Can you provide an insight into your background and outline what sparked your current research interests?

It was during my postdoctoral studies at the Washington University School of Medicine that I began studying the mechanisms that underlie acute neuronal injury – particularly regarding stroke, which is caused by cerebral ischaemia, or the loss of blood flow to the brain. Although the laboratory in which I was based was predominantly focused on understanding the mechanisms by which neurons die in an autonomous fashion, I was fascinated by the potential that stroke could result in non-autonomous neuronal cell death – namely, that other cells mediate the injury. I therefore started to explore how astrocytes respond to the injured environment and whether these cells contribute to injury. As for my current research interests, they are an extension of this work. As a postdoctoral researcher, I was very lucky to have a wonderful mentor who allowed me to study the potential for inflammatory astrocyte signalling to contribute neuronal injury and who encouraged me to continue this initial work in my own laboratory.

What are the core aims and objectives of your laboratory’s work?

The work in my laboratory focuses on elucidating the molecular and biochemical mechanisms by which inflammatory factors upregulated during and following acute injury – for example, in stroke, trauma and epilepsy – can either promote or protect neurons (that is, nerve cells). In particular, we are concentrating on the interactions between neurons and astrocytes.

How is the combined usage of in vitro and in vivo experimentation helping to facilitate your work?

As both in vitro and in vivo models of injury are employed in my research, I am fond of saying that we take a ‘molecules to mouse’ and ‘mouse to molecules’ approach to the essential questions posed. Combining these two approaches is a very powerful method. Our cell culture models allow us to look at the cellular interactions that follow injury with specificity and detail, leading us to make insights into potential therapeutic targets. In turn, we are then able to test these potential therapies in animals as part of an applied research strategy. This is appropriate since mice and humans share many of the same neurobiological properties.

In what ways does cyst(e)ine/glutamate antiporter (system xc-) influence hypoglycaemic neuronal cell death?

We found that the excitotoxic neuronal injury that follows glucose deprivation – aglycaemia – is initiated by glutamate extruded from astrocytes via system xc-, an amino acid transporter that imports L-cystine and exports L-glutamate. Thus, the release of astrocyte glutamate appears to be a primary contributing factor to hypoglycaemic neuronal injury, at least in our cell culture model. Our next steps are to confirm this in an animal model.

Could you discuss your lab’s most exciting findings to date?

Something that is truly unique and exciting is our work on the bimodal actions of IL-1β – intriguingly, it can either contribute to or protect from neural injury via what is essentially the same mechanism: the upregulation of astrocyte system xc-. The concept that IL-1β and system xc- are at the crossroads of injury and protection is the factor that is especially original and intriguing about the work in our lab. Indeed, while our published data predict the ability of IL-1β enhanced cyst(e)ine/glutamate antiporter activity to contribute to injury in cerebral ischaemia and hypoglycaemic injury, we have recently generated new, as-yet unpublished results that indicate this activity could also be potentially protective in direct models of oxidative stress. Hence we posit that IL-1β-mediated upregulation of astrocyte system xc- represents a protective mechanism, which under certain conditions, will ultimately go awry. For these reasons, understanding the regulation of system xc- by IL-1β at the molecular level is of utmost importance, so that we may use this information to devise strategies that harness the beneficial effects and, when appropriate, employ strategies that reduce its activity in order to decrease the probability of neuronal injury.
Astrocyte-neuron interactions

Based in the Department of Biology at Syracuse University, USA, researchers at the Sandra Hewett Lab are making inroads into understanding the molecular and biochemical mechanisms by which upregulated inflammatory factors fuel the progression of acute neuronal injury.
Hewett’s team has found compelling evidence linking the inflammatory genes expressed in parenchymal cells in the central nervous system to both injury and protection.

Hewett outlines, “We have elucidated that IL-1β works to increase transcription of the gene for system xc- [increased xCT mRNA] and stabilises xCT mRNA. Overall, the effect is to increase the number of transporters on the cell’s surface.”

COMBATING HYPOGLYCAEMIA
In addition, the team is also exploring the cellular and molecular mechanisms involved in severe hypoglycaemia, the process whereby brain glucose levels can reach zero. Hypoglycaemia occurs during strokes but is also an event most commonly connected to diabetes – for instance, it occurs in diabetic patients who may take too much insulin, who might not eat enough or who exercise too intensively. It is a serious medical emergency that causes cognitive impairment, seizures, unconsciousness, coma and neuronal cell death. Additionally, it is known that individuals who experience one or more episodes of severe hypoglycaemia are at increased risk of dementia. Hence, it is imperative to understand the cell and molecular processes initiated in the brain by hypoglycaemia.

In spite of solid evidence from previous in vitro and in vivo models that hypoglycaemic neuronal cell death is induced as a result of glutamate excitotoxicity, the cellular source from which glutamate is released – as well as the molecular mechanisms that underpin this process – were incompletely defined prior to the work of the Hewett Lab. “Previous work from my laboratory determined that the astrocyte system xc- contributed to hypoxic neuronal injury via a glutamate-mediated mechanism, thus leading us to attempt to determine whether a similar mechanism might be in play during hypoglycaemia,” Hewett reveals. Excitingly, their results demonstrated that glutamate efflux from astrocytes – via system xc- – contributes to glucose deprivation-induced neuronal cell death in vitro.

SPOTLIGHT ON EPILEPSY
In a further line of research, Hewett is also investigating the cellular and molecular mechanisms that cause seizures in epilepsy. Here, she is collaborating with Dr James Hewett, an associate professor who is also based in the Department of Biology at Syracuse University. Their work in this area stemmed from a finding reported in several studies that the supplementation of polyunsaturated fatty acids (PUFA) – which accumulate in the brain following seizure – can increase seizure threshold in some animal models of epilepsy. “Because nearly 30 per cent of individuals diagnosed with epilepsy do not respond to current anti-epileptic drugs, there is a pressing need to understand the cellular and molecular mechanisms that underlie seizure genesis so that new therapies can be developed,” Hewett emphasises. “Using our mice models, we found that seizure threshold is regulated by the PUFA-metabolising enzyme L-12/15 Lipoxygenase. It could be that PUFAs accumulate in the animals that lack L-12/15 Lipoxygenase and that this is what underlies this effect – but that remains to be experimentally determined.”

FASCINATING FINDINGS

- Hewett and her team discovered that IL-1β fuels the activity and expression of the cysteine-glutamate antiporter (system xc-1) in astrocytes.
- Under conditions of energy deprivation, system xc- induces excitotoxic neuronal cell death; however, the same transporter also drives the synthesis of the antioxidant molecule glutathione.
- Their findings suggest that in addition to its pathogenic role, IL-1β also upregulates processes that protect the brain against oxidative stress.

MOVING FORWARDS
To date, Hewett and her team have made important strides in carving a clearer knowledge about the molecular and biochemical processes that underlie pathophysiological processes in the brain. Looking ahead, it is possible that as a result of their findings the astrocyte will become a more viable therapeutic target to address ischaemic and hypoglycaemic injury than the inhibition of downstream neuronal effectors. However, in order to design the most effective therapies, the researchers are currently planning to focus on forging a deeper understanding of the timing and duration of the dual inflammatory-repair response mediated by IL-1β.