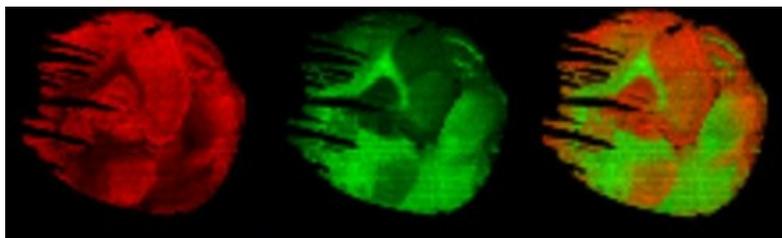


Traumatic Brain and Spinal Cord Injury Research Group



Group leader: **Dr Antonio Belli** (</staff/profiles/cem/NN/belli-tony.aspx>)

Overview

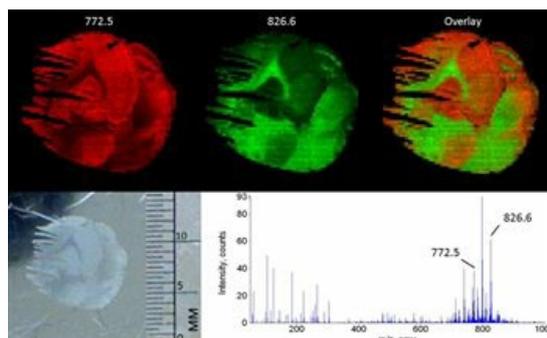
Traumatic brain injury (TBI) is the leading cause of death and disability in the first 4 decades of life and its incidence continues to rise across all age groups. Spinal cord injury (SCI) on the other hand, affects more than 2.5 million people worldwide, with approximately 130,000 new cases each year. SCI can lead to devastating long-term effects and potential therapies only help reduce pain for affected individuals. Trauma to the brain or spinal cord triggers a complex and rapidly evolving interplay of inflammatory, dysmetabolic, degenerative and compensatory mechanisms that determine the fate of the injured tissue. The understanding of these cellular responses and their interconnection with genetic, systemic and environmental factors is key to the development of neuroprotective treatments.

devising long-term effects and potential therapies only help reduce pain for affected individuals. Trauma to the brain or spinal cord triggers a complex and rapidly evolving interplay of inflammatory, dysmetabolic, degenerative and compensatory mechanisms that determine the fate of the injured tissue. The understanding of these cellular responses and their interconnection with genetic, systemic and environmental factors is key to the development of neuroprotective treatments.

Our research group

The TBI and SCI group carries out translational research linked with the activity of the **NIHR Surgical Reconstruction and Microbiology Research Centre (Trauma Research)** (<http://www.srmrc.nihr.ac.uk/>). We study the early response to trauma, i.e. changes that occur in the 'golden hour' and that are particularly challenging to study in a clinical setting, as well as mechanisms of neurodegeneration and long-term cognitive dysfunction. Our lab uses *in vivo* and *in vitro* models that have been developed to mimic the pathophysiological changes seen in impact and acceleration/deceleration injuries. We have particular interest in the mitochondrial response to trauma and how the impairment of calcium homeostasis triggers downstream responses, how these responses are modulated by genetic and epigenetic factors, as well as how spinal cord cavities form, development of antifibrotic agents and identification of new genes involved in CNS axon regeneration. Our research focuses on novel technologies to detect early signatures of damage before this becomes irreversible (e.g. metabolic impairment, brain swelling, neuroinflammation, cavitation etc.) or to identify patients at risk of poor cognitive outcome, mental health disorders, spasticity or epilepsy, thus allowing the development of targeted intervention and personalised treatments. Our interest is also in the factors that lead to poor neurological outcome and early neurodegenerative conditions when repeated TBI occurs in susceptible individuals, with athletes, soldiers and the extreme ages of life being at particular risk.

Our research is cross-disciplinary and links in areas such as Medicine, Psychology, Imaging, Sports and Exercise Sciences, Bioengineering, Chemistry and Computing Sciences.



Current Projects

[Open all sections](#)

- **Gamma oscillations, mitochondrial dysfunction and cognitive impairment following traumatic brain injury (Vreugdenhil, Belli, Toescu, Di Pietro)**

Preliminary research points to mitochondrial damage that leads to energy crisis and damage due to reactive oxygen species and distorted calcium homeostasis. Gamma (30-120 Hz) frequency brain waves are energy-demanding processes synchronising neuronal activity at ms precision required for many cognitive processes. This project tests the hypothesis that mild TBI causes cognitive impairments due to impaired gamma synchronisation, as a result of mitochondrial damage.

We record the induced gamma synchronisation in cultured slices of the rat hippocampus and simultaneously record the mitochondrial membrane potential and calcium concentration using fluorescent dyes and afterwards use immunohistochemistry to test the effect on interneurons involved in gamma synchronisation. The cultures are subjected to a stretch injury, which reproduces a diffuse axonal injury as seen in road traffic accidents.

- **Mild Traumatic Brain Injury and PTSD in UK Military and Civilian Populations (Upthegrove, Belli, Wood, Finnegan, Broome)**

There has been increasing concern in recent years about incidence of post-traumatic stress disorder (PTSD) following mild trauma brain injury (mTBI), with evidence suggesting a strong link between these two conditions. Several explanations have offered for this but a causal link is yet to be established. This project sets to identify the incidence and risks factors for PTSD in cohorts of military and civilian patients with mTBI. Parallel research will establish a translational lab model to with a view developing therapeutic intervention.

- **Early metabolic signatures of traumatic brain injury (Di Pietro, Britton, Bunch, Grover, Foster, Midwinter, Belli)**

TBI triggers a cascade of metabolic, inflammatory, degenerative and pathoanatomical changes that start immediately after injury and may rapidly become irreversible. TBI research has largely focused on changes that occur at some distance from the injury, typically by measuring brain and systemic parameters in intensive care, often when the damage is already established and less likely to respond to intervention. This project explores technological solutions to investigate early signatures of injury that may assist pre-hospital decision-making, prognostication and early therapy. This translational research is carried out with parallel *in vivo*, *in vitro* and clinical studies and avails itself of cross-disciplinary collaborations with Bioengineering and Chemistry.

- **Post-traumatic pituitary dysfunction (Belli, Logan, Toogood, Foster)**

TBI has long been known to be a cause of pituitary dysfunction, although in practice the latter usually remains undiagnosed due to the overlap with typical post-concussional symptoms, such as fatigue, sexual dysfunction, cognitive impairment, low mood, behavioural changes and occasionally psychotic syndromes. Post-traumatic hypopituitarism (PTHP), arises due to stalk trauma or ischaemia of the anterior or posterior pituitary lobe resulting in endocrine abnormalities. The endocrine dysfunction may be reversed when the deficiencies are recognised, with potential benefits for rehabilitation and clinical outcome. The risk factors for PTHP are unknown but this problem has been investigated in combat sports such as boxing, football, ice hockey and martial arts. This projects sets to investigate the incidence and risk factors for PTHP in military and civilian cohorts.

- **Predictors of adverse long-term outcome in mild, severe and repetitive traumatic brain injury (Belli, Logan, Jones, Wood, Grey, Di Pietro, Morrison, Bickerton, Nagy)**

Functional recovery after TBI depends on numerous factors and our current predictive models, typically based on age, Glasgow Coma Scale and basic physiological parameters, have significant limitations that hamper their routine use in clinical practice. Genetic and epigenetic factors also play an important role and explain some of the inter-individual variability in the response to injury. Co-morbidity, systemic inflammation and repetitive neurological insults are also likely to be determinants of long-term outcome and in particular of the risk of early neurodegenerative conditions (e.g. Parkinson's, Alzheimer's and Amyotrophic Lateral Sclerosis). The aim of this project is to identify predictive biomarkers that could (a) highlight patients likely to have poor functional outcome, (b) provide important information for hospital staff, patients and carers to make informed decisions, and (c) form part of a coherent treatment pathway. This research is based on a multimodal battery of assessment including psychometric properties, spectroscopic imaging, functional MRI, Trans-Cranial Magnetic Stimulation, cognitive neurophysiology, functional MRI and blood biomarkers, with particular focus on the mTOR pathway and systemic inflammation.

- **Decorin as an anti-scarring agent after spinal cord injury (Logan, Ahmed)**

Spinal cord injury induces pathological changes such as scarring that impede recovery of function and can also form the focus of post-injury epileptic attacks. We are analysing drugs that will act as antifibrotic therapies and suppress acute post-injury scar formation in the CNS. One such drug is decorin, a small leucine-rich antagonist of TGF- β that attenuates TGF- β activation and signalling through their receptors. We aim to evaluate the therapeutic potential of decorin to inhibit scarring in the spinal cord and brain.

- **Cavitation after spinal cord injury (Ahmed, Logan)**

In most mammals, progressive tissue necrosis occurs after SCI leading to the formation of fluid filled cavities and is potentially a life threatening condition in humans. Several lines of evidence suggest that promotion of angiogenesis improved wound healing and reduces cavitation after SCI. We are using state-of-the-art gene detection studies, including microarray and deep sequencing technologies to identify genes involved in angiogenesis/wound healing with the aim of reducing cavitation after spinal cord injury.

- **Definition of genes that contribute to axon regeneration after SCI (Ahmed, Logan)**

In contrast to adult neurons of the peripheral nervous system, damaged CNS axons do not spontaneously regenerate due to limitations that include; neuronal loss by apoptosis, reduced intrinsic growth capacity of neurons and the presence of a non-permissive environment in the injured adult CNS preventing axon growth. There are three major inhibitory components of CNS myelin, Nogo-66, myelin associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp) that bind a common receptor, the Nogo-66 receptor (NgR1) and associate with the signal transducing receptor, p75 and its co-receptor LINGO-1, signalling inhibition of CNS axon growth through a RhoGTP-mediated pathway. In addition, TAJ/TROY was also identified as a surrogate receptor for p75 since not all neuronal populations that responded to myelin contained p75.

Due to the variety of different molecules involved in blocking axon regeneration after injury, understanding how they function and interact is pertinent to be able to devise ways to overcome these molecules effectively. We are therefore defining the function of genes and assessing their contribution to CNS axon regeneration with a view to devising better therapeutic molecules to enhance axon regeneration.

Recent Publications

- Vagnozzi R, Signoretti S, Floris R, Marziali S, Manara M, Amorini AM, Belli A, Di Pietro V, D'Urso S, Pastore FS, Lazzarino G, Tavazzi B (2012) Decrease In N-Acetylaspartate Following Concussion May Be Coupled To Decrease In Creatine. J Head Trauma Rehabil. 2012 Dec 15. [Epub ahead of print]
- Di Pietro V, Amorini AM, Tavazzi B, Hovda DA, Signoretti S, Giza CC, Lazzarino G, Vagnozzi R, Lazzarino G, Belli A. (2012) Potentially neuroprotective gene modulation in an in vitro model of mild traumatic brain injury. Mol Cell Biochem. 2012 Dec 15. [Epub ahead of print]
- Zaben M, El Ghouli W, Belli A (2012). Post-traumatic Head Injury Pituitary Dysfunction: Does it Matter for Rehabilitation? Disability & Rehabilitation. 2012, July 2010. [Epub ahead of print]
- Hou R, Moss-Morris R, Peveler R, Mogg K, Bradley BP, Belli A (2012). When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury. J Neurol Neurosurg Psychiatry. 2012 Feb;83(2):217-23
- Di Pietro V, Amin D, Pernagallo S, Lazzarino G, Tavazzi B, Vagnozzi R, Pringle A, Belli A (2010): Transcriptomics of traumatic brain injury: gene expression and molecular pathways of different grades of insult in a rat organotypic hippocampal culture model. J Neurotrauma 2010 Feb; 27(2):349-59
- Ahmed Z., Douglas M.L., Read M.L., Berry M., Logan A. (2011) Citron kinase regulates axon growth through a pathway that converges on cofilin downstream of RhoA. Neurobiol Dis 2011 Feb; 41(2): 421-429
- Lagord C, Berry M, Logan A (2002). Expression of TGFbeta2 but not TGFbeta1 correlates with the deposition of scar tissue in the injured spinal cord. Mol Cell Neurosci 2002 May; 20(1): 69-92

Staff

Principal Investigators

Professor Ann Logan (</staff/profiles/cem/NN/Logan-Ann.aspx>)

Dr Zubair Ahmed (</staff/profiles/cem/NN/Ahmed-Zubair.aspx>)

D (</staff/profiles/cem/NN/Upthegrove-Rachel.aspx>) **r Rachel Upthegrove** (</staff/profiles/cem/NN/Upthegrove-Rachel.aspx>)

Dr Emil Toescu (</staff/profiles/cem/NN/Toescu-Emil.aspx>)

Dr Martin Vreugdenhil (</staff/profiles/cem/NN/Vreugdenhil-Martin.aspx>)

Dr Zsuzsa Nagy (</staff/profiles/cem/NN/Nagy-Zsuzsanna.aspx>)

Dr Ana Maria Gonzalez (</staff/profiles/cem/NN/Gonzalez-AnaMaria.aspx>)

Honorary Staff

Professor Martin Berry

Dr Andrea Cavanna - University Hospitals Birmingham NHS Trust, UK

Professor Adrian Williams - University Hospitals Birmingham NHS Trust, UK

Internal Collaborators

Dr Kevin Whitehead (</staff/profiles/cem/PPT/Whitehead-Kevin.aspx>) - School of Clinical and Experimental Medicine, College of Medical and Dental Sciences

Dr Michael Grey (</staff/profiles/sportex/grey-michael.aspx>) - School of Sport and Exercise Sciences, College of Life and Environmental Sciences

Dr Liam Grover (</staff/profiles/chemical-engineering/grover-liam.aspx>) - School of Chemical Engineering, College of Engineering and Physical Sciences

Professor Roy Bicknell (</staff/profiles/iandi/bicknell-roy.aspx>) - School of Immunity and Infection, College of Medical and Dental Sciences

Postdoctoral Researchers

Dr Valentina Di Pietro (</staff/profiles/cem/NN/dipietro-valentina.aspx>)

PhD Students

Sarina Kundi

Shareef al-Mutiri

