Building and Rebuilding Complex Tissues

Event Information

18 July 2024
Robinson College, Cambridge

UNIVERSITY OF CAMBRIDGE
School of Biological Sciences

Practical info

Venue information

Parenting/quiet room - follow signs to the Linnet Room for anyone needing a quiet space, including breastfeeding and pumping.

Breakout room - follow signs to the Auditorium Lounge if you need a space to take calls/meetings.

Lunch and refreshments will be served in the event marquee.

Accessibility information

The venue is wheelchair accessible. The auditorium is fitted with a Hearing Loop - users are advised to select "T" on their earpiece. Please ask the organisers for any assistance.

Wi-Fi

Free Wi-Fi access is available onsite - look for signs at the registration desk and in the event marquee.

Photography and Filming

During the event, photos, screenshots, and videos will be taken for non-commercial educational and promotional purposes and these may be available to the public on all platforms, including on-line and social media.

Emergency information

Fire

The Fire Assembly point is in the University Library Car Park, across Grange Road. If the fire alarms sound please move directly to the car park and await instructions from conference staff or a college porter.

First aid

Please alert conference staff or college porters promptly to any first aid incident that occurs.

Welcome

We are delighted to welcome you to the Building and Rebuilding Complex Tissues meeting which brings together researchers from the UK, Europe and America to explore research progress, opportunities and challenges in tissue development and regeneration.

This is an incredibly exciting field to be working in. From minor cuts to major wounds, many tissues have the capability to heal after trauma or injury. However, this regenerative potential varies greatly in different organ systems, with age, and importantly, across different species. Comparisons of regenerative and non-regenerative systems in different contexts will enable us to understand how successful regeneration occurs and how this knowledge can be used to improve ailments as diverse as birth defects, traumatic injury, age-related pathologies and degenerative diseases.

While most of the research is focusing on recapitulating developmental mechanisms to regenerate lost tissue/cells, there is also evidence of unique regenerative processes that do not recapitulate development. Regenerative biology has been greatly embraced by developmental and stem cell biologists given the overlapping interest in "building" complex tissues. However, there are limited platforms to bring together groups that work on development and regeneration to compare and contrast successful mechanisms and approaches. The goal of this meeting is to facilitate a discussion of similarities and disparities of complex tissue regeneration and developmental processes.

Today's meeting follows a series of local meetings here in Cambridge organised by the Reproduction, Development and Lifelong Health Theme in the School of Biological Sciences which have enabled a range of researchers from across scales and systems to share their research plans and establish new collaborations. We hope this larger meeting will serve as a springboard for further interactions across a wider range of scientists with complementary expertise and to facilitate a discussion of similarities and disparities of complex tissue regeneration and developmental processes. We look forward to continuing to build a network of engaged researchers to advance the field of complex tissue development and regeneration.

Please do keep in touch and reach out to us if you have thoughts and ideas for follow up activities as a result of today's meeting.

Mekayla, Sumru and Ben, Organising Committee

Mekayla Storer
Cambridge Stem Cell Institute and Department of Physiology, Development and Neuroscience

Sumru Bayin
Gurdon Institute

Ben Steventon
Department of Genetics

Conference programme

08:15	**Registration and welcome coffee**
09:30	Opening Remarks, Sumru Bayin
09:40	**Session 1,** chaired by Ben Steventon
09:40	**Jérôme Gros,** Institut Pasteur Mechanical feedback during embryonic self-organization
10:00	**Giulia Paci,** University College London Crafting robust patterns in developing tissues under mechanical stress
10:10	**Swati Sharma,** University of Manchester Investigating retinal cellular dynamics in eye disorders using Zebrafish embryos
10:20	**Aida Rodrigo Albors,** University of Edinburgh Unlocking spinal cord regeneration across species
10:40	**Henry Roehl,** University of Sheffield Dissecting development and redevelopment of the zebrafish larval tail
11:00	**Break**
11:40	**Session 2,** chaired by Sumru Bayin
11:45	**Can Aztekin,** École Polytechnique Fédérale de Lausanne Signaling centers of limb development and regeneration
12:05	**Karen Ching,** University of Edinburgh Uncovering novel liver regeneration and antifibrotic pathways in Acomys (spiny mice)
12:15	**Ziqi Dong,** University of Cambridge Hypoxia regulates the fate of human fetal lung epithelial progenitors
12:25	**Aziz Aboobaker**, University of Oxford Gene regulation in planarian stem cells during regeneration
12:45	**Ragnhildur Thóra Káradóttir,** Cambridge Stem Cell Institute Neuronal regulation of myelin regeneration
13:05	**Lunch and poster session**

Conference programme

14:30	**Session 3,** chaired by Mekayla Storer
14:35	**Rita Mateus,** Technische Universität Dresden, Max Planck Institute of Molecular Cell Biology and Genetics Regeneration triggers a slow growth shift by scaling of morphogen gradients
14:55	**Uri Frank,** University of Galway Cnidarian stem cells do everything
15:15	**Filipa Simões,** University of Oxford Decoding immune-related spatial heterogeneity in the regenerating heart
15:35	**Osvaldo Chara,** University of Nottingham Reaction-diffusion control of spinal cord regeneration in axolotls: a modelling study
15:55	**Break**
16:30	**Session 4: Keynote Speaker,** chaired by Mekayla Storer
16:35	**Ashley Seifert,** University of Kentucky Evolution of regenerative ability
17:20	Poster prizes, sponsored by Qkine
17:30	Closing Remarks, Mekayla Storer
17:40	**Reception drinks**
18:30	End

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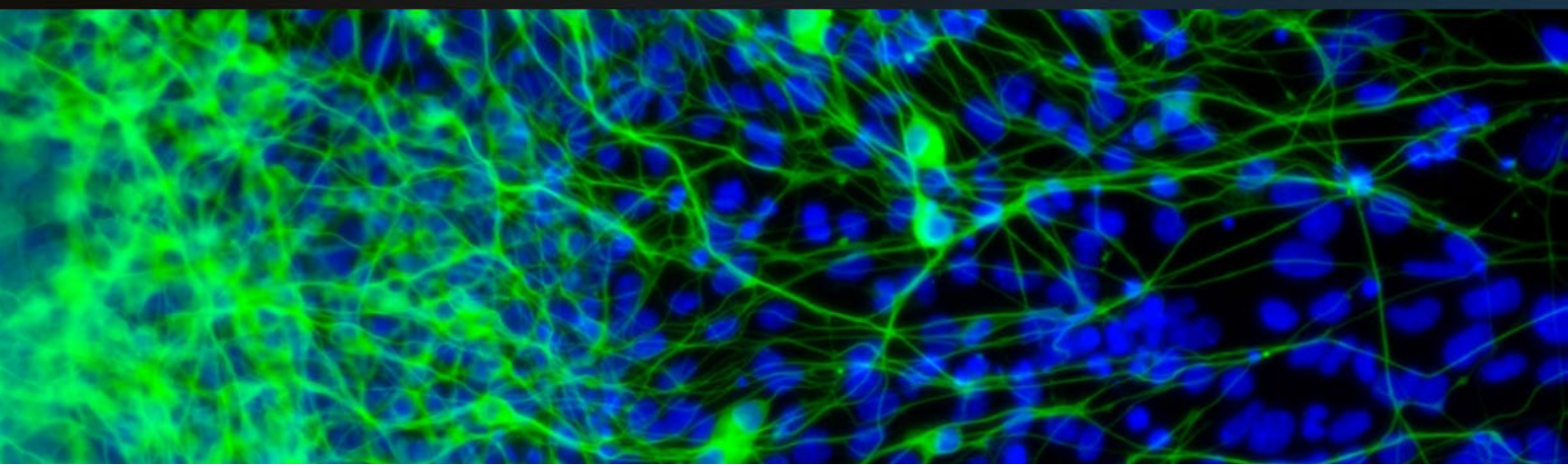

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Speaker profiles

Keynote: Ashley Seifert

University of Kentucky

Ashley W. Seifert is currently a Professor in the Department of Biology at the University of Kentucky where his research group is attempting to uncover the cellular blueprint for complex tissue regeneration in mammals. His research group takes a multispecies approach to identify drivers and inhibitors that regulate regeneration in different mammalian lineages and determine how these mechanisms are curtailed in non-regenerating systems. Following his seminal discovery that spiny mice can regenerate skin and musculoskeletal tissue, his lab has pioneered using these rodents to study the evolution of complex tissue regeneration in mammals. Ongoing work by Prof. Seifert and his group is unravelling how macrophages are required for regenerative healing and more generally how inflammatory cells affect tissue healing outcomes. Additionally, his group has uncovered cellular mechanisms that direct injury signals to regulate the balance between proliferation and cellular senescence; mechanisms that can be affected to drive regenerative healing in laboratory mice. Prof. Seifert received his PhD working with Prof. Martin J. Cohn in the Biology Department at the University of Florida and did postdoctoral research with Prof. Malcolm Maden.

Aziz Aboobaker

University of Oxford

Aziz Aboobaker is interested in regenerative phenomena across the Animal Kingdom, and understanding how some animals can regenerate their whole bodies from small non-descript starting fragments, using adult pluripotent or multipotent adult stem cells to do this. He has used planarian flatworms as a go to model system, these animals have a population of pluripotent adult stem cells which self-renew, up their proliferative rate, migrate and differentiate in order to fuel both regeneration and allow homeostasis in the light of changing nutritional status. He is currently a member of the newly formed Department of Biology at Oxford, where he teaches molecular, cell and developmental biology, as well as some genomics, to undergraduates taking the Oxford MBiol degree.

Can Aztekin

École Polytechnique Fédérale de Lausanne

Can Aztekin received his BSc in Biological Sciences and Bioengineering from Sabanci University in Turkey in 2014, during which he was selected for the Harvard Stem Cell Institute Internship Program. He then earned his MSc in Biomedical Engineering at Koc University in Turkey in 2016. Following this, he obtained his PhD in Developmental Biology from the University of Cambridge in the UK. In 2021, Can joined the Swiss Federal Institute of Technology Lausanne (EPFL) as an ELISIR Scholar and established his own research group, investigating structural regeneration using a comparative approach between regeneration-competent tadpoles and regeneration-incompetent mice. The group combines traditional developmental biology approaches with innovative imaging and single-cell multi-omics methods. Can was awarded the Branco Weiss Fellowship in 2022.

Osvaldo Chara

University of Nottingham

Osvaldo Chara's laboratory develops novel computational and mathematical models to understand tissues structurally and dynamically during development, regeneration and pathological conditions. His lab has developed ForSys, an open-source software capable of inferring static and dynamic mechanical stresses in tissues (Borges et al., 2024. bioRxiv). Using a combination of computational modelling and formal analysis, he discovered how a reaction-diffusion signal can control spinal cord regeneration in axolotls and predicted the diffusivity and half-life of the regeneration-inducing signal (Caliaro et al., bioRxiv, 2023). He developed the first computational model with cell-level spatial resolution of a regenerating spinal cord, which was tested using a transgenic FUCCI axolotl in collaboration with Elly Tanaka's lab (Cura Costa, Otsuki et al., eLife, 2021). Using modelling and image analysis, his lab has uncovered the key cellular mechanisms governing development and regeneration in a variety of axolotl, zebrafish and Drosophila tissues (Kozak et al., Development, 2023; Oliveira et al, Nature Com, 2022; Riquelme-Guzmán et al., Dev Dyn, 2022; Muñoz-Nava et al., Dev Biol 2020; Medelnik et al., Stem Cell Rep 2018; Currie et al., Dev Cell, 2022; Rost, Rodrigo Albors et al., eLife, 2016; Rodrigo Albors et al., eLife, 2015; Roensch et al., Science, 2013).

Uri Frank

University of Galway

Uri Frank got his PhD from the University of Amsterdam. His PhD research was on intraspecific competition in reef-building corals. He then did a postdoc at the National Institute of Oceanography (Haifa, Israel), followed by two postdocs in Germany, one at the University of Jena and the other at the University of Heidelberg. He is currently a professor at the University of Galway. Uri's research interest has gradually shifted from marine ecology to cell and developmental biology. His current research is utilizing the cnidarian animal model, *Hydractinia symbiolongicarpus* (a close relative of jellyfish and corals) to study the mechanisms of stem cell stability and decision-making in the context of development, homeostasis, and regeneration. Research in Uri's lab utilizes molecular biology, genetics, genomics, and chromatin biology of a population of stem cells that are the only known in vivo model of adult pluripotency in a genetically tractable animal.

Jérôme Gros

Institut Pasteur

Jérôme Gros obtained his PhD in 2006 from the University of Marseille-Luminy in France, in the field of Developmental Biology. He then moved to Boston, USA as a postdoctoral fellow in the laboratory of Cliff Tabin in the department of Genetics at Harvard Medical School. In 2012, Dr Gros became an Assistant Professor of Developmental and Stem Cell Biology at the Institut Pasteur in Paris, France where his lab uses an integrative approach ranging from classical embryology, molecular genetics, cellular biology, state-of-the-art live imaging microscopy and biophysics to understand how cells and molecular cues interplay to shape tissues during embryogenesis.

Ragnhildur Thóra Káradóttir

Wellcome-MRC Cambridge Stem Cell Institute

Ragnhildur Thóra Káradóttir is the Director of the Cambridge Centre for Myelin Repair and a group leader at the Cambridge Stem Cell Institute, University of Cambridge. She did her undergraduate degree in Biochemistry at the University of Iceland. For her postgraduate training, she entered the Wellcome Trust 4-year PhD Programme in Neuroscience, at UCL. After completing her PhD She was awarded a Dorothy Hodgkin Fellowship of the Royal Society and then a Wellcome Trust Career Development Research Fellowship to establish her own group at the University of Cambridge. She has >20 years' experience studying neuronal regulation of myelination and remyelination. She has established an interdisciplinary laboratory with expertise in single-cell electrophysiology, in vivo models of myelin regeneration and brain stem cells. Prof. Káradóttir has received multiple awards for her research on neuron – glia interactions, including the Allen Distinguished Investigator Award, the FENS-Kavli Network of Excellence Award, the Lister Institute Research Prize and an ERC Consolidator award. She has over 60 publications in high-ranking journals including Science, Nature, Nature Neuroscience and Neuron. She has trained and mentored 12 postgraduate students and 6 postdoctoral fellows. Several have been successful in receiving independent fellowships.

Rita Mateus

Technische Universität Dresden and Max Planck Institute of Molecular Cell Biology and Genetics

Rita Mateus is a joint group leader at the Max Planck Institute of Molecular Cell Biology and Genetics and the Cluster of Excellence Physics of Life in Dresden, Germany. She has always been interested in understanding how cells coordinate precise growth and form of tissues, allowing them to become fully functional. To this end, Rita did her PhD in Prof. Antonio Jacinto's laboratory in Portugal, where she investigated how, upon injury, the zebrafish caudal fin precisely regenerates its shape and size, over and over, error-free. During her postdoc in the group of Prof. Marcos Gonzalez-Gaitán in Switzerland, Rita turned to development to investigate how morphogens control organ growth, using the zebrafish pectoral fin as a model. Now, in the Mateus laboratory, Rita's team investigates how physical properties guide cells in establishing organ proportionality during organ development and regeneration, with a focus on how cells sense and transduce electrical, mechanical, and chemical cues into regulating organ growth.

Aida Rodrigo Albors

University of Edinburgh

Aida Rodrigo Albors studied Biology at the University of Valencia, Spain. She became fascinated by axolotls when she heard that they can regenerate virtually every body part, including the spinal cord. To learn more about their unique regenerative capacity, she moved to Germany to do her PhD with Elly Tanaka at the Max Planck Institute of Molecular Cell Biology and Genetics and the Centre for Regenerative Therapies, Dresden. Aida discovered that spinal cord stem cells in the axolotl redeploy developmental gene expression programmes to regenerate. To gain a better understanding of why mouse spinal cord stem cells (ependymal cells) are not that efficient at repairing the injured spinal cord, Aida joined Kate Storey at the University of Dundee. She uncovered previously unappreciated immature and mature ependymal cells in mice and hints suggesting that mature ependymal cells cannot revert to an embryonic-like state that supports regeneration. Since April 2023, Aida is a Chancellor's Fellow at the Centre for Regenerative Medicine at The University of Edinburgh. The goal of her lab is to discover new mechanisms of spinal cord regeneration by working across species with diverse regenerative capabilities: axolotl, mice, and spiny mice – the only known mammal that can recover from spinal cord injury.

Henry Roehl

University of Sheffield

Henry Roehl has fifty papers and over 5000 citations to date. His lab has published studies on the role of proteoglycans in axon pathfinding and cartilage tumour formation as well as studies on how Retinoic acid, FGF, WNT and Hedgehog signalling act during development of the zebrafish skeleton. More recently his group has focused on zebrafish larval tail development and regeneration. One current project involves understanding how the Hedgehog and TGF-beta signalling pathways mediate the transition from wound healing to regeneration. A second project aims to compare developmental cell types to those that emerge during regeneration using scRNA-seq with a focus on the WNT signalling pathway. Dr. Roehl is an active member of the research community, serving on the BSDB committee (2012-2017) and co-founding the International Society for Regenerative Biology (isrbio.org, Secretary 2020-Present); he has co-organised an EMBO Regeneration Workshop (Salerno, Italy, 2016) a BSDB meeting (Warwick, 2017) and an ISRB conference (Vienna 2023); he has served on the Wellcome Sir Henry Dale Fellowship Committee and the BBSRC Committees for sLoLa, Pioneer and Responsive Mode grants.

Filipa Simões

University of Oxford

Filipa Simões is a Group Leader and British Heart Foundation Research Fellow at the Institute of Developmental and Regenerative Medicine, DPAG, and a Hugh Price Fellow at Jesus College, University of Oxford, UK. Her research is focused on understanding how immune cells, in particular macrophages, can be programmed by their neighbouring cells to repair the damage caused by a heart attack. Her team uses genomics, spatial transcriptomics and functional in vivo and in vitro assays to dissect the spatiotemporal dynamics of cellular microenvironments, identify intercellular signalling networks and decipher how these converge to define macrophage identity, plasticity and function in the healthy and diseased heart.
Filipa has a degree in Microbiology and Genetics from the Faculty of Sciences, University of Lisbon, Portugal, and a PhD in Biochemistry from the Faculty of Sciences and Technology, University of Coimbra, Portugal, during which research was undertaken at the Weatherall Institute of Molecular Medicine, University of Oxford. She did her postdoctoral work at the Department of Physiology, Anatomy and Genetics, University of Oxford, where she identified distinct functional cell subpopulations in the developing and regenerating epicardium. Through a BHF CRE Transition Fellowship, Filipa identified macrophages as direct collagen contributors to the forming scar during heart regeneration and repair.

Poster Session

13:05-14:30

Poster Session

1

Mechanisms of robustness in vertebrate paraxial mesoderm morphogenesis

Q. Chen, B. Steventon

University of Cambridge, UK

What drives robust tissue morphogenesis during development? A key challenge is to understand how both tissue intrinsic patterning mechanisms and extrinsic mechanical forces contribute to developmental robustness. A defining feature of embryogenesis is the progressive elongation of the anterior-posterior body axis. In vertebrates, this is coupled with the clock-like segmentation of the presomitic mesoderm (PSM). Interestingly, progenitor cell loss, decreased cell number, or cell division defects don't affect PSM elongation in zebrafish embryos. Across the PSM, a spatial expression pattern of three T-box genes (tbxta, tbx16, and tbx6) emerges, in response to gradients of Wnt and FGF activity. I hypothesize that they can act together to enable the re-establishment of tissue elongation rates upon sub-threshold reductions in cell number. I aim to explore the driving forces that contribute to zebrafish PSM morphogenesis robustness by first determining the robustness limit of cell ablation. This will provide the least number of cells required for PSM re-establishment and the dynamic morphological alterations. I will further observe the dynamics of morphogen gradient re-establishment and how this links to the rescue of T-box gene expression. Furthermore, I will explore mechanical input from the adjacent notochord and neural tube that affect the PSM morphogenesis. By elucidating the interplay between the cell intrinsic patterning with extrinsic forces from adjacent tissues, this study aims to provide a comprehensive understanding of the robustness underlying zebrafish PSM elongation. Insights gained from this project will contribute to understanding the fundamental developmental process for future research on multi-scale interactions.

2

Jerboa induced pluripotent stem cells to unravel the mechanisms of limb-size control via inter-species chimeras

I. Goel, R. Tsutsumi, K. Cooper, A. Rosello-Diez
University of Cambridge, UK

Evolutionary developmental biology (evo-devo) aims to understand how developmental mechanisms changed during evolution. The variations of limb size and proportions provides a strong model to study this evolutionary diversity. I aim to define the mechanisms controlling limb size using inter-species chimeras in innovative ways; specifically, limb-specific jerboaàmouse chimeras. Jerboa induced pluri-potent stem cells (jiPSCs) were generated in Kyoto University using a sendai virus based stealth RNA vector and the jiPS cell line was established after analysing with different methods. In this poster, I will present my progress in the generation and characterisation of jiPSCs, including pluripotency assessment by immunocytochemistry and qPCR of established markers, RNA-sequencing and teratoma formation in mouse. These established jiPSCs will then be injected into limbless mouse blastocysts and the resulting chimeras will be analyzed by 3D limb morphometry, in situ hybridization, and immunohistochemistry. Transcriptomics and chromatin-accessibility analyses will identify the gene regulatory networks involved in the control of limb size, i.e., differentially active in jerboa limbs grown within mouse bodies vs. normal jerboa limbs. I hypothesize that if early limb bud cells are placed within the signal environment of a different species, they will adapt their developmental tempo accordingly, leading to a change in limb size, as compared to the donor of limb mesenchyme. This study has the potential to open up new avenues in the field of iPSCs as well as limb chimeras and development.

Poster Session

3 Unravelling mechanisms of neuroepithelial to radial glial transition using novel organoid DamId technologies

A.P.A. Donovan, M. Sutcliffe, M. Lancaster, A. Brand
University of Cambridge, UK

Timely transitions in stem cell identity and competence during brain development underpin the capacity of neural stem cells (NSCs) to produce a vast array of neuronal and glial cell-types. One such transition during the earliest stages of cerebral cortex development is the conversion of symmetrically dividing neuroepithelial cells to neurogenic radial glia. The timing of this transition determines brain size in humans and great apes and deviations in this timing may underlie neurodevelopmental abnormalities in brain growth. Studying these early events in human neurodevelopment has proven challenging due to the lack of early-stage human fetal tissue. Brain organoids derived from human pluripotent stem cells provide a tractable system for this purpose. The neuroepithelial to radial glial transition in human cerebral organoids is characterised by broad transcriptional changes, orchestrated at least in part by the transcription factor ZEB2. How ZEB2 regulates this transition, and how ZEB2 expression is controlled in a timely manner, are two outstanding questions. Here, we combined novel organoid DamID methodologies and chromatin conformation capture to investigate the role of ZEB2 in the neuroepithelial to radial glial transition. Our aim is to construct a comprehensive network of transcriptional and epigenetic regulation that provides broad insights into the mechanisms underlying the regulation of brain size.

4 Can in-vitro cultures recapitulate the transcriptional heterogeneity of oligodendrocytes?

R.Fetit, L.A. Seeker, L.J. Wagstaff, A.Williams
University of Edinburgh, UK

Oligodendrocytes are special cells in the brain and spinal cord that form membrane extensions around neuronal axons which form the myelin sheath. Myelin loss is the cause of many neurodegenerative diseases, including Multiple Sclerosis (MS). We have previously shown that oligodendrocytes, and their progenitors (OPCs), are heterogeneous at the transcriptional level and the proportions of the different subtypes vary in health and disease. We identified 2 OPC subtypes (NELL1+ and PAX3+) and 3 oligodendrocyte subtypes (OPALIN+, RBFOX1+ and SPARC+). Whether this transcriptional heterogeneity can be recapitulated in-vitro is yet to be investigated. Using human embryonic stem cells (hESCs) we generated OPCs and Oligodendrocytes and maintained them for three weeks in-vitro. We then quantified the subtypes using flow cytometry. Finally, we transplanted GFP+ OPCs into immunocompromised myelin-deficient Shiverer (Shi/Shi:Rag2-/-) mice to assess the differentiation of OPCs into different oligodendrocyte subtypes in-vivo. Flow cytometric analysis revealed that at 1 week, OPCs co-express NELL1+ and PAX3+. By three weeks, there is a significant increase in NELL1+ OPCs concomitant with a significant reduction in NELL1+PAX3+ OPCs. Moreover, Oligodendrocytes in culture express all three subtype markers (SPARC+OPALIN+RBFOX1+), the proportions of which do not change from 1 to 3 weeks. Furthermore, we confirmed the presence of the different oligodendrocyte subtypes in the human-mouse chimeras at 6 weeks of age using immunofluorescence. Taken together, our data suggests that in-vitro cultures lack the necessary cues to drive the differentiation of OPCs into distinct oligodendrocyte subtypes, whereby they remain in a "confused" state expressing all three subtype markers.

Poster Session

5 **Inducing cell migration in an ex vivo assay promotes migratory cell fates in early chick embryo explants**

Y. Takahashi, B. Steventon
University of Cambridge, UK

Gastrulation orchestrates the global reorganization of a single-celled epithelial layer into the three primary embryonic germ layers: ectoderm, endoderm, and mesoderm. While the role of genes in influencing cell behaviors, which in turn shape tissue organization and drive the emergence of whole embryos during gastrulation is well-studied, understanding how specific cell behaviors feedback to cell fate decisions remains limited. Previous studies highlight the role of extracellular matrix proteins, like fibronectin (FN), in facilitating cell migration and epithelial-to-mesenchymal transitions. Here, we investigate the impact of FN-coated substrates on cell behavior during gastrula-stage chick embryo development. Our findings show that FN-coated glass induces cell migration in explanted chick anterior primitive streak (APS; mesodermal) and prospective neural plate (PNP; ectodermal) tissues. Bulk RNA sequencing and in situ hybridization chain reaction analyses of APS and PNP explants at 0h and 24h reveal an increase in BMP activity and gene expression changes that mark a transition towards migratory fates within each germ layer. Specifically, APS explants shift from expressing anterior to posterior streak markers and PNP explants transition from expressing neural to neural crest markers. This implicates a potential modulation of BMP signaling—a crucial factor in posterior primitive streak and neural crest development in vivo—by cell behavior. In summary, our results show that inducing cell migration promotes migratory cell fates within embryonic germ layers. Future work includes functional testing to understand BMP spatiotemporal dynamics.

6 **Investigating retinal cellular dynamics in eye disorders using Zebrafish embryos**

S. Sharma, R. Lea, C. Manning

University of Manchester, UK

* Selected for a short talk

The visual function of the eye is dependent on early eye morphogenesis to acquire the necessary three-dimensional shape and size of a mature eye. Alterations in morphogenesis lead to the developmental eye disorders namely Microphthalmia (reduced eye size), Anophthalmia (no eye) and Coloboma (optic fissure closure defects) (MAC conditions) which occur 1 in 10000 births and account for up to 25% of childhood blindness. We analyzed the MAC patients' gene panel which show enriched cell adhesion and cytoskeletal gene mutations. This is medically relevant because translation of patient genes into tractable cellular morphogenesis mechanisms during early development is lagging. We hypothesize that MAC conditions, involving morphogenetic defects, initiate during early development and could result from mutations in cytoskeletal and adhesion components affecting eye morphogenesis. We are particularly focused on FNBP4 (Formin binding protein 4), amongst other cytoskeletal and adhesion MAC patient's genes based on morphogenesis during early development using gene ontology. FNBP4 perturbation in MAC patients have been identified through whole-exome sequencing. However, the mechanistic insights into FNBP4's role in MAC disorders remain unclear. Using RNA in-situ, we show that FNBP4 mRNA is localized to retinal progenitor cells the optic cup during zebrafish development. We find that CRISPR knockout of FNBP4 leads to microphthalmia in Zebrafish embryos. Preliminary findings indicate that FNBP4 knockout leads to microphthalmia, accompanied by increased apoptosis resulting in reduced cell number, suggesting a potential link to alterations in cellular dynamics. Future studies focus on analyzing the local changes in retinal cellular dynamics, shape, size, motility, tension, and global changes in optic cup architecture in FNBP4 mutant resulting in microphthalmia condition. We will further dissect the molecular pathway regulated by FNBP4, shedding light on its role in local-global coupling mechanisms during optic cup morphogenesis, particularly in microphthalmia conditions.

Poster Session

7 **The zebrafish: in the goldilocks zone for investigating the development and regeneration of tissue architecture**

B.D. Crawford
University of New Brunswick, Canada

The molecular and cellular processes underlying the development and regeneration of functional tissue architecture are exquisitely sensitive to myriad mechanical and biochemical signalling systems. They integrate information over poorly characterized spatial and temporal scales, exhibiting stigmergy and emergent properties that are effectively impossible to recapitulate in vitro. On the other hand, good in vivo models are also lacking; results from invertebrate models are difficult to generalize to mammals, and murine systems are expensive, develop slowly and internally severely limiting imaging methods, and can raise problematic ethical considerations. The zebrafish, with its fully sequenced and easily manipulable genome, rapid development as externally fertilized transparent embryos, and availability of thousands of transgenic lines offers an attractive middle ground. My lab has developed a variety of novel techniques, reagents and approaches for the investigation of extracellular matrix remodelling in the intact zebrafish embryo that should appeal to researchers exploring the development and regeneration of complex tissue architecture in vertebrates. This poster highlights a variety of these, giving examples of their use and availability to other researchers.

Poster Session

8 Unravelling lineage decision mechanisms of nestin-expressing progenitors during mouse cerebellum development and regeneration

J.B. Christensen, A.P.A. Donovan, A. Reid, A.H. Brand, N.S. Bayin
University of Cambridge, UK

The cerebellum is a hindbrain structure crucial for motor and social behaviour. The neonatal mouse cerebellum is a powerful system to investigate molecular mechanisms that drive neural stem cell lineage decisions due to its protracted development and high regenerative potential upon injury at birth. Cerebellar nestin-expressing progenitors (NEPs) consist of gliogenic and neurogenic subtypes, and give rise to astroglia and interneurons, respectively. Upon injury at birth, gliogenic-NEPs undergo adaptive reprogramming, switch their fate, and replenish lost neurons through an ASCL1-dependent mechanism. The gene regulatory networks (GRNs) that underlie NEP lineage decisions during development and regeneration and how ASCL1 mediates injury-induced lineage plasticity are unknown. We performed scRNA-seq on NEPs isolated from control and injured (irradiation at postnatal day 1) mouse cerebella at postnatal days 1-5. Through clustering and pseudotime analyses, we investigate NEP subtype lineage dynamics during development and regeneration and predict the GRNs involved in their lineage decisions. Preliminary analysis revealed differentiation trajectories of the gliogenic and neurogenic-NEPs and identified FOXO1 as a potential factor critical for interneuron lineage progression alongside ASCL1 during postnatal cerebellum development. Expression analysis during in vitro differentiation of mouse and human primary cerebellar NEP cultures shows that both ASCL1 and FOXO1 are transiently expressed at early stages of differentiation. Lentiviral overexpression of FOXO1 in primary NEPs increased neuron production, confirming a key role during lineage progression. We are currently investigating how FOXO1 and ASCL1 cooperate during interneuron differentiation, and how ASCL1 function varies during interneuron development and the gliogenic-to-neurogenic switch upon injury in different NEP subtypes by assessing FOXO1 and ASCL1 target genes during neonatal development and upon injury using targeted-DamID, ChIP-seq and scATAC-seq. Our findings provide insights into GRNs driving NEP lineage decisions in different contexts, and how they can be used to understand the causes of neurodevelopmental disorders and develop regenerative therapies.

9 Predicting skeletal regeneration: A mathematical model of skeletal stem cell activity

S. Short, R. Garcia, S. Farhat, R. Desaulniers, L. Schumacher, D. Coutu

University of Ottawa, Canada

Mathematical modelling has provided novel insights into the activity (e.g., self-renewal, proliferation kinetics, and differentiation rate) of a diverse range of stem and progenitor cell populations. Despite this, attempts to model skeletal stem cell (SSC) populations remain limited due to insufficient quantifiable data for model generation – largely stemming from past technical challenges associated with processing and imaging skeletal tissues. Our recently developed methodological pipeline has allowed us to prepare 3D sections of intact, adult mouse femurs, and we have generated the first quantifiable evidence demonstrating the existence of a self-renewing and multipotent population of SSCs in post-natal mice. Herein, we report our development of a stochastic mathematical model which aims to predict SSC population activity, accounting for cell self-renewal, fate/turnover, proliferation kinetics, and differentiation events. Genetic lineage tracing, thymidine analogue incorporation/retention, and imaging cytometry are incorporated to model SSC behaviour as a function of time. Lastly, we review our efforts to validate and improve this model based on new experimental data. The study of SSCs is currently limited by long processing times, high costs, and a need to reduce animal suffering (fracture modelling in rodents, etc.). Computational applications in SSC biology will serve to curb these obstacles by clarifying the complex role of SSC populations using a simulated environment, which will provide novel insight towards developing regenerative-based therapies.

Poster Session

10 Spinal cord elongation enables proportional tissue regulation in the Zebrafish posterior body

D. Saunders, C. Camacho, B. Steventon
University of Cambridge, UK

Early embryos display a remarkable ability to regulate the patterning of tissues in response to changes in tissue size. However, it is not clear whether this ability continues into post-gastrulation stages when cells have largely committed to distinct germ layers. Here, we performed targeted removal of neural fated cells in the zebrafish tailbud using multi-photon ablation. This led to a proportional reduction in the length of both the spinal cord and somitic mesoderm, revealing a capacity to regulate tissue morphogenesis across multiple tissues to build a well-proportioned posterior body. Following analysis of cell proliferation, gene expression, signalling and cell movements, we found no evidence of cell fate switching from mesoderm to neural fate to compensate for neural progenitor loss. Furthermore, we found that somitic mesoderm length is not reduced upon direct removal of an equivalent number of mesoderm progenitors, ruling out the hypothesis that neuromesodermal competent cells enable proportional regulation. Instead, reduction in the numbers of cells across the spinal cord reduces both spinal cord and somitic mesoderm length. We conclude that spinal cord elongation is a driver of somitic mesoderm elongation in the zebrafish posterior body and that this can explain proportional regulation of both tissues upon neural progenitor reduction.

11 Immune-related cellular niches in the regenerating zebrafish heart

E. Razaghi Siahroudi, T. Gungoosingh, S. Tüzüner, K. Çil, C. King, F. C. Simões

University of Oxford, UK

Zebrafish have the remarkable ability to regenerate their heart after injury. Macrophages are critical in this process: they clear up dead cells and debris, participate in fibrosis but also contribute to regeneration through interactions with their tissue microenvironment. However, little is known about the precise regulation shaping macrophage identity and function in response to cardiac injury. By combining single-cell and spatial transcriptomics, we discovered the composition and activation states of various immune cell populations found in distinct spatial territories of the regenerating and homeostatic heart. We uncovered information about macrophage, dendritic, B and NK cell transcriptomes and their corresponding location within the cardiac tissue, including the epicardium, the outflow tract, as well as the injury-zone cardiomyocyte microenvironment. By reconstructing immune-related cellular niches across the regenerating and the homeostatic heart, we were able to discover the molecular signatures mediating such specific cell-cell communication, therefore contributing towards dissecting the regulatory programmes driving macrophage pro-fibrotic and pro-regenerative phenotypes. Further analysis is underway to understand how specific microenvironmental signalling interactions may be enhanced or disrupted to support tissue regeneration. Our findings reveal how knowledge of cardiac niche-specific immune interactions could guide more effective pro-regenerative and anti-fibrotic therapies.

Poster Session

12 Hypoxia regulates the fate of human fetal lung epithelial progenitors

Z. Dong, A. Agarwal, A. Reid, C. Melo, E. Rawlins, N. Wit, J. Nathan

University of Cambridge, UK

* Selected for a short talk

Human embryos develop in a highly hypoxic uterine environment during the first trimester. However, the impact of hypoxia on human lung organogenesis remains poorly understood. In this study, we elucidated this relationship by isolating primary human first-trimester lung epithelial progenitors and cultivating them as fetal lung organoids in a self-renewing expansion medium. The lung epithelial progenitors remained undifferentiated under normoxia, but halted proliferation and initiated spontaneous differentiation towards various airway cell types, but not alveolar cells under hypoxia. Through single-cell transcriptomics, we identified distinct hypoxia-resistant and lineage-primed progenitor populations within normoxic organoids. Following short-term hypoxia exposure, the fate of lineage-primed progenitors diverged towards basal cells and neuroendocrine cells separately, revealing inherent heterogeneity in progenitor differentiation potentials. Activation of the HIF (Hypoxia-Inducible Factor) pathway was observed under hypoxia, and confirmed with HRE (Hypoxia-Response Element) reporters. Chemical stabilization of the HIF pathway under normoxia recapitulated the differentiation phenotype induced by hypoxia. However, differential functions of HIF1a or HIF2a on lung lineage decisions were elucidated through inhibition or stabilization of each homolog individually. Utilizing CRISPRi and transcriptomic analysis, we demonstrated that HIF1a regulated multiple processes in fetal lung progenitors, including proliferation, EGFR signalling, cholesterol homeostasis, and surfactant metabolism. ChIP-seq analysis identified a group of KLF-family genes as direct targets of the HIF pathway, mediating the differentiation of progenitors into basal cells. Moreover, chronic hypoxia directly reprogrammed mature human alveolar type 2 cells into airway cells, suggesting a process akin to bronchiolization of alveoli observed in injured adult lungs. Our findings indicate that hypoxia actively regulates the fate decisions of human lung progenitors during development via the HIF pathway. Additionally, ectopic activation of the developmental program due to localized hypoxia may contribute to the progression of chronic lung diseases.

13 High throughput production of patient-derived 3D bio-printed models of skeletal muscles as a robust platform for screening biological and therapeutics parameters of muscle metabolism in women with Polycystic Ovary Syndrome (PCOS)

Z. Farahbakhsh, L. Cussen, T. McDonnell, C. Miller, M.W. O'Reilly, M. McIlroy

Royal College of Surgeons in Ireland

Polycystic ovary syndrome (PCOS) is a prevalent metabolic disorder affecting approximately 10% of women worldwide. There is an established link between elevated androgen levels and disruptions in skeletal muscle (SkM) energy metabolism. Delineating the mechanistic impact of androgen excess on SkM energy metabolism may provide insights into the origins of metabolic disease in PCOS. Thus far, no animal model has fully replicated the complexity of human PCOS aetiology and pathophysiology, owing to the complex interface of adrenal, 11 oxygenated and gonadal androgens. Current in vitro models predominantly employ transformed or immortalised cell lines that may differ genetically and physiologically. However, primary cells offer a more faithful representation of tissue function, making them superior models for native tissue cells. Our study introduces an innovative approach: a 3D bioprinting model of skeletal muscle in vitro that can closely mimic native tissue characteristics. Our model is made using primaries isolated from tissue biopsies that are obtained from healthy or PCOS patients. Using a non-contact drop-on-demand 3D bio-printer, we optimised the hydrogel composition and cell density to create 3D SkM models. These multicellular skeletal muscles are then embedded within the hydrogel matrix and matured over 7-14 days. Following maturation, they undergo treatment with various steroid ligands for 14 days and are subsequently stained for mitochondrial and lipid droplet markers. Our observations from the in vitro patient-derived 3D-bioprinted models unveiled a distinct maturation in both morphology and structure of muscle tissue, presenting a marked contrast to the more simplistic development observed in 2D models. Additionally, the preliminary findings from our androgen ligand interventions revealed distinct morphological changes in the myocytes treated with various androgens in 3D. Our study demonstrates the potential of 3D bioprinting as a robust platform for understanding the mechanisms contributing to metabolic dysfunction in PCOS, potentially leading to novel treatments.

Poster Session

14 **The node is required for neural patterning but not specification**

A. Neaverson, B. Steventon

University of Cambridge, UK

Hensen's Node is considered to be the organiser in the vertebrate embryo, secreting signals that pattern the main body axes and induce the surrounding ectoderm to acquire neural fate. Node grafting experiments demonstrate that the node is sufficient to generate an ectopic axis with a fully patterned nervous system, but the requirement of the node in normal neural development is less clear. In the chick gastrula, the node can fully regenerate following ablation, and normal development continues. In order to delineate the node's requirement in neural development, we asked how the early neural plate is affected by ablation of the node, the source of neural induction signals. Comparison of single cell RNAseq and HCR-ISH data from control and node-ablated embryos showed that early neural marker genes are unaffected in the absence of the node. Notably, the definitive neural marker SOX2 is expressed in its normal pattern in node-ablated embryos, suggesting that the node is not required for neural induction. To test the extent of self-sufficiency in neural development, the neural plate was isolated from the rest of the embryo and cultured on its own. These cultures form structures resembling the neural tube, and upregulate SOX2, showing that they progress to a committed neural fate in the absence of the organiser. However, they lack anteroposterior organisation, and fail to upregulate the posterior regional marker KROX-20. When the node is included in anterior segments, a fully-formed head develops, with OTX2 and KROX-20 expression in the forebrain and hindbrain, respectively. These findings show that the node is not required for sustained neural induction, but rather for the correct organisation and regional specification of the brain.

Poster Session

15 **Investigating the differential responses of lymphatic microvasculature to regeneration and fibrosis**

L. Connolly, T. Bray, M. Storer, B.J.W.H. Mui
University of Cambridge, UK

Mammalian digits demonstrate a level dependant response to amputation. Amputation through the distal portion of the digit (P3 phalanx) typically results in a regenerative response. However, amputation through the adjacent P2 phalanx results in fibrosis. Which processes facilitate and propagate these differential responses remains unresolved. In recent years the role of the lymphatic system in regeneration has become a point of focus, with lymphatics having been demonstrated to promote intestinal and bone regeneration in mice. Therefore, we aim to investigate how the lymphatic system responds in digit tip regeneration and fibrosis. To investigate this, we are using an inducible lineage tracing system, Prox1CreErt2:tdtomato. With this system, we have observed a difference in lymphatic vessel density between regenerating and fibrotic digits. In fibrosis, lymphatic vessels percolate throughout fibrotic tissue, however vessels are spatially and temporally restricted in the regenerative digits. This observation implies that lymphatic vessels may respond differently in regeneration and fibrosis. We are subsequently beginning to interrogate what underlies these differences using single cell transcriptomics and investigating whether lymphatic vessels have a functional impact on regeneration and fibrosis in the digit by ablating lymphatic vessels temporally using transgenic animals.

16 **Dynamics of growth, collision, and cell division in epithelial monolayers**

C. Falco, D.J. Cohen, J.A. Carrillo, R.E. Baker

University of Oxford, UK

Although tissues are typically studied in isolation, such situations rarely occur in biology, as cells, tissues, and organs coexist and interact across various scales, shaping both form and function. In this work, we adopt a quantitative approach that combines experimental data, mathematical modelling, and Bayesian parameter inference to describe the dynamics of freely expanding and colliding epithelial monolayers. Two simple and extensively studied continuum models are employed, where cells move either randomly or in response to population pressure gradients. Following appropriate calibration, both models successfully replicate the primary features of individual tissue expansions. However, our findings demonstrate that when tissues are not isolated and interactions become relevant, assuming random cell motion can lead to unrealistic behaviour. In such cases, a model that considers population pressure from different cell populations proves more suitable and facilitates comparison with experimental measurements. Additionally, we investigate the dynamics of cell division within epithelial monolayers and demonstrate how a combination of minimal modelling and Bayesian inference can capture mechanical checkpoints in cell-cycle progression.

Poster Session

17 Facilitating regeneration in the brain upon injury via modRNAs

G. Vanacore, A. Boikova, C. Wilson, N.S. Bayin

University of Cambridge, UK

Unlike the rest of the brain, the neonatal cerebellum is highly regenerative and, upon injury at birth, the Nestin-expressing progenitors (NEPs) undergo adaptive reprogramming to replenish the lost cells. Although NEP-like cells exist in the adult cerebellum, it fails to regenerate upon injury. ATAC-seq of NEPs isolated 4 days after injury to the neonatal or adult cerebellum has shown decreased chromatin accessibility of proliferation and neural differentiation-related genes, such as Myc. Similar to the cerebellum, the heart displays age-dependent changes in regenerative capacity and, while Myc expression is high during neonatal cardiac regeneration, its expression is limited following adult heart damage. However, ectopic expression of Myc together with a transcriptional facilitator, Ccnt1, in the adult heart induces cardiomyocyte proliferation and regeneration. In this study, we aim to define the expression profile of Myc and Ccnt1 throughout cerebellum development and adulthood as well as, to determine whether Myc cooperates with Ccnt1 in NEP/NEP-like cells-mediated regeneration. Immunofluorescent analysis of the mouse cerebellum reveals that MYC and CCNT1 expression is variable in neonatal NEPs but declines dramatically in NEP-like cells. To assess whether transient Myc and/or Ccnt1 overexpression induces NEP proliferation and self-renewal, we transfected primary neonatal NEP cultures with modified-RNAs (modRNAs) for one or both (Myc+Ccnt1) vs. control (Gfp-modRNA) and observed a transient increase in proliferation upon combined overexpression of Myc+Ccnt1 but not Myc alone, suggesting that Ccnt1 drives neonatal NEP proliferation in vitro. Moreover, preliminary ex vivo studies, using adult cerebellum slice cultures, suggest that Myc+Ccnt1 overexpression induces astrocytes and NEP-like cell proliferation. Currently, we are investigating the mechanisms whereby Myc+Ccnt1 modRNAs facilitate NEP/NEP-like cell proliferation, and whether transient overexpression with modRNAs can rescue the age-dependent decline in regeneration using an in vivo stroke model. Together, these findings highlight modRNAs as a future therapeutic tool to facilitate brain regeneration upon injury.

18 Deciphering the impact of ECM proteins on cell ingression and mesoderm induction using gastruloids

A.Delahaye, G. Serrano Nájera, B. Steventon
University of Cambridge, UK

During gastrulation, early embryos undergo the specification and reorganization of their germ layers. This transformation necessitates the mesoderm's transition from an epithelial to a mesenchymal state (EMT) to acquire a migratory capacity. This process depends on mesodermal cells remodelling the extracellular matrix (ECM), while the ECM concurrently regulates cell fate. Despite its critical role, studying the developmental impacts of the ECM presents challenges due to its complex protein composition and overlapping functions, impeding traditional knockout methodologies.
Alternatively, in vitro models such as gastruloids could be utilized for studying ECM during gastrulation; however, current models fail to fully replicate the EMT at both morphological and cellular behaviour levels. To address this, we employ mouse embryonic stem cell gastruloids cultured on ECM proteins with crucial roles in embryonic development. Utilizing a reporter cell line, we track pluripotency exit and mesoderm activation, along with high-throughput imaging and computational analysis of live imaging data. This enables quantification of gene expression changes, morphological alterations, and cell migration dynamics. Notably, our observations reveal cell migration on fibronectin only after experimentally inducing mesoderm, while laminin appears to flatten the gastruloids while hindering mesoderm induction.
Now, we aim to enhance our understanding of cell migration dynamics in 3D by using hydrogels. Furthermore, preliminary data suggest that our high throughput pipeline could be used to screen for anti-metastasis drugs, underscoring its translational significance in addressing developmental and pathological processes.

Poster Session

19 Characterizing the basal cell population and clonal dynamics in the human lung

C. Bunn, E. Rawlins

University of Cambridge, UK

Basal cells are stem cells of the pseudostratified airway epithelium in the human lung. During homeostasis, they are responsible for self-renewal and differentiation into multiple airway epithelial cell types and are required for regenerative responses after injury. One key aim for regenerative medicine is to improve the repair response of basal cells in chronic lung diseases. However, there remains a critical knowledge gap in understanding the heterogeneity and long-term clonal dynamics of the basal cell population and its differences during development and homeostasis. This research seeks to address that knowledge gap by functionally assessing and creating a quantitative model of stem cell turnover and clonal dynamics in human fetal tissue, as well as adult human airway epithelium. We hypothesize that a novel tissue culture system preserving the 3D architecture of epithelial tissue while reaching a steady state will mimic the airway epithelial niche at homeostasis. To see if our in vitro model recapitulates the normal airway epithelium, we are comparing with in vivo data using immunofluorescence, scRNA-seq, and qPCR. We are using clonal analysis and lineage-tracing techniques to build a quantitative model of cellular turnover and heterogeneity within the basal cell population. This work addresses unanswered fundamental questions in developmental biology, as well practical knowledge that will be critical to proper implementation of targeted stem cell therapeutics in the human lung.

20 Developing a functional vascularised cardiac organoid system for disease modelling

S. Tüzüner, T. Gungoosingh, B. Psaila, A. Khan, F. Simões

University of Oxford, UK

Our current understanding of how the human heart reacts after a heart attack is limited due to the lack of human-based in vitro models that provide an accurate representation the complexity of human physiology. While the development of new vessels plays a pivotal role in disease modelling, the vascularisation process of the human heart has not been fully elucidated. It is known that immune cells influence the process of angiogenesis, but the role of macrophages in processes like angiogenesis and anastomoses has not been fully elucidated in the heart. Importantly yolk sac derived macrophages and bone marrow derived macrophages have different functions in the homeostatic and the regenerating heart. To circumvent the limitations of current in vitro models, we are using a vascularised ventricular cardiac organoid (CO) system, which contains endothelial cells, fibroblasts, pericytes, and ventricular cardiomyocytes and integrating yolk sac-derived and bone marrow-derived macrophages to assess their effect on blood vessel formation. This allows us to increase the multicellularity and more faithfully recapitulate the complexity of in vivo systems in a petri dish. We have differentiated yolk sac derived macrophages and bone marrow derived macrophages from hiPSCs and conducted phenotyping of these immune cells through flow cytometry analysis, confirming the expression of both general and lineage-specific macrophage markers. Subsequently, we integrated these immune-derived cells into the cardiac organoid system. We are now using this model to address how the cardiac niche is programming tissue resident and monocyte-derived macrophages in situ and how their phenotypic differences contribute to injury repair of our 3D cardiac in vitro model.

Poster Session

21 **Deciphering the cellular mechanisms underpinning structural organisation of skeletal muscle**

M.A. Mendieta-Serrano, S. Theis, T.E. Saunders
University of Warwick, UK

Skeletal muscle formation involves major changes in both cell shape and position. Fast muscle precursors fuse and elongate to form contractile muscle fibres organised in a highly ordered tissue. Such organisation is crucial for the proper function of muscle in generating contractile forces able to propel movement. Yet, despite its physiological importance, it remains an open question as to how complex muscle architecture emerges during embryogenesis. Here, we use high-resolution live 4D imaging in combination with quantitative analysis to elucidate how complex cell organisation emerges during skeletal muscle formation in zebrafish. We observed that as future muscle fibres elongate and fuse, they form a highly polarised array parallel to the dorsal-ventral axis. The fibres also rearrange along the medial-lateral axis, with behaviour akin to a structural (topological) transition in the myotome. This change in topological order corresponds with the emergence of a characteristic helical organisation of the fibres by 36 hpf. In mutants lacking fusion or slow muscles, the cell packing and twisting are perturbed, consistent with a change in the local boundary constraints. Overall, we find that robust muscle formation depends on cells undergoing topology transitions to ensure the emergence of a highly order architecture at the tissue scale.

Poster Session

22 Mechanical confinement triggers the thickening of the neural plate

G. Serrano Nájera, L. Busby, K. Weijer, B. Steventon

University of Cambridge, UK

The internalisation of mesoderm precursors through the primitive streak in birds and mammals has received considerable attention; however, how these are balanced with divisions events across the epiblast is unknown. Using in vivo recordings at cellular resolution, we observed that 40% of cells abandon the epiblast's surface through the neural plate (NP) outside the streak. Blocking mesoderm induction does not affect the ingression events in the NP, suggesting that these cells do not form part of the mesoderm layer. We investigated the fate of cells undergoing ingression outside the streak by labelling small numbers of cells on the surface of the NP. We observe that the cells sink into the layer but they do not cross the basal lamina or acquire a mesenchymal phenotype, suggesting that they do not undergo epithelial to mesenchymal transition.
We observed that the embryo proper does not significantly change in area during gastrulation despite the high proliferation rates. Based on these observations we proposed that mechanical forces may drive the cell sinking in the NP. To test this hypothesis we developed a method to confine avian embryos in the plane of epiboly. Confined embryos present a reduced embryonic area and develop a significantly thicker NP without altering cell division rates or average cross-sectional cell area, suggesting that when the tissue cannot accommodate more cells in the plane, these sink generating a 3-dimensional NP. In summary, our observations suggest that cell sinking outside the streak and the thickening and pseudostratification of the early neural tissue are the consequence of the multi-tissue interactions that confine the NP.

23 Uncovering novel liver regeneration and antifibrotic pathways in Acomys (spiny mice)

K. Ching, J. Man, R. Aird, S. Ferreira-Gonzalez, S.J. Forbes

University of Edinburgh, UK

* Selected for a short talk

Spiny mouse (genus Acomys) is an emerging model for mammalian regeneration research. Their extraordinary repair and regeneration capacity was first described in the skin, but later also in central nervous, renal, musculoskeletal, and cardiac system. Despite the remarkable regenerative capacity of mammalian livers, sustained injury results in accumulation of fibrotic tissue and cirrhosis. Uncovering liver regeneration and antifibrotic pathway in the Acomys will therefore open up new hope for cirrhosis management. The goal of this project is to examine whether Acomys livers will display accelerated regeneration with minimal fibrosis upon injury. We aim to first characterise the cellular phenotypes and then assess the regeneration capacity of Acomys upon acute and chronic liver injury. We also hope to understand the mechanism towards their fibrosis-free healing and translate the findings for therapeutic and diagnostic purposes. Our preliminary findings revealed the loss of hepatocyte zonation pattern and low CD68+ macrophage count in Acomys despite the similar architecture, and cell type-specific marker expression between Acomys and Mus musculus. To investigate their response towards injury, we employed 1) acute injury model of paracetamol overdosing, 2) chronic fibrosis-inducing model of hepatotoxin and 3) surgical model of partial hepatectomy. Upon paracetamol insult, Acomys demonstrated higher tolerance with less hepatic necrosis. However, they showed significantly higher level of cellular senescence than Mus. In chronic injury model, similar phenomenon of cellular senescence induction around the injured area was observed. Cellular senescence has been implicated in tissue repair for both beneficial and detrimental effects. It facilitates wound healing, but prolonged senescence promotes inflammation and hinders regeneration outcome. In surgical model, Acomys was able to restore liver mass within 7 days, which is comparable to Mus. We have also established organoid culture system for biliary cells and monolayer culture for hepatocytes for upcoming functional and mechanistic study.

Poster Session

24 The role of dynamic expression in neurogenesis during development and regeneration

X. Soto
University of Manchester, UK

The development of the brain requires a tight balance between stem cell proliferation and differentiation. Previous work has shown that specific genes, such as the Her/Hes transcription repressor family, are essential for the maintenance of neuronal stem cells and factors such as the microRNA (miR), controls their expression. My own research has shown that during development the generation of new neurons, genes (i.e. Her/Hes gene family) are not simply on or off. Instead, their levels pulse dynamically over time, influenced by the miR, and control whether the cells stay as proliferating progenitors or becoming new neurons.
It is known that the same genes involved in development of the nervous system are reactivated upon spinal cord (SC) injury and are important during SC regeneration. However, the mechanisms are unknown. Therefore, it is not clear whether during SC regeneration and the generation of new neurons are also controlled by the pulses in gene expression. Here, I describe using the zebrafish model to study dynamic gene expression during development of the nervous system and then go on to discuss ongoing work on its role in SC regeneration. This work focus studying Her6 dynamic expression and how miR-9 finely-tune its expression providing an understanding on the mechanism and functional importance of pulsatile gene activity during neuronal cell-fate decisions in development and regeneration. This will grant new insights with potential translational implications for injuries on SC in animals with no regenerative capacity, such as mice and humans.

25 The role of mechanics in liver organoid formation and regeneration

A. Guzman-Herrera, J.Y. Lin Quan, S. Warrington, E. Gentleman, J. Burden, L. Aloia, Y. Mao

University of Cambridge, UK

Mechanics has an important effect on tissue morphology during development and regeneration, influencing how efficiently a tissue repairs itself. Liver is a highly regenerative tissue that has been widely studied at a molecular and genetic level, however, the mechanical aspect remains unclear. In this project we investigate the role of the mechanoenvironment and of tissue mechanics during liver regenerative morphogenesis. To address this, we use Intrahepatic Cholangiocyte Organoids (ICOs), which recapitulate a ductal regenerative response to restore both cholangiocytes and hepatocytes.
We first characterise organoid morphology as they grow and differentiate. ICOs initially form a spherical, translucent, cell monolayer; upon differentiation, they either remain spherical or acquire a more complex, folded and multi-layered morphology. We find that the final morphology of differentiated ICOs correlates with their cell composition, having a cholanciocyte-like or hepatocyte-like cell profile.
Interestingly, a hepatocyte-like folded morphology can also emerge without chemical differentiation. The mechanoenvironment has been shown to induce and regulate cell differentiation, thus we investigate the effect of substrate mechanical properties (i.e. stiffness) on ICOs. Our data suggests substrate stiffness does have an important effect on organoid morphologies and cell profile.
We also look at the mechanical properties of the organoids themselves, how they change as they differentiate and how this affects ICOs ability to respond to further damage. We observe organoids become more 'solid' and, when injured, respond differently compared to young ICOs.
The liver can respond to injury in many ways, but it remains unclear how and why the injured tissue chooses one mechanism over another. We hope that by studying the mechanical aspect of this regenerative process we can better understand it and even improve it in diseased conditions such as fibrosis.

Poster Session

26 Characterising the interplay of signalling and cell mechanics in zebrafish presomitic mesoderm morphogenesis

R. Narayanan, R. Harrison, A. Kader, T. Saunders
University of Warwick, UK

Zebrafish skeletal musculature derives from the presomitic mesoderm (PSM) during embryogenesis. The fast-twitch muscles differentiate from the laterally positioned mesenchymal cells of the PSM. The slow-twitch muscles develop from a medially located pseudoepithelial monolayer of cells – the adaxial cells. Hedgehog (Hh) signalling is required for the slow-twitch fate of these cells. It is unclear if and how Hh signalling affects adaxial cell mechanics, and thereby PSM morphogenesis.
By quantifying adaxial cell dynamics, we find that tension fluctuations at the cell-cell junctions and cell rearrangements in the adaxial cells are comparable to the lateral PSM – a tissue that has been measured to have solid material property. However, in contrast to the lateral layers, we observe the adaxial cell array to be a confluent monolayer. Cdh2-mediated adhesion is required to maintain this confluency in wild type but seems unnecessary in the absence of Hh signalling. This contrasting dependence on Cdh2 is due to Hh signalling impacting movement of cells into the PSM, possibly affecting the tissue rigidity transition in the body axis that underlies its anterior-posterior elongation. Thus, we reveal new understanding of how Hh signalling affects local mechanical forces and material properties during morphogenesis.

27 Crafting robust patterns in developing tissues under mechanical stress

G. Paci, B. Baum, Y. Mao

University College London, UK

* Selected for a short talk

Animal tissues undergo development and take on their functional 3D shape while experiencing continuously changing mechanical forces. Despite decades of work into how genetic and biochemical programs guide morphogenesis, we do not yet understand how developmental patterns are (1) robustly achieved and (2) maintained in the presence of continuous mechanical perturbations. To address these questions, we combine ex-vivo and in-vivo approaches using the Drosophila wing disc as a model system. We have developed a high-throughput assay based on PDMS channels to stretch wing discs of living larvae and study the long-term effects of mechanical forces on development. We find that wild-type larvae that have been mechanically challenged even for a few hours develop into adults with a higher incidence of developmental defects (wing blisters, notches). Intriguingly, adult wing size inversely correlates with constriction width, which we hypothesize could be due to an increase in apoptosis. In larvae with "softened" wing discs, we find no effect on global wing area but severe patterning defects, consistent with tissue fluidity helping prevent extreme cell deformations and cell death but worsening cell mispositioning. Among the developmental defects observed in our assay, phenotypes related to Notch-Delta signalling appear prominently. In the second part of this project, we are investigating the development of sensory organ precursors (SOPs) at the wing margin, which are specified through Notch-Delta signalling during the 3rd instar larval stage and form two cell rows straddling the dorsoventral boundary. Through 2-photon imaging and 3D cell segmentation of cell shapes, we find that 3D cell contacts are crucial in tuning the signalling range and achieving the correct spacing between SOPs. In tissue stretching experiments, we observe that SOPs are stiffer than neighbouring cells which may help confer robustness to the pattern. Indeed, preliminary perturbation experiments show that wing discs with genetically "softened" SOPs have an altered pattern.

Poster Session

28 Celsr1+ stem cells contribute to angiogenesis and vessel formation in the process of tissue regeneration

D. Fan, M. Sabalić-Schoener, M. Sordi, P. Sharpe
King's College London, UK

Mouse incisors are continuously growing organs where growth is fuelled by specific resident stem cell populations. The rate of growth is perfectly balanced by the loss of cells from the incisor tip. In situations where growth rate is increased such as loss of occulsion, a small sub-population of quiescent mesenchymal stem cells, identified by expression of Celsr1, enter mitosis and generate addition cells to accommodate the increase in growth rate. Single cell RNA sequencing analysis combined with experiments in vivo reveals that Celrs1+ stem cells are progenitors of endothelial cells and also interact with immune cells contributing to angiogenesis and vessel formation during rapid periods of incisor growth.

Poster Session

29 **Building the embryo: mechanical forces as regulators of axis elongation**

C. Camacho-Macorra, D. Saunders, B. Steventon

University of Cambridge, UK

In vertebrate embryos, the body axis is segmented into tissue blocks known as somites, which ultimately give rise to the skeletal muscle and vertebrae in the adult body. The establishment of this body axis occurs in a conserved, progressive manner from the anterior to the posterior. Concurrently, as the embryo elongates, a population of progenitor cells localized in the tailbud, termed Neuromesodermal Progenitors (NMPs), contributes to the growth of the spinal cord and mesoderm. In addition, during this process, the morphogenesis of one tissue exerts forces that influence the morphogenesis of neighboring tissues, driving the elongation of the embryo axis.
Recent studies have shown the role of the transcriptional co-activator Yap1, a known sensor of biomechanical forces, is required for a proper body axis formation. Under mechanical stress, Yap1 translocates to the nucleus, where it forms a transcriptional complex with TEAD transcription factors, activating the transcription of target genes. This process can be modulated by Vestigial-like protein 4 (Vgll4), which competes with Yap1 for binding to TEAD, inhibiting its activity. However, the precise mechanisms through which mechanical forces impact the behavior of progenitor cells in the tailbud and contribute to axis elongation in vertebrates remain poorly understood.
In this study, we observe the presence of Yap1 activity in the progenitor niche of the tailbud during axis elongation in zebrafish. Leveraging a mutant line for vgll4b, a zebrafish Vgll4 paralogue, we demonstrate that somitogenesis is affected and the resulting embryos present a shorter body axis. Taking all together, we propose that mechanical forces generated within the tailbud, coupled with a regulated mechanotransduction response in progenitor cells, are essential for proper body axis elongation in vertebrates.

Getting here

Robinson College is situated on Grange Road (CB3 9AN), close to the centre of Cambridge. Grange Road runs between Barton Road and Madingley Road and is parallel to Queens' Road (the 'Backs').

The best way to approach the College by road from the north, south or east is from Junction 12 of the M11. If travelling by car, we recommend the **Park & Ride Service** which will run you into the city throughout the day, as parking in Cambridge City Centre is limited. There is no parking available at Robinson College. The University **Universal Bus Service** has a bus stop on Grange Road outside the College.

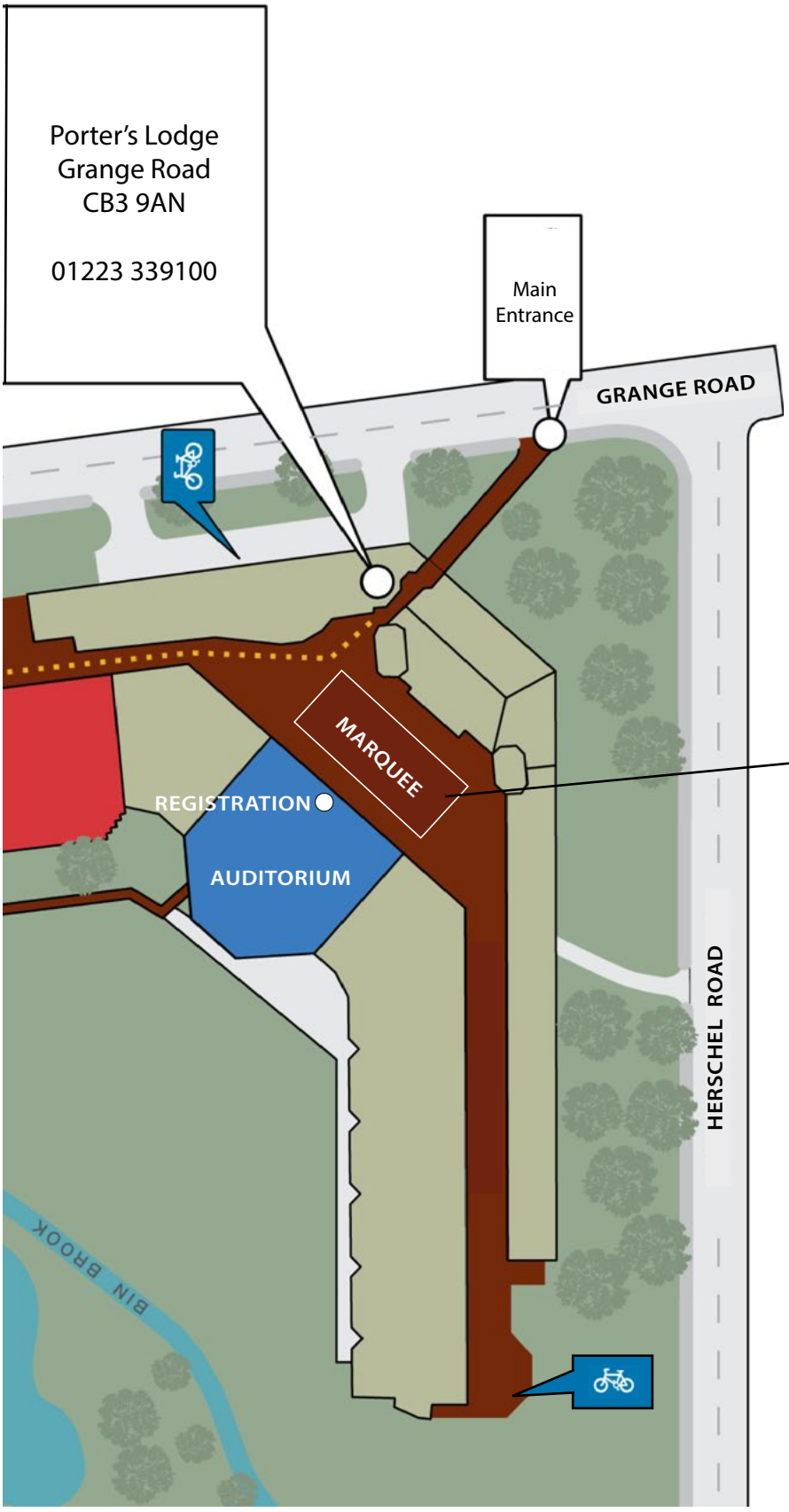
Walking/cycling from Market Square in the town centre:
Go past Great St Mary's, heading towards Senate House.
Follow Senate House Passage, then turn right onto Trinity Lane.
Turn left 30 yards later onto Garret Hostel Lane.
Continue over the footbridge until you reach Queens' Road.
Cross Queens' Road and continue on the footpath running past the University Library.
Arrive on Grange Road, directly opposite Robinson College.

Trains run frequently from London King's Cross, London Liverpool St (slower service), Stansted Airport and Birmingham.

There is bicycle parking on Herschel Road.

More information about directions.

Venue map



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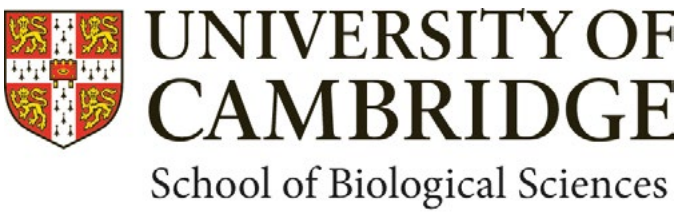

This document was produced by Issy Baker,
School of Biological Sciences, July 2024