the physical manifestations of the condition result from a combination of damage to nerve cells (axons) and the insulating myelin sheath coating the cells (demyelination). This makes the treatment of MS particularly challenging since the central nervous system (CNS - brain and spinal cord) has a limited intrinsic capacity for repair. Current therapies are largely aimed at reducing the inflammation associated with relapses of MS, but have no direct effects on cells of the nervous system to promote tissue repair and are therefore ineffective for a large proportion of patients with existing or ongoing CNS damage (usually seen as primary or secondary progressive disease).

Our MS research group explores the mechanisms that lead to axonal damage in MS with a particular focus on identifying novel molecules that are dysregulated in the natural progression of the disease and identifying suitable targets for therapeutic intervention. Using microarray and next generation sequencing technologies, we have identified several novel molecules that are present on the surface of neurons and are important in neuronal repair. We aim to understand the biology of these molecules and their potential role in the pathogenesis of MS with an aim to modify their expression to develop new treatments for MS. We have already shown a close link with one of these molecules to the pathogenesis of MS, acting on oligodendrocyte precursor cells (OPC) that are normally resident in the CNS and inhibits their differentiation into myelinating oligodendrocytes. We are therefore developing antagonists to these molecules to promote OPC differentiation and thus enhance myelin repair and restoring lost function.

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Current Projects

Defining the role of novel molecules in the pathogenesis of MS (Ahmed, Logan, Berry, Fulton)

The development of a new treatment that promotes repair of axons and their associated myelin sheath would revolutionise the outlook for patients and their carers. Currently, there is no treatment to reverse the axonal damage that occurs in MS. However, we have identified several molecules that might be useful in promoting myelin repair and regeneration in the damage CNS. This is a huge unmet need, particularly for patients with progressive disease (both primary and secondary progressive MS) in which none of the available agents have been shown to be effective.

We will test the hypothesis that antagonism of several of these molecules that are highly upregulated in oligodendrocyte precursor cells will promote their differentiation into myelinating oligodendrocytes and thus enhance myelin repair. Our preliminary experiments also demonstrate that these molecules are present in reactive astrocytes, macrophages/microglia and in MS lesions. Understanding how these molecules are dysregulated in MS may define new molecules for therapeutic utility in the fight against MS.

Neuroprotection in optic neuritis (Ahmed)

Around 10-30% of individuals affected by MS have a clinical presentation that manifests with inflammation of the optic nerve (optic neuritis) followed by the development of relapsing-remitting MS. Optic neuritis leads to loss of vision due to conduction block, demyelination and subsequent loss of retinal ganglion cells in the retina. The underlying immunological basis for different clinical forms of MS and its association to optic neuritis is not well defined. However, MRI studies have shown that people with this condition often have brain lesions and the involvement of the optic nerve. Optic neuritis can result in visual impairment in a proportion of affected individuals and results in retinal nerve loss.

Working with colleagues at the Blizzard Neuroscience Centre, Queen Mary, University of London, UK, we have shown that caspase-2, an orchestrator of apoptosis, is activated in retinal ganglion cells during the development of optic neuritis and its suppression with a nuclease stable siRNA prevents retinal ganglion cell apoptosis and preserves retinal fibre layer thickness. We are currently analysing the utility of these therapeutic molecules in treating individuals affected with this medical condition.

Recent Publications

- Lidster K, Jackson SJ, Ahmed Z, Munro P, Coffey P, Giovannoni G, Baker MD and Baker D (2013) **Neuroprotection in a novel mouse model of multiple sclerosis** (<http://www.ncbi.nlm.nih.gov/pubmed/?term=Neuroprotection+in+a+novel+mouse+model+of+multiple+sclerosis>). *PLoS One* 8(11):e79188
- Ahmed Z (2013) Cannabinoids: **Do they have the potential to treat the symptoms of multiple sclerosis** (<http://www.wjgnet.com/2218-6212/pdf/v3/i4/87.pdf>). *World Journal of Neurology* 3(4):87-96
- Garthwaite G, Batchelor AM, Goodwin DA, Hewson AK, Leeming K, Ahmed Z, Cuzner ML and Garthwaite J (2005) **Pathological implications of iNOS expression in central nervous system white matter: an ex vivo study of optic nerves from rats with experimental allergic encephalomyelitis** (<http://www.ncbi.nlm.nih.gov/pubmed/?term=Pathological+implications+of+iNOS+expression+in+central+nervous+system+white+matter%3A+an+ex+vivo+study+of+optic+nerve+from+rats+with+experimental+allergic+encephalomyelitis>). *European Journal of Neuroscience* 21(8):2127-2135
- Pryce G*, Ahmed Z*, Hankey DJR*, Jackson SJ, Croxford JL, Pocock JM, Ledent C, Petzold A, Thompson AJ, Giovannoni G, Cuzner ML and Baker D (2003) **Cannabinoids inhibit neurodegeneration in models of multiple sclerosis (Cannabinoids inhibit neurodegeneration in models of multiple sclerosis)**. *Brain* 126(Pt 10):2191-2202 *Joint first authors
- Ahmed Z, Doward AI, Pryce G, Taylor DL, Pocock JM, Leonard JP, Baker D and Cuzner ML (2002) **A role for caspase-1 and -3 in the pathology of experimental allergic encephalomyelitis: Inflammation versus degeneration** (<http://www.ncbi.nlm.nih.gov/pubmed/?term=A+role+for+caspase-1+and+%E2%80%933+in+the+pathology+of+experimental+allergic+encephalomyelitis%3A+Inflammation+versus+degeneration>). *American Journal of Pathology* 161(5):1577-1586

Staff

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