NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

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Fri, 13 July 2018 | 2pm | DBS Conference Room 1

Hosted by A/P Christoph Winkler

Chondrolectin interacts with collagen 19a1 to stabilise synapses during motor axon development in zebrafish

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Chondrolectin (*chodl*) is a gene necessary for axon growth and is a suggested downstream target of *smn,* the causative gene in Spinal Muscular Atrophy (SMA). In mouse models, chondrolectin is one of the earliest dysregulated genes and in zebrafish, overexpression of full-length *chodl* partially rescues the phenotype of *smn* knockdown. These findings suggest *chodl* is a key gene in motor axon development and SMA pathology.

To characterise the role of *chodl* in motor axon development we generated a homozygously viable *chodl* mutant zebrafish. The mutants show transiently stalled motor axons, with 75% of axons stopped at the horizontal myoseptum (HM) choice point at 28 hours post fertilisation, compared to none in the control. Neuromuscular junction formation at the HM is impaired at this embryonic time point. Neuromuscular junction deficits persist until at least 3 days post fertilisation, leading to widespread reduction in synapses and thus the startle reaction of the mutant larvae is also deficient. We have determined that *chodl* exerts its function by binding extracellular Col19a1 with its C-type lectin domain, using genetic interactions, in vitro binding assays and *in vivo* rescue experiments. This suggests a novel mechanism of chondrolectin as a signalling molecule which stabilises the pre-synapse on the axon during development.

Utilising the UK zebrafish screening facility at the University of Edinburgh, we undertook a drug screen using the *chodl* phenotype. We found several hits (6/650) that improve axon length by at least 2-fold and are now following up their effect in SMA models. In summary, our results suggest a link between synaptic maturation and axon growth in a novel mechanism facilitated by *chodl.* Screening *chodl* mutants may indicate novel drugs that are relevant to SMA.

This work was supported by the MNDA, the SMA Trust and a BBSRC Alert Call.

Artwork by Ann Nee, DBS, NUS