London Worm Meeting

Date: 6th Nov 2025
Time: 2-5 pm

Location: Sir Alexander Fleming Building
SAFB 120 - Seminar Room
https://maps.app.goo.gl/NmJmnzEtPPJt8cp17

Agenda

2.00-2.25 **Eva Sheardown**, King's College London
Neural regulation of insulin-like hormones in brain-body communication

2.25-2.50 **Carla Lloret-Fernández**, University College London
Cell cycle progression gates sex-specific glia-to-neuron conversion

2.50-3.25 **Lightning talks**

3.25-4.00 **Coffee break**

4.00-4.25 **Iris Hardege**, University of Cambridge
Identification and characterisation of novel nematode neurotransmitter receptors

4.25-4.50 **Luke Slade**, University of Oxford
Adult depletion of the Integrator complex extends C. elegans lifespan and healthspan via defective pre-mRNA processing

4.50-6.00 **Drinks & snacks**

Abstracts

Neural regulation of insulin-like hormones in brain-body communication

Eva Sheardown[1]
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Neurotransmitters and hormones are both found in the brain and control physiological processes in the body. How these two systems interact is not well understood. Discovering the circuitry linking the two will give insight into neural control of physiological functions. In addition, the pattern of these connections can reveal their decision-making functions. Our main hypothesis is that neurotransmitters modulate expression of hormones in the nervous system, and this pattern of regulatory connections produces information processing functions that link neural activity to bodily physiology. To understand the genetic mechanism underlying neuroendocrine control of growth and development, we investigate the regulation of insulin-like peptides (ILPs) in sensory neurons. These ILPs regulate a developmental switch between growth and a specialised larval arrest called dauer (1). The key ILPs regulating this developmental decision are *ins-4, ins-6,* and *daf-28* (2). These ILPs mutually compensate for the loss of individual signals, thereby producing redundancy, where loss of all 3 ILPs is required for a high rate of dauer entry (3). Although much is known about these ILPs, the neural signals regulating them are less well understood. To investigate this, we have tested loss-of-function mutants in genes in neurotransmitter pathways for altered rates of dauer arrest. We implicated several neurotransmitters in regulation of dauer entry. Future experiments using Hybridisation Chain Reaction 3.0 to visualise single transcripts and cell-specific rescue will identify how these neurotransmitters regulate ILPs to uncover the pattern of regulatory connections linking neural activity to body physiology.

1) Zhang, M. G. et al. Development (Cambridge) 149, (2022)
2) Fernandes de Abreu, D. A. et al. PLoS Genet 10, 17–19 (2014)
3) Hung, W. L. et al. Development (Cambridge) 141, 1767–1779 (2014)

Cell cycle progression gates sex-specific glia-to-neuron conversion

C Lloret-Fernández[1]*, M Sammut[1], S Rigg[1], J Pérez-Martín[2], R Hakmi[1], S He[1], J Gehler[1], SPR Gilbert[1], M van der Lans[1], E Dao[1], T Mistry[1], RJ Poole[1]
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Quiescent glia cells act as neural progenitors across the animal kingdom. How their cell cycle re-entry is precisely co-ordinated with their asymmetric cell fate decision to generate neurons is not clear. Using *Caenorhabditis elegans*, we uncover a multi-step sexually dimorphic cell cycle regulatory programme that coordinates the cell division and asymmetric cell fate decision of a differentiated glia neural precursor.

We have previously shown that the AMso glial cells act as sex-specific neural progenitors. Here, we identify the conserved negative cell cycle regulator and APC/C activator FZR-1/CDH1 as a key gatekeeper of the sexually dimorphic division, inhibiting S-phase entry and cell cycle progression through the degradation of CYE-1/Cyclin E and CYA-1/Cyclin A. Upon cell cycle re-entry the AMso undergoes an asymmetric division and the posterior daughter differentiates into the MCM neuron. We find that progression through the cell cycle but not mitosis is required for neuronal differentiation, suggesting a tight co-ordination between the cell cycle and developmental regulators. We demonstrate that the asymmetric cell fate decision is orchestrated by the interaction of the kinase *pig-1/MELK* with the Wnt-asymmetry pathway and the proneural bHLH transcription factors *hlh-2/Daughterless* and *hlh-14/Ascl1*. We find that the cell cycle gates the expression of these developmental regulators in two different ways. Firstly, *fzr-1* regulates the sexually dimorphic expression of *pig-1*, Wnt-asymmetry pathway components and *hlh-2* in the AMso, independently of its role in S-phase entry. Secondly, we show that the asymmetric expression of *hlh-14* is dependent on S-phase entry and requires the CMG-component *psf-2* but not the Wnt-asymmetry pathway. Lastly, we demonstrate that the conserved cyclin-dependent kinase *cdk-1/Cdk1* additionally regulates the asymmetric cell fate decision at the G2-M transition, acting in parallel to both the proneural genes and the Wnt-asymmetry pathway.

Altogether, our findings uncover a tightly integrated programme where discrete cell cycle stages act as molecular checkpoints that license neuronal fate. This work highlights a previously unrecognised role of consecutive cell cycle regulators acting as temporal and sex-specific gatekeepers of glia-to-neuron cell fate conversions.

Identification and Characterisation of Novel Nematode Neurotransmitter Receptors

Iris Hardege[1]
[1]Department of Zoology, University of Cambridge

Ligand-gated ion channels (LGICs) play important roles in synaptic communication and in the regulation of behaviour. The pentameric cys-loop superfamily of LGICs (pLGICs), which contains mammalian nAChRs and GABA receptors, has undergone vast gene expansion in nematodes and includes channels gated by classical and non-classical neurotransmitters, including monoamines. This diversity in nematode receptors has long been harnessed for anti-parasitic applications including the compounds levamisole and ivermectin. However, until recently the majority of genes encoding pLGICs in the nematode model organism *C. elegans* remained uncharacterised.

Using Two-Electrode Voltage Clamp (TEVC) recordings in *Xenopus* oocytes we have undertaken several deorpahnisation studies of uncharacterised *C. elegans* pLGICs. In this way, we identified ligands for several novel channels, ranging from cholinergic to monoamine-gated channels which are either excitatory or inhibitory, including excitatory and inhibitory channels gated by the same neurotransmitter. Interestingly we also found that excitatory and inhibitory receptors gated by the same neurotransmitter are frequently expressed within the same neurons. We are now studying the distribution of these channels across the *C. elegans* nervous system, as well as their importance in behaviour, to understand how an anatomically small nervous system harnesses this level of receptor complexity.

Adult depletion of the Integrator complex extends *C. elegans* lifespan and healthspan via defective pre-mRNA processing

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Tight regulation of transcription is integral to development of multicellular organisms. Multiple complexes exist that assist in regulation of the core transcription complex, and many of these are essential for cell and organismal viability. One such complex is Integrator, which was originally discovered due to its role in production of small non-coding RNAs, but subsequently discovered to have additional roles in regulating protein-coding gene transcription. Loss of integrator activity blocks development in many organisms including *C. elegans*. However, what role integrator plays in ageing is unknown. We used RNAi to knock down integrator subunits in adult worms. Surprisingly, silencing of the catalytic subunit *ints-11* led to extension of lifespan and healthspan. Using tissue-specific RNAi, we showed that knock-down of *ints-11* activity in the somatic gonad and germline had the strongest effect on lifespan, implying that *ints-11* function in these tissues in adult worms shortens lifespan. By examining the transcriptome and proteome of *ints-11* knockdown animals, we uncovered a possible mechanism for lifespan extension, due to defective mitochondrial function resulting from failure of splice-leader transcription in the absence of integrator function. Impaired mitochondrial function may extend lifespan through stimulation of small non-coding RNAs. Indeed, *ints-11* knockdown did not extend lifespan in animals lacking the small RNA biogenesis factor *mut-16*, implying that *ints-11* knockdown requires small non-coding RNAs to result in lifespan extension. Taken together, our results uncover a striking example of how molecular processes essential to development can have negative effects on the ageing process, and demonstrate a new link between transcriptional regulation and small RNA mediated signalling mediated via mitochondrial dysfunction.

Abstracts Lightning talks

RNAi screen of *C. elegans* nuclear hormone receptors in search for novel anthelmintic targets

Agnieszka Carvalho

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Nuclear hormone receptors (NHRs) are ligand-responsive transcription factors which regulate reproduction, development and metabolism. Recently, nematode NHRs were proposed as putative targets of novel anthelmintic agents addressing a growing problem of multi-drug resistance in parasitic nematodes. In this study we use model nematode *Caenorhabditis elegans* to test this hypothesis and investigate developmental and metabolic function of nematode NHRs. In screen of 176 *C. elegans* NHRs RNAi performed on the background of N2(WT) and *sbp-1(ep79)* nematodes we found 25 NHRs that modulate *C. elegans* development. The two most severe phenotypes were observed in *nhr-61* and *nhr-56* RNAi nematodes. We found that silencing of *nhr-61* induced severe developmental delay in N2(WT) nematodes and further exacerbated *sbp-1(ep79)* developmental impairment. Furthermore, we observed that *nhr-61* RNAi significantly reduced *sbp-1* and *acdh-1* promoters' activity, and reduced FAT-7 expression levels indicating that NHR-61 modulate expression of genes within metabolic pathways. We also observed that silencing of *nhr-56* exacerbated *sbp-1(ep79)* developmental delay but had no effect on development of N2(WT) *C. elegans*. Knockdown of *nhr-56* resulted in significant reduction of *sbp-1* promoter activity indicating that NHR-56 may regulate development within SBP-1 pathway. Additionally, we observed an uncoordinated phenotype in N2; *nhr-56* RNAi nematodes and noted significant reduction in crawling and swimming speed. Homology search identified NHR-56 and NHR-61 as *Caenorhabditis* spp.-specific NHRs indicating their regulatory function is crucial for development and locomotory fitness of free-living nematodes. Overall, we found no evidence that single NHRs can constitute an efficacious target for novel anthelmintic agents.

Elucidating Novel Signalling Components Through Partial Suppression of the Oomycete Recognition Response in *C. elegans*

Domenica Ippolito and Michalis Barkoulas

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Our lab has recently identified oomycetes as natural pathogens of *Caenorhabditis elegans*, and we have employed these novel pathosystems to investigate the mechanisms by which nematodes detect such pathogens and subsequently activate a protective transcriptional program termed the oomycete recognition response (ORR). A defining feature of the ORR is the induction of chitinase-like (*chil*) genes, including *chil-27*, predominantly within the epidermis.

We have utilized the induction of *chil-27p::GFP* following exposure to a harmless pathogen extract—which elicits the immune response without causing infection—as a proxy for pathogen recognition. This approach facilitated a series of forward genetic screens, enabling the identification of components of the pathogen recognition machinery operating within neurons, the intestine, and the epidermis, thereby underscoring the importance of inter-tissue communication in orchestrating the immune response upon infection threat. Whereas previous investigations have largely focused on mutants exhibiting a complete abrogation of *chil-27* induction upon exposure to the pathogen extract, we have also begun to characterize mutants displaying only partial attenuation of *chil-27* expression. These partially unresponsive mutants are challenging to map using the classical CB4856 mapping strain, as it partially modifies the phenotype. Nonetheless, they offer a unique opportunity to dissect potentially redundant and parallel contributions of molecular effectors, signalling pathways, or sensory tissues involved in pathogen recognition.

One of our recent screens identified a role for *sid-3*, a gene implicated in systemic RNA interference and encoding a non-receptor tyrosine kinase of the activated Cdc42-associated kinase (Ack) family, as well as for *usp-4*, the ortholog of human Ubiquitin-specific Peptidase 4. Here, we present the characterization of these newly identified regulators, focusing on their tissue-specific functions and link to the known signalling network. Although our findings suggest that the RNAi machinery is not involved in oomycete recognition, they point instead to the involvement of endosomal and proteasomal pathways.

Elucidating the molecular machinery governing ORR induction will deepen our understanding of pathogen recognition mechanisms in *C. elegans* and can provide valuable insights into oomycete recognition across diverse animal species.

Dissecting the Negative Engram of Aversive Memory in *C. elegans*

Hiba Daghar

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The nematode *Caenorhabditis elegans* exhibits diverse forms of learning and memory that, much like in the mammalian brain, are encoded within distributed neural networks rather than a specialized learning centre. Recent work from our lab has shown that when *C. elegans* is trained to associate an odour with both a reward and a punishment, two distinct engrams are formed, yet only one is behaviourally expressed. We hypothesize that specific neurons within each engram govern the behavioural expression of memory. Specifically, for expression of repulsion after aversive learning, we have shown that the circuit requires neuromodulation by the neuropeptides PDF-1 and 2. To identify the neurones driving repulsion, we generated a conditional knockout allele of the neuropeptide receptor *pdfr-1* by inserting LoxP sites into its locus using CRISPR/Cas9 genome editing. We are crossing the *pdfr-1*-LoxP line with Cre-driver strains that express recombinase in defined neuronal populations, enabling targeted dissection of the negative engram network. Here, we present preliminary results comparing our conditional *pdfr-1* mutants with the existing *pdfr-1* null allele, as well as with pan-neuronal and *odr-2*-specific knockout lines.

State-Dependant Sexual-Signalling in *Prisionchus exspectatus*

Khan Taufiq

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Pheromonal communication represents one of the most ancient yet least understood forms of biological signalling. To understand the complexities of this chemical language, nematodes have emerged as powerful model organisms. However, most commonly studied nematode species are androdioecious, comprising males and hermaphrodites, which limits our understanding of male–female pheromonal interactions. To address this gap, we employed the dioecious species *Pristionchus exspectatus* to investigate state-dependent variation in pheromone-mediated behaviour. We hypothesised that female attractiveness is influenced by physiological and environmental conditions, specifically starvation, reproductive status, and age. To test this, we performed chemotaxis assays under a range of controlled conditions. Our results indicate that optimal female attractiveness occurs in young, well-fed, and virgin individuals, suggesting that pheromonal signalling in *P. exspectatus* is finely tuned to reproductive state and energy balance.

Exploring the Potential Role of the CMG Complex and S-phase Gene Expression in an Epithelial-to-neuron Transdifferentiation

Matan-Elle Cohen

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Transdifferentiation, the conversion of one differentiated cell type into another, is a fundamental biological process for development and regeneration. What the core mechanisms are, and whether they are shared or distinct between transdifferentiations occurring with (indirect) or without (direct) cell division, remains unclear. Preliminary evidence from the Poole Lab points to the CMG helicase complex involvement in both processes. Importantly, the lab also observed that direct transdifferentiation can occur concomitantly with S-phase marker expression in the absence of DNA replication; a ‘pseudo S-phase’.

In this study, I investigated the role of the CMG component psf-2/GINS and the presence of a ‘pseudo S-phase’ in the sexually dimorphic epithelial-to-neuronal Y-to-PDA switch in *C. elegans*. This model allows for a unique comparison of direct (hermaphrodite) and indirect (male) transdifferentiation mechanisms within the same lineage. I assessed psf-2 depletion effect on neuronal identity with a temperature-sensitive allele and analysed S-phase gene expression with fluorescent reporters. I also generated novel CRISPR-engineered psf-2 strains for future enhanced time-resolved depletion and expression analysis studies.

I showed that *psf-2* is required for the indirect male transdifferentiation and production of the PDA neuron. Conversely, the direct hermaphrodite switch neither requires *psf-2* nor undergoes a ‘pseudo S-phase’, indicating that distinct transdifferentiation mechanisms can exist within one lineage. Surprisingly, the non-dividing K' rectal cell also expressed S-phase markers, hinting at a broader role for this phenomenon in cellular plasticity. By highlighting *psf-2* and ‘pseudo S-phase’ as key plasticity components, this study provides new insights with potential applications in regenerative medicine.

Modelling Novel Dopamine Transporter Mutations *in C. elegans*

Max Cadogan

University of Reading, UK

Dopamine Transporter Deficiency Syndrome (DTDS) is an extremely rare disorder, with only fifty documented cases. This disorder presents as an infantile parkinsonism and is caused by autosomal recessive mutations in slc6a3, encoding the dopamine transporter (DAT), which mediates the reuptake of dopamine from the synaptic cleft. Such mutations cause aberrant post-translational processing of the protein, resulting in retention in the endoplasmic reticulum (ER) and a lack of cell surface presentation, and reduced DAT activity, preventing the efficient synaptic clearance of dopamine. Recently, seven novel DTDS-associated allelic variants have been identified in infants presenting with parkinsonism symptoms. We have generated *C. elegans* models for each of these variants via CRISPR-Cas9 engineering in the *C. elegans* orthologue, *dat-1*. We have harnessed *C. elegans* behaviours under dopaminergic control, including the basal slowing response (BSR) and swimming-induced paralysis (SWIP), to elucidate the in vivo impact of these variants. We find that *C. elegans* carrying the majority of these variants behave similarly to *dat-1*deletion worms, exhibiting a strong SWIP phenotype without a defect in the BSR, indicating dysfunctional DAT-1 activity. However, two of these novel variants do not exhibit a strong SWIP phenotype, indicating that these mutants may have functioning DAT-1 protein. These variants are, however, defective in the BSR, indicating that these mutations may cause disease via different molecular mechanisms. Further investigation has indicated that disrupted dopamine biosynthesis may contribute to the molecular pathology of some of these mutations, encouraging us to examine the expression of genes regulating dopamine synthesis, degradation and regulation.