

## **Report on the ISN Symposium on Neurodegeneration and Proteostasis held in conjunction with the 2 nd Proteostasis & Disease Symposium 5 – 7 Nov 2014**

The 2 nd Proteostasis & Disease Symposium was held 5 – 7 November 2014 in the city of Wollongong, situated 80 km south of Sydney, Australia. Wollongong is a vibrant, multicultural city, situated on one of Australia's most picturesque coastlines. Regarded as Australia's 'most liveable' regional city, Wollongong combines a relaxed, coastal atmosphere with cosmopolitan dining, shopping and culture. Sitting beneath the spectacular Illawarra Escarpment, on the shores of the Pacific Ocean, the city is bordered by the Royal National Park to the north and Lake Illawarra to the south.

The 2014 Proteostasis & Disease Symposium was attended by ~90 researchers and postgraduate students, with 8 international invited speakers and 7 national invited speakers delivering outstanding lectures across a broad range of topics. A total of 49 lectures and 24 posters were presented over the 3-day meeting, with the oral presentations divided into the following sessions: Neurodegeneration and Proteostasis (Sponsored by ISN), Protein biogenesis and trafficking, Protein folding/misfolding, Protein modifications/ aggregation, Stress response and chaperones, Protein degradation, Proteostasis systems. Further details and speaker biographies are available (<http://proteostasis.com.au/2014/>).

The ISN Symposium on Neurodegeneration and Proteostasis was chaired by Professor Brett Garner, from the University of Wollongong, and all lectures were delivered to a full auditorium. The session comprised 4 outstanding presentations that are summarised below.

### **Professor Neil Cashman, University of British Columbia, Vancouver, Canada (Invited International Speaker): "Identification and therapeutic targeting of misfolding-specific epitopes"**

Professor Cashman (Brain Research Centre, University of British Columbia, Vancouver) described his work on the propagation of SOD1 misfolding in amyotrophic lateral sclerosis (ALS). He presented work that indicated that expression of ALS causing mutants of TDP-43 and FUS can kindle SOD1 misfolding and its subsequent cell to cell propagation. Professor Cashman's work centres on identifying neutralising antibodies that may quell the intercellular propagation of misfolding. He proposed that misfolding of one single protein can be the catalyst for proteostasis collapse and therapeutically neutralising the toxic or propagating species may be beneficial. In this light, he also presented work describing antibodies directed towards amyloid-beta species and to cancer related cell surface misfolded proteins.

### **Professor Lars Ittner, University of New South Wales, Sydney, Australia (Invited National Speaker): "Dendritic tau mediates neurodegeneration"**

Professor Ittner (University of New South Wales, Sydney) presented his work on the role of tau in mediating amyloid- $\beta$  toxicity on Alzheimer's disease mouse models. In particular, he showed how tau mediates the localization of Fyn kinase to the post-synapse that in turn sensitizes NMDA receptors to mediate amyloid- $\beta$  induced toxic hyperexcitation. He then moved on to show how this mechanism could be targeted with specific peptides to prevent memory deficits and death in Alzheimer's disease mouse models. Finally, he presented novel data on the role of tau in acute brain damage associated with stroke.

### **Professor Philip Beart, Florey Institute of Neuroscience & Mental Health, University of Melbourne, Australia (Invited National Speaker): "Autophagy good and bad: A genuine target for neuropathologies?"**

Professor Beart (Florey Institute of Neuroscience & Mental Health, Melbourne) gave a contemporary account of autophagy as a catabolic mechanism eliminating misfolded proteins, aggregates and damaged organelles. He placed his presentation in the context of the overall thrust of the meeting where protein load can influence eventual neuronal injury in

neuropathologies. Here recruitment of autophagy in a neuro-protective or neuro-toxic mode may depend upon “load” of cellular debris and toxic aggregates, and the effective injurious milieu. Energy availability may also be a determinant factor via the process of mitophagy. The clinically approved agent, rilmenidine, an autophagy activator, was found to provide cytoprotection in various cellular models of injury, but was ineffective in the SOD-1 model of Motoneuron disease. How autophagy may be beneficial or toxic is poorly understood and further insights are needed into this “switch”. This is a topic of growing contemporary interest as a “druggable” target with numerous teams internationally seeking to exploit its beneficial action in neurodegenerative conditions.

**Dr Mark Greenough, Florey Institute of Neuroscience and Mental Health, Parkville, Australia: “A novel role for presenilin in CTR1-mediated copper uptake”**

Dr Greenough focused on regulation of Cu uptake and Alzheimer’s disease. Presenilin (Florey Institute of Neuroscience & Mental Health, Melbourne) presented a (PS) is the catalytic component of  $\gamma$ -secretase, a multiprotein aspartyl protease that cleaves the amyloid precursor protein to release C-terminal amyloid beta ( $A\beta$ ) peptides. Dr Greenough and colleagues (C. Mawal, I. Volitakis, J. Camakaris, C. Opazo, A. Bush) have generated data demonstrating that PS interacts with the CTR1 (copper transporter 1) in cultured cells and primary mouse hippocampal neurons and the results are consistent for a role in the presentation of CTR1 at the cell surface, where it affects copper uptake/re-uptake in neurons. Dr Greenough hypothesized that mutations in PS that cause early-onset familial Alzheimer’s disease (FAD) may alter PS function and disrupt CTR1 mediated copper uptake. Studies to investigate whether this could exacerbate AD pathogenesis are currently being undertaken.

**ISN Symposium on Neurodegeneration and Proteostasis - Chair and Speakers**



(Left to Right: Prof Neil Cashman, Prof Phil Beart, Prof Brett Garner, Dr Mark Greenough, Prof Lars Ittner)