London Worm Meeting

Date: 30 Apr, 2025
Time: 2-5 pm
Location: UCL, G08 Sir David Davies LT, Roberts Building
Registration link:
https://www.eventbrite.co.uk/e/london-worm-meeting-tickets-1321225784889?aff=oddtdtcreator

Agenda

André Brown – Brown lab, Imperial College London
Computational ethology for disease modelling and drug screening

Padraig Gleeson – Gleeson lab, University College London
The OpenWorm Project - towards a biologically constrained computational model of C. elegans

KangBo Ng - Goering group – Francis Crick Institute
Mitotic feedback oscillations balance sensitivity and stability in a cell polarity network

Coffee break

Henry Nvenankeng – O'Connor lab, University of Southampton
EAT-2, a novel drug target for the mitigation of parasitic nematode infections

Eva Sheardown – Ch'ng lab, King's College London
Brain to body communication: the interface between neurotransmitters and hormones in C. elegans

Sam Taylor – Labbadia lab, University College London
An ER-to-cytosolic stress response promotes proteostasis and reproductive health

Abstracts

André Brown – Brown lab, Imperial College London

Computational ethology for disease modelling and drug screening

A key bottleneck in some neuroscience experiments is behaviour quantification. We have used megapixel camera arrays to record all of the wells of 96-well plates with enough resolution for pose estimation. We use this approach to measure behavioural profiles of *C. elegans* in 10k conditions per day. Computational ethology at this scale opens new directions in disease modelling and drug screening. I will discuss our work using this approach to model dozens of genetic diseases, perform drug repurposing screens, and use genome-scale RNAi to identify phenotypes for genes without previously known roles in behaviour.

Padraig Gleeson – Gleeson lab, University College London

The OpenWorm Project - towards a biologically constrained computational model of C. elegans

The OpenWorm project (http://openworm.org) is a global, online collaboration of computational and experimental neuroscientists, software developers and interested volunteers with an ambitious long-term goal: creating a cell-by-cell computer model of the worm *C. elegans* which reproduces the behaviour of the real animal in as much detail as possible. The project takes a unique Open Science approach to development, and provides a community resource which consolidates our anatomical and physiological knowledge of the worm, allowing investigators to examine the mechanistic underpinnings of how behaviour is generated by a complete nervous system. I will provide an update on the overall roadmap of OpenWorm, and highlight a number of subprojects: development of biologically constrained models of worm locomotion, creation of a unified web resource for anatomical, functional and extrasynaptic connectomic datasets (https://openworm.org/ConnectomeToolbox) and creation of a Large Language Model (LLM) customised with curated information on worm anatomy and physiology.

KangBo Ng - Goering group – Francis Crick Institute

Mitotic feedback oscillations balance sensitivity and stability in a cell polarity network

During development, cells must balance their ability to sustain robust and durable changes in state in response to transient signals with their ability to remain sensitive to changes in signals over time. Lineage specification in the *C. elegans* embryo relies on a series of tightly choreographed asymmetric divisions in germ lineage blastomeres that rely on their polarization by stage-specific cues. Here we show that proper cue-dependent polarization of blastomeres relies on a CDK-1 entrained oscillation in feedback within the PAR cell polarity network. Blastomeres are born in a low feedback regime that promotes symmetry-breaking and proper orientation of molecular asymmetries in response to cues. Increased CDK-1 activity at mitotic entry shifts blastomeres to a high feedback regime that consolidates asymmetries into well-defined PAR domains that are needed to drive division asymmetry. Feedback then drops during anaphase, resetting the cycle. Critically, whereas high CDK-1 activity was required to maintain stable PAR protein localization during mitosis, disruption of the oscillation into the low CDK-1 state compromised both symmetry-breaking and cell contact-induced polarity reversal that is critical for the apposition of germ line and intestinal cell lineages and their subsequent internalisation at gastrulation. We propose that feedback

oscillations allow cells to sample distinct feedback regimes and thus optimise network behaviour in time - in this case switching between an early rheostat-like regime in which newly born cells sample and respond to their environment and a later, switch-like regime that promotes pattern stability and robust signalling to downstream pathways. We suggest that temporal oscillations may be a general mechanism for satisfying the dual requirements for sensitivity and robustness in developmental systems.

Henry Nvenankeng – O'Connor lab, University of Southampton

EAT-2, a novel drug target for the mitigation of parasitic nematode infections

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Nicotinic acetylcholine receptors (nAChRs) are fast acting ligand gated ion channels that have been widely studied in vertebrate and invertebrate organisms. In insects, they are among the most thoroughly studied receptors as they are important targets for several naturally occurring and synthetic compounds that exhibit potent insecticidal activities. Over the past two decades highly selective targets for naturally occurring and synthetic chemicals have been identified within this receptor class, for the effective control of insect pests in agriculture and veterinary medicine. EAT-2, a nAChR that regulates feeding behaviors in the free living nematode *Caenorhabditis elegans*[1] has characteristics that make it attractive as a novel druggable target for mitigating plant parasitic worms and other helminths. Its uniqueness among nAChR as they lack key vicinal cysteine residues that are essential for ligand binding, its dependence on EAT-18, an auxiliary protein with no known orthologs for functional expression, and a phylogeny that reveals conservation within the Nematoda suggest possibilities for it as a novel, selective pharmacophore. In plant parasitic nematodes (PPNs)pharmacological data are consistent with EAT-2 regulating stylet thrusting, the parasitic behavior required for root invasion, feeding and hatching of juveniles. Pharmacologically disrupting EAT-2 function could interrupt these behaviors and serve as a target to mitigate parasitic nematodes. Using *C. elegans* as a surrogate model animal in a bioassay that scored for drug effect on feeding behaviors, to screen for EAT-2 selective compounds, we have identified nicotine, mecamylamine and some other compounds as possible modulators of the receptor. Validating drug targets in whole organisms is somewhat challenging. However, in recombinant systems these targets can be expressed in non-native cells and tested for activity. We functionally expressed EAT-2 in *X. laevis* oocytes by co-injecting mRNA for EAT-2 and the auxiliary protein EAT-18d. Receptor function was confirmed by testing acetylcholine, the natural agonist of the receptor and then the compounds identified as modulators of the receptor. These compounds were identified as antagonists of the receptor. When tested on infective juveniles of the PPN *Globodera rostochiensis*, they inhibited stylet thrusting with varying potencies. This finding is significant because by inhibiting stylet thrusting in PPNs we may interrupt the hatching of infective juveniles, the subsequent invasion of host plants and potentially break parasitism.

Reference: McKay, J. P., Raizen, D. M., Gottschalk, A., Schafer, W. R., & Avery, L. (2004). eat-2 and eat-18 Are Required for Nicotinic Neurotransmission in the Caenorhabditis elegans Pharynx. *Genetics*, *166*(1), 161–169. https://doi.org/10.1534/GENETICS.166.1.161

Eva Sheardown – Ch'ng lab, King's College London

Brain to body communication: the interface between neurotransmitters and hormones in C. elegans

Neurotransmitters and hormones control physiological processes in the body, however how these two systems interact is not well understood. Using *C. elegans* we are trying to underpin the circuitry linking the two signalling pathways to give insight into neural control of physiological functions.

Sam Taylor – Labbadia lab, University College London

An ER-to-cytosolic stress response promotes proteostasis and reproductive health

In order to preserve healthy tissue function, eukaryotic cells must efficiently regulate protein homeostasis (proteostasis) within different membrane bound organelles. To this end, cells utilise specific stress response pathways such as the Heat Shock Response and Unfolded Protein Response to rapidly neutralise the threat of misfolded proteins in different compartments. However, how cells integrate these different pathways to achieve global proteostasis and long-term tissue health remains poorly understood. Here, we report a new intercompartmental stress response from the ER to the cytosol in the nematode worm *C. elegans* that is crucial for maintaining cytosolic proteostasis and reproductive health. Loss of the key ER HSP70 chaperone HSP-3 (a worm ortholog of GRP78/BiP) elicits an HSF-1/DAF-16-dependent transcriptional response that results in a robust increase in cytosolic HSP70 and sHSP family chaperones, lipid metabolism enzymes, detoxification pathways, and proteasomal subunits. We find activating this response greatly suppresses intestinal polyQ aggregation and improves organismal robustness without increasing lifespan. Furthermore, an inability to activate this response results in a profound reduction in fecundity under conditions of ER stress. Our findings expand our understanding of how cells achieve concerted regulation of different stress response pathways to preserve tissue-health. Future work to better understand the precise regulatory mechanisms of this pathway may highlight new avenues to prolong cell and tissue health by ameliorating suboptimal proteome states, which are pervasive in disease and ageing settings.