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TEMASEK LIFESCIENCES LABORATORY

22 March 2016 (Tuesday), 11am
The Auditorium (Level 1)

Hosted by: Dr Yu Fengwei

Roles of spastic paraplegia gene products in organising axonal endoplasmic reticulum in Drosophila

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I completed my Bachelor's degree at Cambridge University in 1981, and my PhD in the use of gene trapping in bacterial genetics at Trinity College Dublin in 1985. I was a postdoctoral fellow with Prof Walter Gehring in the University of Basel (1985-1988), and after 4-5 years as a Faculty member at Warwick University (UK), I have been a Faculty member of the Department of Genetics in Cambridge University since 1993, including 4 years as Head of Department from 2009-2013. My main interests are membrane traffic and organisation in neurons, mechanisms of neurodegeneration that are related to this, and development of genetic tools and community resources for these purposes. Major achievements include widely used tools including enhancer trapping, and targeted neuronal inactivation using tetanus toxin, characterisation of the roles of endocytic proteins and discovery of novel non-endocytic roles including T-tubule organisation, the discovery of roles in BMP signaling pathway for hereditary spastic paraplegia genes, and the pioneering of methods to study axonal endoplasmic reticulum. My current work focuses mainly on formation and roles of axonal ER, and I am also a co-PI on the community resource, Virtual Fly Brain.

The length of motor axons entails significant engineering for their formation and maintenance. Failures of this are seen in the Hereditary Spastic Paraplegias (HSPs), with lower limb weakness, and degeneration of longer upper motor axons. To date over 60 causative Spastic Paraplegia Genes (SPGs) are known. Several encode endoplasmic reticulum membrane proteins, with intramembrane hairpins that curve and model ER membrane. Two of these protein families, reticulons and REEPs, are together required for formation of most tubular ER in yeast. To test whether they are also required for formation or maintenance of axonal ER, we have developed markers in *Drosophila*, and mutants that lack members of these protein families. Our analyses suggest widespread if not ubiquitous occurrence of ER in axons, and we see a range of loss-of-function phenotypes, and partial redundancy of gene function. Mutant phenotypes include partial loss of ER from distal but not proximal axons, thus recapitulating the susceptibility of longer distal axons in the human diseases, and some loss of continuity of the ER network in axons. We have therefore established *Drosophila* axons as a system to assay organisation of axonal ER, and the roles of spastic paraplegia genes in this process. We propose an important role for ER continuity in axons, and models of pathology that may involve regional or long-range transmission of calcium signals in axons.

Recent Publications:

1. NC O'Sullivan, TR Jahn, E Reid, **CJ O'Kane*** (2012) Reticulon-like-1, the Drosophila orth-olog of the Hereditary Spastic Paraplegia gene reticulon 2, is required for organization of endoplasmic reticulum and of distal motor axons. Hum Mol Gen 21:3356-65
2. C Blackstone, **CJ O'Kane**, E Reid (2011) Hereditary spastic paraplegias: membrane traffic and the motor pathway. Nat Rev Neurosci 12:31-42
3. X Wang, RC Shaw, HTH Tsang, E Reid, **CJ O'Kane*** (2007) Drosophila spichthyin inhibits BMP signaling and regulates synaptic growth and axonal microtubules. Nature Neuroscience 10:177-85.