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<th>Supervisor</th>
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<th>Rotation Project Description</th>
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<td>Professor Julie Ahringer</td>
<td>Gurdon Institute</td>
<td><strong>The regulation and roles of chromatin organization in development</strong>&lt;br&gt;The structural organization of the genome is functionally important for the regulation of gene expression and other genomic processes. Chromatin regions with different activities have preferential locations in the nucleus and diverse architectural features have been described, such as contact between cis-regulatory elements, self-interacting topologically associated domains (TADs), and a “compartmentalized” structure in which active and inactive chromatin regions are segregated and interact like with like. Broad domains of particular histone modifications are also prevalent and may help determine spatial structure because they are retained through mitosis whereas chromatin interaction domains are not.&lt;br&gt;Despite these advances, we know relatively little about how these structural features form and modulate genome function or how chromatin is regulated in cell-type specific manner. We use the power of functional genetics and genomics in <em>C. elegans</em> to address these questions, combining the strengths of model organism genetics with genome-wide chromatin phenotyping and FACS sorting for cell-type specific assays. We combine wet-lab and computational approaches to a range of problems including cell-type regulation of chromatin in development, the formation and functions of heterochromatin, and the regulation of chromatin domains and their relationship with higher order structure.&lt;br&gt;A possible rotation project would be:&lt;br&gt;Constitutive heterochromatin is a fundamental component of the genome that is essential for safeguarding and regulating genome functions. It comprises regions that are more compacted, repeat rich, and transcriptionally inert. We recently characterized a network of <em>C. elegans</em> heterochromatin proteins that collaborates with small RNA pathways to ensure transposon repression, DNA repair, fertility, and growth (1). Interestingly, we discovered that the tumor suppressor p53 and DNA repair pathways mediate the slow growth defect of heterochromatin mutants, linking heterochromatin with genes involved in tumorigenesis. This project will further investigate the nature of the growth impairment induced by heterochromatin dysfunction by testing for interactions with candidates such as homologues of the myc oncogene.&lt;br&gt;(1) McMurchy AN, Stempor P, Gaarenstroom T, Wysolmerski B, Dong Y, Aussianikava D, et al. (2017) A team of heterochromatin factors collaborates with small RNA pathways to combat repetitive elements and germline stress. eLife, 6:7931.</td>
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<td>Professor Michael Akam</td>
<td>Zoology</td>
<td><strong>This lab is not available for a PhD place</strong>&lt;br&gt;<strong>Mechanisms of segmentation and patterning in short germ arthropods</strong>&lt;br&gt;Although my lab is not available for a Ph. D. project, I would be happy to discuss a range of rotation projects in the general area of arthropod axial patterning and segmentation. One possible topic would be to use multiplex hybridisation chain reaction to study early axial patterning in the centipede embryo.</td>
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Electroreception, i.e., the detection of weak electric fields in water (primarily used for detecting prey/predators), is phylogenetically widespread within vertebrates but was lost in the lineage leading to neopterygian fishes - gars, bowfin and teleosts. However, electroreception was originally discovered in 'weakly electric' teleosts, which use modified muscle/nerves as ‘electric organs’ to generate weak electric fields. These are the mormyriforms (mormyrids plus gymnarchids) and the unrelated knifefishes (which include the electric eel, a ‘strongly electric’ fish). Both groups have ‘ampullary organs’ that detect low-frequency environmental electric fields (e.g. those around other animals), and 'tuberous organs' that detect high-frequency electric organ discharges (used for electrolocation, communication, etc).

The sister groups of both weakly electric teleost fish groups have ampullary electroreceptors (e.g. catfishes, sister-group to the knifefishes), but tuberous electroreceptors are unique to weakly electric teleosts. The independent evolution of ampullary and tuberous electroreceptors at least twice within teleosts (see Baker et al., 2013, *J. Exp. Biol.* 216: 2515-22) is a striking example of the convergent evolution of novel cell types, most plausibly from the mechanosensory hair cells (closely resembling the vestibular hair cells of the inner ear) of 'neuromasts': tiny sense organs distributed in lines over the head and trunk that detect local water flow. We and others showed that electroreceptors in all non-teleost jawed vertebrates are also lateral line placode-derived (see Baker et al., 2013, *J. Exp. Biol.* 216: 2515-22) and share close developmental, physiological and evolutionary links with hair cells (Modrell et al., 2017, *eLife* 6, e24197). The hypothesis that teleost electroreceptors independently evolved from neuromast hair cells remains untested.

We have preliminary data on ampullary organ development in a catfish (sister-group to the weakly electric knifefishes), including expression of candidate genes identified via differential RNA-seq in a knifefish (collaboration with Harold Zakon, UT Austin, USA), supporting the hypothesis that ampullary electroreceptors evolved from hair cells in the common ancestor of catfishes and knifefishes.

The rotation project aims to characterise electrosensory organ development at the molecular level for the first time in a mormyrid (unrelated to catfishes and knifefishes), by cloning candidate genes and validating their expression using *in situ* hybridisation at a range of stages, followed by vibratome and/or cryosectioning. (Mormyrid cDNA and fixed embryos are available in the lab.) In the longer-term, electrosensory organ development would be studied in both mormyrid and knifefish embryos, including fate-mapping of lateral line placodes, differential RNA-seq analysis to discover molecular differences and commonalities between ampullary organs, tuberous organs and neuromasts (both within species and across the different weakly electric teleost groups), plus analysis of gene function by CRISPR/Cas9, in collaboration with labs with breeding colonies.

Overall, this work will shed light on the molecular pathways underpinning the development and convergent evolution of teleost electrosensory organs, i.e., the mechanisms underlying sensory hair cell diversification in both development and evolution.
Axis elongation is a key process in body plan formation. In vertebrates, this developmental process is essential for the diversification of axial structures. These include externally apparent structures like fins, limbs, wings and tails, which are known defining features of particular groups of vertebrates. This implies that different modes of axial elongation are inherently linked to the evolutionary diversification of vertebrate forms, although the underlying mechanisms remain unknown.

To shed light on this question, our laboratory investigates the molecular and cellular dynamics of axis elongation in the most basal chordate available for study, the invertebrate chordate amphioxus. We have found that even when amphioxus are devoid of axial specialisations, they elongate in a similar way to vertebrates and produce similar cell types that might cross talk in a similar way. We focus in understanding the birth of these cells in their developmental context, their behaviours, their cell fate choices and ultimately their molecular cell identity via single cell RNA-sequencing. We currently focus on two areas of the embryo:

**BRAIN**: Brain and spinal cord seem to be functionally and structurally a continuum. However, some preliminary results in the lab suggest that this is the end product of fusing two parallel developmental programs: anterior CNS and posterior CNS.

**First Possible Rotation Project – Dual Origin Of The Chordate Central Nervous System**: would be to determine the anterior-posterior limits of these two contiguous developmental units. This can be done by *in situ* hybridisation with specific neuronal markers at the specific time point when we see the separation of these two modules. Depending on the availability of live embryos, this approach will be combined with the use of small-molecule inhibitors to test the implication of specific signalling pathways on the specification of these boundaries *in vivo*. This can be followed up as a PhD project adding on full characterisation of mutant and wild type phenotypes, where relative neuronal populations will be quantified and molecularly defined via single-cell RNA-seq.

**TAILBUD**: The recent discovery of neuromesodermal progenitors (NMPs) in different vertebrates has revealed the cell repertoire of the tailbud to be more complex than previously thought and to include a subset of bipotent progenitor cells able to give rise to mesodermal and neuronal precursors. Our current research in the lab suggests that this could be also the case in the tailbud of amphioxus. We have recently found that Notch signaling influences the allocation of progenitor cells between nervous system and axial mesoderm.

**Second Possible Rotation Project – Cell Fate Decisions In The Amphioxus Tailbud**: would be to investigate the cross talk between Notch and Nodal or Notch and Wnt in the allocation of these presumptive neuromesodermal progenitor cells in the amphioxus tailbud. To this aim embryos will be incubated with small-molecule inhibitors and phenotypes will be scored, as it is usual practice in the lab, with structural markers and via *in situ* hybridization. This project can be followed up as a PhD project adding on fine-tuning of the treatments and further characterization of the distinct phenotypes, in order to understand the molecular and cellular dynamics of cell fate decisions within the amphioxus tailbud.
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**Zoology**

We investigate the relation between neuronal circuits and behaviour with an emphasis on the diversification of circuits and the role of genes in specifying different neuronal networks and their assembly during development. We use state of the art *Drosophila* neurogenetics ranging from molecular genetics (CRISPR/cas9), to neuronal circuitry morphology (confocal microscopy) and function (calcium imaging and thermo/opto-genetics) to behaviour (FIM- Frustrated total internal reflection Imaging Method) to understand how Hox genes orchestrate the diversification of motor circuits during nervous system development.

**Project 1) Diversification of neuronal networks underlying region specific behaviours.**

All animals perform several innate behaviours, like breathing, feeding, walking. The neuronal circuits controlling these patterns of movement are located along the nervous system and their location coincides with the muscles and effectors on which they act. We are investigating how these different circuits diversify from an identical set of neuronal stem cells, which is repeated in each segment of the developing nervous system of the fruit fly. The project focuses on the role played by the Hox genes, which are conserved known regulators of cellular identity along the body. The project aims to understand how the Hox genes control the morphology and connectivity of segment specific neurons, and how this influences their activity and ultimately behaviour.

**Project 2) Development of neuronal connectivity that integrates different behaviours.**

The different behaviours performed by an animal need to be properly integrated between each other to produce a meaningful output. In *Drosophila*, for example, the movements of crawling have to be integrated with the movements of feeding. Long and short range intersegmental projections face the challenge of traversing generic Hox domains (which regulate cellular identity along the body). What is the regional identity of such cells? Can they grow out of their Hox domain expressing the local Hox code or do they need to abandon their regional identity to be able to reach another Hox domain? Do certain neurons that connect distant circuits, from the abdomen to the thorax for example, express a combined Hox code from both regions (e.g. Ubx + AbdB)? We know nothing about the set of principles that governs the intersegmental connectivity in any system. This is what we are investigating taking advantage of neurons with intersegmental projections.

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**Gurdon Institute**

**Time to wake up: regulation of stem cell quiescence and proliferation**

Stem cell populations in tissues as varied as blood, gut, and brain, spend much of their time in a mitotically dormant, quiescent, state. A key point of regulation is the decision between quiescence and proliferation. The ability to reactivate neural stem cells *in situ* raises the prospect of potential future therapies for brain repair after damage or neurodegenerative disease. Understanding the molecular basis for stem cell reactivation is an essential first step in this quest.

In *Drosophila*, quiescent neural stem cells are easily identifiable and amenable to genetic manipulation, making them a powerful model with which to study the transition between quiescence and proliferation. These stem cells exit quiescence in response to a nutrition-dependent signal from the fat body, a tissue that plays a key role in the regulation of metabolism and growth. My lab...
combines cutting edge genetic and molecular approaches with advanced imaging techniques to study the reactivation of Drosophila neural stem cells in vivo. This enables us to deduce the sequence of events from the level of the organism, to the tissue, the cell, and finally the genome.

Rotation projects include:

1) How do environmental signals influence neural stem cell behaviour? What are these signals and how are they received by the stem cell niche and transmitted to neural stem cells?

2) What are the transcriptional and epigenetic changes in neural stem cells in the transition from quiescence to proliferation?

3) What role do non-coding RNAs play in controlling neural stem cell behaviour?

Selected publications:

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PDN

Cell fate decisions in real time: investigating the relationship between signalling and transcription dynamics.

To make and organize different tissues, cells must decipher information from developmental signalling pathways. Currently we know little about how the information is encoded and decoded, to generate the right balance and arrangements of cell types. Dynamic signalling properties –duration, fold-change and periodicity– are likely sources of information but, with few ways to measure these in living embryos, their importance is unresolved. Cells face the challenge of transmitting this information accurately, so that cell-surface signals are translated into correct transcriptional responses, but how this is achieved mechanistically remains a major question. Using leading-edge live imaging approaches (e.g. see reference below), including the MCP/MS2 system to detect transcription in real time, we are addressing these questions, focussing on the Notch pathway where levels and dynamics of signalling are crucial for functional outcomes. Some of our ongoing projects investigate (i) how activity and specificity are encoded within Notch responsive enhancers (ii) the relationship between signaling dynamics and cell-fate decisions (iii) the relevance of cell-cell organization and mechanics for signaling outcomes. A range of projects are possible, please come and discuss if interested.

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**PDN**  
**Optogenetic manipulation of cell polarity in the zebrafish brain**  
My lab uses optogenetics and live confocal imaging within the zebrafish neural tube. We test the role of cell polarity in building epithelial integrity during organ development and in breaking it during disease. Our hope is to unravel parallel mechanisms of epithelial development and disease *in vivo*.  

In combination with high resolution *in vivo* imaging, we use a new optogenetic approach to directly manipulate the polarity, signalling and division of single cells within the developing zebrafish brain. Along with CRISPR-mediated functional knock down experiments, this allows us to explore **how cell polarity and division are linked** during development such that cells can divide without disrupting the strict organization of the tissue. We are also testing the **role of polarity dysregulation in tissue disruption** by optogenetically manipulating polarity-linked signalling pathways (such as the PI3K pathway) in the already established zebrafish neural tube epithelium. We have recently started a collaboration with the Zernicka-Goetz lab to compare the mechanisms behind *de novo* polarisation in mESC culture and the zebrafish neural tube and the role that cell contact mediated force might play in this process. There is scope for expanding some of this work as a joint PhD project with a bioengineering or biophysics laboratory.

**Example rotation projects are:**

1. **Dissecting Pard3 function and oligomerisation using light**  
Optogenetics and light-induced phase separation will be used to manipulate the subcellular location and oligomerisation of the key apical scaffolding protein, Pard3. This will allow us to test the function of different domains within the protein and to assess the effect of altering Pard3 location on neuroepithelial cell behaviour during zebrafish neural tube development.

2. **Using light to model and manipulate PI3K signalling during brain formation:** Experiments in culture have suggested that the PI3K signalling pathway is key for the development of apicobasal polarity in epithelial tubes. Confocal 4D imaging and optogenetics will be used to determine the timing and importance of PI3K pathway signalling during the more complex development of vertebrate organs *in vivo*.

3. **Determining the role of cell-cell adhesions in directing *de novo* polarisation:** Inducible CRISPR Cas9 functional knock down approaches in the zebrafish neural tube and mESC culture models will be used alongside confocal 4D imaging to determine the ability of cells lacking functional adhesion proteins to polarise and divide appropriately during the establishment of epithelial tubes.

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**Zoology**  
**Using Two-Colour Coincident Detection Microscopy to test γ-TuRC composition in *Drosophila* cells**  
**Co-supervisor: Dr. Steven Lee, Department of Chemistry**  
In this project, the student will use a novel two-colour coincident detection microscopy technique to examine the protein composition of an essential cell component, the gamma-tubulin ring complex (γ-TuRC). In cells, γ-TuRCs are recruited to microtubule organising centres (MTOCs), such as centrosomes, where they template the formation of new microtubules. How γ-TuRCs are recruited to different MTOCs, at different times, and in different cells remains unclear. One hypothesis is that γ-TuRC composition can vary and that this can influence γ-TuRC recruitment. We have already confirmed this for one γ-TuRC component, Mozart1, which is expressed only in the *Drosophila* testes (https://doi.org/10.1016/j.cub.2018.05.044). We now want to test...
other components. In the past, this has been difficult primarily because biochemical experiments typically assay the whole population of γ-TuRCs, which could contain complexes of mixed composition. Using two-colour coincident detection microscopy, however, we can now assess the composition of individual complexes. In this technique, developed by Dr. Steven Lee in the Department of Chemistry (who will co-supervise this project), two different γ-TuRC components are fluorescently labelled: one in green, one in red. Complexes that pass through a stationary focal point on the microscope are then assessed for the presence or absence of the green and red fluorophores. Information on the percentage of complexes that contain both proteins, or just one protein, can be extracted. Our lab has now generated endogenously-tagged fluorescent lines for multiple γ-TuRC components. The student will initially image Drosophila embryos, but, if successful, other cell-types will be tested. During the project, the student will gain experience not only in a specialised form of light microscopy, but also in Drosophila husbandry and CRISPR techniques (to generate new fluorescent lines for other γ-TuRC components).

**Investigating microtubule formation in developing and adult Drosophila neurons:** Our lab has established techniques to image dendritic arborisation neurons in living Drosophila larvae, pupae and adults. We have screened for proteins important for microtubule formation in these neurons and will now follow up on some of the leads by trying to understand how these proteins function within the neurons at the molecular level. Microtubules are typically nucleated by γ-tubulin ring complex (γ-TuRC) but it remains unclear if γ-TuRC mediated microtubule nucleation is important for the maintenance of adult neurons. This is an important consideration, as γ-TuRCs are a potential target for anti-cancer therapy and current microtubule-binding anti-cancer drugs lead to a painful condition known as chemotherapy induced peripheral neuropathy. We are therefore developing tools to examine the effect of perturbing γ-TuRCs within the neurons in an inducible manner. We are taking various approaches, including generating potential temperature-sensitive γ-tubulin mutants and generating versions of γ-tubulin that respond to auxin-induced degradation. Once a system has been established, we will test the effect of inhibiting γ-tubulin on neuronal function. The rotation student will join these projects working closely with a postdoc in the lab. A suitable PhD project will then be identified should the student want to continue.

**Purifying Drosophila γ-TuRCs for structural determination and activity assays:** γ-TuRCs are multiprotein complexes that template the formation of new microtubules within cells. The structure of budding yeast γ-TuRCs has been elucidated using electron microscopy, but Drosophila and human γ-TuRCs are more complex, containing additional proteins with unknown function. The student will purify Drosophila γ-TuRCs from embryo extracts using MBP-tagged fragments of a γ-TuRC binding protein. The purified complexes will be used in microtubule nucleation assays where specific γ-TuRC binding proteins and kinases will be tested for their ability to activate the γ-TuRC. The complexes will also be sent to our collaborator, Leifu Chang, who will attempt to solve the structure of the using cryo-electron microscopy. During the rotation project, the student will purify γ-TuRCs from Drosophila embryos and begin to establish nucleation assays. The PhD project would be a continuation of this work, including using the knowledge from the γ-TuRC structure to design specific mutations in the γ-TuRC that can be tested in the fly.
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| Genetics | Mammalian epigenetic inheritance and epigenetic control of genome function.  
(Other projects can also be generated depending on the interests of the student)  
**Project 1:** Mechanisms underlying non-genetic inheritance in mammals. 50% of our genome is repetitive and much of this is composed of transposable elements such as endogenous retroviruses that are epigenetically silenced. Metastable epialleles are partially silenced endogenous retroviruses exhibiting variable epigenetic states between individuals with an impact on endogenous genes and mammalian phenotype in vivo. Two classic genetic models suggest that such metastable epialleles are environmentally sensitive and that they undergo transgenerational epigenetic inheritance. We have conducted a genome-wide screen for such elements which are acting as a new model to explore the properties and heritability of variably methylated mammalian retrotransposons. The student will have an opportunity to contribute to one of several components of this programme.  
**Project 2:** KRAB-zinc finger proteins (KZFPs) and the targeting of epigenetic states to non-repetitive regions of the genome.  
KRAB-zinc finger proteins are vertebrate specific factors that are believed to have evolved to target repressive chromatin states to retrotransposons. Some however play specific roles at unique regions of the genome. We have been characterising three of them.  
In this project the student will contribute to the analysis of a rather special KZFP that appears to prefer regions of the genome that are associated with activating marks. The student will either contribute to the analysis of mice that are mutant for this KZFP to decipher the transcriptome of cell types that lack this protein or will contribute to the biochemical characterisation of proteins that interact with this KZFP.  
**Project 3:** Mammalian epigenetic control: Chromosome architecture and topology in vivo – new insights from genomic imprinting.  
Comparative analysis of chromatin topology on the two parental chromosome homologues at an imprinted domain allows us to distinguish long range cis-interactions that regulate expression from those that package chromatin more generally. We have characterised the long range interactions at a 3Mb domain encompassing an imprinted locus in mouse and have used CRISPR-Cas9 to generate a series of four different CTCF binding site mutations. The student will contribute to the characterisation of these mutants assessing in mouse embryonic tissues to determine their contribution to the behaviour of each of the two chromosome homologues.  
**Project 4:** Genomic imprinting and the epigenetic control of mammalian lactation.  
Genomic imprinting is believed to have evolved to control prenatal resource control and the interaction between mother and fetus via the placenta. However, increasing evidence indicates that imprinting plays an important role in postnatal processes including adult neurogenesis, non-shivering thermogenesis, and lipid metabolism. We are testing the hypothesis that imprinting controls postnatal nutritional control by lactation by combining imaging approaches with transcriptomic and epigenomic technology in different cell populations of the dynamic mammary gland during mouse pregnancy, lactation and involution. The student will have an opportunity to contribute to one of several components of this programme.  

| All |
| **Professor Chris Jiggins**<br>e.jiggins@zoo.cam.ac.uk | **Zoology**<br>We study the remarkable diversity of wing patterns in tropical *Heliconius* butterflies. We are interested in the general question of how evolutionary changes in phenotype and patterns are controlled in the DNA sequence of an organism. Our recent work has identified potential enhancer elements that control specific elements of the *Heliconius* wing patterns and putative upstream patterning factors that interact with these elements. We are therefore starting to understand the novel gene interactions that give rise to novel wing patterns. We are interested in following up on this work and potential projects could include, but are not restricted to the following:<br>1) Analysis of ATAC-seq data to further refine localisation of enhancer elements. We are currently generating data using this technique which will be available for analysis.<br>2) Genome editing to test the function of patterning elements. We are using CRISPR/Cas9 editing techniques in *Heliconius* to investigate gene function in wing patterning and subject to availability of butterfly stocks a rotation student could carry out injections for gene knockouts of candidate wing patterning genes identified in population analyses. | **All** |

| **Dr Felipe Karam Teixeira**<br>fk319@cam.ac.uk | **Genetics**<br>Our lab studies the development of the germline, the immortal cell lineage that provides the continuity of life. Using Drosophila as a model, we combine developmental, genetics, microscopy, high-throughput sequencing analyses (small RNA-seq, RNA-seq, Ribo-seq) to build a systematic and unbiased understanding of diverse aspects governing germline biology *in vivo*. In particular, we are interested in dissecting the mechanisms protecting the germline genome against selfish DNA modules such as transposons (Teixeira et al, 2017), as well as in using germline stem cells as a model for understanding the control of stem cell self-renewal, growth, and differentiation *in vivo* (Sanchez et al, 2016).<br>1) Mechanisms safeguarding genome integrity during germline development: Accumulation of unrepaired damage in the germ line can lead to infertility and tumor development. The major threat to the germline genome is provided by selfish DNA modules known as transposons – mobile units that compose a large fraction of our genomes and that aim to increase in copy number by mobilization. Exploiting classic genetics tools in flies (Malone et al, 2015; Teixeira et al, 2017), we aim to understand, at the single-cell level, how germ cells assess, control, and respond to transposon activity during development. Current projects involve developmental, microscopy, and next-generation sequencing in combination with transgenic reporters and FACS sorting to study how molecular checkpoints operate in germ cells during development.<br>2) Small RNA- and chromatin-mediated regulation of alternative splicing: Transposable elements can drive genome evolution, but their enhanced activity is detrimental to the host and must be regulated. We have recently uncovered a novel mechanism by which an evolutionary conserved small RNAs (known as piRNAs) control transposon activity by regulating chromatin states and alternative splicing (Teixeira et al, 2017). Building on this, current projects aim to dissect the emerging and exciting relationship between chromatin states, transcription, and splicing regulation *in vivo*. This is being achieved by combining genetics (using nuclease deficient Cas9 (dCas9) protein fusions), | **All** |
biochemical (Mass Spec), and genomic (ChIP-seq and qPCR) approaches.

3) Protein synthesis regulation controlling stem cell self-renewal and differentiation: Accumulating evidence indicate that regulation of protein synthesis plays critical roles during development, tissue homeostasis, and tumorigenesis. Yet, the study of spatiotemporal regulation of gene expression and its function in controlling stem cells has been mostly restricted to chromatin-based mechanisms. Translational regulation is prominent in the germ line, and we have previously identified many translation factors as being critically required for stem cell self-renewal and differentiation in vivo (Sanchez et al, 2016). Using genetics, microscopy, and bioinformatic analysis, we aim to build a refined molecular understanding of how protein synthesis control – a new frontier in gene regulation – governs key aspects of germline stem cell development in vivo.

References:

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Micro-environmental control of gut renewal.

The intestinal epithelium constantly regenerates from stem cells, which adjust their behaviour to the changing physiological conditions the gut is exposed to. For example, stem cell proliferation rates can transiently increase to speed up regeneration after tissue loss or in response to the diet, before reverting to steady-state levels once correct tissue size is reached. In turn, this plasticity is essential for intestinal function, as lack of regeneration causes tissue atrophy whereas unrestricted stem cell proliferation promotes cancer.

The molecular mechanisms of gut maintenance and tissue differentiation resemble largely those used during development. For example, the same signalling pathways that control tissue growth during development control cell fate decisions in the adult or become misregulated in cancer. We use the genetically tractable *Drosophila* gut to identify the secreted and physical factors regulating gut plasticity.

Rotation projects will enable students to learn about *Drosophila* genetics, cellular and molecular biology and confocal microscopy. Students will have the option of expanding on the project for their PhD.

Rotation project - Investigation of the crosstalk between the intestinal epithelium and the visceral mesoderm.

Reciprocal interactions between the mesoderm and the intestinal epithelium are key during gut development. In the adult, the visceral mesoderm acts as a niche for intestinal stem cells by providing proliferative signals, however it is not known whether the physical changes that it undergoes during gut resizing influence stem cell proliferation. Understanding how these decisions are coordinated would be particularly relevant to physiological situations leading to local gut remodeling such as intestinal inflammatory diseases.
Upon global damage of the intestinal epithelium, a particular region of the visceral mesoderm undergoes remodelling, but why this particular region is not clear. The rotation project aims to further investigate intrinsic properties of this region using electron microscopy (with help from the CAIC facility – PDN) and atomic force microscopy (with the help of Kristian Franze’s lab, PDN). The student will also characterise the changes to the visceral mesoderm upon dietary restriction as the gut shrinks.

A potential PhD project would involve developing long-term imaging of the gut ex vivo and in vivo to capture the events coordinating gut regeneration and to further identify if distension of the visceral mesoderm regulates stem cell proliferation.

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Development of neural networks – plasticity & critical periods

During late stages of nervous system development, plasticity mechanisms endow the system with tuning and self-regulatory properties that are necessary for network function to emerge. These tuning phases, associated with heightened levels of plasticity, are universal and often called ‘critical periods’. Importantly, errors that occur during critical periods lead to permanent mis-adjustment and network instability in later life, the cause of neuro-developmental psychiatric disorders and seizures.

To investigate the cellular and molecular mechanisms of plasticity, we focus on synapse formation and dendritic growth. We use live and super-resolution imaging, electrophysiology and behavioural analysis, working with the motor network of the Drosophila embryo and larva to study interlinked questions:

1. What determines the critical period of heightened plasticity, its onset and closure? The Drosophila motor system has a precisely defined critical period of two hours in late embryogenesis. We find that this correlates with the onset of synaptic transmission, of inhibitory transmitter expression and the ingrowth of astrocyte glia into the synaptic neuropil. An intrinsic clock could be an alternative mechanism.

2. Novel regulators of structural plasticity: We identified reactive oxygen species (ROS), commonly thought of as destructive agents associated with aging and neurodegeneration, as novel regulators of neuronal plasticity. We also discovered DJ-1 (aka PARK7) as a conserved ROS sensor. How do ROS and DJ-1 convert changes in neuronal activity into adjustments of dendritic growth and synapse formation? Regulation of local mRNA translation might be involved.

3. Neuron-glia interactions during plasticity: When neurons are activated we find they generate ROS at the plasma membrane via NADPH oxidases, best known in the context of immune responses. Do these ROS signal to neighbouring neurons or glia? And do glia use ‘immune’ pathways to sculpt neuronal arbors? Preliminary evidence suggests they might.

4. Damage and regeneration: A genetic screen for modifiers of excitotoxicity-induced degeneration identified some unexpected candidates. Contrary to current views, we think that that glia and/or target muscles might generate retrograde signals that regulate local degeneration of their partner nerve terminals.
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Our lab uses *Drosophila* to study mitochondrial DNA (mtDNA), including its transmission, recombination, and interaction with the nuclear genome. We are also keen on developing more genetic tools to understand how mtDNA impacts health and wellbeing.

**Rotation project:** Seeing is believing: Observing mitochondrial DNA heteroplasmy using super-resolution imaging: The mitochondrial genomes are dispersed throughout the mitochondrial network as histone-free nucleoids. Given that there are multiple copies of mtDNA within each cell, pathogenic mitochondrial mutations often arise among thousands of wild-type genomes (i.e. heteroplasmic), and once their level exceeds a certain threshold, phenotypic manifestation of the genetic defects occurs. Thus, selectivity in the transmission of functional versus pathogenic genomes in somatic cells affects the expression of disease phenotype as we age. Whereas selective transmission in germline governs the heritance of mtDNA mutations from mother to progeny, and thus its evolution. These fundamental processes occur in the context of the developing organism and are manipulated by the nuclear genome. Recently, we have developed *Drosophila* as a powerful model to study how an organism sets the rules governing mtDNA transmission. We showed that there is a quality control mechanism (i.e. purifying selection) that hampers the transmission of detrimental mitochondrial mutations in the germline. However, we know very little about how it works. In this rotation, the student will use a heteroplasmic line containing two mitochondrial genotypes that differ for 7% at the sequence level. She/he will design DNA probes specific for each genome and perform fluorescent in situ hybridization to colour-code the two genotypes (i.e. oligo-paints). She/he will then apply super-resolution microscopy to study the distribution of the two genomes in the *Drosophila* oocytes (in collaboration with George Sirinakis & Edward Allgeyer). This study will also reveal whether individual mitochondria or nucleoids are heteroplasmic, and obtain detailed images of mtDNA nucleotide structure, size and distribution etc.

Dr Juan Mata
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**Translational control of cellular development**

We are interested in how gene expression is regulated and coordinated during processes of cellular development. We address these questions in the fission yeast *Schizosaccharomyces pombe* and, more recently, in the Apicomplexan parasite *Toxoplasma gondii*, the causative agent of toxoplasmosis. Both organisms are unicellular, and undergo complex differentiation processes.

We are studying the translational programs that drive these developmental programs using ribosome profiling, an approach that provides a genome-wide view of translation with single-nucleotide resolution. Our studies with *S. pombe* reveal complex regulation of translation, although very little is known about its importance and regulation. We are also investigating gene expression control at other levels, such as RNA degradation, and how it is integrated with translational control. Rotation projects will focus on the regulation of gene expression at the posttranscriptional level, using *S. pombe* as a model system. PhD projects would address similar question in either *S. pombe* or *T. gondii*.


| **Professor Eric Miska**  
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| **Lab website:**  
| www.ericmiskalab.org  
| **Gurdon Institute/Genetics**  
| Our group is interested in a mechanistic understanding of the roles of RNA and Epigenetics in development and physiology. Potential projects could include:  
| 1. Molecular genetics of the Piwi/piRNA pathway in the germline of *C. elegans*.  
| 2. Plasticity and epigenetic inheritance in *C. elegans*.  
| 3. The role of RNA modifications in *C. elegans* development.  
| 4. The role of epigenetics in the evolution of animal form: nature versus nurture in Lake Malawi cichlids.  
| 5. Developing an epigenetic clock of development and ageing in African cichlids.  
| **All**  

| **Dr Cahir O’Kane**  
| c.okane@gen.cam.ac.uk  
| **Lab website:**  
| http://www.gen.cam.ac.uk/research-groups/okane  
| **Genetics**  
| **1. Mechanisms organising the axonal endoplasmic reticulum compartment.** The tubular smooth ER compartment is thought to run throughout the lengths of axons. It is not highly active in protein synthesis, but other roles may include calcium or lipid homeostasis, or conductance of signals along axons, and mutations that affect it can cause axonal degenerative diseases including hereditary spastic paraplegia. Our goal is to understand the mechanisms that organise smooth tubular ER along axons in *Drosophila*, using mutant or transgenic lines that affect spastic paraplegia or functionally related genes.  
| **2. Co-supervised by Liria Masuda-Nakagawa**  
| **Circuitry of Sensory discrimination in the higher brain of *Drosophila larva***  
| Sensory cues guide animal behavior and the discrimination of sensory representations is essential for the formation and retrieval of memory. The aim of our projects is to understand the neural circuits that underlie sensory discrimination in the higher brain. We use Drosophila larval brain as a model, with the advantage of a simple brain of 10,000 neurons; a full brain connectome in progress; and the powerful genetic tools available for Drosophila. Specific projects: 1) anatomical characterization, by targeting expression of molecular markers, of the circuitry regulating the activity of the memory center, the mushroom bodies, 2) functional characterization of novel neurons in the discrimination circuitry, by olfactory discrimination behaviour assays, by activating neurons using optogenetics, 3) functional analysis of circuit connectivity by calcium imaging of live brains, by activating neurons with optogenetics. This work will give a comprehensive understanding of the circuitry of sensory discrimination, and its regulation.  
| **All**  

| **Professor Ewa Paluch**  
| ekp25@cam.ac.uk  
| **Lab website:**  
| https://www.pdn.cam.ac.uk/directory/ewa-paluch  
| **PDN**  
| **The mechanobiology of cell shape**  
| The Paluch lab investigates the basic principles underlying animal cell morphogenesis. A precise control of shape is key to cell physiology, as precisely orchestrated cell shape changes underlie fundamental processes like cell division, cell migration and epithelial morphogenesis. Cell shape deregulation is at the heart of many diseases and developmental disorders. Yet, how cells regulate their own shape remains poorly understood. Because cell morphology is intrinsically controlled by mechanical forces acting on the cell surface, interdisciplinary studies integrating approaches from physics into biology are required to truly understand cell shape. The lab combines biology, physics, engineering and quantitative imaging to investigate the regulation of cell shape. We  
| **2 & 3**
work with various model systems, including cultured cancer and embryonic stem cells and developmental organoids; projects in other model organisms are also possible in collaboration with other groups in the programme. We use classical cell and molecular biology techniques, biophysical measurements (atomic force microscopy, optical tweezers), super-resolution imaging (SIM and STORM, to investigate the nanoscale architecture of the cytoskeleton), advanced electron microscopy, automated image analysis (including neural networks-based), and microfabrication (to generate 3D environments with controlled geometries and mechanics). The lab is currently moving from University College London (http://www.ucl.ac.uk/lmcb/users/ewa-paluch) to Cambridge; rotations are available after the New Year.

There are various projects available, depending on the student’s background and interests. Examples of projects:

(1) Investigating cell shape changes in gastruloids, embryoid bodies that recapitulate symmetry breaking and some of the morphogenetic events of early mouse development.

(2) Investigating the molecular basis of force generation during morphogenesis in *Drosophila*, in collaboration with Bénédicte Sanson’s lab.

(3) Investigating the coupling between cell shape and cell fate in various model systems.

There is no requirement for a background in physics, most previous students have been biologists, the only requirement is curiosity, an open mind, and enthusiasm for learning new concepts.

Dr Emma Rawlins
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**This lab is not available for a PhD place.**

**Cellular mechanisms of mammalian lung development**

Changes in the cellular structure of the lung are a feature of many human lung diseases. In spite of this tremendous disease burden, surprisingly little is known about the cellular and genetic mechanisms which control lung embryonic development and postnatal growth/maintenance. We are using mouse genetics, and increasingly human embryonic lung organoids, to dissect the control of lung progenitor cell behaviour at the level of single progenitor cells. This approach allows the mutant cells to be analyzed in a quantitative manner in vivo, or by live imaging in organ culture systems. We have also recently started to study cell fate choice in human embryonic lung samples (Nikolic et al., 2017).

Specific projects:

1. *Which signals direct multipotent progenitor cells to produce alveolar descendants?* Of particular interest, can we use our results from the mouse system as a basis for improving the differentiation of human embryonic organoids?

2. *What is the response of individual lung embryonic progenitor cells to signalling pathways?* Are all of the progenitors of equal potential at the early stages of lung branching morphogenesis?

Possible collaborative projects are also available with Pietro Cicuta (e.g. investigating the requirement of physical forces for alveologenesis) or Ben Simons.


**Lab website:**
http://www.gurdon.cam.ac.uk/research/rawlins

**Gurdon Institute**
**Drosophila Sox genes in segmentation and CNS development.**

Sox domain proteins are highly conserved transcriptional regulators involved in many aspects of metazoan development. In all animals where they have been studied, Group B Sox proteins (Sox1, 2 and 3 in vertebrates; Dichaete and SoxNeuro in insects) act redundantly to control key aspects of neural cell specification and differentiation. In addition, in all insects examined to date, Dichaete-class Sox proteins have a role in early development with experimental evidence in flies, beetles and spiders pointing to conserved functions during embryonic segmentation.

We have generated a wealth of genomic data on Sox protein binding in the *Drosophila* embryo and, more recently, in fly tissue culture cells. We have also recently generated genomic binding profiles for Opa - a protein Dichaete interacts with during segmentation in both flies and beetles - and Vnd - a homeodomain protein that both Dichaete and SoxN interact with during early neural cell specification. Using these data we are exploring the genetic redundancy exhibited by Sox genes at the genomic level, with a view to understanding how highly related DNA binding proteins show unique and shared binding events, and how Sox proteins interact with partner proteins to direct transcriptional regulation.

In addition to genomic approaches, we have recently generated a number of novel genetic tools to study Sox function in vivo. These include versions of Dichaete and SoxN tagged with fluorescent proteins at their endogenous loci to facilitate imaging studies of their dynamic expression during embryogenesis. We have used genome engineering approaches to swap Dichaete and SoxN coding sequences at their endogenous loci, facilitating a detailed analysis of the true extent to which these genes are functionally redundant.

We have rotation projects available on the computational analysis of genomic binding profiles, further genomic analysis in vivo and in tissue culture cells, imaging based studies of Sox expression and genetic analysis of Sox redundancy.


Ferrero E, Fischer B, Russell S (2014) SoxNeuro orchestrates central nervous system specification and differentiation in *Drosophila* and is only partially redundant with Dichaete. Genome Biology 15:R74
| Dr Bénédicte Sanson | PDN | Morphogenesis of early embryos: mechanisms underlying cell behaviours *in vivo*
| bs251@cam.ac.uk |  | Our group investigates the mechanisms of morphogenesis, in other words how embryos and organs acquire their complex three-dimensional shapes. To understand this, we need to study the role of genetic programs in shaping tissues, but also to consider the physical environment of the embryo, for example how the embryonic architecture imposes stresses on cells and tissues (reviewed in Heisenberg & Bellaiche, 2013, *Forces in tissue morphogenesis and patterning*, Cell, doi:10.1016/j.cell.2013.05.008).
| Lab website: [http://www.pdn.cam.ac.uk/staff/sanson/](http://www.pdn.cam.ac.uk/staff/sanson/) |  | Working with interdisciplinary collaborators, we strive to analyse genetic programming and physical forces together, using a range of approaches, from developmental genetics and imaging to computational analysis and modelling of cell behaviours. As a model organism, we use *Drosophila* embryos because they are easy to image and to manipulate genetically. We image live embryos labelled with fluorescent proteins to analyse the cytoskeleton dynamics, the changes in cell shapes and the movement of cells relative to each other. We focus on a window of developmental time spanning gastrulation and segmentation, investigating conserved morphogenetic processes such as axis extension and tissue boundary formation ([https://www.pdn.cam.ac.uk/directory/benedicte-sanson](https://www.pdn.cam.ac.uk/directory/benedicte-sanson)). Failure in these in human embryos can cause serious developmental complications, for example neural tube defects when axis extension does not happen properly. Our methods include imaging FP-tagged proteins in live transgenic embryos, confocal and super-resolution microscopy, image analysis, computational tracking of cell and tissue geometries and mathematical modelling.
|  |  | A range of projects are available in the lab for rotations leading to a PhD. This year, there is a possibility of co-supervision with Ewa Paluch on a super-resolution project. |
| Dr Emília Santos | Zoology | **This lab is not available for a PhD place.**
| es754@cam.ac.uk |  | We are interested in the genetic and developmental basis underlying organismal diversification using cichlid fish species as a model system. Cichlids are one of the most species rich vertebrate families (~2500 species) showing extreme diversity in their colour patterns, body shape lateral line and craniofacial and feeding morphology. They are a fascinating system because despite this diversity, they are genetically very similar but morphological very diverse allowing for in depth comparative developmental studies between closely related species. They are a well characterized model in evolutionary ecology, phylogenetics and genomics and are an emerging model system for developmental biology. This is mostly due to the recent increase in genomic resources, the viability of hybrid crosses and to the application of the genome modification method - CRISPR/Cas9.
| Lab website: [https://emiliapsantos.com/](https://emiliapsantos.com/) |  | We are currently focusing on the study of variation of sexually dimorphic pigmentation patterns that are important for male-male competition and female choice. Despite the evolutionary significance of vertebrate colour patterns, the genetic and developmental mechanisms underlying their diversification remain elusive and were mostly studied in organisms that show little variability. We use a combination of quantitative and population genomics, developmental genetics and behavioural tools to address the questions presented. |
Fine scale genetic mapping and expression analysis of a genomic variant associated pigment pattern variation in cichlid fishes

Egg-spots are circular pigmentation markings present on the anal fins of approximately 1500 species of cichlid fishes. They consist of a central circular area of xanthophores and iridophores (orange and silver pigment cells respectively) surrounded by an outer transparent ring. They are a novel trait characteristic of the most species rich cichlid lineage – the haplochromines – which show extreme sexual dimorphism. Males are large and extremely colourful, with females being smaller and dull in colouration. Egg-spots are highly variable trait, varying in colour, number and arrangement, both within and between species. They function as badges of status, being sexually selected via female choice in some species and via male-male competition in others.

We are interested in dissecting the genetic and developmental processes underlying eggspot pattern variability. We have recently identified a 9kb genomic region that is associated with eggspot number variation in Astatotilapia calliptera. This region harbours one gene that is implicated in melanophore development in mammals. Many questions remain open:

a) How and where is this gene expressed throughout development?
b) Is this gene expressed differently between individuals with low and high eggspot number?
c) What is the causal mutation in this 9kb region leading to a high or low number of eggspots?
d) What is the function of this gene in pigmentation patterning?

This rotation project would address one or more of these questions. You would use gene expression techniques, such as in situ hybridization and qPCR, microscopy tools to visualize pigmentation development, as well as gene sequence and gene function analysis using crispr/cas9.

Characterization of lateral line development in cichlid fishes

Cichlid fishes differ greatly in lateral line morphology, this variation is associated with different habitats in feeding mode. Lateral line is a sensory system existing in aquatic vertebrates and is used to detect vibrations, movement and pressure changes in the surrounding environment. We are interested in understanding the genetic and developmental basis of variation in cichlid lateral line between two cichlid species - a generalist (Astatotilapia calliptera) and a sonar feeder (Aulonocara stuartgranti) – that have different lateral line morphologies. This rotation project would consist in characterizing lateral line development in embryos and larvae of both cichlid species by studying sox2 expression, a gene known to be expressed throughout the development of this sensory system in zebrafish. You will use cloning, in situ hybridization and microscopy techniques.
# Epithelial polarity in flies and mammals

Cell polarity is essential for most cell functions and for several key developmental processes, such as cell migration, axis formation and asymmetric stem cell divisions, whereas a loss of polarity is a critical step in the formation of tumours. We are analysing how cells become polarised and how this polarity controls the organisation of the cytoskeleton and intracellular trafficking. Part of the group studies the *Drosophila* oocyte, since its polarity defines the anterior-posterior axis of the future embryo. The rest of the group focuses on epithelial polarity, where we are comparing secretory (the follicle cells) and absorptive epithelia (the adult midgut) in *Drosophila* with a typical mammalian epithelium (mouse intestinal organoids). Much of our work depends on advanced imaging, ranging from live imaging growing microtubules and protein secretion to super-resolution imaging of polarity factors using custom-built microscopes with adaptive optics. Possible projects include:

1) **Characterising novel epithelial polarity factors in intestinal organoids**

More than 80% of tumours derive from epithelial tissues, and one of the hallmarks of these tumours is a loss of epithelial polarity, with the extent of depolarisation correlating with the malignancy of the tumour. We currently know very little about how polarity is disrupted during the process of tumorogenesis, however, as many of the factors that polarise normal epithelial cells remain to be identified. We have recently discovered that different types of *Drosophila* epithelia polarise by different mechanisms, and have found that the fly intestine is a good model for endodermal epithelia in mammals. The aim of the project will be to test whether these novel factors play conserved roles in polarising the epithelial cells of the mouse intestine, using intestinal organoids as a model.

2) **Counting polarity proteins with super-resolution microscopy**

The lateral polarity and tumour suppressor proteins, Scribbled, Discs large and Lgl are often referred to as a complex, but there is little evidence that they interact in interphase cells. We have tagged the endogenous copies of Dlg and Lgl with SNAP and HALO tags and have generated homozygous viable and fertile lines, in which every copy of each protein carries the tag. The project will involve attaching oligonucleotides to the SNAP and HALO tags, so that we can use DNA PAINT to image the two proteins simultaneously with 10nm resolution and determine the extent to which they localise to the same complex. Since the attachment of oligonucleotides to SNAP and HALO is 80% efficient and each blink represents a single molecule, we can then count the number of molecules in polarity complexes in different regions of the cell.

3) **Live imaging of epithelial polarisation in the *Drosophila* adult midgut**

The enterocytes of the *Drosophila* midgut are continuously produced during adult life from basal intestinal stem cells and the new enterocytes then polarise as they integrate into the epithelium from its basal side. This therefore provides a rare opportunity to observe cells polarising de novo. The aim of the project will be to set up conditions for live imaging of the adult gut ex vivo and to follow the localisation of specific polarity factors (tagged with fluorescent proteins) as the enterocytes integrate.
Establishing the vertebrate body plan is a progressive process that begins during gastrulation and continues throughout the elongation of the embryonic body. During this time, cells must coordinate cell fate decisions with the dynamic cell behaviours that build and elongate the 3D structure of the embryo. While the gene regulatory networks (GRNs) that govern cell specification and pattern formation are well conserved, the rates of cell movements, cell growth and cell proliferation are highly species-specific. This is most clear for posterior progenitor populations such as neuromesodermal progenitors (NMPs). Mammalian embryos such as the mouse elongate their body axis by the progressive addition of cells during posterior growth, and NMPs have been shown to be important in this by acting as a bipotent stem cell population, continually allocating cells to the spinal cord and pre-somatic mesoderm. However, externally developing embryos such as the zebrafish have been selected for a rapid mode of development that allows for the development of a fully swimming tadpole within 24 hours. Here, most of the spinal cord and paraxial mesoderm territory is set aside during gastrulation, with axis elongation being largely driven by a convergence and extension of these early specified progenitors. In the absence of posterior growth, zebrafish NMPs act as a quiescent population of undifferentiated progenitors, that commit to either the caudal-most spinal cord or paraxial mesoderm only at the very end of somitogenesis. To what degree are these differences in NMP cell population dynamics due to autonomous properties of the progenitor populations and the GRNs that drive them? And to what degree are they a consequence of more global properties of the developing embryo, in terms of growth rates and morphogenesis?

**Rotation project (co-supervised by Prof. Ben Simons):**
Together with the Cambridge Advanced Imaging Centre (CAIC), we have developed a microscope tracking capability to allow for continuous imaging of posterior body development by light-sheet imaging, allowing us to generate a complete picture of the cell behaviours that generate axis elongation in zebrafish. Cell tracks of the NMP population have been generated and validated, with the fates of the cells as either spinal cord or mesoderm assigned to each track. The rotation project will analyse this tracking data in order to ask whether or not there is some behaviour of the cells that is in some way predictive of their eventual cell fate. Practically, this will mean extracting various statistics from the tracking data and seeing whether or not this correlates with either fate. We will then see where this leads us in terms of generating testable predictions in terms of the mechanism of cell fate decision making.

**Potential PhD project (co-supervised by Prof. Ben Simons):**
Tracking data such as that described above for zebrafish can be used to generate 3D simulations of how pattern emerges in the tailbud over time. These models can be used to generate testable predictions on a) the minimal GRN structure required to generate the pattern, b) the clonal output of the cell population in terms of the timing and ratios of cells moving into either spinal cord or mesodermal compartments and c) the impact that alterations in growth rates and/or rates of convergence and extension occurring in the system. This will allow us to probe the evolvability of this system by tuning various aspects of the model, and comparing this to clonal and gene expression data from other species such as the mouse. The PhD project will benefit greatly from co-supervision by Ben Simons. The aim will be to apply approaches from statistical physics to probe conserved and divergent characteristics of the NMP system. Using this top-down approach, we hope to uncover fundamental characteristics of NMP cell fate decisions that shed
| **Professor Azim Surani**  
a.surani@gurdon.cam.ac.uk | **Gurdon Institute** | **Specification and programming of the mammalian germline for development**  
Our lab is investigating diverse aspects of preimplantation, and early postimplantation mouse and human development. This includes specification of primordial germ cells and resetting of the germline epigenome for totipotency, and the inheritance of genetic and epigenetic information.  
Recent references:  
Irie et al., 2015; *Cell* 160, 253-268  
Tang et al., 2015, *Cell* 161, 1453-1467  
Murakami et al., 2016, *Nature* 529, 403-407 | All |

| **Dr Erica Watson**  
edw23@cam.ac.uk | **PDN** | **The epigenetic effects of abnormal folate metabolism during development**  
Exposure to environmental stressors can lead to changes in the epigenome that increase disease risk not only in the exposed individual but also in their unexposed children and grandchildren. The mechanism behind this type of non-conventional inheritance is not well understood. However, the mechanism is likely epigenetic in nature. To explore this question, we work with the hypomorphic *Mtrr*⁰ mouse model that is unable to metabolize the vitamin folate². Folate metabolism is required to transmit methyl groups destined for the methylation of DNA, histones, and RNA. The *Mtrr*⁰ mutation causes widespread epigenetic instability and developmental phenotypes (e.g., congenital malformations) that appear up to four wildtype generations later.  
The recent focus of our lab is tracking differential DNA methylation patterns that appear in *Mtrr*⁰⁺/+ mice (F0 generation) through to the wildtype F2 generation using unbiased and biased methods. We aim to address whether these persistent DNA methylation marks affect gene expression and cause congenital malformations (G. Blake & E. Watson, in prep). We have also initiated an RNA-sequencing experiment in collaboration with the Miska lab to assess non-coding RNA content in the sperm of *Mtrr* mutant males (i.e., the maternal grandfather). A potential project will be to analyze the RNA-sequencing results and explore possible repercussions of altered non-coding RNA expression on development.  
Our lab also focuses on the role of folate metabolism in placental development. The placenta is important for nutrient and gas exchange between the mother and fetus. Defects in its development can have drastic effects on the growth and survival of the fetus. We have evidence that the *Mtrr*⁰ mutation affects placental development to varying degrees of penetrance. Recent findings show that placental phenotypes are strongly correlated to congenital malformations⁴. Remarkably, the mechanism behind neural tube defects, which are famously associated with folate deficiency in humans, is not well understood. A potential project would be to explore whether neural tube defects associated with folate deficiency are caused by placental phenotypes using embryo manipulation techniques.  
Other projects are possible, please come and discuss them.  
| **Dr Tim Weil**<br>tw419@cam.ac.uk | Zoology | **The function of bimolecular condensates in translational regulation**<br>Biomolecular condensates are micron-scale, membraneless structures composed of RNAs and proteins. Often termed "bodies" or "granules", these cellular compartments are important in maintaining homeostasis and regulating cellular changes. They have also been implicated in pathogenesis and neurodegeneration. One key aspect of bimolecular condensates is their ability to transition between different biophysical states.<br><br>This project will focus on testing the role of the conserved biomolecular condensate, Processing (P) bodies, in mRNA metabolism. Previous work in the lab has shown the importance of P bodies in regulating differential translation in *Drosophila* development. In addition to imaging and biochemical approaches to test the function of P bodies, this project will explore the role of low-complexity domains and RNA - RNA interactions in the formation of these bodies. The long-term aim of this research is to understand how P body dynamics are regulated in vivo and what factors control P body - RNA interactions.<br><br>**Calcium wave(s) at egg activation**<br>Egg activation is a conserved process that is required to prepare an egg for fertilisation and embryogenesis. In all animals, egg activation is associated with at least one transient increase in the cytosolic calcium concentration. This "calcium wave(s)" is required for the resumption of the cell cycle, reconfiguring of the cytoskeleton, cortical granule exocytosis, translation of maternal transcripts and other downstream events.<br><br>This project aims to establish the mechanisms that drive the initiation, propagation and recovery of the calcium wave(s) in eggs at activation. We use *Drosophila* as our model system due to its genetic and imaging tractability. This rotation project will use methods already successfully applied in the laboratory, including in vivo advanced imaging of genetically encoded calcium indicators, genetic analysis of key pathways, pharmacological disruption and physical micro-manipulation. | All |

| **Dr Rob White**<br>rw108@cam.ac.uk | PDN | **Super-resolution imaging of chromatin and nuclear organization in Drosophila spermatocytes**<br>(Co-supervisor: Kevin O'Holleran, Cambridge Advanced Imaging Centre)<br><br>The 3-D organization of chromatin within the nucleus is likely to play a major role in defining cell fates with the specific sub-nuclear localisation of active and inactive genes, the organization of topological domains and transcriptional hubs. The new techniques of super-resolution microscopy offer powerful approaches to investigate 3-D chromatin organization. In this project we will apply super-resolution microscopy to investigate the organization of the Drosophila spermatocyte nucleus. These nuclei have key advantages for imaging as they are up to 25X the volume of normal somatic cell nuclei and individual chromosomes and chromatin fibers are easily visualized. In addition they are undergoing a clear well-characterised transcriptional program with the specific expression of several thousand spermatogenesis genes. We have many reagents and mutants available to probe 3-D chromatin organization in these nuclei, to investigate the link between nuclear architecture and gene regulation. | 2 & 3 |
| Dr Phil Zegerman  
[zegerman@gurdon.cam.ac.uk](mailto:zegerman@gurdon.cam.ac.uk)  
Lab website: [http://www.gurdon.cam.ac.uk/research/zegerman](http://www.gurdon.cam.ac.uk/research/zegerman) | Gurdon Institute | How do metazoans prevent mutagenesis during rapid early embryonic divisions?  
The early embryonic divisions of many metazoa are extremely rapid but must be highly faithful because these divisions give rise to all the cells of the adult including the germ line. This project will address the paradox of how embryonic cells divide extremely rapidly, with high rates of DNA replication in the absence of checkpoints, without accumulating mutations.  
To measure mutagenesis during early vertebrate divisions, an assay will be developed using a reporter injected into *Xenopus laevis* embryos. Mutations rates will be compared pre- and post- the mid-blastula transition (MBT). This will employ mathematical approaches, including fluctuation analysis, to determine the rate of mutation per division. Mutagenesis will also be compared in embryos stimulated to undergo extra rapid divisions after the MBT and in embryos with no endogenous checkpoint activity. This rotation project will provide the framework to address a fundamental developmental question, which may also provide insight into how somatic cells prevent mutagenesis to avoid tumourigenesis.  
References  
Collart, C., Smith, J.C., and Zegerman, P. (2017). Chk1 Inhibition of the Replication Factor Drf1 Guarantees Cell-Cycle Elongation at the *Xenopus laevis* Mid-blastula Transition. *Developmental Cell* ***42***, 82-96 e83. | All |
| --- | --- | --- |
| Professor Magda Zernicka-Goetz  
[mz205@cam.ac.uk](mailto:mz205@cam.ac.uk)  
Lab website: [http://www.pdn.cam.ac.uk/zernickagoetzlab](http://www.pdn.cam.ac.uk/zernickagoetzlab) | PDN | (1) Controlled differentiation of human embryonic stem cells to human embryo-like structures  
Human embryogenesis has remained mysterious due to the ethical and technical difficulties to study human embryos. We have recently succeeded at developing culture conditions that allow the development of human embryos until day 13, the ethical limit for human embryo culture. On day 13 of development, human embryos begin the process of gastrulation, whereby the three germ layers of the human body form. In order to study this process, we propose to build synthetic human embryo-like structures combining extra-embryonic and embryonic stem cells, as we have recently done for the mouse. One of the major limitations to achieve this aim is the lack of human extra-embryonic stem cells. The aim of this proposal is to differentiate novel extended potential human embryonic stem cells to an extra-embryonic fate, in order to generate synthetic human embryo-like structures.  
The pluripotent character of human embryonic stem cells is known to be primed for differentiation, meaning the cells present bias to specific lineages, which is thought to limit their differentiation potential. With this mind, a number of studies have recently reported novel human embryonic stem cell lines with an unbiased pluripotent state, or an extended potential and so able to generate both embryonic and extra-embryonic tissues in *vivo*. The first aim of this project is to apply these new culture regimes to generate *in* | All |
### How does the early mammalian embryo measure the time?

Developmental timing is critical for early embryogenesis but the clock that sets the timing of the first morphogenetic events in mouse embryogenesis remains a total mystery. Cells in the early mouse embryo polarise de novo following an intrinsic timer that does not count cell numbers but the time elapsing after the act of fertilisation. Here, we aim to reveal the nature and universality of this developmental timer by: (1) identifying its molecular regulators; 2) determining how its timing influences developmental decisions; 3) undertaking comparative embryological studies to determine whether its mechanism is used in diverse mammalian species. We have already established the necessary approaches for studying the timing mechanisms for the development of cell polarity in mouse embryos. These include tools such as advanced high resolution live embryo time-lapse imaging in combination with the use of optogenetic, FRET sensor and CRISPR-CAS9 technologies.

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