TEMS

Temasek External Monthly Seminar

TEMASEK LIFESCIENCES LABORATORY

ALL ARE WELCOME

31 October 2017 (Tues), 10.30am

The Auditorium (Level 1)

Hosted by: Dr Koh Tong Wey

Tackling Rare Disease in Flies: A Case for Parkinson Disease

Dr Hugo Bellen

Baylor College of Medicine, United States



Mutations in *PLA2G6*, a phospholipase, cause neurodegenerative disorders in human, including autosomal recessive Infantile Dystrophy and early onset Parkinsonism (PARK14). Phospholipases typically hydrolyze glycerol phospholipids. Here we show that loss of *iPLA2-VIA*, the fly homologue of *PLA2G6*, reduces lifespan, increases bang sensitivity and affects synaptic transmission. Surprisingly, loss of *iPLA2-VIA* does not affect the phospholipid composition of brain tissue but rather disturbs sphingolipid metabolism. The resulting increase in ceramides and sphingolipids impair the function of retromer and lysosomes. Reducing the levels of ceramides alleviates lysosome stress and suppresses neurodegenerative phenotypes. Similarly, enhancing the function of the retromer suppresses neurodegeneration. Our data indicate that loss of *iPLA2-VIA* disrupts sphingolipid metabolism and impairs retromer function via a negative feedback loop leading to the demise of neurons. I will discuss the implications for other forms of Parkinson's disease.

Hugo Bellen, DVM, PhD, Howard Hughes Investigator and Professor at Baylor College of Medicine, has made major contributions to our understanding of nervous system development, synaptic transmission, and neurodegeneration. His group uses flies to examine the function of human genes associated with neurodevelopmental and neurodegenerative phenotypes. His research demonstrates the benefits that emerge from studies in model organisms to improve diagnosis and human health.

Recent Publications:

1. Liu, L., MacKenzie KR, Putluri N, Maletic-Savatic, M. and **Bellen, H.J**. 2017. The glia-neuron lactate shuttle and elevated ROS promote lipid synthesis in neurons and lipid droplet accumulation in glia via APOE/D. *Cell Metabolism*, in press.
2. Nagarkar Jaiswal, S., Lee, P-T., Campbell, M.E., Chen, K., Anguiano-Zarate, S., Cantu Gutierrez, M., Busby, T., Lin, W-W., He, Y., Schulze, K.L., Booth, B.W., Evans-Holm, M., Venken, K.J.T., Levis, R.W., Spradling, A.C., Hoskins, R.A. and **Bellen, H.J.** 2015. A library of MiMICs allows tagging of genes and reversible spatial and temporal knockdown of proteins in Drosophila. *eLife* 4:e05338. PMID: 25824290; PMCID: PMC4379497.
3. Yoon, W.H., Sandoval, H., Nagarkar-Jaiswal, S., Jaiswal, M., Yamamoto, S., Haelterman, N.A., Putluri, N., Putluri, V., Sreekumar, A., Tos, T., Aksoy, A., Donti, T., Graham, B.H., Ohno, M., Nishi, E., Hunter, J., Muzny, D.M., Carmichael, J., Shen, J., Arboleda, V.A., Nelson, S.F., Wangler, M.F., Karaca, E., Lupski, J.R. and **Bellen, H.J.** 2017. Loss of Nardilysin, a mitochondrial co-chaperone for α-ketoglutarate dehydrogenase, promotes mTORC1 activation and neurodegeneration. *Neuron* 93: 115-131. PMID: 28017472; PMCID: PMC5242142.