

Final Report - ISN Symposium on Neurodegeneration and Proteostasis 2017

a. Basic information (title of the Symposium and meeting, dates, organizer, venue, etc.)

The “ISN Symposium on Neurodegeneration and Proteostasis” was a highlight of the 3rd International Proteostasis and Disease Symposium that was held at The Novotel, Wollongong, Australia, from 20th to 22nd November 2017. The meeting was organized by the following committee members who are based at the University of Wollongong.

Assoc Prof Heath Ecroyd (Co-chair)
Senior Prof Mark Wilson (Co-chair)
Professor Brett Garner
Dr Lezanne Ooi
Dr Kara Perrow
Professor Marie Ranson
Dr Amy Wyatt
Associate Professor Justin Yerbury

b. Speakers

Michele Vendruscolo, University of Cambridge, UK (Invited)
Natura Myeku, Columbia University, USA (Invited)
Julie Atkin, Macquarie University, Australia (Invited)
Shu Yang S, Macquarie University, Australia (Selected from abstracts)
Mauricio Cabral-da-Silva MC, Wollongong University (Selected from abstracts)

c. A short description of the highlights of the symposium

This was the 3rd Neurodegeneration and Proteostasis Symposium held in Wollongong and was the largest so far. We had 110 registrants, including 8 from the UK, 7 from the USA, and 95 national researchers. The larger Proteostasis meeting was held over 3 days and featured 9 invited international speakers and 6 invited national speakers, including some of the most globally eminent researchers in this diverse field. There were a total of 46 oral presentations, 30 posters, and 10 additional talks in a dedicated student session. The ISN Symposium on Neurodegeneration and Proteostasis was held on the 22nd of November and was very well attended.

Dr Vendruscolo present his work on the metastable subproteome and its association with Alzheimer’s disease. Increasing evidence suggests that the formation of amyloid and tau deposits is associated with the dysregulation of highly expressed and aggregation-prone proteins, which make up a metastable subproteome. He identified specific components of the protein homeostasis system associated with metastable proteins by using a gene co-

expression analysis. The results reveal the importance of the protein trafficking and clearance mechanisms, including branches of the endosomal–lysosomal and ubiquitin–proteasome systems, in maintaining the homeostasis of the metastable subproteome associated with Alzheimer’s disease.

Dr Myeku presented her work on receptor-mediated proteasome activation as a means to stop trans-synaptic propagation of tauopathy. Her work showed that activation of synaptic proteolysis upon stimulation of a specific GPCR present on dendritic membranes, induces tau clearance restricted to post synaptic compartments and this improved cognitive performance in a mouse model. She proposed a new therapeutic strategy of GPCR (Gs-coupled receptor) - mediated degradation of pathological synaptic tau via pituitary adenylate cyclase-activating polypeptide (or other ligands). She also proposed the repurposing of GPCR-targeted drugs, which account for 27% of marketed drugs, for the treatment of tauopathy in Alzheimer’s disease.

Dr Atkin presented her work on therapeutic strategies based on proteostasis in Amyotrophic Lateral Sclerosis (ALS)/Motor Neuron Disease (MND). She identified eight misfolded ALS/MND proteins that inhibit ER-Golgi transport, implying that this is a common, upstream disease mechanism: mutant SOD1, TDP-43, FUS, Cyclin F, C9ORF72 dipeptide repeat proteins, hnRNPA1, hnRNPA2, and ubiquilin-2; and also misfolded, wildtype SOD1 and TDP-43, thus linking ER-Golgi transport to sporadic disease. She proposed that restoring ER-Golgi transport may be effective therapeutically. Her data showed that Rab1 can restore ER-Golgi transport and prevent ER stress, inclusion formation and apoptosis, in cells expressing ALS/MND proteins. She generated novel compounds, that enhance Rab1 activity and are protective in vitro and in vivo, that are now being developed by her as novel therapeutics in ALS/MND.

Dr Yang presented her work on proteostasis abnormalities in ALS patient skin fibroblasts. She provided data supporting the hypothesis that the ubiquitinproteasome system (UPS) plays an important role in MND pathogenesis, and examined whether UPS dysfunction could be detected in skin fibroblasts from ALS patients. Using immunofluorescence staining, UPS inhibition was shown to cause accumulation of ubiquitinated TDP-43 inclusions, a hallmark pathology of ALS, in ALS fibroblasts. A flow cytometry based UPS reporter assay-GFPu assay was used in these fibroblasts to investigate whether UPS function was inhibited. She reported significant accumulation of GFPu, indicating UPS dysfunction, in familial ALS patients with mutations in CCNF, TARDBP, UBQLN2 and C9orf72. She also found that an increase in GFPu accumulation of in CCNF patient fibroblasts collected at an earlier compared to later disease state, suggesting that UPS dysfunction may be used to monitor disease progression. This may prove useful for pathogenic studies and have short-term diagnostic and prognostic utility for this rapidly progressive disease.

Dr Cabral-da-Silva presented his work on the use of iPSC-derived microglia (iMG) as a tool for investigating Alzheimer’s disease. He developed a microglial differentiation protocol that was used to derive iMG from sporadic AD patients and healthy controls. Characterization of iMG revealed the upregulation of several microglia-related gene targets during progression of the protocol. SPI1 and IRF8, two of the main microglial lineage commitment genes, were upregulated by 10 days of differentiation. Further maturation upregulated a set of genes

regarded as the TGF- β 1 dependent molecular and functional signature in microglia (C1QA, GAS6, GPR34, MERTK, P2Y12 and PROS1). Microglial-specific genes TMEM119 and ITGAM were also detected. The cells produced by this protocol may be used for in vitro assessment of microglial function in order to identify a potential phenotype associated with AD.

d. Number of attending people

110

e. Travel subsidies for the speakers of the ISN symposium

Dr Myeku \$2000 AUD

Dr Vendruscolo \$2000 AUD

f. Budget; detailed ISN budget, how the ISN funds were utilized

Travel expenses – International speakers (Vendruscolo and Myeku)

\$2000 per person	\$4000
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Registrations fees – Invited speakers (Vendruscolo, Myeku and Atkin)

\$690 per person	\$2070
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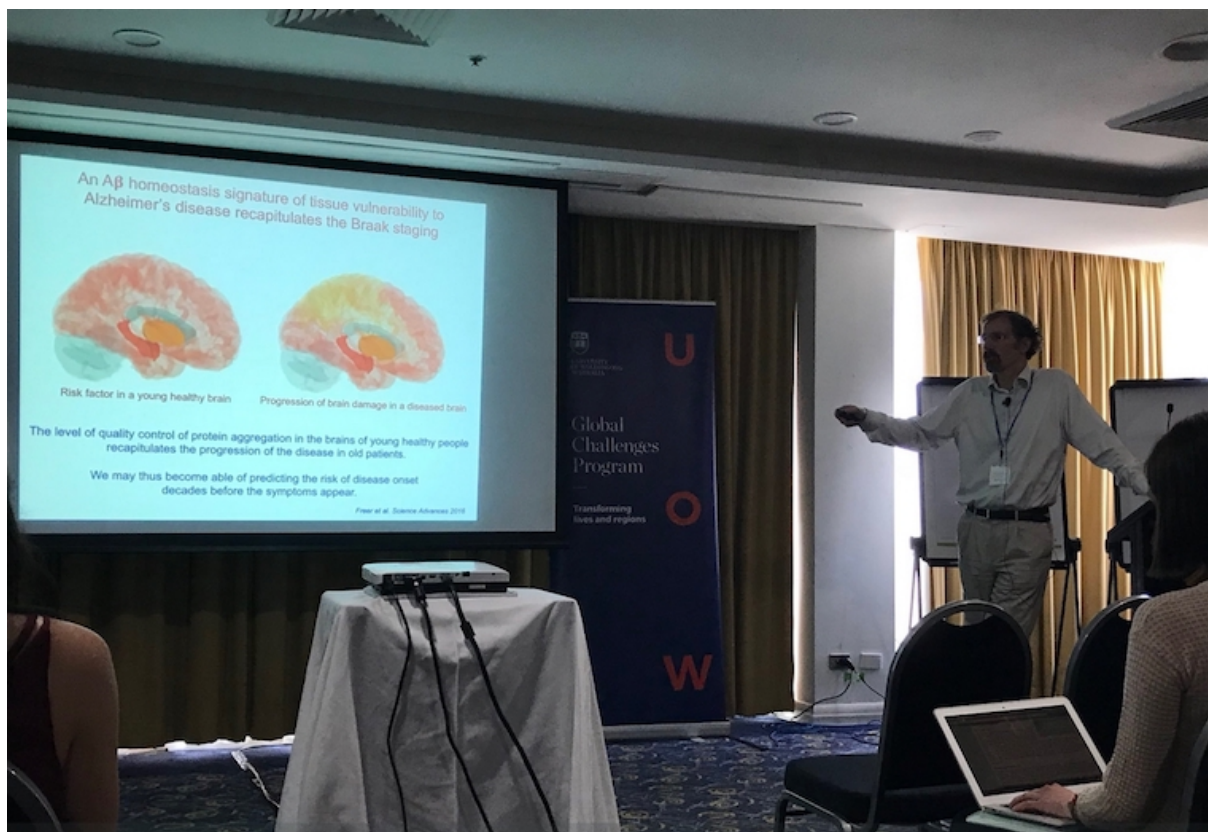
Taxi fare from Sydney Airport for Dr Vendruscolo	\$90
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Total \$6160 AUD

g. Photos



Dr Julie Atkin (ISN Symposium Invited Presenter)



Dr Michele Vendruscolo (ISN Symposium Invited Presenter)



Mark Wilson and Heath Eckroyd (conference chairs)

h. Comments of at least 3 attendants about the Symposium

Dr Simon Brown, Senior Research Fellow.

“The Neurodegeneration and Proteostasis Symposium that was held as part of the Proteostasis and Disease Symposium at Wollongong in Nov 2017 was an outstanding event. We got to hear presentations from leading researchers from the USA, UK and Australia and also hear from younger researchers who are also conducting cutting edge research. The talks spanned multiple neurodegenerative conditions including AD, ALS/MND, and a vast array of new methods and animal models were presented and discussed. The Symposium was well attended with over 100 delegates and the Chair ensured there was plenty of time for questions and discussion. This symposium size was ideal and encouraged lots of interactions and cross fertilisation of ideas from different disciplines. I am looking forward to the next Wollongong Neurodegeneration and Proteostasis Symposium!”

Ms Sonia Sanz-Munoz, PhD student. "The ISN Symposium on Neurodegeneration and Proteostasis Symposium held in Wollongong in November 2017 was a fantastic meeting. The symposium was really well organized and the presence of important international speakers together with an incredible number of local scientific talks made the 3 days of the Proteostasis and Disease Symposium a complete scientific gathering. Besides the high quality of the science, the fact that it is still a small meeting made it great for networking, which is always important specially for early career researchers and students."

Ms Claudia Keilkopf, PhD student “The ISN Symposium on Neurodegeneration and Proteostasis was a very well run meeting, all events went smoothly. The talks were very interesting showcasing leading research in the proteostasis field and the diversity of topics covered many aspects. From a student's perspective, the poster session gave a great opportunity to discuss our projects and to talk to the invited speakers.”

i. The budget used for each speaker must be specified separately

Dr Myeku, Airfare contribution from USA \$2000 AUD, conference registration \$690 AUD.

Dr Vendruscolo, Airfare contribution from UK \$2000 AUD, conference registration \$690 AUD. Airport transfers \$90.

Dr Atkin, conference registration \$690 AUD.