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PROGRAMME

11 – 13 March 2026
Vienna, Austria

Symposium for the next generation of stem cell researchers

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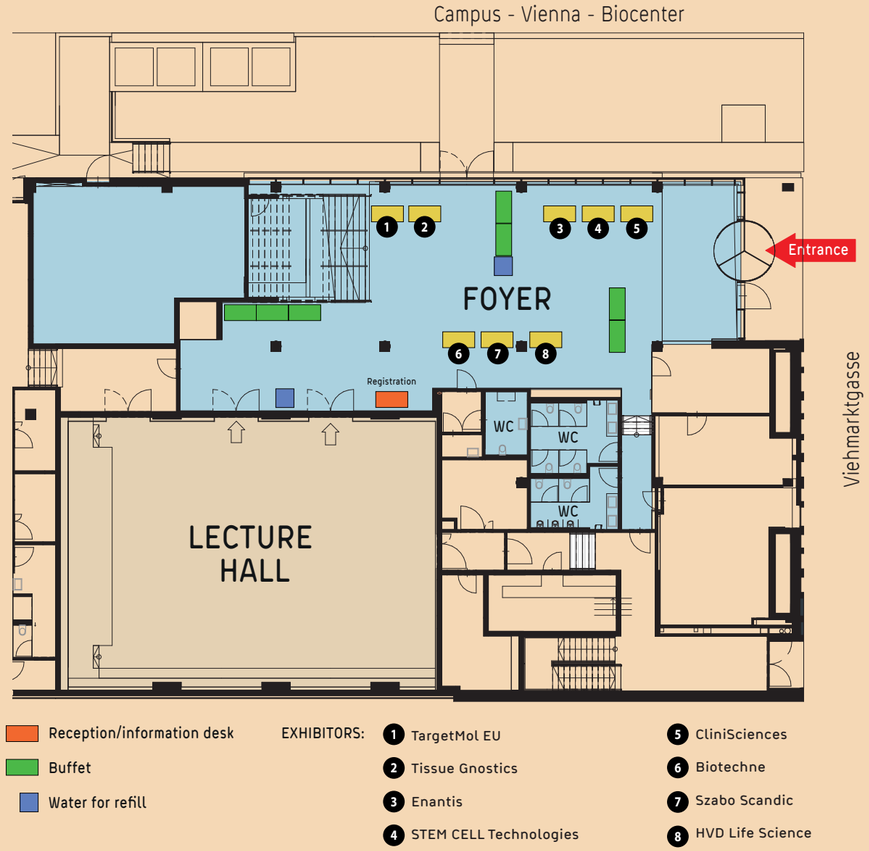

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Programme

DAY 1 - Wednesday, March 11

09:30 **Panel talk**

11:00 **Registration & welcome get together**

12:00 **Welcome & introduction**

Keynote lecture I

12:15 **Marianne Bronner (California Institute of Technology)** Gene regulatory subcircuits controlling neural crest stem cell fate along the body axis

13:15 *lunch break*

SESSION 1: Developmental plasticity

14:15 **Stefanie Grosswendt (Berlin Institute of Health & Max Delbrück Center)** Cell communication uncovered in single-cell resolved neighborhoods

14:45 **Chloe Roffay (IMP - Research Institute of Molecular Pathology)** Uncovering the forces driving specification and morphogenesis of extraembryonic amnion during human gastrulation

15:00 **Irene Zorzan (Babraham Institute)** New approaches to study the regulators of human trophoblast development

15:30 *break*

16:00 **Undine-Sophie Deumer (University of Cambridge)** Ability of committed progenitor cells to rewire their fate under homeostatic conditions

16:15 **Mekayla Storer (Cambridge Stem Cell Institute)** At the tip of Regeneration – Insights from tissue mechanics and the extracellular matrix

16:45 **Luis Miguel Cerron Alvan (Max Perutz Labs)** Wt1 acts as a rheostat switch to guide early post-implantation fate and has isoform specific lineage-inductive potential

17:00 *break*

17:30 **Noelia Anton-Bolaños (University Medical Center Utrecht)** Mirroring Human Brain Development and Disease Using Brain Organoids as Avatars

18:00 **Giulio Di Minin (CRO National Cancer Institute)** Be Happy (and Haploid): The Role of Cell Size and Metabolic Constraints in Haploid Stem Cell Stability

18:15 **POSTER SESSION I**

20:00 *Symposium Dinner [on site]*

DAY 2 - Thursday, March 12

SESSION 2: Signaling and Patterning

09:00 **Lucie Zilova (Centre for Organismal Studies)** Development Without Constraints: Organoids as Testbeds for Alternative Developmental Pathways

09:30 **Amy Wilkinson (Babraham Institute)** Investigating the role of transcription factors in anteroposterior patterning of human post-implantation epiblast

09:45 **Tiago Rito (University of Hong Kong)** In vitro embryology and tissue design: tuning axial progenitors to make the human backbone.

10:15 *break*

10:45 **Anastasios Balaskas (Max Planck Institute for Molecular Genetics)** An advanced head-to-tail mouse gastrulation model with hypoxia-mediated neural patterning

11:00 **Gavin Schlissel (Stanford University)** Extracellular Hedgehog diffusion, and evolution of novel morphogen gradients

11:30 *break*

12:00 **Vikas Trivedi (EMBL-Barcelona)** Understanding constraints on tissue patterning: Bridging networks, mechanics and metabolism

12:30 **Irene Amblard (Imperial College London)** CDX factors instruct neural crest regionalisation programmes

12:45 group picture & lunch

SESSION 3: Neurodevelopment and neurodegeneration

14:00 **Evgenia Salta (Netherlands Institute for Neuroscience)** Single-cell molecular mapping of human adult hippocampal neurogenesis in Alzheimer's disease

14:30 **Elisa Gabassi (University of Innsbruck)** Aged human brain organoids capture hallmarks of neural ageing and reveal PHF2 and ZNF93 as regulators of LINE-1 repression

14:45 *break*

15:15 **Eduardo Leyva Díaz (Instituto de Neurociencias de Alicante)** Dissecting neuronal identity: from worms to vertebrates

15:45 **Irene Varela (Institute of Science and Technology Austria)** Beyond inside-out: Tracing the Origins of Projection Neuron Fate and Diversity in the Mouse Neocortex

16:00 **POSTER SESSION II**

18:00 **end of sessions - free evening for attendees**

DAY 3 - Friday, March 13

SESSION 4: Automation

09:00 **Ewa Ozga (University of Edinburgh)** Array-CNCC: precise aggregation and arrayed plating facilitate quantitative phenotyping of human cranial neural crest cells and craniofacial disease modelling

09:15 **Athina Patra (Leiden University Medical Center)** OtoNeurons in a Dish: Generating Spiral Ganglion Neurons from Human Induced Pluripotent Stem Cells

09:30 **Daniel Paull (The Jackson Laboratory / The New York Stem Cell Foundation)** Scaling biology at the intersection of automation, stem cells, and AI

10:00 *break*

SESSION 5: Stem cell models for human health

10:45 **Eleonora Conti (Human Technopole)** Human trigeminal ganglion organoids enable modelling of host-virus interactions of herpesviruses

11:00 **Margherita Turco (Friedrich Miescher Institute for Biomedical Research)** Organoid Systems as a Window into Women's Reproductive Health

11:30 *break*

12:00 **Nicole Amberg (Medical University of Vienna)** Regional dynamics of tumor initiation in neural stem cells upon oncogenic germline mutations/tumor predisposition syndromes

12:15 **Johannes Bargehr (Cambridge Stem Cell Institute)** Immune niche conditioning in cardiac repair

12:45 *lunch*

13:45 **Elisa Laurenti (Cambridge Stem Cell Institute)** Why do human haematopoietic stem cells lose function ex vivo?

14:15 **Francesco Boccellato (University of Oxford)** A YAP1–DKK1–Wnt mechanochemical circuit defines the human gastric regenerative niche

14:30 *break*

Keynote lecture II

15:00 **Lorenz Studer (Sloan Kettering Institute)** Developing human PSC-based cell therapies for CNS and PNS disorders

16:00 **Closing remarks**

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Keynote lecture 1

Gene regulatory subcircuits controlling neural crest stem cell fate along the body axis

Marianne Bronner, California Institute of Technology

During embryonic development, neural crest stem cells arise within the forming central nervous system, but then migrate from their site of origin along defined pathways to populate numerous sites and differentiate into diverse cell types, including the craniofacial skeleton, peripheral nervous system, outflow tract of the heart and skin melanocytes. However, neural crest populations differ along the body axis with respect to migration pathways and derivatives. For example, only cranial neural crest cells give rise to cartilage and bone of the face, only cardiac neural crest cells contribute to the heart and only vagal and sacral neural crest cells contribute to the enteric nervous system. To identify gene regulatory networks (GRNs) that confer axial level specific identify, we have performed single cell transcriptome analysis of these different neural crest populations along the body axis. By functionally testing GRN subcircuits specific to the neural crest contributions to the head, heart and gut, we aim to define transcriptional and signaling components of axial level-specific neural crest GRNs. Finally, by comparing transcriptomes of neural crest cells across numerous species ranging from cyclostomes to amniotes, we infer evolutionary changes that may have contributed to evolution of neural crest stem cells in the vertebrate lineage.

Keynote lecture 2

Developing human PSC-based cell therapies for CNS and PNS disorders

Lorenz Studer , Sloan Kettering Institute

Human pluripotent stem cells (PSCs) present a powerful tool for studying human disease and developing novel cell-based therapies in regenerative medicine. Our group has established strategies to coax human PSCs into many specific neuronal and glial cell types, on demand and at scale. For some neural lineages, such as midbrain dopamine neurons, these efforts have translated into a first-in-human clinical trial using clinical-grade, "off-the-shelf" dopamine neurons for treating patients with advanced Parkinson's disease (PD). I will provide an update on the results from this trial and discuss next steps in clinical development, as well as the development of next-generation dopamine neuron products to further enhance the clinical impact of PD cell therapies.

In the peripheral nervous system (PNS), we have pioneered the development of cell therapies in preclinical models of Hirschsprung's disease, a congenital disorder of the enteric nervous system. I will present genetic fate-mapping data that provide surprising insights into early competency restrictions during the specification of human PSC-derived vagal and enteric neural crest lineages. These insights enable a new class of protocols to derive enteric neural lineages at unprecedented efficiencies. Furthermore, they reveal a broader mechanism by which early competency can be harnessed to develop CNS differentiation protocols that capture all major regional identities in a highly systematic manner.

SESSION 1: Developmental plasticity

Cell communication uncovered in single-cell resolved neighborhoods

Stefanie Grosswendt [1,2]

Tobias Christaller[1,2,7], Philipp Stachel-Braum[1,2,7], Henrike Scherrer[1,2,7], Elmir Mahammadov[1,2,7], Fabian Gademann[1,2], Brittany Moser[3], Alessia Petrella[2], Valentina Beliaeva[4], Shriya Lele[1,2], Julia Batki[5], Helena Radbruch[6], Annette Hammes[2], Malte Lücken[4], Zev J. Gartner[3], Stefanie Grosswendt[1,2]
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Cells communicate through ligand–receptor (L–R) interactions that occur in specific combinations and contexts to coordinate gene expression and function. However, current omics technologies cannot jointly capture spatial proximity and deep transcriptome-wide profiles of cells, limiting the analysis of L–R combinations between individual cells. We developed CellMate-seq, a method that tags neighboring cells for deep single-cell transcriptomic profiling. Applied to the mouse embryo, CellMate-seq identified thousands of neighborhoods, which we annotated with a new single-cell atlas augmented with positional information. Many of these neighborhoods contained neural crest cells whose migration and specification is directed by various interacting cell types. By analyzing neural crest cells with one of its major interaction partners, the cardiopharyngeal mesoderm, we uncovered distinct L–R combinations that are linked to anatomical positions, highlighting how local context shapes cell communication. Together, we provide a framework that opens new avenues for studying the combinatorial logic of cell communication and its role in development.

Uncovering the forces driving specification and morphogenesis of extraembryonic amnion during human gastrulation

Chloe Roffay [1]

S. Jay [1], O. Drozdowski [1], C. Horenburg [1], E. Hannezo [2], D. Pinheiro [1]
[1] IMP
[2] ISTA

Extraembryonic tissues provide key molecular signals and mechanical support to the growing embryo. For instance, the extraembryonic amnion, which forms a fluid-filled sac surrounding the embryo, was recently shown to trigger germ layer specification during gastrulation, by secreting BMP ligands. Despite the key roles of extraembryonic tissues in embryo development, little is still known regarding their molecular and biophysical programs, particularly in human. Using a 2D stem cell-based model of human gastrulation, termed gastruloid discs, we found that amnion cells undergo a sharp columnar-to-squamous transition concomitantly with fate specification. Via biophysical modelling, direct force measurements, pharmacological and genetic perturbations, we showed that this morphogenetic transition is amnion-intrinsic and it is driven by active wetting, i.e. a transition from tensile to adhesion-dominated cellular states. Molecularly, active wetting is implemented via a rewiring of cytoskeleton composition, from actomyosin to keratin-based cytoskeletal networks, akin to a bistable toggle-switch in gene regulatory networks. Strikingly, blocking shape changes at the colony edge results both in defective cellular states in the amnion and impaired gastruloid disc morphogenesis within the embryonic compartment. Together, our findings establish that a cytoskeletal toggle switch couples fate specification to tissue architecture in the human amnion and suggest an unexpectedly active mechanical role for extraembryonic tissues in shaping the embryo proper.

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New approaches to study the regulators of human trophoblast development

Irene Zorzan
Babraham Institute

The placenta is essential for nutrient and gas exchange between mother and foetus, and its proper development is critical for pregnancy success. To overcome the lack of physiologically suitable models, we established a tissue-engineered system that recapitulates the receptive endometrium. Excitingly, this system sustains early postimplantation development of human embryos and of stem cell-based embryo models called blastoids. Importantly, our system promotes advanced stages of postimplantation trophoblast development, including the trophoblast plate and early villus structures. Single-cell RNA-sequencing of the embryo-endometrial interface at day 14 uncovers predicted molecular interactions between conceptus and endometrium. Disrupting signalling interactions between extravillous trophoblast and endometrial stromal cells caused defects in trophoblast outgrowth, demonstrating the importance of crosstalk processes to sustain embryogenesis. This platform opens up the opportunity to study the molecular mechanisms regulating early trophoblast development in human postimplantation embryos.

Ability of committed progenitor cells to rewire their fate under homeostatic conditions

Undine-Sophie Deumer [1, 2]
Maria T. Bejar [1, 2], Harikrishnan Ajit [1, 2], Jesus Eduardo Rojo Arias [1], Denise Tran [1], Davide Rossetti [1, 2], Greta Skrupskelyte [1, 2], Joo-Hyeon Lee [1, 3], Maria P. Alcolea [1, 2]
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[3] Memorial Sloan Kettering Cancer Center, New York, USA

Epithelia represent our bodies' first barrier of defence, protecting us against environmental aggressions and perturbations. To this end, epithelial cells can rewire their cell fate programme according to specific tissue needs. This guarantees rapid and efficient repair of injured tissue by enabling lineage-committed cells to reacquire stem cell-like behaviour in response to damage. However, much less is known about the importance of cell fate rewiring/plasticity for tissue maintenance in the absence of perturbations.

The oesophageal epithelium is an ideal system to study plasticity in homeostasis due to its simple tissue architecture. This squamous stratified epithelium consists of one layer of progenitor cells that differentiate by stratifying into suprabasal layers, forming a protective epithelial barrier. Differentiated squamous cells are known to express Kruppel-like factor 4 (Klf4). Recently, a subpopulation of basal cells expressing Klf4 has been identified, and was concluded to be committed to differentiation.

Here, we study the behaviour of this early committed cell population in the oesophageal epithelium, marked by expression of Klf4 in the basal layer. Through lineage tracing, using a novel in-house KLF4-Cre mouse line, we have found that Klf4+ cells, despite initial commitment marker expression, can form long-lasting clones. Using single-cell RNA sequencing, we have been able to find that Klf4-derived clones may rewire their transcriptional signature under homeostatic conditions. By combining our KLF4-mouse with lines carrying mutations often found in both healthy aging and tumorigenesis, we have shown that the expression of Klf4 influences mutant clone dynamics. Taken together, our results indicate that committed cells may rewire their fate, re-acquiring progenitor features under normal homeostatic conditions, and that this plastic phenotype may be repurposed by mutant clones to increase their fitness. We hypothesize that fate plasticity may be a process that operates during tissue maintenance to support tissue integrity long-term.

At the tip of Regeneration – Insights from tissue mechanics and the extracellular matrix

Mekayla Storer
Cambridge Stem Cell Institute

Tissue regeneration is rare in mammals, but distal digits can regrow following amputation, unlike proximal injuries. While the molecular cues are well-studied, the physical microenvironment's role remains unclear. We identified the extracellular matrix (ECM) and tissue mechanics as key regulators of amputation responses. We show that regenerative regions are soft with high hyaluronic acid (HA) content, while non-regenerative areas are stiff with dense collagen. Strikingly, depleting HA inhibits regeneration, while stabilizing HA with the link protein, HAPLN1, reduces scarring and promotes bone repair. These findings suggest that ECM modulation may be a potent strategy to unlock mammalian regenerative potential.

Wt1 acts as a rheostat switch to guide early post-implantation fate and has isoform specific lineage-inductive potential

Luis Miguel Cerron Alvan [1, 2]
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Exit from naïve pluripotency is essential for establishing post-implantation epiblast identity and enabling subsequent germ-layer specification. However, we do not yet fully understand how early embryonic cell fate decisions are regulated, or which gene-regulatory network (GRN) factors initiate post-implantation epiblast formation. To identify candidate initiators, we performed a targeted pooled gain-of-function screen across a curated set of potential regulators with high likelihood of influencing the naïve-to-post-naïve transition in mouse embryonic stem cells. Surprisingly, the screen nominated Wt1, which is best known for roles in later organogenesis and has not been reported to function prior to gastrulation, revealing an unexpectedly early capacity to trigger post-implantation gene-regulatory programs. Inducible WT1 expression rapidly dismantles naïve pluripotency and markedly accelerates progression along a developmentally coherent trajectory toward an E5.5–E6.5 epiblast-like transcriptional state, even under conditions that normally stabilize naïve pluripotency.

Genome-wide profiling showed that WT1 binding increases during exit from naïve pluripotency and is enriched at promoters and active EpiLC enhancers marked by p300/H3K27ac, frequently overlapping sites bound by established transition regulators. Consistent with this regulatory context, WT1 promotes acquisition of key aspects of the formative programme, including the attenuation of the naïve GRN and activation of key regulators of early post-implantation identity. To test whether WT1 also shapes lineage competence in a multilineage context beyond monolayer differentiation, we used embryoid body differentiation. In this setting, two WT1 isoforms exhibited unexpectedly distinct functions: one preferentially promoted neuroectodermal and neural programs, whereas the other preferentially promoted mesodermal and stromal programs, while both advanced shared post-implantation programs. Although WT1 is not detectably induced during human pluripotency progression, forced WT1 expression activates human orthologs of WT1-responsive genes and preserves the isoform-linked bias in developmental output, indicating conserved regulatory capacity across species and raising the possibility that WT1 can modulate the tempo of post-naïve progression. Together, these findings reveal an unexpectedly early role for WT1 as an instructive transcription factor that promotes formative and early post-implantation epiblast identity and tunes lineage competence before germ-layer specification."

Mirroring Human Brain Development and Disease Using Brain Organoids as Avatars

Noelia Anton-Bolaños
University Medical Center Utrecht

Human brain development is shaped by both exceptional interindividual genetic diversity and an unusually prolonged developmental timescale, yet experimental systems that capture these dimensions remain limited. I will present recent advances in human brain organoid models that enable the study of both genetic variability and long-term maturation in vitro. Using multi-donor cortical Chimeroids, generated by co-developing cells from multiple individuals within a single organoid, we show that human genetic background strongly modulates susceptibility to neurotoxic exposures, affecting both the penetrance and molecular phenotype of vulnerable cell types. In parallel, by maintaining human cortical organoids for up to five years in culture, we demonstrate that organoids transcriptionally and epigenomically age in step with the human brain and retain an intrinsic developmental clock. Mixing progenitors of different developmental ages reveals that neural cells record and recall the passage of time, executing age-appropriate fate programs when placed in permissive environments. Together, these approaches expand the scope of human brain organoids to study how genetic diversity and developmental time shape human brain maturation and vulnerability.

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Be Happy (and Haploid): The Role of Cell Size and Metabolic Constraints in Haploid Stem Cell Stability

Giulio Di Minin [1,2]

Markus Holzner [2], Anton Wutz [2]
[1] CRO National Cancer Institute
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Why are complex organisms generally linked to a diploid genome? Derivation of haploid embryonic stem cells from several mammalian species has shown that cells with a single set of chromosomes can grow, differentiate, and integrate into complex cellular systems both in vitro and in vivo. However, during passages, these cells often lose their haploid state and spontaneously become diploid, indicating the presence of mechanisms that safeguard diploidy. Surprisingly, DNA content itself is not the main driver of the process: we demonstrate that diploidization is a controlled, redox-dependent process that links mitochondrial ATP production with mitotic accuracy. This metabolic checkpoint—similar to the Warburg effect seen in cancer cells—is closely connected to cell size and mitochondrial signaling, forming a key physiological barrier to maintenance of the haploid state. Based on these findings, we rationalise a strategy to promote haploid stem cell stability by modulating the NADPH oxidation rate. Stable haploid embryonic stem cells offer a powerful platform for forward genetic approaches, and we illustrate their use in dissecting complex processes, including the molecular mechanisms driving the transformation of neural stem cells into medulloblastoma precursors.

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SESSION 2: Signaling and Patterning

Development Without Constraints: Organoids as Testbeds for Alternative Developmental Pathways

Lucie Zilova

Elin Stahl, Miguel Angel Delgado Toscano, Anastasia Paneva, Ishwariya Saravanan and Joachim Wittbrodt
Centre for Organismal Studies Heidelberg University, Heidelberg, Germany

In vitro organoid development utilizes a remarkable ability of embryonic stem cells or progenitor cells to autonomously self-organize in higher order structures with sophisticated microarchitecture often closely resembling cell type compositions, 3D structure, and the function of the organ. As organoids show remarkable similarities to their in vivo counterparts, we naturally tend to infer that corresponding structures are formed by the corresponding cellular processes in both systems. However, the extent to which organoids recapitulate native, embryonic morphogenetic mechanisms remains unclear. Here we show an example of alternative mode of cellular assembly that leads to similar structural outcome – the formation of the lens. We used medaka fish derived pluripotent cells as a model for generation of complex ocular organoids composed of both retina and lens tissues. By following progenitors of respective tissues, we show that fish retinal organoids efficiently formed embedded lenses in the process that employs the molecular pathways including expression of key transcription factors and utilization of extracellular signaling pathways as the embryo. In contrast to in vivo development, organoid cells did not follow canonical process of lens formation and used an alternative mode of cellular assembly to generate the lens.

The goal of many organoid studies is to replicate in vivo conditions as closely as possible. Unconstrained environment of organoids on the other hand offers a unique opportunity to observe alternative developmental pathways which are not apparent in vivo. Such studies would thus expand our understanding of the plasticity, robustness and adaptability of developmental programs.

Investigating the role of transcription factors in anteroposterior patterning of human post-implantation epiblast

Amy Wilkinson [1]

A. Bendall [1], I. Zorzan [1], J. Srinivasan [1], C. Penfold [1], S. Elderkin [1], P.J. Rugg-Gunn [1]
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Introduction: The early post-implantation period of human embryo development sees a dynamic progression in the development of the epiblast – the cell lineage that will give rise to all cell types of the future fetus. A key aspect of this progression is the establishment of the anteroposterior (A-P) axis which ensures that all future body structures form in the correct place from head to tail. While work in model organisms has defined many conserved molecular principles of A-P patterning, differences in timing, lineages, and transcription factor expression in humans means that downstream transcriptional mechanisms enacting A-P patterning in human embryos are largely unknown. This study aims to investigate the roles of transcription factors in the in A-P patterning of human epiblast.

Methodology: Published data was reanalysed to shortlist transcription factors with candidate roles in A-P patterning. Human pluripotent stem cells (hPSCs) were then used to model the pre- to post-implantation epiblast transition, which encompasses the window of A-P axis specification. Knockouts were generated in the naïve (pre-implantation-like) state and then capacitated to the primed (post-implantation-like) state. Their phenotype was examined by RT-qPCR, RNA sequencing, immunofluorescence, and flow cytometry. In order to gain mechanistic insights, CUT&RUN was performed in primed hPSCs to identify putative target genes.

Results: MEIS3 was identified as a candidate with a potential role in anterior specification of human epiblast. While MEIS3 knockout in hPSCs did not affect the naïve state or the ability to transition to the primed state by capacitation, subsequent culture in primed conditions resulted in instability in MEIS3 knockout hPSCs. This was characterised by the presence of differentiated cells with a mesendoderm bias. MEIS3 knockout hPSCs also exhibited a reduced efficiency for neuroectoderm differentiation. MEIS3 is known to regulate transcription in conjunction with various co-factors. One such co-factor, PBX1, was found to bind at genomic sites enriched for the MEIS3 motif and to bind nearby genes associated with neural lineages.

Conclusions: This study identifies the transcription factor MEIS3 as a putative regulator of A-P patterning in human development. Absence of MEIS3 in hPSCs may confer a more posterior identity, indicated by instability of the pluripotent state and a bias for differentiation to posterior lineages. Mechanistically, MEIS3 may cooperate with its co-factor, PBX1 to activate anterior genes, hence contributing to A-P patterning. Emerging results will further our understanding of transcriptional mechanisms underlying body plan formation during early human embryo development.

In vitro embryology and tissue design: tuning axial progenitors to make the human backbone.

Tiago Rito

HKU, School of Biomedical Sciences, HK, Hong Kong

The vertebrate body forms through the coordinated activity of multiple progenitor pools that can be replicated in vitro. However, current stem cell models of trunk development still lack many key features. One of these is the robust, midline presence of a notochord, essential for signaling and tissue patterning.

Using single-cell transcriptomics in chicken embryos, we spatially mapped progenitor populations and applied these insights to human pluripotent stem cells. By precisely timing key signaling pathways, we created a 3D model of human trunk development that includes a notochord alongside neural and somitic tissues. This improved model offers new insights into notochord formation and ventral tissue patterning in a more realistic tissue environment.

An advanced head-to-tail mouse gastrulation model with hypoxia-mediated neural patterning

Anastasios Balaskas [1,2]

Isabelle Kraus [1,3], Hatice Ö. Özgüldez [1], Persia Akbari Omgba [1,4], René Buschow [1], Adriano Bolondi [1], Idan Berlad [5], Jacob H. Hanna [5], Helene Kretzmer [1,3], Aydan Bulut-Karslioğlu [1]
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The developing mammalian embryo is guided by the continuously changing signals that it receives from maternal tissues and its microenvironment. The dynamic cell-cell and cell-environment interactions that together shape the embryo largely remained unexplored until the advance of stem cell-based embryo models. These revealed the self-organizing properties of cells in response to endogenous and exogenous cues. Among the latter, restricted oxygen (hypoxia) emerged as a critical microenvironmental regulator that influences cell type diversification in multicellular systems. Here we built a modular embryonic stem cell–based head-to-tail model of mouse gastrulation by developing an antero-posterior (AP) assembly strategy under hypoxia, termed Hypoxic Anterior-Posterior gastruloids (HAP-gastruloids). Unlike conventional gastruloid models, HAP-gastruloids feature stage-appropriate anterior neural tissues that recapitulate the morphological organization and transcriptional identity of fore- and midbrain, including spatial organizer regions such as the midbrain–hindbrain boundary. These anterior tissues develop in synchrony with posterior tissues such as the spinal cord, somites, and gut endoderm derivatives, ultimately yielding a unified structure. We show via genetic and environmental perturbations that timed hypoxia is essential to boost anterior neural cell identities and their patterning through HIF1a. These results underline the key beneficial role of hypoxia in early development and offer a uniquely modular system to investigate antero-posterior phenotypes for basic discovery and translation.

Extracellular Hedgehog diffusion, and evolution of novel morphogen gradients

Gavin Schlissel

Stanford University

Developmental pattern formation relies on secreted signaling proteins to determine cell fates within a patterning field. These signaling proteins must travel through a crowded extracellular matrix, which is composed of insoluble and heavily modified proteins. It has long been appreciated that the extracellular matrix might affect cell-cell communication, however the extracellular matrix is resistant to most legacy biochemical, structural, or genetic analysis and so it has been difficult to understand mechanistically how the extracellular matrix could influence the movement of extracellular signaling molecules. I developed in situ single-molecule microscopy approaches to understand how secreted signaling proteins move through an intact extracellular matrix in live cells and tissues. My work revealed a new model for extracellular diffusion, and identified previously unappreciated mechanisms that evolution has modulated to regulate the size of Hedgehog signaling gradients in tissue- or organism-specific ways. I will discuss my past, ongoing and future efforts to understand how signaling proteins interact with the extracellular matrix, and how those mechanisms inform our understanding of animal patterning.

Understanding constraints on tissue patterning: Bridging networks, mechanics and metabolism

Vikas Trivedi
EMBL-Barcelona

CDX factors instruct neural crest regionalisation programmes

Irene Amblard [1]
Christos Kalaitzis [2], Irina Balaguer Balsells [2], Juan M. Vaquerizas [1,2], Vicki Metzis [1,2]
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During development, neural crest cells (NCCs) generate distinct subtypes along the head to tail axis, but how these subtypes are positioned and specified remains an open question. Using a strategy to track early regionalisation events in mouse embryos, combined with spatial transcriptomics and quantitative stem cell models, we find that dynamic changes in CDX transcription factors explain NCC subtype identity at discrete positions in the body. The data demonstrate that different CDX factors preconfigure NCCs to adopt discrete HOX codes, explaining how distinct subtypes emerge at the correct position in the body. Together, these findings define a CDX-driven mechanism that couples early epiblast regionalisation to NCC subtype positioning, and support a hybrid origin for vagal NCCs at the head to trunk transition.

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SESSION 3: Neurodevelopment and neurodegeneration

Single-cell molecular mapping of human adult hippocampal neurogenesis in Alzheimer's disease

Evgenia Salta

Netherlands Institute for Neuroscience

The notion of exploiting the regenerative potential of the human brain in physiological aging or neurological diseases represents a particularly attractive alternative to conventional strategies for enhancing or restoring brain function. Harnessing adult hippocampal neurogenesis in human Alzheimer's brain may provide novel strategies to prevent or counteract dementia, by enhancing the 'fitness' and plasticity of a hippocampal network that is critical both for memory formation and for memory deterioration in Alzheimer's disease. Insights into the molecular and cellular regulatory networks maintaining homeostasis of the human neurogenic microenvironment are currently missing.

We employ single-nucleus RNA sequencing technology in the human adult hippocampal neurogenic niche to profile cell type-specific molecular signatures of adult hippocampal neurogenesis and their changes during the course of AD pathology and in resilient brains. We identify distinct immature neuronal profiles that may be linked to mechanisms of vulnerability and resilience to Alzheimer's dementia. Further understanding of what these cellular populations can do in the healthy and diseased adult human brain may open up novel therapeutic avenues.

Aged human brain organoids capture hallmarks of neural ageing and reveal PHF2 and ZNF93 as regulators of LINE-1 repression

Elisa Gabassi [1]

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Studies of human brain ageing have been constrained by limited access to patient-derived tissue and the lack of physiologically relevant in vitro models. While models derived from induced pluripotent stem cells (iPSCs) would offer a valuable tool for investigating various aspects of human diseases and physiological processes, iPSC-type reprogramming results in the loss of age-related signatures and limits the ability to faithfully recapitulate late-onset conditions in vitro. In this study, we present the first 3D human brain organoid model based on inducible progerin overexpression that robustly recapitulates canonical hallmarks of ageing. Induced ageing in organoids resulted in loss of epigenetic integrity, marked by a 40% reduction in H3K9me3-enriched heterochromatin, a two-fold increase in DNA damage, mitochondrial dysfunction, and accumulation of senescent cells. Transcriptomic profiling identified a distinct age-associated gene expression signature closely mirroring that of aged human post-mortem cortical tissue, including significant downregulation of synaptic genes such as SYN1, CALM2, and CAMK4. Among the differentially expressed genes, we identified consistent downregulation of the histone demethylase PHF2 (PHD Finger Protein 2) in both aged organoids and human post-mortem cortical samples. ChIP-seq analysis revealed that PHF2 occupies genomic regions enriched for motifs recognised by the KRAB zinc-finger protein ZNF93, a key regulator of LINE-1 retrotransposon repression. Consistent with disruption of this regulatory axis, aged organoids exhibited a 20% increase in LINE-1 expression, accompanied by re-localisation of ZNF93 from the nucleus to the cytoplasm, suggesting that PHF2 is required for proper ZNF93 chromatin recruitment. Together, these findings identify the interaction between PHF2 and ZNF93 as a regulatory element safeguarding genome integrity during human neural ageing. This inducible brain organoid model provides a powerful, human-specific platform for dissecting molecular drivers of brain ageing and genome instability, with broad implications for modelling neurodegenerative disease.

Dissecting neuronal identity: from worms to vertebrates

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The generation of neurons involves not only fate choice during development, but also the establishment and long-term maintenance of both shared and specific neuronal identity across diverse neuron types. While developmental and in vitro differentiation approaches have revealed key determinants of neuronal specification, the transcriptional logic that stabilizes neuronal features after fate commitment remains less well understood.

Work in the invertebrate model Caenorhabditis elegans has revealed a conserved role for CUT homeobox transcription factors as regulators of pan-neuronal gene expression, acting in parallel with neuron type-specific fate determinants. These findings suggest that neuronal identity is built from the coordinated deployment of shared and subtype-specific transcriptional programs, rather than from independent, cell-type–restricted modules.

We extend these principles to vertebrate systems using direct neuronal reprogramming, providing a framework to test how conserved transcriptional programs are engaged, stabilized, or disrupted during rapid cell identity transitions. Together, these approaches aim to illuminate general principles by which neuronal identity is established and maintained across development, reprogramming and evolution.

Beyond inside-out: Tracing the Origins of Projection Neuron Fate and Diversity in the Mouse Neocortex

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The six-layered neocortex regulates cognitive and behavioral functions through precisely organized networks of excitatory projection neurons (PNs). During development, the myriad cortical PN subtypes are produced by specialized stem cells known as radial glial progenitors (RGPs). According to the canonical hierarchy of cortical neurogenesis, multipotent RGPs sequentially produce distinct laminar PN identities via temporally regulated neurogenic divisions. Yet, it remains unclear how individual RGPs produce the full spectrum of cortical PNs, as well as the diversity of RGP-derived PN lineages in the developing neocortex.

A key obstacle in addressing these questions lies in finding a robust framework for PN classification. Lineage studies have traditionally relied on layer position as a proxy for PN diversity; yet, as different PN subtypes occupy the same cortical layer, lamination alone does not adequately define PN identity. A complementary classification is based on axonal projection patterns, which divide PNs into two major categories: intra-telencephalic (IT) and extra-telencephalic (ET) PNs. This projection-based classification represents a technical challenge, since no straightforward tracing method can comprehensively capture the full axonal diversity of adult IT-PNs and ET-PNs. However, developing PNs share exuberant axonal projections that are stabilized or eliminated during the first postnatal weeks. Here, we demonstrate that developmental callosal projections prospectively identify IT-PNs in all cortical layers. By leveraging exuberant projections to the corpus callosum, we establish an axonal tracing strategy that distinguishes IT-PNs from ET-PNs in early postnatal mice, resolving the PN classification bottleneck.

Our results indicated that deep-layer PN subtypes acquire distinct cardinal IT/ET projection identities at birth. To examine the temporal regulation in the genesis of cortical PNs that migrate to the deep layers, we determined their birthdates by combining our axonal tracing approach with single-pulse EdU labeling. We observed that many deep-layer IT-PNs and ET-PNs are born asynchronously yet ultimately populate the same cortical layers. These findings uncouple PN identity from laminar birth order, challenging classical models. Instead, they suggest that projection identity is specified prior to laminar positioning, pointing to an early neurogenic fate decision that governs projection subtype specification.

To elucidate the lineage architecture underlying RGP production of IT- and ET- PNs, we combined Mosaic Analysis with Double Markers (MADM) with early postnatal callosal axon tracing. For this, we used a tamoxifen (TM)-inducible Emx1-CreER recombinase driver line to induce MADM clones from cortical RGPs at embryonic stages E12.5 and E13.5. Our classification of MADM clones based on early axonal projection patterns revealed that, at the onset of neurogenesis, multipotent RGPs undergo early PN-subtype fate diversification and generate distinct ET-PN and IT-PN sub-lineages that progress in parallel rather than sequentially.

ET-PNs arise exclusively from small, self-consuming lineages, whereas IT-PNs are produced through both small lineages and larger translaminar outputs generated by fate-restricted RGPs. Although individual RGP divisions displayed variable outcomes, population-level analyses uncovered a quantitatively and temporally stereotyped neurogenic program emerging from early progenitor state transitions. Mechanistically, we identified POU3F transcription factors as candidate regulators of IT-PN fate restriction, acting via non-canonical, sequence-independent mitotic chromatin binding.

Together, our work provides a revised view of the canonical inside-out model via a linear sequence of neurogenic divisions, and demonstrates that RGP-derived pure lineages of IT-PNs exist in the developing mouse neocortex, revealing greater heterogeneity in the pool of cortical RGPs than previously appreciated."

SESSION 4: Automation

Array-CNCC: precise aggregation and arrayed plating facilitate quantitative phenotyping of human cranial neural crest cells and craniofacial disease modelling

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Introduction

The development of the face is highly sensitive to genetic and environmental perturbations, with craniofacial malformations present in over one-third of congenital birth defects. Facial formation starts early during embryonic development, with a large contribution from transient and migratory multipotent cranial neural crest cells (CNCCs). CNCCs emerge from the neural plate border and migrate to populate the facial prominences. Given the early and inaccessible window for human facial development, assessment of the molecular and cellular mechanisms driving developmental malformation relies greatly on the use of in vitro cellular models.

Methodology

While several methods exist for modelling craniofacial development from human pluripotent stem cells (hPSCs), we have leveraged a protocol that first generates neuroectodermal spheres (neurospheres) to model the embryonic origin of the neural crest. This approach has been used to model facial development, evolution, and disease; however, it is currently challenging to explore early developmental stages due to the variable size and asynchronous attachment of the neurospheres. Here, we have developed and characterised a robust and reproducible human differentiation protocol to facilitate quantification of the earliest CNCC specification and migration events – processes that may be adversely affected in disease. This included the introduction of single cell aggregation to standardise neurosphere size, growth, and attachment. When plated, neurospheres spontaneously attach and form a ring of migratory CNCCs. Through addition of surface coatings, we further synchronised this step to quantify CNCC migration rates and compare cellular and molecular features between treatment conditions.

Results

We next demonstrate the utility of this protocol, which we refer to as 'Array-CNCC', for craniofacial disease modelling. We first provide proof-of-concept quantitative analysis of a mosaic co-culture system which facilitates side-by-side comparison of genetically distinct cells within the same aggregate at finely controlled proportions. This approach is amenable to downstream analyses such as live imaging, fluorescence-activated cell sorting, and single-cell RNA-sequencing. In combination with quantitative immunofluorescence, this approach facilitates exploration of the impact of genetic changes on cell type diversity and patterning. Secondly, we utilised the Array-CNCC setup to explore the impact of exogenous factors, namely different extracellular matrix surface coatings, on the efficiency of neurosphere attachment, and the proliferation, migration, spatial patterning, and cell states of the emerging CNCCs. We further analysed the impact on CNCC transcriptional state and patterning with RNA sequencing of both the early isolated and later expanded CNCCs from a range of conditions, in direct comparison to the original CNCC derivation protocol.

Conclusions

Together, we show that the Array-CNCC protocol is amenable to multiplexed screening of genetic or environmental impacts on early CNCC specification and cell states. The mosaic protocol further enables co-culture of both control and test cells within the same neurospheres for highly controlled phenotyping. Moreover, the highly reproducible neurospheres lower the need for excessively large differentiations using prohibitively large volumes of media. Altogether, this protocol enables enhanced disease modelling with quantitative cellular and molecular readouts."

OtoNeurons in a Dish: Generating Spiral Ganglion Neurons from Human Induced Pluripotent Stem Cells

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Introduction

The human inner ear relies on specialized sensory cells and neurons to enable hearing and balance. According to the World Health Organization (WHO), by 2050, nearly 1 in 10 people is expected to experience some form of hearing impairment due to hereditary genetic factors, age-related sensorineural degeneration, or ototoxic medications. Although cochlear implants and hearing aids can partially improve hearing, no existing treatment fully restores inner ear function. A key limitation is the essentially absent regenerative capacity of spiral ganglion neurons, which transmit signals from hair cells to the brain. Human induced pluripotent stem cell-derived inner ear organoids (hiPSC-derived IEOs) are emerging as a powerful in vitro model; however, their use in scalable investigations is limited by off-target cell induction, inter- and intra-experimental variability, and labor-intensive workflows. Therefore, we employ a high-throughput 2D platform of hiPSC-derived inner ear neurons (OtoNeurons) to investigate their role in physiological and pathological conditions.

Methodology

scRNA-seq data from the Inner Ear Organoid Atlas (IODA) were analyzed to identify a cell-surface marker specific to otic vesicle-like cells. OC90 expression was validated by immunocytochemistry and confocal microscopy in hiPSC-derived IEOs across multiple differentiation time points. In parallel, the timing of otic neuroblast delamination from otic vesicles in hiPSC-derived IEOs was mapped to define the optimal window for cell isolation. At day 21, IEOs were dissociated, and otic vesicle-like cells were purified by fluorescence-activated cell sorting (FACS) from off-target populations. Sorted OC90+ cells were subsequently cultured on PDMS plates coated with PLO/laminin in a defined 2D system with growth factor supplementation to generate hiPSC-derived inner ear neurons (OtoNeurons). The results were evaluated by protein expression and transcriptomics.

Results

Among our key findings is the identification of OC90 as a marker of otic vesicle-like cells, with immunostainings showing luminal localization in organoids at day 21. OC90 is expressed by SOX2+ sensory epithelial cells within SOX10+ otic vesicles. In parallel, at day 18, ISL1+ neuroblasts were observed delaminating and in close proximity to SOX10+ otic vesicle-like cells. At day 21, FACS analysis showed that OC90+ cells comprise 10% of the dissociated organoid population, enabling the enrichment of otic cells from off-target cells. Upon culture in a well-defined 2D system, OC90+ sorted cells generated TUJ1+/PRPH+ neurons. Ongoing work focuses on identifying inner ear neuron-specific markers and distinguish them from pan neuronal markers. To further improve otic neuronal differentiation and assess maturation efficiency, samples have been submitted for single-nucleus RNA sequencing (snRNA-seq).

Conclusions

Together, our findings support the development of a purified, simple and scalable organoid-to-2D platform that minimizes off-target cells inherent to hiPSC-derived IEO cultures and enables the generation of an otic-enriched neuronal population. This establishes the first purified otic neuron system compatible with high-throughput drug screening, supporting the discovery of otoprotective agents and regenerative interventions. "

Scaling biology at the intersection of automation, stem cells, and AI

Daniel Paull

The Jackson Laboratory / The New York Stem Cell Foundation

Complex diseases demand cellular models that mirror patient diversity at scale. Achieving this requires reimagined infrastructure that overcomes the inherent challenges of cell biology at scale. Over the past decade, we have developed an integrated, automated platform that unifies high-throughput approaches with AI at multiple stages of the experimental and discovery pipeline.

By utilizing the NYSCF Global Stem Cell Array®, we can automate the generation and differentiation of induced pluripotent stem cells (iPSCs) into a variety of cell types, including neurons, cardiomyocytes, and 3D organoids. These automated workflows facilitate high-throughput modeling of neurological and other complex disorders across genetically diverse patient cohorts, providing a robust platform for disease modeling and drug discovery.

To capture subtle phenotypes, we combine our automated culture system with sequencing, high-content imaging, and deep learning-based phenotypic profiling. This pipeline generates morphological embeddings from patient cells that power machine learning models capable of detecting disease signatures and resolving individual-level variation across large experimental batches.

The utility of this platform has been demonstrated through the successful identification of disease signatures in fibroblasts from patients with Parkinson's Disease and Infantile Neuroaxonal Dystrophy. We are currently expanding the application of this platform to iPSC-derived lineages, broadening its potential impact on disease research and drug discovery. This integrated platform aims to accelerate the discovery of disease mechanisms and therapeutic targets, potentially transforming how we model and treat complex diseases. WERBUNG – Enantis HOCHFORMAT

SESSION 5: Stem cell models for human health

Human trigeminal ganglion organoids enable modelling of host-virus interactions of herpesviruses

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The trigeminal ganglion (TG) is composed of peripheral sensory neurons which transmit pain, temperature and touch information from the face to the brain. Developmentally, it originates from placodal progenitors, which are specified in the ectoderm through gradients of BMP4 and FGF, and which are marked by the expression of SIX1. Initially, placodal progenitors can give rise to a variety of sensory derivatives besides the TG, and only a subpopulation of progenitors later acquires a trigeminal fate, marked by the co-expression of SIX1 and PAX3, and gives rise to the TG. The TG is involved in several human pain and viral pathologies, including migraine and latency of herpesviruses. These remain poorly understood in part due to a lack of human in vitro models of this tissue. To address this, we here generated the first human pluripotent stem cell (hPSC)-derived trigeminal ganglion organoid (TGO) as a model to investigate trigeminal development and pathology.

For this, we first differentiated organoids composed almost exclusively of SIX1+ placodal progenitors by exposing hPSCs to a timely sequence of BMP4 and FGF. The placodal progenitors in the organoids are for the most part unpatterned, with the potential to develop towards virtually all placodal derivatives. Subsequently, through a high-content chemical compound screen, we identified signalling pathways (i.e. TGFß, Wnt and cAMP) guiding the differentiation of these placodal progenitors specifically towards a SIX1+/PAX3+ trigeminal fate. At later differentiation timepoints, these trigeminal progenitor-enriched organoids develop into TGOs which closely model the native tissue. Indeed, TGOs are composed of distinct somatosensory neuron populations, including pain-sensing, temperature-sensing and mechano-sensing neurons, mirroring the ganglion neuronal diversity. Notably, TGO neurons are functional, as they fire action potentials in response to sensory stimuli. In addition to neurons, glial cells also develop in TGOs in the form of both resident glia populations of the ganglion, namely Schwann cells and satellite glia. scRNA-seq analysis highlights how TGO neuronal and glial populations transcriptionally match their counterparts in human primary TG, further supporting their identity. These two cellular components self-organise in TGOs in a ganglion-like cytoarchitecture, resembling the native tissue from a structural perspective, as highlighted by high-resolution imaging and spatial transcriptomics.

Importantly, TGO sensory neurons are susceptible to herpesvirus infection, as both herpes-simplex virus 1 and varicella zoster virus can productively replicate in the organoids. TGOs also functionally respond to these viral insults with interferon production, developing virus-specific immune responses.

Overall, TGOs model the human TG in their cellular composition, structure, and function, making them an invaluable tool to study TG development, physiology and pathology. Given their susceptibility to herpesviruses and their scalability, they open new experimental avenues for the modelling and investigation of viral latency in the ganglion.

Organoid Systems as a Window into Women's Reproductive Health

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Women's health, and particularly reproductive and maternal health, have been historically underfunded and understudied. Organoid systems are now transforming our ability to model human reproductive tissues and uncover their unique biology. The endometrium, the mucosal lining of the uterus, plays a central role in women's reproductive health, undergoing cyclical shedding, regeneration, and differentiation under the influence of ovarian hormones. Dysregulation of these processes contributes to common conditions such as infertility, endometriosis, hyperplasia, and adenocarcinoma. Using tissue-derived endometrial organoids that faithfully recapitulate the morphology, function, and gene expression of the epithelium in vivo, we model the menstrual cycle to investigate the mechanisms that regulate epithelial regeneration and differentiation, and how these may differ in women with fertility. These tools can also be combined with organoids from the placenta to model maternal-fetal interactions during pregnancy. Together, these systems provide a powerful window into women's reproductive health and its disorders.

Regional dynamics of tumor initiation in neural stem cells upon oncogenic germline mutations/tumor predisposition syndromes

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Tumor predisposition syndromes (TPS) contribute to more than 10% of pediatric brain tumors and significantly increase the risk of aggressive malignancies. TPS-associated brain tumors occur in multiple brain regions, with disease severity often linked to tumor location. Thus, one must consider the importance of the microenvironment in cancer initiation.

We hypothesize, that distinct microenvironments harbor different vulnerable time points/stem cell identities that undergo oncogenic transformation in a brain region-specific manner. Our experimental model is based on TPS patient-derived iPSCs and brain region-specific organoid cultures to model tumor development in vitro. We have established highly reproducible hindbrain and forebrain organoid protocols that efficiently induce regional patterning. We focus on the two ultra-rare and highly aggressive TPS termed Constitutional Mismatch Repair Deficiency (CMMRD) and Rhabdoid Tumor Predisposition Syndrome (RTPS) to not only understand critical time windows of oncogenic transformation and the region-derived cues contributing to tumor initiation, but also to dissect TPS-specific mechanisms affecting neural stem cell behavior during development.

Within 2 months of culture, we have identified tumor-like lesions in both, forebrain and hindbrain CMMRD-derived organoids. These organoids show a disruption of germinal zone morphology and development of tumor-like lesions, characterized by loss of the apical adherence junction belt, a differentiation block and the formation of hyperproliferative zones. In order to link region-specific physiological outcomes to the (epi)genetic and transcriptomic landscapes, we have performed TSO500 panel sequencing, methylation profiling with nanopore sequencing and snRNAseq. We have uncovered distinct signatures between control and TPS-derived organoids, with additional pathological mutations.

Our platform offers an unparalleled opportunity to establish a highly relevant translational model for affected patients. Overall, our research seeks to improve the diagnostic and therapeutic options for brain tumor patients by extracting novel biomarkers with predictive value for the clinics.

Immune niche conditioning in cardiac repair

Johannes Bargehr

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Heart failure affects nearly one million people in the UK, with a five-year mortality of 50%. Heart transplantation, the only therapy replacing lost contractile myocardium, is available to ~200 patients annually and carries lifelong risks and complications. Regenerative medicine using human pluripotent stem cell (hPSC)-derived cardiomyocytes (CM) offers a scalable approach to remuscularise infarcted myocardium. Intramyocardial transplantation of hPSC-CM has resulted in stable cardiac grafts augmenting host heart function following myocardial infarction in rodents and non-human primates. However, a major hurdle is poor grafting efficiency which is driven by ischaemia and inflammation impairing survival, proliferation and vascular supply of transplanted cells. The Bargehr lab uses broadly immunoevasive hiPSC lines, locally immunosuppressive strategies and immunomodulatory approaches to reduce myocardial cell death and enhance cardiac engraftment. This involves both in vitro and in vivo models to study innate and adaptive immune responses to assess the efficacy of immunomodulation. Furthermore, to study the cardiac niche and graft arrhythmias immediately post-transplantation ex vivo heart perfusion models are used. Collectively, immunomodulation promises to provide insights into disease-modifying pathways in heart failure and catalyse clinical translation of cardiac cell therapy.

Why do human haematopoietic stem cells lose function ex vivo?

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Hematopoietic stem cells (HSCs) have the unique capacity to produce all blood cell types over the lifespan. HSC transplantation is life-saving for many cancer patients and in the context of gene therapy (GT) for patients of many monogenic inherited disorders. Ex vivo culture is a fundamental step for HSC-based GT and for expansion, however, a major challenge arises from the loss of HSC function during ex vivo culture. Recent work from our laboratory has demonstrated that more than 66% of functional HSCs are lost within the early adaptation to ex vivo culture (approximately 24 hours) and here I will discuss examples of HSC stress responses that contribute to this functional loss.

First, we uncovered that during adaptation, HSCs transiently upregulate stress response and JAK/STAT signalling target genes. Inhibition of JAK/STAT signalling during adaptation leads to three-fold improved HSC regenerative capacity after ex vivo culture.

Second, we have combined scRNAseq and low-input metabolomics to generate a kinetically resolved predictive model of metabolomic switches occurring during the first division of human HSC ex vivo in GT culture conditions and upon induction of differentiation. We identify that metabolic shifts occur dynamically over 72 hours of culture but are most pronounced in the first 24 hours and are independent of cell cycle progression. Flux through one carbon metabolism was dynamically changed in the first 24 hours of culture. Pharmacological inhibition of key one-carbon metabolism enzymes changed HSC and progenitor survival, cell cycle and regenerative capacity ex vivo.

Collectively, our data contribute to a better understanding of the interplay between stem cell stress, metabolism, and regeneration during clinically relevant human HSC culture, and will aid in the identification of new preclinical strategies to improve HSC function ex vivo.

A YAP1–DKK1–Wnt mechanochemical circuit defines the human gastric regenerative niche

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Healthy tissue homeostasis is maintained by regenerative cells that are typically confined within spatially defined stem cell niches. The adult human stomach epithelium is organised into deep invaginations called gastric glands, which open into the gastric lumen through structures known as foveolae. In these glands, epithelial regeneration is driven by WNT beta catenin signalling and is spatially restricted to the isthmus, a narrow region located just below the foveola. However, the mechanisms underlying this precise spatial confinement of regeneration remain poorly understood.

To address this question, we applied spatial transcriptomics to human gastric tissue to map gene expression across distinct anatomical regions of the gland. Regional gene enrichment analyses revealed that components of the WNT beta catenin pathway are specifically enriched at the isthmus, a finding corroborated by increased nuclear accumulation of beta catenin in epithelial cells of this region. In contrast, expression of DKK1, a potent inhibitor of WNT beta catenin signalling, was enriched from below the isthmus toward the gland base. Notably, YAP1, a mechanosensitive transcriptional co activator of the Hippo pathway, was predominantly phosphorylated and cytoplasmic at the isthmus, while it accumulated in the nucleus in regions overlapping with DKK1 expression.

Based on these observations, we hypothesised that cellular compression induces YAP1 nuclearisation, leading to DKK1 expression, inhibition of WNT beta catenin signalling, and suppression of regeneration below the isthmus.

To test this hypothesis, we generated gastric organoids and mucosoids from biopsies of healthy human donors. While organoids provide a robust model for studying epithelial regeneration, mucosoids previously developed and patented in our laboratory are planar, stem cell driven epithelial cultures maintained at an air liquid interface that produce mucus on the apical surface and can differentiate into all major gastric epithelial lineages. Importantly, mucosoids enable the study of epithelial homeostasis, a state that cannot be stably achieved in continuously expanding organoid cultures. Treatment of gastric organoids with DKK1 resulted in a marked reduction in regenerative capacity. In mucosoids, YAP1 nuclear accumulation and DKK1 expression increased from two weeks after seeding, concomitant with a strong decline in cell regeneration. Pharmacological induction of YAP1 nuclearisation using TRULI led to premature DKK1 expression and a block in regeneration, supporting a direct mechanistic link between YAP1 activity and DKK1 regulation.

Finally, to determine whether the YAP1 DKK1 Wnt mechanochemical circuit is sufficient to generate a spatially confined regenerative niche, we developed a mathematical model of a gastric gland cross section. In this model, cells are represented as mechanically coupled elements that respond to compression by producing DKK1. Simulations revealed that cell loss at the foveola acts as a driving force for regeneration at the isthmus. Increasing cell death rates mimicking chronic damage caused by Helicobacter pylori infection predicted gland shortening and loss of the DKK1 mediated regenerative brake. Consistent with this prediction, analysis of human biopsies from Helicobacter pylori associated atrophic gastritis showed cytoplasmic YAP1 localisation, reduced DKK1 expression, and expanded epithelial regeneration.

Together, our findings demonstrate that cellular sensing of mechanical compression plays a central role in spatially regulating gastric regeneration, with the YAP1 DKK1 axis acting as a key mechanochemical brake that defines the human gastric regenerative niche at the isthmus."

Poster Session 1 - Wednesday, March 11 2026

Please note that although all posters will be displayed at the same time, the presentations will take place on different days.
Please check the list below for the day of your presentation

No.	Name	Affiliation (University / Institute / Company)	Abstract title
1	Anna Chantzara	University of Patras	McIdas controls early steps of multiciliogenesis in ependymal cells
3	Nadezhda Romanova	Medical University of Vienna	Neural crest enhancers: an evolutionary perspective
5	Daan de Groot	IMBA	Bonsai: Tree representations for distortion-free visualization and exploratory analysis of single-cell omics data
7	Ewa Ozga	University of Edinburgh	Array-CNCC: precise aggregation and arrayed plating facilitate quantitative phenotyping of human cranial neural crest cells and craniofacial disease modelling
9	Ana Villalba Requena	Institute of Science and Technology Austria (ISTA)	Rptor/mTORC1 Function Globally Prevents Cortical Microcephaly and Cell-autonomously Promotes Postnatal Neuron Survival in a Cell Type Specific Manner
11	Beate Kratschmann	St. Anna CCRI	Modeling Adrenal Medulla Development to Identify Vulnerable Windows for Cancer Initiation
13	Eleftheria Parasyraki	Francis Crick Institute	Deciphering the spatiotemporal developmental programme of cell diversity in the neural tube
15	Georgios Kritikos	University of Patras	Modulation of GemC1 induces widespread chromatin changes during neural stem cell and ependymal lineage commitment
17	Guilherme Ventura	IMP	Understanding the mechanical basis of morphogenetic pace during vertebrate gastrulation
19	Henrike Schwarzenbacher	Berlin Institute of Health (BIH)	The anatomical organization and function of intercellular communication events in the embryo
21	Iskra Sainova	Bulgarian Academy of Sciences (BAS)	Investigation on the different stages of embryogenesis in embryoids, derived from laboratory-incubated primordial germ cell-like cells, totipotent and/or extended pluripotent stem cells
23	Ines Fischer	Ludwig Boltzmann Institute for Traumatology	Regeneration in Full Bloom: Early Epidermal Signaling in Axolotl Limb Healing
25	Chiara Azzi	Babraham Institute	LIN28A regulates developmental timing through translational homeostasis in neural progenitors
27	Kristína Mitrová	Medical University of Vienna	Micropatterned Neuruloids identify FGF2 and Retinoic Acid as Antagonizing Signals in Cranial Neural Crest Fate Specification
29	Lisa Neuschitzer	Max Perutz Labs	Towards Scalable Dopaminergic Neuron Production: Line-Specific Optimization of WNT and SHH Patterning in Human iPSCs
31	Lidija Milojkovic	IMBA	Inhibition of ppERK1/2 Nuclear Function is Crucial for the Maintenance of Neural Stem Cell Quiescence
33	Elisa Toscano	MaxWell Biosystems	NEXT-GENERATION ELECTROPHYSIOLOGY FOR FUNCTIONAL CHARACTERIZATION OF HUMAN NEURAL ORGANOIDS AND ASSEMBLOIDS
35	Lena Bohaumilitzky	IMP	From dynamic morphogen gradients to complex tissue mechanics
37	Manon d'Arco	Nantes Université	Generation of iPScs-derived functional T cells in thymic organoids and disease modelling of APECED syndrome
39	Martina Podlesnic	University of Innsbruck	Single-cell profiling of striatal organoids derived from Leigh syndrome patients indicates an imbalance of neuronal subtypes during early neurodevelopment
41	Manon Ressaire	St. Anna Children's Cancer Research Institute	3D modelling of fusion-driven sarcomagenesis
43	Mewanthi Flaminia Kaluthantrige Don	Human Technopole	Human basal radial glia morphotypes are transcriptionally distinct and exhibit different cell fate determination
45	Michael Bindl	Max Perutz Labs	Mechanism of endo-mesodermal lineage choice
47	Michael Zabolocki	IMBA	Cerebral Organoids Uncover Mechanisms of Neural Activity Changes in Epileptogenesis
49	Moritz Becker	Max Perutz Labs	Mechanisms Regulating the Emergence of Formative Pluripotency in Humans
51	Johannes Grillari	Ludwig Boltzmann Gesellschaft, Institute for Traumatology	Toward Standardized MSC-EV Manufacturing: Effects of hTERT Immortalization and Collection Media on EV Functionality
53	Nikola Popovic	Leiden University Medical Center	Human PSC-derived cardiac organoids incorporating macrophages reveal inflammation-induced physiological alterations
55	Mona Christensen	Medical University of Vienna	Decoding the Regulatory Logic of Cell Fate Convergence in Craniofacial Development
57	Patricia Parzer	Medical University of Vienna	Development of a humanized 3D in vitro microenvironment to study nerve regeneration and axon repair
59	Piero Rigo	King's College London	Characterising human hippocampal neurogenesis during development and in adulthood
61	Shweta Verma	Manipal Academy of Higher Education	Repositioning Netrin-1 as a Priming Agent Enhances Regenerative Potency of Wharton's Jelly-Derived Mesenchymal Stromal Cells Secretome and Extracellular Vesicles
63	Thomas Bargehr	University of Natural Resources and Life Sciences Vienna	Selection and characterization of a physiological human umbilical cord-derived mesenchymal stem cell line for the production of extracellular vesicles
65	Rozalina Galimullina	Medical University of Vienna	Developmental timing shapes oncogenic rewiring in Ewing Sarcoma
67	Sofia Angelini	University of Innsbruck	CLN3 mutations drive early neurodevelopmental and lysosomal defects in iPSC-derived cortical organoids
69	John Mains-Sheard	Monash University	Establishing new models of organ-specific inter-species chimeras to study hindlimb growth regulation

Poster Session 2 - Thursday, March 12 2026

Please note that although all posters will be displayed at the same time, the presentations will take place on different days.
Please check the list below for the day of your presentation

No.	Name	Affiliation (University / Institute / Company)	Abstract title
2	Aditi Kulkarni	University of Cambridge	SIRT2-mediated mitochondrial bioenergetic reprogramming enhances synaptogenesis during human neuronal development
4	Birgit Ritschka	IMP	Senolytic treatment restores repair capacity in a human stem cell-derived model of retinal pigment epithelium aging
6	Bence Fogel	St. Anna CCRI	Exploring neuroblastoma initiation through developmental similarity
8	Daniel Ming-Kang Lee	Max Planck Institute for Molecular Genetics	Regulatory Principles of PRC2 in Cell Fate Decisions During Gastrulation
10	Despoina Korrou Karava	University of Patras	MCIDAS-Driven Ectopic Expression Initiates Reprogramming of Human Primary Astrocytes to the Ependymal Lineage
12	Dunja Alexandra Al-Nuaimi	CeMM Research Center for Molecular Medicine GmbH	Investigating the Mechano-Energy Axis in Epithelial Morphogenesis
14	Elisa Reinthaler	Medical University of Vienna	Role of the CoREST complex in trophoblast identity
16	Fatemeh Safari	AO Research Institute	Deciphering osteoclast-chondrocyte interactions in an organoid model
18	Jahnavy Joshi	Manipal Academy of Higher Education	Inflammatory priming of Mesenchymal Stromal Cells decreases angiogenic potential and enhances immunomodulatory function
20	Flavia Millesi	Medical University of Vienna	Human Spinal Cord Organoids on Spider Silk Fibers as a System for Injury and Regeneration Modeling
22	Justus Kleifeld	IMBA	Insulin/IGF signaling controls adult neural stem cell quiescence and maintenance
24	Gregor Gryglewski	Medical University of Vienna	Compositional analysis of ventral forebrain organoids in Tourette's Syndrome
26	Kapil Jain	ETH Zürich	Confinement and Matrix Mechanics Induce Cancer Cell Reprogramming
28	Javier Bregante Boix	Max Planck Institute of Molecular Cell Biology and Genetics	AP1 signaling as a regulator of maladaptive responses in liver regeneration
30	KATHARINA WIENER	St. Anna Children´s Cancer Research Institute (CCRI)	Organoid modelling of embryonal kidney tumor development
32	Michaela Kress	Medical University Innsbruck	Surface coatings impact on transcriptomic signatures and electrical properties of iPSC derived human nociceptors
34	Katherina Tavernini	IMBA	Establishing a Quiescent State: The Role of Niche Patterning in Human Radial Glia
36	Kaja Moczulska	Center for Brain Research Medical University Vienna	Contributions of the Central Nervous System to Skeletal Development During Embryogenesis
38	Margarita Dillinger	LMU/Biomedical Center/Physiologische Genomik	Neuronal replacement after stroke - from transplantation to reprogramming
40	Luciana Isaja	Fondazione Human Technopole	Decoding NeuroCOVID: Integrative multi-omics and patient-derived stem cell models to unravel chronic neuroinflammation in long-COVID
42	Marina Signer	Institute of Human Biology	Mouse neural organoids access macroglia phenospace
44	Teea Wang	Queen Mary, University of London	Investigating Neuroinflammation in Traumatic Injury Using Human Stem-Cell Derived Organoids with Amyotrophic Lateral Sclerosis Gene Mutation
46	Mattia Pitasi	Max Perutz Labs	Mapping the synergisms network in the exit from naïve pluripotency
48	Nora Papai	bit.bio discovery	CRISPR screens in human iPSC-derived neurons and glia for target identification and validation
50	Nikita Vaulin	Medical University of Vienna	Ex machina: explainable machine learning to decode the regulatory logic of cell-fate specification
52	Paraskevi Athanasouli	Institute of Science and Technology Austria	Unraveling the mechanisms of roof plate specification in the developing neural tube
54	Philipp Stachel-Braum	Berlin Institute of Health / Max-Dellbrück-Center Berlin	CellMate-seq identifies combinatorial ligand-receptor interactions between individual cells
56	Sienna Müller	Max Perutz Labs, University of Vienna	Cell-ECM adhesion remodelling during skin development
58	Sophie Gobeil	Institute of Science and Technology Austria	Lineage origin of spinal cord cell type diversity
60	Sowmya Sunkara	CeMM - Research Center for Molecular Medicine GmbH	A bioengineered in-vitro trauma platform reveals Extracellular matrix-dependent regulation of axon repair
62	Tobias Christaller	Berlin Institute of Health	CellMate-seq captures diverse embryonic cell-cell interactions at single-cell resolution
64	STAVROS TARAVIRAS	Medical School, University of Patras	Rebuilding the Ependymal Barrier: Cell Reprogramming Strategies for Hydrocephalus
66	VIKAS CHAUDHARY	Leiden University Medical Center	Tracing Lineage Imprints: How Cellular Origin Influences iPSC Fate Commitment
68	Michael Oberhuemer	University of Vienna	Mapping Genetic Dependencies in Human Naïve Pluripotency
70	Abel Vertesy	IMBA	High-throughput neural connectivity mapping in organoids reveals wiring-defined neuronal subtypes and aberrant wiring in TSC

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Poster Abstracts

Poster number: 1

McIdas controls early steps of multiciliogenesis in ependymal cells

Anna Chantzara[1], Georgia Lokka [1], Despoina Korrou-Karava [1], Konstantina Kaplani [1], Georgios Spyroulias [2], Zoi Lygerou [3] & Stavros Taraviras [1]

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A primary neurogenic niche in the adult brain is the lateral ventricles' subventricular zone (SVZ), where adult neural stem cells reside and generate new neurons throughout life. This niche is structurally and functionally supported by ependymal cells. These cells, originating from the same progenitor as neural stem cells, radial glial cells bear on their apical surface multiple motile cilia which are synchronously beating, playing a crucial role in cerebrospinal fluid flow. Impairment of multiciliated ependymal cells can lead to developmental conditions such as hydrocephalus – a pathological condition defined by cerebrospinal fluid accumulation and elevated intracranial pressure.

The commitment of cells towards the ependymal lineage is driven by a strictly regulated molecular pathway governing the generation of multiple basal bodies and ciliogenesis. Geminin family proteins, Geminin, GemC1 and McIdas, are major upstream regulators of this pathway. While our previous work established how Geminin and GemC1 influence the choice between adult neural stem cells and ependymal cells, respectively, our current research explores the specific role of McIdas in the pathway. Our findings show that upon McIdas deletion, radial glial cells still commit to the ependymal lineage, evidenced by the expression of p73 and Foxj1, factors essential for differentiation. However, these cells fail to produce multiple basal bodies, halting the generation of multiciliated ependymal cells and causing hydrocephalus in McIdas mutant mice. Our work provides a physical, molecular, and functional characterization of the population that emerges in place of multiciliation ependymal cells following McIdas loss, integrating high-resolution imaging with single cell RNA sequencing and proteomic analyses. In addition, we investigate the contribution of potential cell cycle alterations in impaired ciliogenesis in the absence of McIdas. In conclusion, although McIdas is not essential for the initial commitment towards the ependymal cell fate, it is critical in early stage multiciliogenesis and maintaining the balance between different ependymal subpopulations.

Such insights into the specific mechanisms governing multiciliogenesis provide a foundation to induce multiciliated ependymal cells generation even in the absence of McIdas. This approach could restore ciliary function within the brain ventricles, opening new possibilities for hydrocephalus treatment strategies.

Poster number: 2

SIRT2-mediated mitochondrial bioenergetic reprogramming enhances synaptogenesis during human neuronal development

A. Kulkarni[1,2], Sunan Li [2], András Lakatos [1], Zu-Hang Sheng [2]

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Neurons rely heavily on oxidative phosphorylation to meet the energetic demands of synaptogenesis and maturation, making the regulation of mitochondrial metabolism a vital component of neuronal development. Recent work shows that the deacetylase sirtuin-2 (SIRT2) acts on axonal adenine nucleotide translocase (ANT1/2) to facilitate adenosine triphosphate (ATP) export from the mitochondria. However, our understanding of how this influences synaptic development and maturation remains elusive. Here, we assess the role of SIRT2 in neuronal development by overexpressing mitochondrial-targeted SIRT2 (mito-SIRT2) in human iPSC-derived neurons and cortical organoids. Mito-SIRT2 driven reprogramming significantly increases mitochondrial respiration, ATP production and pre-synaptic density in the distal axon of iPSC-derived neurons. Scaling this metabolic enhancement to organoids that recapitulate cortical cell type-diversity and 3D architecture results in a significant increase in synaptic density. Our data suggest that ATP may be a limiting resource during human synaptogenesis, highlighting the fundamental connection between energy metabolism and synaptic maturation.

Poster number: 3

Neural crest enhancers: an evolutionary perspective

Nadezhda Romanova[1,2], Nikita Vaulin [1], Rozalina Galimullina [1], Mona Christensen [1], Alek Erickson [3], Igor Adameyko [1,3]

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Neural crest cells (NCCs) are a transient, multipotent stem cell population that gives rise to an exceptionally diverse range of derivatives. This diversity is particularly pronounced during craniofacial development, where cartilage, skeletal elements, neural system components, and parts of the dentition share a common neural crest ancestry. Consequently, both normal and pathological variation in craniofacial morphology is tightly linked to NCC migration, differentiation, and the gene regulatory networks controlling these processes. However, the evolutionary origin and diversification of craniofacial NCC regulatory elements, and how these relate to their regulatory functions, remain poorly understood.

In this study, we investigate the evolutionary dynamics of neural crest–associated enhancers active during human craniofacial development. Using a recently generated single-cell atlas of human craniofacial NCCs, we identified stage-specific enhancers associated with NCC gene regulatory programs. To assess their evolutionary conservation, we performed cross-species genome comparisons across 22 mammalian species using whole-genome multiple sequence alignments, enabling classification of NCC enhancers according to their degree of sequence preservation and subsequent analysis of their regulatory architecture and potential functional effects.

Focusing on the primate lineage, we identified conserved and primate-specific enhancer sets based on sequence preservation relative to human reference enhancers. Integration with gene set enrichment analysis revealed that genes linked to primate-specific enhancers are enriched in collagen formation pathways, potentially highlighting processes associated with the prominent craniofacial remodeling characteristic of this lineage. Moreover, stage-specific expression analysis revealed that the greatest difference in expression between genes associated with primate-specific enhancers and other genes occurs at the ninth week of embryonic development – a critical period for chondro- and osteogenesis in craniofacial structures.

Together, these findings suggest that evolutionary changes in neural crest gene regulatory networks may contribute to craniofacial diversification in primate and human evolution. Our integrative and comparative approach provides a framework for investigating the evolutionary dynamics of developmental regulatory programs.

Poster number: 4

Senolytic treatment restores repair capacity in a human stem cell-derived model of retinal pigment epithelium aging

Birgit Ritschka[1], C. Etl [1], F. Becerril Perez [2], K. Ishihara [1,3], M. Leyva Gonzalez [1], S. Almedawar [4], H. Neubauer [4], R.A. Bakker [4], E.M. Tanaka [2]

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Retinal pigment epithelium (RPE) dysfunction and loss are hallmarks of age-related retinal degenerations. While fetal RPE cells possess proliferative potential, adult RPE cells fail to replenish damaged structures, leading to irreversible vision loss. To study this transition, we utilize a rapid and reproducible protocol to differentiate human embryonic stem cells (hESCs) into mature, functional RPE.

We demonstrate that long-term culture of hESC-RPE effectively mimics biological aging, characterized by declining cell numbers, hypertrophy, and impaired phagocytosis. Transcriptomic profiling revealed that these cells acquire aging-associated signatures observed in human donor RPE in vivo, specifically involving complement activation, inflammaging, and metabolic stress. Within

this model, a subset of RPE cells enters a senescence-like state characterized by increased senescence-associated-β-galactosidase activity and enrichment of senescence-associated secretory signatures.

Notably, treatment with the senolytic inhibitor Navitoclax preferentially eliminated these cells and partially reversed aging-associated transcriptional signatures, increasing global transcriptomic similarity to young cultures and attenuating complement/inflammatory and stress-response modules.This molecular shift translated into a functional rescue, significantly improving repair capacity in an RPE injury assay. Our findings establish a tractable human platform for studying retinal aging and suggest that reducing senescent cell burden can improve RPE repair responses, supporting senescence-targeted approaches for treating age-related retinal degeneration.

Poster number: 5

Bonsai: Tree representations for distortion-free visualization and exploratory analysis of single-cell omics data

Daan H. de Groot[1,2], Sarah X. Morillo Leonardo [1], Mikhail Pachkov1 & Erik van Nimwegen [1]

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Introduction

The astonishing development of a multi-cellular organism from a single fertilized egg cell crucially depends on the tight coordination of gene expression differentiation with cell division and morphogenesis. Single-cell transcriptomics datasets provide a very promising way to study this process, offering genome-wide measurements at single-cell resolution. However, there are three central challenges: they are high-dimensional, noisy, and provide only snapshots of information.

Together, these challenges obstruct the extraction of accurate time-resolved gene expression dynamics. To still explore these datasets, the field has, for lack of a better alternative, relied on embeddings like t-SNE or UMAP, even though such methods are known to distort the intrinsic structure of the data.

Methodology

To address this, we developed Bonsai, which reconstructs the most likely tree that relates any set of high-dimensional objects while rigorously accounting for heterogeneous measurement noise.

Results

Although Bonsai can be used to explore data from a broad range of fields, it is particularly natural for studying differentiation processes, where all cells are related through a cell-division tree. To validate this, we applied Bonsai to a well-characterized blood cell dataset where it recapitulated known differentiation trajectories based on only one snapshot of scRNA-seq data. Moreover, Bonsai finds convincing evidence that NK cells can derive from both myeloid and lymphoid ancestors in vivo, a novel and biologically significant result.

Conclusions

With Bonsai, we present a completely new method of exploring single-cell omics data that can be used to study differentiation trajectories based on high-dimensional and noisy snapshots of any experimental system.

Poster number: 6

Exploring neuroblastoma initiation through developmental similarity

Bence Fogel[1], Polina Kameneva [1], Florian Halbritter [1]

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Neuroblastoma is a pediatric cancer of developmental origin arising from the sympathoadrenal lineage. Multiple putative cells of origin have been proposed based on single-cell transcriptomic comparisons between normal developing sympathoadrenal populations and neuroblastoma tumor cells, highlighting substantial intratumoral heterogeneity. Most tumor cells resemble sympathetic neuroblasts, but there are also subsets of tumor cells with similarity to Schwann cell precursors, chromaffin cells, and early neural crest progenitor cells. Importantly, the degree of similarity varies across tumor cells.

We hypothesize that the degree of similarity to human embryonic sympathoadrenal cell types reflects the transformation status of individual tumor cells. Here, similarity refers not only to which developmental reference cell type a tumor cell most closely matches, but also how strongly its transcriptomic profile aligns with that reference. We propose that progressive deviation from normal developmental programs corresponds to more advanced malignant transformation.

To test this, we trained logistic regression models on single-cell transcriptomic data derived from human embryonic sympathoadrenal populations. These models were applied to neuroblastoma single-cell datasets to calculate similarity scores for each tumor cell relative to defined developmental reference types.

We have observed that tumor cells are distributed along a continuous similarity spectrum and can be stratified into subgroups ranging from the most similar to the least similar cells, independent of which specific developmental reference cell type they most closely resemble. Differential gene expression analysis across these subgroups identified candidate genes that are progressively up- or downregulated with increasing deviation from normal developmental cell types.

Our framework establishes a bridge between normal human development and tumor-associated cellular transformation by enabling quantitative comparison of normal developing cell types with their malignant counterparts and by identifying gene regulatory programs associated with progressive transformation.

Poster number: 7

Array-CNCC: precise aggregation and arrayed plating facilitate quantitative phenotyping of human cranial neural crest cells and craniofacial disease modelling

Ewa Ozga[1], K. M. Milto [1], M. Demurtas [2], L.B. Bates [1], G. Grimes [1], T. Azami [1], J. Su [1], C. De Angelis [1], M. Trizzino [2], J. Nichols [1], H. K. Long [1]

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Introduction

The development of the face is highly sensitive to genetic and environmental perturbations, with craniofacial malformations present in over one-third of congenital birth defects. Facial formation starts early during embryonic development, with a large contribution from transient and migratory multipotent cranial neural crest cells (CNCCs). CNCCs emerge from the neural plate border and migrate to populate the facial prominences. Given the early and inaccessible window for human facial development, assessment of the molecular and cellular mechanisms driving developmental malformation relies greatly on the use of in vitro cellular models.

Methodology

While several methods exist for modelling craniofacial development from human pluripotent stem cells (hPSCs), we have leveraged a protocol that first generates neuroectodermal spheres (neurospheres) to model the embryonic origin of the neural crest. This approach has been used to model facial development, evolution, and disease; however, it is currently challenging to explore early developmental stages due to the variable size and asynchronous attachment of the neurospheres. Here, we have developed and characterised a robust and reproducible human differentiation protocol to facilitate quantification of the earliest CNCC specification and migration events – processes that may be adversely affected in disease. This included the introduction

of single cell aggregation to standardise neurosphere size, growth, and attachment. When plated, neurospheres spontaneously attach and form a ring of migratory CNCCs. Through addition of surface coatings, we further synchronised this step to quantify CNCC migration rates and compare cellular and molecular features between treatment conditions.

Results

We next demonstrate the utility of this protocol, which we refer to as 'Array-CNCC', for craniofacial disease modelling. We first provide proof-of-concept quantitative analysis of a mosaic co-culture system which facilitates side-by-side comparison of genetically distinct cells within the same aggregate at finely controlled proportions. This approach is amenable to downstream analyses such as live imaging, fluorescence-activated cell sorting, and single-cell RNA-sequencing. In combination with quantitative immunofluorescence, this approach facilitates exploration of the impact of genetic changes on cell type diversity and patterning. Secondly, we utilised the Array-CNCC setup to explore the impact of exogenous factors, namely different extracellular matrix surface coatings, on the efficiency of neurosphere attachment, and the proliferation, migration, spatial patterning, and cell states of the emerging CNCCs. We further analysed the impact on CNCC transcriptional state and patterning with RNA sequencing of both the early isolated and later expanded CNCCs from a range of conditions, in direct comparison to the original CNCC derivation protocol.

Conclusions

Together, we show that the Array-CNCC protocol is amenable to multiplexed screening of genetic or environmental impacts on early CNCC specification and cell states. The mosaic protocol further enables co-culture of both control and test cells within the same neurospheres for highly controlled phenotyping. Moreover, the highly reproducible neurospheres lower the need for excessively large differentiations using prohibitively large volumes of media. Altogether, this protocol enables enhanced disease modelling with quantitative cellular and molecular readouts.

Poster number: 8

Regulatory Principles of PRC2 in Cell Fate Decisions During Gastrulation

Ming-Kang Lee[1], Sebastian Mackowiak[1], Daniel Felismino[1], Jeron Venhuizen[1], Maria Walther[1] & Alexander Meissner[1]

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Polycomb repressive complex 2 (PRC2) represents an epigenetic mechanism that controls the spatiotemporal gene programs by modifying histone H3K27 methylation. Mutations in PRC2 subunits are lethal around gastrulation in mice, underscoring its fundamental roles in cell fate decisions during mammalian development. Here, we employ a protein degradation strategy combined with an embryoid model termed Trunk-like Structure (TLS) to address how direct loss of PRC2 obstructs cell fate decisions. We show that acute PRC2 loss causes gastrulation failures, resulting from ectopic expression of anterior and lateral genes, challenging the canonical posterior transformation in Polycomb mutants. H3K27me3 enrichment predicts lineage sensitivity, but does not determine gene responsiveness to PRC2 loss. Importantly, lineage-specific genes and pluripotent genes exhibit differential temporal dependencies on PRC2. While repression of lineage genes constantly requires PRC2 activity, pluripotent genes are only upregulated under early PRC2 loss, but are not responsive to late PRC2 depletion. Finally, we show that transient PRC2 loss is sufficient to irreversibly disrupt the cellular programs and cause developmental failures. Our work uncovers the principles of PRC2-mediated repression in temporal, tissue, and gene-specific contexts and propose an increasing dependency on PRC2 during dynamic cell fate transitions.

Poster number: 9

Rptor/mTORC1 Function Globally Prevents Cortical Microcephaly and Cell-autonomously Promotes Postnatal Neuron Survival in a Cell Type Specific Manner

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The generation of faithful cell-type diversity and correct projection neuron numbers is essential for cerebral cortex development. Corticogenesis is however susceptible, and genetic interference of critical signaling pathways including Mtor/Rptor lead to microcephaly. How the loss of Rptor/mTORC1 function affects the cortical developmental programs at the single cell level is however not known. Here, we utilized Mosaic Analysis with Double Markers (MADM) technology to probe Rptor gene function upon sparse single cell- or global tissue-wide ablation. We found that cumulative tissue-wide effects drive the etiology of cortical microcephaly upon loss of Rptor, rather than deficits in projection neuron genesis. Conversely, Rptor function is cell-autonomously required for postnatal projection neuron survival in a highly cell-type-specific manner. Collectively, our results suggest that the fine balance of precise cell-type-specific cell-autonomous Rptor/mTORC1 function in concert with non-cell-autonomous tissue-wide effects is essential for the development of a properly-sized cerebral cortex with accurate projection neuron diversity.

Poster number: 10

MCIDAS-Driven Ectopic Expression Initiates Reprogramming of Human Primary Astrocytes to the Ependymal Lineage

Despoina Korrou Karava[1], K. Kaplani[1], A. Chantzara[1], G. A Spyroulias[3], Z. Lygerou[2], S. Taraviras[1]

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[2] *Department of General Biology, Medical School, University of Patras*
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Hydrocephalus is a neurological disorder characterised by enlarged ventricles due to the inadequate absorption of cerebrospinal fluid (CSF). The primary intervention, surgical shunt placement, merely manages the manifestations rather than addressing the aetiology, which compromises patient quality of life.

The ventricular lining in hydrocephalic patients is damaged, resulting in the absence of ependymal cells. These cells, which normally reside there, use their unique ciliary structures to propel and circulate CSF. Our team previously identified MCIDAS as a master regulator of ependymal cell differentiation during embryogenesis. Recent studies have successfully demonstrated that cortical murine astrocytes can be reprogrammed into functional ependymal cells through the ectopic expression of MCIDAS using lentiviruses.

Our current study uses human primary astrocytes as a more representative model for direct lineage reprogramming kinetics. We hypothesise that using Adeno-associated viruses (AAVs) to overexpress MCIDAS will provide a safer and more efficient means of converting human astrocytes into the ependymal lineage. To enhance clinical relevance, we are modelling the reactive scarring observed in hydrocephalic patients. We stimulate primary astrocytes with the inflammatory cytokines IL-1? and TNF-? before MCIDAS overexpression, seeking to directly reprogram these inflamed cells.

By targeting the restoration of functional ependymal cells, our findings suggest that MCIDAS is a strong candidate for developing a disease-modifying therapeutic strategy against Hydrocephalus.

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Poster number: 11

Modeling Adrenal Medulla Development to Identify Vulnerable Windows for Cancer Initiation

Beate Kratschmann, T. Eckhardt, B. Fogel, A.K. Mautner, P. Kameneva

St. Anna Children's Cancer Research Institute

Trunk neural crest linage, including Schwann Cell Precursors (SCPs), Sympathoblasts, and Chromaffin cells, can give rise to neuroblastoma (NB) or pheochromocytoma (PC). By modeling adrenal medulla development and interrogating how germline mutations selectively perturb this process, we aim to identify which developmental states are particularly vulnerable to oncogenic transformation.

Our project establishes a human pluripotent stem cell (hPSC)-based differentiation platform that recapitulates the formation of key adrenal medulla cell types. Building on established protocols for generating sympathetic neurons (Frith et al., 2019; Saldana-Guerrero et al., 2024), we expanded this system by performing a bioinformatically guided morphogen screen to promote chromaffin cell enrichment. This protocol is applied to hPSC lines harboring germline mutations associated with NB and PC predisposition (ALK(R1275Q), SDHB+/–, PHOX2B+/–), enabling systematic assessment of their effects on cell fate decisions. Additionally, we will utilize CRISPR/Cas9-mediated gene editing to introduce secondary mutations at precise developmental timepoints, aiming to pinpoint the timing and context in which secondary mutations drive tumorigenesis.

Preliminary results demonstrate that morphogen optimization substantially increases the yield of CART+ chromaffin cells while maintaining the co-existence of SCPs and sympathoblasts. Furthermore, first experiments with PHOX2B+/- cells indicate a differentiation block maintaining early marker expression (SOX10) while failing to express maturation marker (TH) to the same extent as the isogenic wildtype control.

This modelling approach allows to dissect the cellular and temporal mechanisms underlying pediatric cancer initiation and to identify the factors that define the oncogenic susceptibility.

Poster number: 12

Investigating the Mechano-Energy Axis in Epithelial Morphogenesis

Dunja Alexandra Al-Nuaimi[1], Sowmya Sunkara [1], Sarah Dobner [2], Laura De Rooij [2], Abdel Rahman Abdel Fattah [1]

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Epithelial morphogenesis relies on the capacity of cells to locally coordinate, self-organize, and decide to morph. This mechanical process is guided by continuous interactions with the extracellular matrix (ECM), through remodeling, and fueled by metabolic activity. However, how multicellular scale cell-ECM interactions couple with metabolism to define emerging local mechanics and lead to tissue-wide morphological organization remains poorly understood.

To address this, we leverage a minimal in vitro human pluripotent stem cells (hPSCs) model where cell-ECM interactions lead to tissue-wide gastrulation-like organization. This system enables dynamic investigation of the mechano-energy axis, integrating (i) multi-omics approaches, including metabolomics and transcriptomics, with (ii) dynamic assessment of ECM motion and mechanical state within the morphing tissue. We show an ECM-metabolic feedback drives a glycolytic phenotype in parallel with the regulation of mechanosensitive molecular players and the emergence of local symmetry-breaking events within the developing epithelium.

By expanding the integration of mechanical and metabolic data to cell patterning, future studies will aim to unravel how mechano-energy shifts dictate epithelial fate decisions in coordination with tissue-scale morphogenetic programs.

Poster number: 13

Deciphering the spatiotemporal developmental programme of cell diversity in the neural tube

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Embryonic development generates a remarkable variety of cell types, yet how this diversity is established remains unclear. The vertebrate neural tube exemplifies this process, producing diverse cell types through coordinated spatial and temporal transcriptional programs. However, how spatial and temporal regulatory programs integrate at the molecular level to control cell identity remains unclear. Recent work has shown that in the ventral spinal cord, cis-regulatory element (CRE) accessibility changes over developmental time but is largely invariant across space. This is unexpected given that the spinal cord is organised into distinct spatial domains defined by unique transcription factor (TF) identities. These observations suggest that temporal regulators establish chromatin accessibility landscapes through epigenetic modifications, which then modulate spatial TFs binding to drive temporal changes in gene expression and cell fate specification. How temporal chromatin is established and how spatial TFs respond to it is unknown.

Here, we used an established in vitro neural tube differentiation system to determine how temporal chromatin is established. We assessed the role of DNA methylation and demethylation in temporal chromatin accessibility, by profiling 5-methylcytosine (5mC) and 5-hydroxylmethylcytosine (5hmC), a marker of active DNA demethylation, in neural progenitors across developmental time, and comparing this to ATAC-seq data. We found that early and late CREs undergo DNA demethylation at early and late time points, respectively, coinciding with gain of accessibility. However, early CREs retain low 5mC and high 5hmC at late time points, when they are no longer accessible. This suggests that while DNA methylation and demethylation regulate the timely opening of temporal CREs, their subsequent closing occurs through a DNA methylation–independent mechanism.

Future work will characterise the mechanisms underlying CRE closing, their interplay with DNA methylation, and how spatial TFs respond to dynamic temporal chromatin states. Together, our data identify DNA methylation as a regulator of dynamic temporal chromatin accessibility and propose a hierarchical chromatin programme governing CRE regulation in neural cell fate specification. This work is expected to establish fundamental principles of spatiotemporal cell fate specification in the developing neural tube and beyond.

Poster number: 14

Role of the CoREST complex in trophoblast identity

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The human placenta is essential for fetal development and depends on the controlled differentiation of human trophoblast stem cells (hTSCs) into cytotrophoblast (CTB), syncytiotrophoblast (STB), and extravillous trophoblast (EVT) lineages. Disturbances in these processes are associated with pregnancy complications. However, the epigenetic mechanisms that maintain trophoblast stem cell identity are still not fully understood.

In this study, we examined the role of the CoREST complex (RCOR1, RCOR2, RCOR3, LSD1, and GSE1) in regulating hTSC fate. We hypothesized that CoREST supports the stem cell state by repressing genes linked to differentiation.

We performed shRNA-mediated knockdowns of individual CoREST subunits in hTSC cultures and assessed the effects using cellular imaging, RT-qPCR, Western blotting, immunofluorescence, and Quant-Seq transcriptome analysis.

All CoREST subunits were expressed in the nucleus of hTSCs under self-renewal conditions and during STB differentiation. Knockdown of any subunit resulted in loss of the typical cobblestone morphology, reduced proliferation, and increased cell death. Cells acquired an elongated phenotype consistent with cellular stress. Transcriptome analysis showed downregulation of genes involved in cell-cycle progression and maintenance of the CTB stem state, including transcription factors such as GATA2 and MSX2. At the same time, genes associated with migratory and invasive behavior characteristic of EVT were upregulated, together with altered expression of STB markers. Gene Ontology analysis confirmed reduced cell-cycle activity and enrichment of migration- and antiviral-related pathways after CoREST depletion.

Together, these results show that the CoREST complex is required for proliferation, survival, and maintenance of the hTSC state. By preventing inappropriate activation of differentiation programs, CoREST helps preserve trophoblast stem cell identity during placental development.

Poster number: 15

Modulation of GemC1 induces widespread chromatin changes during neural stem cell and ependymal lineage commitment

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During the development of the telencephalon, embryonic radial glial cells (RGCs) act as the primary progenitors that differentiate into two distinct cell populations: quiescent neural stem cells (NSCs) and ependymal cells (ECs). While NSCs reside in neurogenic niches to maintain adult neurogenesis, ECs form a ciliated epithelium essential for brain homeostasis and cerebrospinal fluid circulation. We have formerly shown that GemC1, a member of the Geminin superfamily, is implicated in cellular differentiation events of multiciliated cells and that it is a key regulator protein for ependymal lineage commitment in the CNS. Furthermore, deletion of GemC1 forces RGCs to adopt an NSC identity, whereas its overexpression drives cell differentiation toward the ependymal lineage.

In this study we investigate the epigenetic landscape changes by which GemC1 expression modulates cell fate. Sequencing analysis from our laboratory show that GemC1-deficient cells exhibit altered chromatin organization at multiple loci, where loss of GemC1 affects chromatin dynamics and targeting of SWI/SNF and Polycomb complexes. These findings provide a novel insight into the mechanisms by which GemC1 regulates cell fate decisions. Our results suggest that GemC1 functions as a specific factor for SWI/SNF recruitment, preferentially to promoter and enhancer regions enriched for ciliogenic transcriptional factors such as Foxj1 and p73. Through ChIP-qPCR analysis, we are evaluating the levels of active (H3K27ac) and repressive (H3K27me3) histone modifications at the promoters of ependymal-associated genes. Ultimately, this work demonstrates that the NSC and ependymal lineage commitment is governed by tightly interconnected epigenetic networks, providing a clearer understanding of post-natal neural progenitor plasticity.[

Poster number: 16

Deciphering osteoclast-chondrocyte interactions in an organoid model

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Interactions between the immune system and cartilage play a crucial role in maintaining tissue homeostasis. Osteoclasts (OC), as immune-derived cells residing in skeletal tissues, localize to the hypertrophic zone of cartilage, suggesting that they may directly or indirectly regulate chondrocyte responses to biological and biochemical cues. Furthermore, the incidence of osteoarthritis (OA) is higher in women than in men, indicating potential intrinsic sex-specific differences in chondrocyte biology. This study aims to elucidate how OCs interact with chondrocytes, determine whether OCs alter chondrocyte responses to inflammatory factors, and investigate whether these interactions differ between male- and female-derived cells. To address these questions, we established a human osteoclast–chondrocyte organoid model using cells from both male and female donors. Organoids were generated using a 3:1 ratio of human chondrocytes to OCs. After 7 days of culture, the organoids displayed a distinct self-organized structure, with centrally located OCs surrounded by an outer chondrocyte layer. TRAP staining confirmed the presence and localization of OCs in the organoid core separated from the chondrocytes. These preliminary findings demonstrated an in-vitro spatial arrangement resembling in vivo tissue architecture, where OCs and chondrocytes maintain distinct yet interacting layers. Ongoing analyses will be performed including validation of these structural features and the application of spatial transcriptomics to characterize spatially resolved gene expression. This approach will enable identification of changes induced by OC–chondrocyte interactions and identify potential cell-intrinsic sex-associated differences in chondrocyte behavior in the presence or absence of OC, independent of systemic hormonal influences.

Poster number: 17

Understanding the mechanical basis of morphogenetic pace during vertebrate gastrulation

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Embryogenesis relies on the timely succession of differentiation and morphogenetic steps that shape the developing embryo. Remarkably, the pace of these broadly conserved processes varies significantly across species. A striking example is teleost gastrulation, the crucial process that specifies and shapes the germ layers, which takes 2x longer in medaka (Oryzias latipes) than zebrafish (Danio rerio) in the same laboratory conditions. While such pace differences are well-known in these and other species, it remains poorly understood how time is controlled during development. Recent work using in vitro models provides evidence that interspecies differences in the rate of biochemical reactions and metabolism are involved in setting the pace of differentiation. It is unknown, however, whether and how these molecular parameters set the pace of morphogenesis in vivo. Morphogenesis is a tissue-scale process, set by the interplay between active cell-intrinsic forces and resisting tissue material properties, which are not easily derived from subcellular molecular turnover.

In this project, we aim to define which biophysical parameter scales the pace of gastrulation movements in medaka and zebrafish. For this, we are using in vivo single-plane illumination microscopy to quantitatively characterize medaka gastrulation, which remains poorly understood. We are focusing on mesoderm internalization as it is the first morphogenetic movement of gastrulation and for which we have recently identified the controlling biophysical mechanism in zebrafish. Our preliminary results suggest that the cell movements that power internalization are indeed slower in medaka, supporting that this is a good model to understand the biophysical basis of pace. In the future, we will combine interspecies cell transplantations, in vitro force measuring and theoretical modeling to define the relative contributions of cell-intrinsic forces and tissue material properties to setting the pace of gastrulation movements. This project aims to uncover how developmental pace is controlled from the molecular to tissue scale level.

Poster number: 18

Inflammatory priming of Mesenchymal Stromal Cells decreases angiogenic potential and enhances immunomodulatory function

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Stem cell based regenerative therapies have garnered significant attention over the past decade for their potential to repair and modulate damaged or inflamed tissues. Among various stem cell types, mesenchymal stromal cells (MSCs) have emerged as highly promising candidates owing to their immunomodulatory and immunoevasive properties. Increasing evidence suggests that much of the therapeutic efficacy of MSCs is mediated through their paracrine factors which are collectively termed the MSC secretome, which includes majorly soluble bioactive molecules and extracellular vesicles. The secretome varies with tissue source and microenvironmental cues, and has recently been recognized as a safer, cell-free alternative to conventional cell transplantation strategies. In our study, we investigated the impact of a novel inflammatory priming approach on the regenerative and immunomodulatory potential of Wharton's jelly derived MSCs (WJ-MSCs). Cells were isolated from Wharton's jelly of umbilical cord, characterized by morphology, surface marker profiling and multilineage differentiation as per ISCT criteria, and then primed using a cytokine cocktail comprising IL-1?, TNF-?, and IL-17. The primed WJ-MSCs exhibited a marked increase in the expression of anti-inflammatory and immunoregulatory genes, including TSG-6, IL-6, and CCL-20, compared to unprimed controls. ELISA confirmed negligible residual levels of the priming cytokines IL-1? and IL-17 in the secretome, indicating minimal carryover effects. Proteomic profiling revealed enrichment of biological processes related to extracellular matrix remodeling, tissue regeneration, and immune regulation. Functionally, the primed secretome was able to shift macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype and exhibited significantly reduced angiogenic potential in vitro.

The findings suggest that inflammatory priming serves as a potent regulatory cue that enhances the secretory activity of MSCs by activating intracellular signaling pathways associated with cytokine response, ECM reorganization, and immunomodulation. The resultant secretome exhibits a distinctly anti-inflammatory profile, characterized by increased release of ECM associated proteins

and reduced angiogenic signaling. Such reprogramming of MSCs under controlled inflammatory stress likely mimics the physiological repair microenvironment without causing any permanent genetic alterations, enabling the generation of a therapeutic secretome tailored for inflammatory conditions. These findings open new avenues for developing targeted acellular therapies for inflammatory diseases, and further research can focus on the formulation, delivery and maintaining the consistency of the primed secretome as therapeutics.

Keywords: Regeneration, Anti-inflammation, MSC secretome, Priming

Poster number: 19

The anatomical organization and function of intercellular communication events in the embryo

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Cell communication is fundamental to tissue organization and function during development, where coordinated interactions between cells shape spatial patterning and cell fate decisions. We recently developed CellMate-seq, a single-cell RNA-sequencing method designed to profile cellular neighbourhoods by uniquely tagging individual cells of partially dissociated tissues. This strategy enables deep transcriptional profiling of neighbouring cells at single-cell resolution while preserving information about their cellular surrounding, enabling the study of local cell interactions at unprecedented resolution. Applied to the E9.5 mouse embryo, we identified diverse combinations of receptor-ligand pairs, 'L-R dialogues', between neighbouring cells, such as neural crest cells and one of their major interaction partners, the cardiopharyngeal mesoderm. However, to understand how intercellular communication is orchestrated for the neural crest across the embryo, we need to analyse the spatial organization of these L-R interactions. To this end, we generated an advanced single-cell atlas augmented with absolute positional information. By transferring these spatial coordinates to CellMate-seq neighbourhoods, we found that certain parts of the L-R dialogues are specific to distinct embryonic regions. This spatial specificity is predominantly driven by the cardiopharyngeal mesoderm, which presents different ligands to neural crest cells at distinct anatomical locations. To assess the functional relevance of such region-specific signals, we tested the responsiveness of regional neural crest populations to selected ligand candidates using a newly established neural crest ex vivo model. Overall, our framework provides access to the anatomical organization and function of location-specific cell communication in developing tissues.

Poster number: 20

Human Spinal Cord Organoids on Spider Silk Fibers as a System for Injury and Regeneration Modeling

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Spinal cord injury (SCI) remains a major unmet clinical challenge, partly due to the lack of human-relevant in vitro models that recapitulate spinal architecture and injury responses. While spinal cord organoids derived from human induced pluripotent stem cells (iPSCs) offer a promising approach, their use in reproducible injury modeling requires further structural and functional validation.

Here, we report the establishment of a human spinal cord organoid system using a directed differentiation protocol incorporating caudalizing and ventralizing cues. Organoids display appropriate regional patterning and cellular diversity, including neural progenitors, ventral spinal identity markers, motor neuron markers, and glial populations.

We define a maturation timeline up to day 45, at which organoids exhibit neuronal network formation. This baseline characterization forms the foundation for subsequent controlled injury modeling and structural engineering approaches aimed at improving spatial organization and regenerative assessment.

This platform provides a reproducible human model to study spinal cord development and injury mechanisms, with future integration of biomaterial-guided structural support to enhance translational relevance.

Poster number: 21

Investigation on the different stages of embryogenesis in embryoids, derived from laboratory-incubated primordial germ cell-like cells, totipotent and/or extended pluripotent stem cells

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The main general idea is directed to understanding of the internal protective mechanisms in the initial stages of cell differentiation, which underline the protection against malignant transformation on the one hand and degenerative changes on the other. Induced pluripotent stem cells (iPSCs) could be derived from any types of cells from adult organism in various differentiation stages, even from mature differentiated cells of the adult organism, by treatment with appropriate recombinant vectors about reprogramming by transfer of genes Oct4, Klf4, Sox2 and c-Myc or by incubation in the presence of specific chemical cocktail, containing the protein products of these genes (Yamanaka factors). Sub-populations of the derived iPSCs could be applied about derivation of different organoids, by respective appropriate incubation. Other sub-populations of iPSCs could be applied about derivation of primordial germ cells (PGCs)-like cells, of extended pluripotent stem cells (EPSCs) and/or of totipotent-like stem cells (TLSCs). For this goal, iPSCs should be reprogrammed by transfer of specific genes or to be incubated in the presence of chemical cocktail, containing the protein products of these genes. Additionally, specific pathways should be activated, but other should be inhibited. One of the ways is by epigenetic modifications, including by DNA methylation. Among the responsible factors are Bone Morphogenic Proteins (BMPs), WNTs and enzymes histone methyltransferases, respectively. The derived PGCs-like cells, EPSCs and/or TLSCs should be in vitro-incubated in appropriate conditions (including directed to derivation of male and female gametes from the received PGCs-like cells). The next step is related with formation of blastoids (3D-complex systems – possessing XX and/or XY sex chromosomes, respectively).

Poster number: 22

Insulin/IGF signaling controls adult neural stem cell quiescence and maintenance

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Adult neural stem cells (NSCs) in the dentate gyrus generate new neurons throughout life and provide plasticity to the adult brain. In adulthood, most NSCs reside in a state of quiescence, and because their self-renewal capacity is limited, activation is intrinsically coupled to their depletion. Sustaining lifelong neurogenesis while avoiding premature stem cell exhaustion therefore requires tight regulation of NSC fate. An important component of this regulation is the integration of extrinsic factors such as exercise and diet. Yet, the molecular mechanisms by which NSCs integrate and respond to external signals remain largely unknown.

Here, we investigate Insulin/IGF signaling as a potential mechanism for extrinsic regulation of NSC behavior. Insulin/IGF levels are modulated systemically in response to diet and exercise and are known to influence neurogenesis and other somatic stem cell populations. However, their specific role in regulating adult NSC fate is only incompletely described.

By combining conditional knockout (cKO) of the IGF1 receptor (IGF1R) with in vivo lineage tracing, we analyzed how impaired Insulin/IGF signaling affects NSCs over time. 1-month IGF1R cKO led to an increase in NSC numbers, which was accompanied by reduced NSC proliferation and a sharp decrease in neuronally committed progeny. In contrast, prolonged IGF1R ablation resulted in reduced stem cell numbers, suggesting defects in their long-term maintenance. Together, these data support a model where disruption of Insulin/IGF signaling increases NSC quiescence and compromises self-renewal.

At the molecular level, we find that IGF1R cKO affects the proneural transcription factor ASCL1, a central driver of NSC activation and lineage commitment. Disrupting Insulin/IGF signaling in vitro, by Insulin withdrawal or pharmacological inhibition of the

downstream kinase AKT, reduced ASCL1 protein without altering its mRNA, indicating a post-transcriptional mechanism. This effect required HUWE1, an E3 ligase previously shown to target ASCL1 for proteasomal degradation, and suggests that AKT modulates HUWE1-dependent turnover of ASCL1, thereby tuning abundance of a fate-determining factor.

Together, our findings indicate that Insulin/IGF signaling promotes NSC proliferation and maintenance, at least in part mediated through AKT-dependent regulation of the HUWE1-ASCL1 axis. This reveals a mechanism where extrinsic signaling converges on the pro-activation factor ASCL1 to control NSC fate in response to the systemic environment.

Poster number: 23

Regeneration in Full Bloom: Early Epidermal Signaling in Axolotl Limb Healing

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Tissue regeneration is initiated by rapid restoration of the epidermis, a process that critically influences downstream healing and regenerative outcomes. Whereas mammalian wound repair is typically characterized by scarring, the axolotl (Ambystoma mexicanum) is capable of complete limb regeneration, providing an exceptional system to uncover mechanisms that support regenerative competence. In this study, we investigate injury response of epidermis during axolotl limb regeneration, focusing especially on early re-epithelialization following amputation. Building on our identification of a conserved mammalian wound response defined by rapid and sustained phosphorylation of ribosomal protein S6 (p-rpS6), we demonstrate that axolotl injury causes a specific and spatially confined induction of p-rpS6 within the epidermis. This response suggests the existence of distinct epidermal signaling states associated with regenerative progression. We combine proteomics, phospho-proteomics, and high-resolution imaging to map signaling dynamics during wound healing leading into regeneration. By defining how epidermal signaling landscapes are established and maintained after injury, our work aims to reveal conserved principles of tissue regeneration and clarify the role of epidermal responses in guiding blastema formation and regenerative growth.

Poster number: 24

Compositional analysis of ventral forebrain organoids in Tourette's Syndrome

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[1] *Brady et al. 2022. Mol Psychiatry 27, 5007–5019.*
[2] *Dai et al. 2022. J Neurol 269, 6116-6126.*

Our previous investigation on Tourette's Syndrome (TS) revealed a mispatterning of basal ganglia organoids that might explain the deficiency of striatal interneurons observed post-mortem 1. Here, we cultured a larger set of induced pluripotent stem cell (iPSC) lines from a total of 13 TS and 13 control participants to derive organoids patterned to a ventral forebrain fate using the Wnt antagonist XAV939 and the Shh agonist purmorphamine. We performed single-cell RNA sequencing at 30 days of terminal differentiation and carried out compositional analysis to assess differences in emerging basal forebrain cell types. In TS compared to typically developing controls, significant increases were observed in early neural progenitor cells expressing markers of hypothalamic floor plate (FOXA1/2, SHH, LMX1A, PITX2), together with consistent increases in differentiating cells assuming fates of excitatory neurons additionally expressing VGLUT2, BARHL1/2, CALB2. In line with our previous findings, reductions in FOXG1+ ventral forebrain progenitors, as well as SST+ interneurons, were observed. Alterations in FOXG1+ and VGLUT2+ cells were corroborated by corresponding alterations in cell counts using immunohistochemistry. The current findings suggest developmental aberrations with fate shifts in additional regions modulating basal ganglia circuitry in TS. Due to their size and location, the implicated regions are difficult to access via post-mortem dissection or neuroimaging. Our findings have strong potential for clinical practice, where deep brain stimulation to block the activity of the subthalamic nucleus arising from the posterior hypothalamus can alleviate symptoms in treatment resistant and severe cases 2.

Poster number: 25

LIN28A regulates developmental timing through translational homeostasis in neural progenitors

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The order, duration and tempo at which developmental process takes place is critical for the build-up of a full organism. Imbalances in the speed of tissue development and stem cells differentiation can result in tissue overgrowth or deficits. Yet, despite its importance, how biological timing operates at the molecular level remains elusive. Recent findings show that faster developmental pace correlates with globally increased protein production and degradation rates in mouse neural progenitors compared to human. However, little is known about how developmental systems regulate protein metabolism to set developmental rates.

RNA binding protein (RBPs) are central in the dynamic control of the RNA life cycle and impact the overall rate of protein turnover through post-transcriptional regulatory mechanisms. The conserved RBP LIN28A is known to regulate developmental timing in C. elegans, but whether it functions as a heterochronic factor in mammalian development is still unclear. To investigate how LIN28A influences the induction and the rate of differentiation between developmental programs and its impact on protein homeostasis, we generated a Lin28A::3xFLAG::HALO endogenous knock-in mouse embryonic stem cell line to temporally control LIN28A depletion using HaloPROTACs. LIN28A degradation increases the proportion of neural progenitors and alters neuronal output in mouse stem-cell to spinal cord differentiations, indicating a role in coordinating differentiation dynamics. At the molecular level, LIN28A depletion globally impacts protein synthesis during early development. Direct LIN28A targets are enriched for cytoplasmic translation factors and ER resident genes involved in protein folding and cholesterol synthesis. These targets become dysregulated upon LIN28A knockdown, triggering an Unfolded Protein Response in the early stages of differentiation, suggesting emerging proteostatic stress. Altogether, our results uncover a fundamental role for LIN28A in the regulation of protein homeostasis to control developmental timing.

Poster number: 26

Confinement and Matrix Mechanics Induce Cancer Cell Reprogramming

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Mechanical forces are pervasive signals that shape cell behavior and tissue organization. Whether such physical cues alone can drive cancer cells to undergo transitions between functional states remains unclear. Here, we show that sustained lateral confinement induces progressive identity shifts in epithelial breast cancer cells, accompanied by remodeling of nuclear and chromatin architecture and the emergence of a transient, highly plastic intermediate state with improved genomic stability and stem-like potential. Embedding these partially reprogrammed cells into three-dimensional collagen I matrices spanning stiffness reveals that matrix mechanics dictates subsequent trajectories, with compliant matrices enabling further state transitions and denser matrices restricting them. Quantitative analysis of nuclear morphology and chromatin organization identifies discrete architectural states and defines an image-derived "organization landscape" that captures distinct states of these transitions. Together, these findings reveal a mechanical route for altering cancer cell identity and demonstrate that physical constraints alone can be leveraged to guide cancer cells toward more potential states responsive to therapeutic intervention.

SYStem

Poster number: 27

Micropatterned Neuruloids identify FGF2 and Retinoic Acid as Antagonizing Signals in Cranial Neural Crest Fate Specification

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Neurulation is a process in which the embryonic ectoderm is patterned mediolaterally into four distinct cell fates: precursors of the CNS, PNS (neural crest), sensory organs (the placodes), and future epidermis. As embryonic development progresses, these cell fates are gradually sub-specified and fine-tuned into more specialized cell types. Utilizing a stem cell-based human neuruloid model that gives rise to the 4 afforementioned cell types, we aim to study signalling factors, which guide these inherent cell types towards auxiliary transcription programmes, resulting in certain fate subspecifications. We have found the neural crest cell type is particularly sensitive to retinoic acid and fibroblast growth factor 2 signalling in this regard. The other neuruloid-inherent tissues also show a reaction to these factors. Our results have the potential to shed deeper insight into the developmental dynamics of the embryonic head ectoderm, which gives rise to an incredible variety of cellular functions, resulting from the afforementioned cell fate subspecifications.

Poster number: 28

AP1 signaling as a regulator of maladaptive responses in liver regeneration

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The adult liver exhibits a remarkable regenerative capacity that relies on hepatocytes and ductal epithelial cells. During chronic liver injury, when hepatocyte-mediated regeneration is compromised, ductal cells become key drivers of tissue repair. However, how ductal cell states dynamically respond to injury and how these responses influence long-term regenerative outcomes remain poorly understood.

Here, we generated a single-cell, time-resolved map of ductal cell heterogeneity during acute and repetitive liver injury using an in vivo diet-based mouse model. Following acute liver damage, ductal cells underwent transient compositional changes, including the emergence of two damage-induced populations, namely reactive and proliferative states. Upon injury resolution, ductal cell heterogeneity was fully restored, coinciding with histological recovery of the liver, despite AP-1 transcription factor motifs were persistently accessible.

In contrast, repetitive injury led to the progressive persistence of a reactive, pro-inflammatory ductal cell state beyond the damage phase. This persistence was associated with hallmarks of chronic liver disease, including increased ductal cell numbers, ductal cell senescence, periductal fibrosis, and enhanced immune cell infiltration. Functionally, repetitive liver damage resulted in a marked decline in the organoid-forming capacity of ductal cells, with the persistence of the reactive state preceding functional impairment, suggesting that prolonged exposure to a pro-inflammatory milieu progressively exhausts the regenerative capacity of ductal cells.

Mechanistically, integration of our in vivo damage-repair time-course data with in vitro ductal organoids revealed that AP-1 signaling is transiently induced in ductal cells in response to acute damage but must be subsequently downregulated to enable proliferative regeneration. In chronic injury settings, persistent AP-1 activation correlated with maintenance of the reactive ductal state and inflammatory signaling. Comparative analyses across multiple mouse models of chronic liver disease and human cholangiopathy single-cell datasets identified AP-1 signaling as a conserved master regulator of maladaptive ductal cell responses. Together, these findings demonstrate that while transient AP-1 activation supports regenerative responses, its sustained activation in chronic injury promotes ductal dysfunction, inflammation, and fibrosis. Targeting AP-1 signaling may therefore represent a promising therapeutic strategy to restore ductal cell regenerative capacity in chronic liver disease.

Poster number: 29

Towards Scalable Dopaminergic Neuron Production: Line-Specific Optimization of WNT and SHH Patterning in Human iPSCs

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High-purity ventral midbrain (VM) dopaminergic neurons derived from human pluripotent stem cells are essential for disease modeling, drug screening, and potential cell replacement therapies. While robust guided differentiation protocols exist for human embryonic stem cells, induced pluripotent stem cells (iPSCs), especially heavily modified lines, often require thorough line-specific optimizations.

In this study, we aimed to adapt and optimize a floor plate-based differentiation protocol for an iPSC line that is engineered to express dCas9-KRAB. Our aim is to obtain highly enriched dopaminergic neuron populations (>95% purity) for genetic screens in order to understand the role of RNA metabolism in synucleinopathies. Neuroectoderm was induced by dual SMAD inhibition, followed by ventralization via Sonic Hedgehog (SHH) signaling and caudalization via WNT pathway activation (GSK3β inhibition). We systematically varied CHIR99021 dose (0-1.0 µM), the timing of FGF8b addition, and compared SHH alone with SHH plus the agonist purmorphamine.

Optimization revealed strong condition-dependent effects on survival and patterning. High WNT activation caused pronounced cell loss, whereas lower WNT conditions frequently produced insufficient ventralization, with persistent PAX6 expression and loss of VM identity. Increasing ventralization with SHH plus purmorphamine improved expression of VM floor plate markers (FOXA2, LMX1B) while maintaining OTX2, but caudal VM markers such as EN1 remained low and off-target lineages (for example BARHL1-positive populations) persisted.

These results highlight the challenge of transferring hESC-based protocols to modified iPSC lines and the need for line-specific tuning of developmental signals. Ongoing work involves optimizing morphogen dose and timing to improve reproducibility and ventral midbrain specification and evaluating small-molecule alternatives to recombinant SHH. We are also exploring whether early WNT and SHH transcriptional responses plus culture metadata, such as passage number, seeding density and recovery after thawing, can support more systematic, predictive optimization to reduce trial-and-error.

Poster number: 30

Organoid modelling of embryonal kidney tumor development

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Wilms tumor (WT) is a malignancy of embryonal kidney development and the most common pediatric renal tumor. Despite high survival rates (>90%), relapse and severe late treatment effects remain a challenge. Over 40 somatic and germline mutations have been identified as potential WT drivers, highlighting WT's genetic diversity and offering new paths for risk stratification and therapy. Histological and genetic characteristics of WT suggest its origin in nephron progenitor cells (NPCs). Open key questions include: 1 Are NPCs the sole source of WT? 2 What genetic/epigenetic traits make NPCs tumor-prone? 3 How do driver mutations exploit this vulnerability to trigger malignancy? However, appropriate human models to study tumorigenesis during development are rare.

We aim to simulate WT development using a customized kidney organoid model based on in vitro differentiation of human embryonic stem cells (hESCs). This allows us to mimic stages of embryonic kidney development relevant for WT, including both mesodermal progenitor stages and mature structures like tubules, glomeruli, and podocytes. Capturing this entire complexity is key to understanding mutation effects across cell types. We previously optimized a published differentiation protocol to generate kidney organoids from two hESC lines. From these parental stem cell lines, we derived isogenic onocogene-inducible lines, which we are using to assess the effects of developmental timing on tumor initiation. In a pilot study, we show that the oncogenic SIX1 Q177R mutation indeed influences nephrogenesis and disrupts organoid formation when activated in an NPC-like state.

Our adapted models will enable investigating the effects of tumor driver mutations in a developmentally and genetically relevant context. In future we are planning to apply time-resolved single-cell RNA-sequencing to dissect intra- and inter-cellular changes upon inducing drivers of Wilms tumor.

Poster number: 31

Inhibition of ppERK1/2 Nuclear Function is Crucial for the Maintenance of Neural Stem Cell Quiescence

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Adult neurogenesis occurs in specialized regions of the mammalian brain. One is the dentate gyrus of the hippocampus. There, quiescent adult neural stem cells (aNSCs) seldomly activate to generate new neurons that integrate into the existing hippocampal circuitry to modulate its functions. Activation is linked to depletion due to the poor self-renewing ability of aNSCs. Quiescence is therefore essential to maintaining adequate, healthy neurogenesis as we age.

Despite its importance, little is known about the molecular mechanisms maintaining aNSC quiescence. These cells exist in a very complex niche and receive multiple inputs from their environment. Nevertheless, quiescence can be faithfully mimicked in vitro: active aNSCs grow in the presence of FGF, while quiescence is induced by addition of BMP4.

Using this setting, we asked whether the ability of BMP to induce quiescence could be linked to its modulation of the FGF-driven MAPK/ERK signalling pathway, which has been associated to cell proliferation and neuronal differentiation. We found that levels of phosphorylated (activated) ERK are higher in quiescent than in active aNSCs. However, this increase in ERK activation is not translated into an increase in ERK transcriptional activity. In fact, quiescent cells exhibit reduced expression of conventional direct targets of ERK, including negative-feedback-regulators (Dusp6 and Spry2). Indeed, we found that ERK is excluded from the nucleus of quiescent aNSCs. The change in subcellular localization of ERK depends on PEA15, which retains ERK in the cytosol and is highly upregulated in quiescent aNSCs. Furthermore, preliminary data indicated the increase in ppERK1/2 in quiescent cells could be due to reduced negative regulation because of PEA15 and ERK1/2 binding. We are currently investigating the functional consequences of the shift in ERK localization, its phosphorylation increase and how it affects aNSCs' ability to acquire and sustain quiescence.

Poster number: 32

Surface coatings impact on transcriptomic signatures and electrical properties of iPSC derived human nociceptors

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Human iPSC derived nociceptors (iNocs) generated with currently available do not sufficiently reflect mature phenotypes and similarities to human nociceptors in situ. We hypothesize that surface coating materials impact differentiation and maturation of iNOCs and assessed different extracellular matrix components and materials mimicking physiological cellular interfaces and how they impact on iNocs morophology, transcrioptomes and function.

We compared most commonly used substrates Matrigel®, laminin (LA), a mixture of poly-L-lysine and laminin (PLL/LA,) fibronectin, fibronectin, gelatin, thrombospindin and neurosik. On day 36 in vitro, we assessed general morphology. Of the three conditions showing best morphologies we and harvested cells for bulk mRNA sequencing followed by assessment of differentially expressed (DE) genes and assessed functional properties using multi-electrode array recordings.

Best permoring cotaings were ILA, PLL/LA and Matrigel®. Cells growing on PLL/LA formed clusters while cells cultured on Matrigel and LA-coating remained largely dispersed. Pathway analysis of DE genes revealed functional enrichment of pathways related to ECM organization, cell differentiation and integrin binding. DE ion channels were reflected by differences in electrophysiological properties of iNocs on the three different coatings.

Our results indicate an important role of ECM coatings for iNocs phentopyes and functions.

Poster number: 33

NEXT-GENERATION ELECTROPHYSIOLOGY FOR FUNCTIONAL CHARACTERIZATION OF HUMAN NEURAL ORGANOIDS AND ASSEMBLOIDS

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Human-induced pluripotent stem cell (hiPSC)-derived 3D neural models (e.g. organoids, assembloids, etc.) are crucial tools for replicating human brain development and studying neurological disorders like Alzheimer's and Parkinson's disease. High-density microelectrode arrays (HD-MEAs) offer a label-free, non-invasive approach to real-time, high-resolution electrophysiological recordings from neural organoids, assembloids, and tissue explants.

We used the MaxOne and MaxTwo HD-MEA platforms, each featuring 26.400 electrodes per well, to record extracellular action potentials from various 3D neural models across different scales, ranging from cell population networks down to single-cell and subcellular levels. We showcased the flexible selection of recording electrodes, enhancing the data's reproducibility and statistical power. Key parameters, including firing rate, spike amplitude, and network burst profile, were extrapolated. The AxonTracking Assay was employed to trace action potential propagation along axonal branches and analyze conduction velocity, latency, and axonal morphology. This breakthrough assay enables high-resolution analysis of disease models targeting axon initial segment, development, and conduction.

The here presented HD-MEA platforms' capability for targeted electrode selection improves data consistency and enables more comprehensive statistical insights. Furthermore, automated data visualization and metric extraction make these systems a robust and user-friendly choice for in-vitro disease modeling and drug testing in both acute and longitudinal studies.

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Poster number: 34

Establishing a Quiescent State: The Role of Niche Patterning in Human Radial Glia

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Quiescence is a reversible state characterized by profound metabolic, transcriptional and signaling changes. Quiescence contributes to long-term homeostasis in adult tissues by slowing the depletion of stem cells. During development, neural stem cells (NSCs) acquire quiescence in distinct areas of the mouse brain, the neurogenic niches, to ensure lifelong generation of new neurons. Proliferating NSCs, intermediate progenitors and immature neurons are present in neurogenic niches of the human brain, even at old age. However, quiescent human NSCs are yet to be identified and characterized. This is due to a combination of poor accessibility, relatively low numbers and high resemblance to other cell types such as astrocytes. To overcome these problems and evaluate the competence of human NSCs to acquire, maintain and exit quiescence, we developed an in vitro approach based on BMP4 addition, a molecule that induces a quiescence-like state in mouse NSCs. We tested the ability of BMP4 to promote quiescence hallmarks in human NSCs from different developmental times and regional identities. Our results show that radial

glia - and not neuroepithelial - NSCs drop proliferation and upregulate GFAP, a quiescence-associated marker, in response to BMP4. Furthermore, re-activation requires patterning to known neurogenic regions. The main processes regulated by BMP4 are comparable between mouse and human NSCs. However, there is little overlap in the gene expression changes induced by BMP4 in the two species. This newly identified transcriptional profile of BMP-induced quiescence might allow us to identify prospective quiescent human NSCs in vivo using available datasets. Overall, our results show that defined subsets of human NSCs can acquire a quiescent-like state and that their profile could be used to identify quiescent NSCs in the human brain.

Poster number: 35

From dynamic morphogen gradients to complex tissue mechanics

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Seminal work showed that a few morphogens, i.e. diffusible molecules that form dynamic signalling gradients in vivo, are sufficient to trigger both patterning and morphogenesis during development. While past studies focused on the regulatory logic, and molecular players, by which morphogens specify cell fate, much less is known about how morphogens encode the cell behaviours, and mechanical forces, driving morphogenesis. Recent work, from us and others, identified a central morphogenetic role for the morphogen Nodal, a highly conserved inducer of meso- and endoderm (mesendoderm) patterning, during zebrafish gastrulation. This now provides an exciting entry point to investigate the logic, and molecular effectors, by which Nodal elicits a complex range of cellular behaviours, from motility to changes in adhesion, ultimately resulting in collective gastrulation movements.

Since both Nodal signalling concentration and duration were previously shown to regulate mesendoderm specification and patterning in vivo, we established a minimal in vitro assay to quantitatively link mesendoderm progenitor behaviours and mechanics to Nodal dynamics. This approach revealed that cell protrusions, a well-established proxy for cell motility, show a dose-dependent response to increasing Nodal/Activin-A concentrations. Regardless of the exact concentration of Nodal/Activin-A signals in the media, however, pulsed rather than sustained induction, showed that mesendoderm cells become irreversibly protrusive after 2-hours. These findings support that while Nodal concentration sets the magnitude of mesendoderm motility, signalling duration triggers the irreversible switch towards a motile state. In line with this, we found that sustained Nodal signalling (about 2 hours) is also necessary in vivo for successful mesendoderm morphogenesis. This logic contrasts with previous findings on how Nodal encodes cell fate, where concentration and duration are thought to be more interchangeable parameters.

To identify the molecular effectors by which Nodal regulates mesendoderm motility and morphogenesis, we performed RNAsequencing of in vitro progenitors induced by sustained or pulses of Nodal/Activin-A signals. In addition to well-established Nodal targets, several cytoskeleton and adhesion-related genes were found to be strongly upregulated (and with gene-specific kinetics) in response to Nodal signalling, that we are now functionally testing using CRISPR/Cas9. Altogether, this systematic approach aims to uncover the logic, and molecular mechanism, by which Nodal co-encodes both fate and morphogenetic programs.

Poster number: 36

Contributions of the Central Nervous System to Skeletal Development During Embryogenesis

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Embryonic organogenesis depends on coordinated interactions between stem and progenitor populations across developing tissues. While extensive work has focused on how non-neural organs influence central nervous system (CNS) patterning, whether the CNS reciprocally contributes to peripheral tissue development remains poorly understood. Here, we examine the role of the CNS in embryonic organogenesis.

Using early genetic ablation strategies, we generated embryos lacking a functional CNS. Unexpectedly, CNS-deficient embryos survived until embryonic day 18.5, enabling analysis of late developmental stages in the near absence of neural tissue. Despite preservation of overall body plan organization, we observed pronounced and reproducible defects in skeletal morphogenesis, suggesting that proper bone development depends on CNS-derived signals.

To assess whether these phenotypes arise from CNS loss, we employed blastocyst complementation to reintroduce CNS progenitors. Complemented embryos developed into viable animals with restored CNS. These results demonstrate efficient reconstitution of the neural compartment in an otherwise CNS-deficient developmental context.

Together, our findings support a reciprocal relationship between neural and skeletal progenitor systems and indicate that the CNS contributes to coordinating systemic organogenesis during embryonic development.

Poster number: 37

Generation of iPScs-derived functional T cells in thymic organoids and disease modelling of APECED syndrome

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Autoimmune-polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED) is an autoimmune disease targeting multiple organs. It is caused by a loss-of-function mutation in AIRE, the principal transcription factor regulating self-antigen expression in thymic epithelial cells (TECs), essential in establishing self-tolerance. We have developed an iPSc-derived thymic organoid system to model AIRE function in TECs and generate mature T cells and regulatory T cells (Tregs) for future cell therapy applications.

We first set up and conducted the directed differentiation of AIRE WT iPS cells towards a hematopoietic stem and progenitor cell (HSPC) identity, and obtained reproducible results showing the emergence of a population characterized by the expression of hematopoietic markers CD34, CD43, CD44 and CD45, resembling cord blood CD34+ progenitor cells. A large fraction of these cells also expresses CD7, presenting a phenotype resembling the hematopoietic progenitors that enter the thymus in vivo. We then conducted the directed differentiation of AIRE WT and AIRE KO iPScs towards a TEC precursor (TEP) identity (EPCAM+ CD205+). AIRE WT TEPs were aggregated with the CD34+ HSPCs to form iPSc-derived thymic organoids, cultivated over a five-week period. Flow cytometry analysis revealed the emergence of a CD45+ compartment comprising double negative, double positive and immature simple positive (ISP) CD4+ cells on day 21. This compartment started to mature towards a T lymphocyte population (CD45+ CD3+) comprising double negative and simple positive (SP) CD4+ and CD8+ cells on day 28. On day 35, the generated T cell compartment became more abundant and almost exclusively comprised SP cells positive for TCR??, highlighting their mature state and functional potential.

Our results demonstrate the differentiation potential of iPSc-derived HSPCs towards mature and functional T cells within an iPSc-derived thymic organoid system. This platform now enables us to conduct comparative studies between AIRE WT and AIRE KO conditions to explore AIRE's role in T cell selection, and provides a foundation for the development of Treg-based cell therapy approaches for APECED, including lentiviral-mediated FoxP3 expression strategies.

Poster number: 38

Neuronal replacement after stroke - from transplantation to reprogramming

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Stroke is the second leading cause of death worldwide and one of the leading causes of long-term disability. Although around 13.7 million people per year experience a stroke, effective treatments to promote tissue repair and functional recovery are lacking. By using neuronal replacement strategies, which have approached clinical trials for some neurological diseases in recent years, we hope to contribute to the understanding and improvement of this novel treatment method also for stroke. Towards this aim, we compare different approaches of neuronal replacement – mouse into mouse fetal neuron transplantation as the gold standard and human astrocyte-to-neuron conversion in immune-deficient mouse models. The former has the advantage of exploring

transplant development without any species barriers and immunosuppression. The later probes the development of avoiding immunosuppression also in patients in future converting the patients' own glial cells as source for new neurons. Exploring this in a mouse model, however, requires the use of RAG1-knock-out mice lacking B- and T-cell immunity.

To mimic an ischemic stroke, we established a photothrombotic lesion model with adequate lesion size in the murine cerebral cortex. This model is beneficial due to its high reproducibility, flexible control of location and infarct size, easy manipulation, and minimal trauma. One week after the lesion, we graft either mouse embryonic cortical cells or human iPSC-derived astrocytes directly into the lesion site.

Immunostaining at 4 and 12 weeks post-transplantation (wpt) showed that cells survive well for 4 and 12 wpt and differentiated already at 4wpt into about 50% neurons with the mature neuronal marker NeuN. While some of them were still immature co-expressing Doublecortin, Doublecortin+ neurons had vanished by 12wpt. Sox9+ astrocytes or Olig2+ oligodendrocytes compose about 20% of the transplanted cells by 12wpt. Using Visium HD spatial transcriptomics showed adequate maturation of the transplanted neurons closely resembling host cortical pyramidal neurons.

We investigated tissue remodeling effects of the transplanted cells on the host environment and see strong improvement of the otherwise prominent scar around the lesion, that is much improved upon transplantation, which is also reflected in the spatial transcriptomics. In addition, the accumulation of macrophages in the lesion core is gone, and instead we observed vascularization generating a network almost indistinguishable from the surrounding host cerebral cortex. Thus, transplanted neurons mature to neurons closely resembling the host cortical projection neurons and the lesion scar is much improved.

To develop the most effective neuronal replacement approach, we compared the murine neuron transplantation with a human reprogramming approach. Transplantation of human iPSC-derived proliferating astrocytes transduced with the phospho-deficient form of the proneural transcription factor Neurogenin2 into an ischemic stroke lesion resulted in their conversion to neurons in vivo. Indeed, the majority of cells 4 weeks after transplantation are neurons as assessed by Doublecortin and NeuN immunostaining, while a few still express the astrocyte marker Sox9. We are now exploring their further maturation and integration.

Taken together, transplants exert a beneficial effect on the stroke lesion site and differentiate into adequate neurons resembling the host neurons. Network integration is now the final step to evaluate the quality of the transplants.

Poster number: 39

Single-cell profiling of striatal organoids derived from Leigh syndrome patients indicates an imbalance of neuronal subtypes during early neurodevelopment

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Leigh syndrome (LS) is a severe neurological disorder that is characterized by progressive loss of mental and movement abilities and typically results in death within two to three years, usually due to respiratory failure. LS arises from mutations in mitochondrial genes leading to dysregulated ATP production. NDUFS4, which is commonly mutated in patients, invokes alterations in various brain regions including the striatum. The underlying pathophysiological mechanisms driving this rare disease remain unclear. Induced pluripotent stem cell (iPSC) derived brain organoids have emerged as powerful in vitro tools to study nervous system development. Brain organoids recapitulate early stages of nervous system development and by that serve as valuable models to investigate disease mechanisms. In this study, we aim to exploit LS-iPSC-derived organoid models to elucidate differences on transcriptome level in early striatal organoid development. To this end, we derived striatal organoids from iPSCs carrying a NDUFS4 mutation and their isogenic controls. Single-cell transcriptomic profiling revealed a shift in neuronal subtype composition in LS organoids, with an expansion of glutamatergic neurons and a concomitant reduction in GABAergic neurons. Cell type prioritization highlighted GABAergic neurons as the most perturbed. Differential expression analysis demonstrated downregulation of OXPHOS-related genes at both the gene and pathway levels, with GABAergic neurons showing particular susceptibility to these changes. Comparing DEGs across cell types, we identified 23 consistently dysregulated genes. Network analysis using STRING further refined the candidates to NR2F1, FOXP2, and ETV1. These three genes are involved in differentiation by PAX6 regulation, neurite outgrowth of striatal medium spiny neurons in mouse and mediating gene expression based on mitochondrial membrane potential, respectively. Further investigation of the regulome by decoupleR revealed a perturbation of the majority of transcription factors regulating NR2F1 and ETV1. Together, our findings reveal an early imbalance of GABAergic and glutamatergic neuronal subtypes and nominate gene candidates implicated in the phenotype of LS organoids, advancing mechanistic insight into LS and pointing to potential intervention strategies.

Poster number: 40

Decoding NeuroCOVID: Integrative multi-omics and patient-derived stem cell models to unravel chronic neuroinflammation in long-COVID

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Long COVID is characterized by persistent symptoms lasting more than one year after acute SARS-CoV-2 infection without alternative explanation. Among its most disabling features are neurological and neuropsychiatric manifestations—collectively termed NeuroCOVID—including memory impairment, reduced concentration, fatigue, sleep disturbances, and mood disorders. These symptoms significantly affect daily functioning and quality of life, yet their biological basis remains poorly understood. The NeuroCOV Consortium aims to elucidate the cellular and molecular mechanisms underlying heterogeneous NeuroCOVID trajectories by integrating deep clinical phenotyping with advanced human stem cell–based models. We hypothesize that persistent immune dysregulation and chronic neuroinflammatory processes drive long-term alterations in brain homeostasis, influencing susceptibility or resilience to neurological impairment. We are conducting high-resolution multi-omics profiling of peripheral blood mononuclear cells (PBMCs) from well-characterized patients recruited in two European cohorts (Italy and Germany). By integrating detailed clinical data with immune-associated transcriptomic signatures, we seek to identify pathways linked to distinct neurological phenotypes and to enable patient stratification beyond clinical presentation alone. Based on this stratification, we are establishing a NeuroCOVID-specific human induced pluripotent stem cell (hiPSC) biobank representing the spectrum of neurological manifestations. Patient-derived hiPSCs are differentiated into three-dimensional neural models to recapitulate key aspects of human cortical organization and to investigate long-term neurobiological alterations in a physiologically relevant context. To explore neuroimmune interactions, we are implementing complementary experimental strategies that allow us to examine both direct cellular interactions and broader inflammatory influences within the neural environment. This approach enables the distinction between intrinsic neuronal alterations and extrinsic immune-mediated effects. In parallel, we are developing scalable and semi-automated analytical workflows to quantitatively assess cellular phenotypes and functional changes in a systematic manner. Through integrated molecular and functional analyses, we aim to identify convergent pathways driving chronic neuroinflammation and neuronal dysfunction in Long COVID. By linking patient-derived immune signatures with stem cell–based disease modeling, this project seeks to uncover patient-specific molecular drivers of NeuroCOVID vulnerability and resilience, paving the way for biomarker discovery and targeted therapeutic strategies.

Poster number: 41

3D modelling of fusion-driven sarcomagenesis

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Ewing sarcoma (EwS) is an aggressive malignancy of bone and soft tissue that predominantly affects children and young adults. Despite its genetically simple landscape - most commonly driven by the pathognomonic EWSR1::FLI1 fusion oncogene - faithful disease modeling has remained challenging. A central limitation is the unresolved identity of the cell(s)-of-origin, hindering efforts to accurately recapitulate tumor initiation and early progression in experimental systems.

The cellular origin of EwS remains controversial, with both mesenchymal and neural crest–derived progenitors proposed (Thomas G P Grünewald et al. Nat Rev Dis Primers. 2018). To address this question, we leveraged neuromuscular organoids (NMOs), an emerging three-dimensional (3D) human stem cell–derived model that integrates these developmental lineages (Faustino Martins et al. Cell Stem Cell. 2020). NMOs comprise co-developing spinal cord neurons and skeletal muscle cells that self-organize into functional neuromuscular networks, thereby providing a developmentally relevant context to study early oncogenic events.

Using human embryonic stem cells engineered with a tamoxifen-inducible EWSR1::FLI1 system, we generated fusion-expressing

NMOs to model transformation in a multicellular 3D environment. We successfully established organoids in which EWSR1::FLI1-expressing cells progressively colonize the tissue and achieve near-complete dominance within 100 days. These fusion-expressing NMOs display distinct cellular dynamics, altered self-organization, and sustained expansion over long-term culture, representing - to our knowledge - the first 3D human system that supports stable propagation of EWSR1::FLI1-driven cells.

Building on this platform, we are developing next-generation 3D EwS models that recapitulate early sarcomagenesis and incorporate key components of the tumor microenvironment. This approach provides a tractable and physiologically relevant system for dissecting fusion-driven mechanisms and for advancing preclinical therapeutic testing.

Poster number: 42

Mouse neural organoids access macroglia phenospace

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Macroglia—astrocytes in the brain and Müller glia in the retina—are essential regulators of central nervous system homeostasis. Stem cell-derived mouse neural organoids could be modular, rapidly developing systems to explore matured, homeostatic mammalian brain physiology. Here we establish an atlas of mouse neural organoids, assess fidelity across brain regions and retina, and dissect macroglial-neuron interactions through perturbation. Mouse neural organoids recapitulate developmental pace, enabling access to complex mammalian neuron-macroglial programs in vitro after several weeks of culture. Comparative analysis between brain and retinal macroglia uncovers cell-type-specific inflammation and interferon-induced states across neuronal and glial populations. Transcriptomic mapping to in vivo datasets validates high similarity between organoid and native tissue macroglia. From these inflammatory responses, we identified Oncostatin M as a potent activator driving glial transition to a reactive phenotype and established robust quantitative immunohistochemistry readouts characterizing this phenotype. Through comprehensive single-cell perturbation screening, we mapped the Müller glia perturbation space and found distinct glial states that correlate with degeneration-linked photoreceptor responses. Our findings establish mouse neural organoids as a relevant, rapidly developing, and scalable platform for dissecting macroglial function and neuron-glia crosstalk in health and disease.

Poster number: 43

Human basal radial glia morphotypes are transcriptionally distinct and exhibit different cell fate determination

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Basal radial glia (bRG) are key neural progenitors driving human neocortical expansion. They exhibit remarkable morphological heterogeneity, yet the stability and functional significance of their distinct morphotypes remains unclear. Using human cortical brain organoids combined with long-term live imaging and morphology-resolved spatial transcriptomics (CellShape-seq), we show that bRG morphotypes display distinct morphodynamic behaviors, proliferative capacities and transcriptional profiles. While bifurcated bRG remodel extensively during mitosis to produce morphologically diverse progeny, multipolar cells are most morphologically flexible during interphase. Multipolar bRG further show the greatest proliferative capacity and the transcriptional signature related to progenitor state. Bifurcated bRG are least proliferative and are enriched for the multifunctional gene expression regulator YBX1. Pharmacological inhibition of YBX1 depletes bifurcated bRG, reduces neurogenesis and promotes glial commitment. Our findings link progenitor morphology, gene expression and fate, providing a framework for understanding the cellular logic of human cortical development.

Poster number: 44

Investigating Neuroinflammation in Traumatic Injury Using Human Stem-Cell Derived Organoids with Amyotrophic Lateral Sclerosis Gene Mutation

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with a typical survival of 3-5 years after symptom onset and no effective disease-modifying therapies. Epidemiological evidence links traumatic brain injury (TBI) to increased ALS risk, but the mechanisms by which TBI interacts with ALS-linked mutations to shape neuroinflammatory responses remain poorly defined. Conventional rodent models incompletely capture human-specific inflammatory and glial phenotypes, underscoring the need for human-relevant experimental systems.

Here, the aim was to define mutation-specific neuroinflammatory responses to traumatic injury using human induced pluripotent stem cells (iPSC)-derived cortical organoids carrying ALS-associated mutations. Cortical organoids generated from iPSC lines harboring TDP-43 Q331K, TDP-43 M337V, FUS R495X, or isogenic/wild-type controls were subjected to a controlled traumatic impact paradigm. Neuroinflammatory responses were analyzed at 3-, 7-, and 14-days post-injury using cytokine profiling and immunofluorescence for glial markers and disease-associated proteins (pTDP-43, FUS, NOS2).

Traumatic impact successfully induced injury-related neuroinflammation across all genotypes, confirming the utility of this platform as a human model for TBI-ALS interactions. This study validates a genetically tractable human cortical organoid system for probing how ALS-linked mutations influence post-traumatic responses.

Poster number: 45

Mechanism of endo-mesodermal lineage choice

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During gastrulation, cells self-organize while undergoing fate transitions to establish the three germ layers, ectoderm, mesoderm, and endoderm. The onset of this process is accompanied by the formation of the primitive streak at the posterior side of the epiblast. Here, cells first acquire a mesendodermal precursor identity, defined by the marker Brachyury (T), and subsequently differentiate to endoderm, a transition linked to the expression of Foxa2. While our knowledge of the precise cell fate trajectories in the embryo is increasing, the genetic requirements for the stepwise acquisition of definitive endoderm identity remain largely unknown. To monitor the progression in the endo-mesodermal trajectory, we engineered embryonic stem cells (ESCs) to express fluorescent reporters fused with marker genes for early gastrulation (T) and definitive endoderm (Foxa2). To then understand the genetic dependencies of each transition, we performed genome-wide CRISPR screens in established monolayer differentiation regimes. I am currently investigating candidate genes by taking advantage of RNAseq and ChIPseq to further uncover how they regulate the endo-mesodermal lineage choice.

SYStem

Poster number: 46

Mapping the synergisms network in the exit from naïve pluripotency

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Gene regulatory networks (GRNs) are the main instructors of cell differentiation, and they importantly coordinate precise and ordered transitions in cell identity during development. Despite the transcriptional programs defining pluripotent states being well described, we still lack a comprehensive understanding of how genetic redundancy and cooperativity help in the contribution to shaping early developmental cell state transitions. A key example of such transitions is the exit from naïve pluripotency, corresponding to the switch between the pre- and post-implantation epiblast. This differentiation event represents one of the earliest and most important fate transitions in mammalian development, as it coincides with the acquisition of differentiation competence, right before the onset of gastrulation.

In the mouse system, many genes have already been implicated to play a role in the exit from naïve pluripotency, yet no single-gene perturbation is sufficient to fully prevent this transition, suggesting that the naïve exit is controlled by partially redundant gene activities acting in a coordinated manner. Here, we use the exit from naïve pluripotency in mouse embryonic stem cells (mESCs) as a simple yet insightful model to systematically map the genetic interactions that drive this developmental transition. We establish an optimized combinatorial CRISPR screening setup that enables balanced, simultaneous disruption of two genes per cell, allowing for the assessment of genetic synergism across a vast combinatorial genetic space. Using this approach, we perform a targeted genetic screen surveying roughly 280,000 gene pairs, selected from candidates previously linked to naïve exit. This dataset provides an extensive and quantitative catalogue of genetic interactions ranging from purely additive to strongly synergistic. Network-level analysis reveals both expected functional relationships within known pathways and previously underappreciated genetic players, uncovering how multiple modules jointly dismantle the naïve GRN and promote progression toward formative pluripotency. Selected gene pairs will be validated by generating bulk double knockouts, high-throughput transcriptomics, and clonal line generation for mechanistic follow-up.

Together, this work establishes a solid framework for systematically dissecting genetic redundancy and synergism in the context of development and provides new insight into the cooperative logic underlying the exit from naïve pluripotency.

Poster number: 47

Cerebral Organoids Uncover Mechanisms of Neural Activity Changes in Epileptogenesis

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Neurological disorders often originate from progressive brain network dysfunction that starts years before symptoms appear. How these changes emerge in the developing human brain remains elusive due to a lack of tractable model systems. Here, we show a cerebral organoid model of Tuberous Sclerosis Complex (TSC) that recapitulates hallmarks of epileptogenesis in vitro. We compare extracellular recordings from TSC organoids with intraoperative electrocorticography from TSC patients, revealing striking functional similarities, including pathological high-frequency oscillations – an electrical biomarker for epileptogenic tissue. In TSC, a human-specific interneuron subtype derived from the caudal ganglionic eminence drives pathological network phenotype through perturbed synaptic transmission, as confirmed by extracellular recordings during pharmacological treatments, miniature inhibitory postsynaptic current recordings, and electron microscopy of inhibitory synapses. This leads to an altered excitation/inhibition (E/I) ratio and increased spontaneous firing. Moreover, inhibiting the overproliferation of its progenitors via long-term epidermal growth factor receptor inhibition prevented the onset of this pathological phenotype at both functional and morphological levels. Our work shows that organoids enable mechanistic analysis of emerging neural network phenotypes, enabling anti-epileptogenic drug testing in a human brain development model.

Poster number: 48

CRISPR screens in human iPSC-derived neurons and glia for target identification and validation

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To advance systematic functional genomics in human CNS cell types, we engineered CRISPR-Ready iPSC-derived models, enabling precise CRISPR-based perturbations in multiple cell types, including ioGlutamatergic Neurons, ioMotor Neurons, ioMicroglia, and ioOligodendrocyte-like cells. These models facilitate pooled CRISPR activation (CRISPRa), CRISPR interference (CRISPRi), and CRISPR knockout (CRISPRko) screens with single-cell RNA sequencing (scRNA-seq) readouts, allowing for high-dimensional mapping of gene function in disease-relevant contexts. We are expanding screening readouts to functional assays, including phagocytosis, autophagy and cytokine secretion.

Using a library of 150 CNS disease–associated genes across all four cell types, we captured cell-type-specific transcriptional responses. Neurons highlighted regulators of synaptic activity and mitochondrial function; microglia revealed immune-signaling and metabolic programs; oligodendrocyte-like cells showed alterations in myelination and lipid metabolism. Comparative analyses uncovered shared signatures and lineage-specific vulnerabilities, underscoring the context dependence of gene function in the CNS.

This CRISPR screening platform provides an end-to-end workflow for target discovery and validation - moving from perturbation to mechanism to functional effect - and enables scalable dissection of human neural disease mechanisms.

Poster number: 49

Mechanisms Regulating the Emergence of Formative Pluripotency in Humans

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The transition from pre- to post-implantation epiblast is an early developmental milestone in which pluripotent cells extinguish naïve identity, acquire formative competence, and become able to execute subsequent lineage decisions while retaining broad developmental potential. Because this period is ethically and technically difficult to access in vivo, the molecular rules governing the naïve-to-formative transition remain incompletely defined in humans. Here, we establish a human-specific in vitro model that faithfully transitions naïve human embryonic stem cells (hESCs) towards formative pluripotency. Time-resolved transcriptomic profiling confirms that this system recapitulates key in vivo differentiation trajectories. Strikingly, our data indicate that the tempo of progression is predominantly governed by intrinsic factors rather than external cues. Comparative analysis with mouse datasets reveals a mixture of conserved and species-divergent transcriptional dynamics, underscoring the necessity of human models to resolve human-specific regulatory logic. Based on this in vitro system, we performed a genome-wide CRISPR knockout screen to identify genes required to dismantle the naïve state and enable the establishment of the formative state. This unbiased approach yielded candidate regulators, several of which have been validated as drivers of the naïve-to-formative transition. Current efforts focus on mechanistic dissection of these hits, defining how they reshape transcriptional and chromatin states to enforce shutdown of the naïve gene regulatory network and initiate the formative state.

SYStem

Poster number: 50

Ex machina: explainable machine learning to decode the regulatory logic of cell-fate specification

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The machinery of cell fate decision is fueled by stochasticity, environmental factors, and a plethora of subtle cues encoded in the genome. While single-cell transcriptomics and epigenomic profiling have significantly deepened our view of these processes, they have generated a vast amount of data that remains difficult to analyze comprehensively. In this work, we present a strategy to utilize novel sequence-to-function deep learning models, such as Enformer and AlphaGenome, to decode the regulatory landscapes underlying cell fate decisions.

We apply this machine learning-driven analysis to the neural crest, a multipotent migratory population whose derivatives span diverse tissues. By fine-tuning these models on multi-modal single-cell data, specifically scRNA-seq and scATAC-seq, we repurpose them for high-resolution interpretation of regulatory logic. We employ in silico experimentation strategies, such as mutagenesis and identifying high-importance nucleotides, to test hypothetical sequence perturbations and validate candidates for laboratory analysis. Furthermore, we leverage model reasoning, specifically the analysis of attention matrices, to infer novel cis-regulatory elements and rank their interactions with genes of interest, such as Twist1, during the formation of skeletogenic mesenchyme.

Finally, we illustrate how these fine-tuned regulatory landscapes can address developmental and evolutionary questions. These technical approaches reveal principles that resonate far outside neural crest biology, offering a transferable set of recipes for anyone seeking to explore the logic of regulatory systems across diverse biological contexts.

Poster number: 51

Toward Standardized MSC-EV Manufacturing: Effects of hTERT Immortalization and Collection Media on EV Functionality

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Mesenchymal stromal cell–derived extracellular vesicles (MSC-EVs) are emerging as promising cell-free therapeutics due to their immunomodulatory, regenerative, and pro-repair properties. However, clinical translation of MSC-EVs is hindered by substantial biological and technical variability arising from donor heterogeneity, limited replicative lifespan of primary cells, phenotypic drift during in vitro expansion, and inconsistencies in culture and collection conditions. Addressing these challenges is critical for developing scalable, standardized, and clinically relevant MSC-EV manufacturing platforms.

In this study, we evaluated hTERT-immortalized (telomerized) MSCs as a stable and reproducible EV producer platform and systematically assessed the influence of EV collection media on EV characteristics and biological activity. hTERT-immortalized MSCs derived from different tissue sources were compared with their parental primary counterparts with respect to cell phenotype, proliferation, differentiation potential, and EV properties. In parallel, EVs produced by telomerized MSCs were collected in four xeno-free media, enriched using tangential flow filtration (TFF), and functionally compared to corresponding unconditioned media controls.

Our results demonstrate that hTERT immortalization does not alter MSC morphology, surface marker expression, tri-lineage differentiation capacity, or cellular doubling time, while enabling unlimited and stable in vitro expansion. Importantly, EVs derived from telomerized MSCs were indistinguishable from those of primary MSCs in terms of size, particle concentration, cargo composition, and key biological functions, including anti-inflammatory, anti-fibrotic, wound-healing, and proliferative activities in vitro. These findings establish hTERT-immortalized MSCs as a robust and reliable cell factory for continuous MSC-EV production.

Furthermore, we show that EV collection media exert a pronounced influence on EV yield and functional bioactivity. EVs collected in different xeno-free media displayed distinct biological effects, some of which overlapped with activities observed in corresponding unconditioned media, underscoring the importance of carefully distinguishing EV-specific effects from medium-derived components. Collectively, this work highlights the dual importance of standardized producer cell platforms and optimized collection conditions for generating consistent, clinically translatable MSC-EV preparations.

Poster number: 52

Unraveling the mechanisms of roof plate specification in the developing neural tube

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In developing embryos, organizing centers produce morphogens and profoundly influence the patterning and growth of adjacent tissues. Perturbations in the sizes of organizing centers have severe developmental consequences, yet the mechanisms involved in robustly controlling the specification and growth of these centers are poorly understood. One such example is the roof plate (RP) of the vertebrate neural tube, a key organizing center that controls dorsal neural tube patterning. How RP identity is specified and segregates from adjacent neural crest (NC) and dorsal neural progenitor lineages is unclear. Here, we use 2D mouse neural organoids that recapitulate dorsal neural tube patterning to investigate the dynamics of RP fate specification. Our analysis so far indicates that Lmx1a, a master-regulator of RP identity, is activated earlier in development than previously thought. Quantifications of the gene expression patterns in organoids in response to defined activation or inhibition of BMP and Wnt signaling indicate that the two signaling pathways synergistically activate Lmx1a expression, but have distinct effects on NC specification. To uncover additional regulatory links, we used single-cell RNA sequencing at different time points of differentiation. To infer the differentiation trajectories associated with RP, NC and dorsal progenitor differentiation, we are employing deep learning-based methods for trajectory inference. Our preliminary data allowed us to identify potential cross-regulatory interactions between NC, RP and dorsal neural progenitor-associated transcription factors. We will next validate these regulatory links and their relationship to cell fate decisions using high-resolution lineage tracing, live imaging of fluorescent fate reporters, and perturbations, combined with dynamical systems modeling. These approaches will allow us to determine when and how RP, NC and dorsal neural fates become restricted, thereby uncovering key principles of controlling the size of organizing centers in developing tissues.

Poster number: 53

Human PSC-derived cardiac organoids incorporating macrophages reveal inflammation-induced physiological alterations

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Cardiovascular disease remains a leading cause of death worldwide, yet progress in developing new treatments is hindered by the limited physiological relevance of many preclinical models. Human pluripotent stem cell (hPSC)-derived organoids offer a promising platform to model human tissue biology, including cardiac development and disease. However, most cardiac organoid models lack immune components, despite their important roles in cardiac physiology and pathology.

We have developed a cardiac organoid ("cardioid") model that incorporates macrophages to better mimic the multicellular environment of the human heart. Macrophages were successfully introduced and maintained within the cardioids. To investigate their functional role, the organoids were exposed to lipopolysaccharide (LPS) and interferon-gamma (IFN-γ), to simulate systemic inflammation. This treatment induced a pro-inflammatory phenotype, as evidenced by increased CD80 expression and elevated levels of pro-inflammatory cytokines, including IFN-γ, CXCL10 and IL-6.

Functionally, these inflammatory stimuli led to prolonged calcium transients and contraction durations in macrophage-containing cardioids; responses not observed in organoids lacking immune cells. While further investigation is required, these findings suggest that macrophages can modulate cardiac organoid physiology under inflammatory conditions.

While our current study has focused on acute inflammatory responses, the model offers opportunities to explore broader roles of macrophages in cardiac tissue, including contributions to remodelling, metabolism, and electrophysiology. Overall, this model provides a new platform for studying immune–cardiac interactions and has potential applications in further disease modelling and drug discovery, particularly in the context of inflammation-associated cardiac dysfunction.

SYStem

Poster number: 54

CellMate-seq identifies combinatorial ligand-receptor interactions between individual cells

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Cells communicate with their neighbors through ligand-receptor (L-R) interactions to coordinate their behavior and fate. While signaling is often studied one pathway at a time, it is well recognized that pathways influence each other and jointly affect the cell. For a systems-level understanding of intercellular communication, it is therefore essential to identify which cells interact and what combinations of signaling pathways they use. To this end, we developed CellMate-seq, an approach that uniquely barcodes neighboring cells for subsequent deep scRNA-seq, together with a computational framework to identify their L-R combinations. Applying CellMate-seq to the E9.5 mouse embryo, we uncovered comprehensive sets of L-R pairs ('modules') used together by subpopulations of interacting cells. For instance, for interactions between cardiopharyngeal mesoderm and neural crest cells, we identified eight L–R modules which form cell-state and location-specific 'dialogues.' Although neural crest cells vary in their differentiation state, it is the mesodermal neighbors that primarily drive the differences between these L–R dialogues by exposing neural crest cells to varying sets of ligands at distinct anatomical locations. Overall, CellMate-seq unlocks the potential of single-cell transcriptomics to study the L-R combinations that underlie the language of cells.

Poster number: 55

Decoding the Regulatory Logic of Cell Fate Convergence in Craniofacial Development

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Despite their ectodermal origin, cranial neural crest cells generate bone and connective tissues similar to mesoderm. However, the regulatory basis of this cell fate convergence remains unclear. To investigate this, we characterized transcriptional and epigenomic states during early craniofacial development by comparing single cell RNA-sequencing and ATAC-sequencing of E9 mouse cranial neural crest and mesodermal cells. These data capture gene expression and chromatin accessibility within the same cells, enabling analysis of transcriptional states and regulatory element usage during early craniofacial mesenchyme emergence.

In parallel, we generated CUT&RUN datasets from embryonic mouse heads targeting key neural crest transcription factors (Tfap2a, Sox10, FoxD3, Ets1, Twist1) together with H3K4me1 profiling. Ongoing integrative analyses link transcriptional states, chromatin accessibility, and transcription factor occupancy to identify candidate regulatory elements associated with cranial neural crest progression toward mesenchyme.

Together, these datasets provide a multi-omic framework to investigate regulatory dynamics underlying craniofacial mesenchyme formation.

Poster number: 56

Cell-ECM adhesion remodelling during skin development

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Epithelial tissues, including the skin epidermis, both shape organs and provide a protective barrier. The developing epidermis is composed of heterogeneous cell populations with varying levels of cellular fitness, which are expected to arise from genetic mutations, metabolic differences, and mechanical cues. To maintain tissue homeostasis and facilitate proper skin formation, cell competition selectively identifies and eliminates less fit cells, allowing more fit cells to clonally expand. However, the precise molecular and mechanical underpinnings of both fitness sensing and cellular elimination in the epidermis remain obscure. Cell–extracellular matrix (ECM) adhesions act as physical anchor points through which epidermal cells use integrin adhesion receptors to attach to their underlying basement membrane, composed of ECM proteins including collagen IV and laminin 332. We hypothesize that integrin-mediated cell–ECM adhesions serve as a key fitness-sensing mechanism by translating tissue-level mechanical cues into single-cell behaviours that collectively preserve epidermal homeostasis. Although the roles of integrin-mediated cell-ECM adhesion are well established in homeostatic epidermis, the mechanisms that underlie assembly of cell-ECM adhesions in epidermal development are not well described. Moreover, the possibility that heterogeneity in cell-ECM adhesion could play a role in epidermal fitness and cell competition has not been tested. This project aims to fill both these knowledge gaps. First, we begin by characterizing expression and localization of collagen IV, laminin 332, integrinβ1, and the basolateral polarity protein Scribble, through embryonic development in the mouse epidermis, at both the mRNA (via qPCR) and protein level (via immunofluorescence). We find that integrin localization to the basement membrane increases with development, and correlates with a thickening and increased recruitment of basement membrane ECM. However, with the exception of laminin 332, which exhibits an expected increase, mRNA levels of all other components we examined remain stable across developmental time. These results suggest that basement membrane assembly and maturation is largely orchestrated post-transcriptionally. Second, to interrogate the functional role of integrinβ1, we generated a short-hairpin RNA (shRNA) to knockdown integrinβ1. We first tested for its efficacy in vitro using 2D culture of mouse keratinocytes. Our preliminary findings in vitro show successful knockdown of integrinβ1 with decreased mRNA expression and reduced focal adhesion formation. Our ongoing experiments use our lab's powerful ultrasound-guided in utero lentiviral nanoinjection strategy to obtain mosaic expression of our integrinβ1 hairpin in epidermal progenitors in intact developing embryos. This strategy will enable us to functionally understand how a reduction in cell-ECM adhesion could translate to changes in epidermal cell fitness and survival during the process of epidermal morphogenesis. We can also assay for effects on basement membrane assembly in vivo. Ultimately, our study will uncover fundamental insights on the role of cell-ECM adhesion dynamics and their role in establishing and maintaining tissue fitness in epithelia.

Poster number: 57

Development of a humanized 3D in vitro microenvironment to study nerve regeneration and axon repair

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Most studies investigating nerve regeneration and axonal repair after peripheral nerve injury rely on rodent models, yet species-specific differences hinder translation to humans. In vitro cultures studying the interaction of SCs and neurons could provide an alternative but the limited access to human SCs and human neuronal cells fostered the use of cell lines that insufficiently mimic the behavior of original cell types. Moreover, animal-derived components such as fetal bovine serum (FBS) can alter cell response. Additionally, most protocols still rely on 2D culture systems, which lack the spatial complexity and physiological cues found in vivo. Thus, there is an urgent need to develop humanized 3D in vitro models, which could serve as a valuable tool for preclinical testing of therapeutic strategies.

To this end, we are developing a 3D in vitro model incorporating primary human SCs embedded and iPSC-derived motor neurons (MN) in a biocompatible, placenta-derived human hydrogel (provided by Dr. Karl Schneider, Center for Biomedical Research and Translational Surgery, MedUni Vienna), cultured with human serum and recombinant growth factors. After maturation into MNs, a standardized lesion will be punched into the hydrogel and replaced with a human SC-loaded hydrogel and analyzed alongside with controls. The regenerative performance on axon regeneration (neurogenic effect) of SCs will be evaluated by the speed of axon regeneration and quantity of axons regenerating into the SC-loaded hydrogel at different time points using spinning disc microscopy of living cultures and fixed and immunostained 200 µm sections at different time points.

SY Stem

Poster number: 58

Lineage origin of spinal cord cell type diversity

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The complexity and specificity of movement in vertebrates is driven by a rich diversity of spinal motor and interneuron cell types. During development, eleven spinal cord progenitor domains generate an equivalent number of cardinal neuron types, each containing numerous motor and interneuron subpopulations. How progenitor domains, individual progenitors, and post-mitotic diversity relate to each other however is still unknown. Intrinsic and/or extrinsic factors could shape the identity and proportions of post-mitotic cells. We performed high-resolution single-progenitor lineage tracing in the embryonic mouse spinal cord using mosaic analysis with double markers (MADM). Our quantitative study of lineage progression revealed that nearly all spinal cord progenitors undergo highly variable numbers of proliferative, neurogenic, and gliogenic cell divisions. The nascent clonally-related neurons migrate radially over large distances, can span the dorsoventral axis, and even cross the spinal cord midline. Subsequent molecular and morphometric analysis confirms high levels of progenitor multipotency, with one progenitor capable of producing several molecularly and morphologically distinct neuron types, as well as astrocytes. These findings redefine spinal cord development as a flexible process in which lineage variability—rather than rigid progenitor identity—drives the generation of cellular diversity.

Poster number: 59

Characterising human hippocampal neurogenesis during development and in adulthood

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Introduction

Hippocampal neurogenesis is essential in mice, contributing to the rapid growth of neural tissues during development and supporting learning, memory and mood regulation in adults. In rodents, hippocampal neurogenesis reaches its highest rates around birth and declines to low levels during the first few postnatal months. Contemporarily, most neural stem cells (NSCs), i.e. the source of neurogenesis, become quiescent, allowing for the lifelong maintenance of NSCs and neurogenesis. Conversely, human hippocampal NSCs and neurogenesis remain poorly characterised during development, while their persistence in adults is still debated. However, human hippocampal neurogenesis rates peak around gestational week (GW) 14, raising the possibility that NSCs become quiescent before birth.

Methodology

We used single-cell spatial transcriptomics and immunofluorescence to characterise human hippocampal NSCs and neurogenesis in the developing brain, and to assess whether NSCs become quiescent during gestation. Thereafter, harnessing the acquired knowledge about human hippocampal NSCs and neurogenesis in the embryo, we asked whether cells with molecular properties similar to embryonic NSCs and their immediate progeny, i.e. immature neurons, could be found in published single-nucleus RNA sequencing (snRNA-Seq) datasets of the adult human hippocampus.

Results

At mid-gestation, after the peak of neurogenesis at GW14, we observed a large fraction of NSCs in a non-proliferative state expressing genes related to quiescence, suggesting, by analogy with mouse hippocampal neurogenesis, the formation of a reservoir of quiescent NSCs that could support long-term postnatal neurogenesis. In adult human hippocampi analysed using snRNA-Seq, we found many cells displaying transcriptomic profiles similar to those of embryonic NSCs and immature neurons, suggesting abundant neurogenesis may occur in the adult human hippocampus.

Conclusion

Altogether, our results are compatible with a model whereby human hippocampal NSCs become quiescent around mid-gestation and are maintained in adults, while hippocampal neurogenesis declines sharply during gestation, but it may persist throughout adulthood.

Poster number: 60

A bioengineered in-vitro trauma platform reveals Extracellular matrix-dependent regulation of axon repair

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Traumatic brain injuries (TBI) often lead to diffuse axonal injury (DAI), that is the severing of neurons. These injuries do not affect neurons in isolation. The extracellular matrix, a protein niche surrounding neurons, is concurrently disrupted. Despite continuous neuron-ECM crosstalk, the contribution of ECM damage to axonal repair remains poorly understood, largely due to the structural complexity of brain tissue.

To address this gap, we employ a minimal in vitro human pluripotent stem cell (hPSCs)-derived neuron injury model. Here, neurons are generated via NGN2 induction where we locally injure axons, focusing on laminin interactions as regulators of axonal recovery post-trauma. We engineered a high-precision trauma (HiT) platform capable of inducing an array of spatially defined axon-severing injuries in 2D neuronal cultures. This approach enables (i) a systematic dissection of neuron-laminin interactions by isolating neuronal responses from supporting cell types and (ii) an assessment of molecular and metabolic consequences of axonal injury, ECM damage, or their combination. Using immunofluorescence, metabolic profiling, transcriptomics, and particle image velocimetry, we characterize rapid ECM remodeling and spatiotemporal cellular dynamics in response to localized axonal injury. We demonstrate, using transcriptomic profiling, that trauma upregulates metabolic pathways while suppressing axon guidance ones, but online the presence of laminin. Further confirmed the activity of these metabolic pathways using metabolomics.

By expanding the work to comparative analysis with human post-mortem TBI brain samples, we aim to validate the conservation of these signatures, highlighting mechano-metabolic feedback that link ECM dynamics and axon recovery. Together, this work establishes a scalable human in vitro platform to uncover ECM-driven mechanisms of axonal injury and repair in TBI.

Poster number: 61

Repositioning Netrin-1 as a Priming Agent Enhances Regenerative Potency of Wharton's Jelly-Derived Mesenchymal Stromal Cells Secretome and Extracellular Vesicles

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Tissue regeneration depends on precisely coordinated processes involving cell proliferation, migration and extracellular matrix remodelling. WJMSCs are recognised as potent regenerative agents owing to its strong paracrine activity and diverse secretory profile. This study explores the potential of Netrin-1 as a priming factor to augment the regenerative capacity of WJMSC-derived secretome and extracellular vesicles (EVs). In the study, WJMSCs with and without priming were characterized to assess phenotypic stability and priming efficacy.

Comparative analysis between primed and unprimed WJMSCs secretome and EVs was performed through a series of functional assays encompassing fibroblast proliferation and migration, endothelial tube formation to evaluate angiogenic potential, and macrophage functional analyses through nitric oxide quantification and flow cytometry-based assessment of surface markers to verify polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype.

Netrin-1 priming markedly enhanced fibroblast proliferation and migration with treatment of both WJMSC derived secretome and EVs. HUVEC tube formation assays demonstrated a pronounced increase in angiogenic potential upon treatment with primed secretome compared to unprimed controls, whereas EV-treated groups exhibited no significant difference in tube length between primed and unprimed groups. Both primed EVs and secretome stimulated HUVEC proliferation, with primed secretome eliciting the most robust response. Treatment with netrin-1 primed WJMSC secretome and EVs significantly promoted macrophage polarization from the pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype.

Overall, our findings demonstrate that netrin-1 priming substantially amplifies the regenerative and immunomodulatory functions of WJMSC secretome. This approach provides a promising cell-free and tunable strategy for enhancing tissue repair through the synergistic combination of targeted priming and the inherent paracrine potential of MSCs.

Poster number: 62

CellMate-seq captures diverse embryonic cell-cell interactions at single-cell resolution

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Cells interact and communicate to regulate their gene expression and function, for example, through complex ligand-receptor (L-R) mediated signaling. Secreted ligands primarily affect receptive cells that are in spatial proximity. Which L-R pairs are used between cells, and which responses are induced downstream, is furthermore influenced by the specific state of the interacting cells. Thus, the analysis of local cell interactions at the systems level requires precise profiling of the transcriptional states of neighboring cells, including all their expressed communication factors.

However, currently available omics technologies cannot simultaneously provide information on spatial proximity and deep transcriptome-wide expression profiles for cells. They either provide deep transcriptional information per cell while losing the neighborhood information (single-cell RNA-seq) or preserve spatial context but capture comparatively few transcripts per cell (spatial transcriptomics). This fundamental trade-off limits our ability to study L-R interactions comprehensively.

Here, we introduce CellMate-seq, a method that combines a two-step dissociation procedure, in which membrane-bound barcodes are used to uniquely tag cells within their native cellular neighborhoods for subsequent scRNA-seq. Applying CellMate-seq to the E9.5 mouse embryo identified thousands of neighborhoods comprising diverse cell types. For instance, we recovered neural crest cells together with a wide range of different interaction partners they meet on their migratory paths throughout the embryo.

CellMate-seq enables the systematic analysis of sets of L-R pairs that together mediate the communication between individual neighboring cells. Notably, we find that spatial transcriptomics fails to detect most L-R pairs between neighbors, due to the substantially lower per-cell data depth.

In summary, CellMate-seq enables a systems-level view of local cell-cell interactions by combining spatial neighborhood information with deep single-cell transcriptomes, paving the way for decoding intercellular interactions in development, homeostasis, and disease.

Poster number: 63

Selection and characterization of a physiological human umbilical cord-derived mesenchymal stem cell line for the production of extracellular vesicles

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Introduction

Mesenchymal stem cells (MSCs) are widely investigated as cell-based therapies to treat a multitude of diseases due to their regenerative capabilities. In recent years, the interest in MSC-derived therapeutic applications shifted towards the secretome of MSCs, indicating that paracrine factors as well as extracellular vesicles (EVs) released by MSCs are major contributors to therapeutic efficacy. Using EVs as a cell-free therapeutic approach overcomes the shortcomings of cell-based therapies, e.g. tumorigenesis and immune reactions. However, clinical translation is currently limited by MSC donor-to-donor variability and the lack of scalable EV production systems.

To address these limitations, we characterize and establish an immortalized umbilical cord–derived mesenchymal stem cell line (ucMSC) to achieve scalable EV production in 2D and 3D culture formats.

Methods

Primary ucMSCs were immortalized using lentiviral transduction, resulting in multiple clones. These clones were then compared to primary ucMSCs to identify those displaying comparable growth behavior, surface marker expression, and tri-lineage differentiation potential.

Further, EVs were produced from three selected clones and their primary counterpart under hypoxic 2D culture conditions using antibiotic-free, xeno-free and phenol red-free medium. EVs were isolated by ultracentrifugation from the conditioned medium and characterized/quantified using nanoparticle tracking analysis (NTA). Functional potential of EVs is currently being assessed using angiogenesis and scratch wound assays. Moreover, 3D EV production will be investigated using gelatin methacryloyl (GelMa)–encapsulated MSCs cultured in a vertical wheel bioreactor.

Results

An assessment of growth characteristics indicated that the clones had significantly longer doubling times and increased linear cell dimensions than primary cells, while still maintaining the typical spindle-shaped morphology of MSCs. Additionally, the clones expressed the surface markers characteristic of MSCs and demonstrated tri-lineage differentiation potential. Furthermore, EVs were successfully produced and subsequently quantified using NTA.

Conclusion

Immortalized ucMSCs provide a stable platform for EV production, unlike primary MSCs that enter replicative senescence at a certain stage. Even though the clones show slower proliferation and increased cell dimensions compared to primary MSCs, cells retained stemness marker expression, supporting their usability as a standardized EV source. We will compare the 2D and 3D cell culture formats with respect to EV yield and the functional biology of the harvested EVs.

Poster number: 64

Rebuilding the Ependymal Barrier: Cell Reprogramming Strategies for Hydrocephalus

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Hydrocephalus is a neurological disorder characterized by the abnormal accumulation of cerebrospinal fluid (CSF) within the brain's ventricles. A key contributor to its pathophysiology is the dysfunction of multiciliated ependymal cells lining the ventricles. These cells are critical for regulating CSF flow and composition and for supporting neural stem cells in the ventricular/subventricular neurogenic niche. Disruption of this niche and its structural organization plays a substantial and enduring role in the progression of hydrocephalus. Current management relies largely on neurosurgical diversion of CSF, a treatment associated with significant morbidity and a high failure rate, highlighting the pressing need for novel therapeutic approaches.

We have shown that ectopic expression of GemC1 and Mcidas reprogram mouse and human astrocytes into functional ependyma. Additionally, we demonstrated that Mcidas expression supports ependymal cell regeneration in two distinct postnatal hydrocephalus mouse models—one involving intracranial hemorrhage and the other a genetic form of hydrocephalus—. Our results show restoration of the ependyma and improvement in the structural integrity of the neurogenic niche of mice with hydrocephalus.

Collectively, our findings indicate that GemC1 and Mcidas can directly reprogram cells toward ependymal identity. In addition, our results support the concept that replacing or restoring ependymal cells in hydrocephalus may offer a viable avenue for developing new treatments.

SY Stem

Poster number: 65

Developmental timing shapes oncogenic rewiring in Ewing Sarcoma

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Ewing sarcoma (EwS) is an aggressive pediatric malignancy driven by chromosomal rearrangements that generate the EWS–FLI1(EF1) fusion oncogene. Although EF1 functions as a master transcriptional regulator, its transforming capacity is highly dependent on cellular context, and the precise cell of origin of EwS remains unresolved. One of the potential candidate cell types is suggested to be a skeletogenic neural crest cell (NC), which can generate into osteogenic cell fates and tolerate EF1 expression.

To investigate how developmental stage influences oncogenic outcomes, we established a human induced pluripotent stem cell (iPSC)-based model enabling differentiation into neural crest and NC-derived mesenchymal states, combined with inducible EWS–FLI1 expression. Oncogene activation was performed at distinct stages of differentiation (early NC, cranial NC, and mesenchymal derivatives), followed by single-cell RNA sequencing to resolve cell-state-specific transcriptional responses.

Upon induction of the oncogene at different time points of NC-MSC differentiation (early-NC, cranial NC and MSC), we observed the upregulation of the same gene expression programs in single-cell RNA-seq data as in Ewing sarcoma cell lines. Nevertheless, the resulting cellular trajectories and transcriptional landscapes were strongly dependent on the developmental stage at which the oncogene was initiated. While certain induced states showed substantial similarity to patient tumor transcriptomes, others diverged, suggesting that initiation timing and cell type context may contribute to tumor heterogeneity.

Integration with human embryonic single-cell atlases revealed that both induced cells and primary tumors exhibit signatures consistent with the co-option of developmental programs, including neural crest regulatory modules and partial epithelial-to-mesenchymal transition-like features.

Together, our data suggest that the developmental identity of a cell at the moment of EWS–FLI1 activation constrains and directs the oncogenic rewiring process, dictating which embryonic programs are hijacked and potentially influencing tumor formation and heterogeneity.

Poster number: 66

Tracing Lineage Imprints: How Cellular Origin Influences iPSC Fate Commitment

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The extent to which developmental history constrains pluripotent reprogramming and subsequent self-organization remains unclear. Here, we use gastruloids to directly test whether cellular identity is fully reset by reprogramming or leaves a lasting imprint on their differentiation potential. We engineered mouse embryonic stem (ES) cells with a doxycycline-inducible reprogramming cassette via piggyBac transposition and established multiple clonal lines, which were characterized for pluripotency, transgene copy number, and reprogramming efficiency. Based on induction efficiency, a single clonal line was used to generate gastruloids, from which ectodermal and mesodermal populations were prospectively isolated by fluorescence-activated cell sorting. Each population was subsequently reprogrammed into induced pluripotent stem cells (iPSCs), generating two isogenic iPSC lines derived from distinct germ-layer progenitors. We then investigated how the iPSC's past shapes its ability to self-organize. To this end, we compared axial organization, patterning dynamics, and transcriptional trajectories in gastruloids derived from parental ES cells and from each of the two iPSC lines. This analysis allowed us to evaluate the extent to which prior developmental identity is retained through reprogramming. This work establishes gastruloids as a sensitive platform for dissecting lineage memory and provides new insight into the reversibility of early embryonic cellular and regulatory states.

Poster number: 67

CLN3 mutations drive early neurodevelopmental and lysosomal defects in iPSC-derived cortical organoids

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Juvenile neuronal ceroid lipofuscinosis (JNCL), also known as Batten disease, is a rare and severe pediatric neurodegenerative disorder caused by mutations in the CLN3 gene. The disease is characterized by progressive vision loss, cognitive and motor deterioration, and premature death, with no effective therapies currently available. Despite its devastating effects, the early molecular and developmental mechanisms of CLN3-associated neurodegeneration are largely unknown, in part because of the lack of human-relevant experimental models.

In this study, we used induced pluripotent stem cell (iPSC)–derived cerebral organoids to investigate early neurodevelopmental defects associated with CLN3 mutations. Four iPSC lines were analyzed: WT, CLN3 KO, and two mutant lines carrying the D416G variant, associated with a severe clinical phenotype, and the R405W variant, linked to a milder, predominantly vision-related form of the disease. In parallel, iPSCs were differentiated into small molecule neural progenitor cells (smNPCs). Organoids were analysed at days 30 and 60 of differentiation, while smNPCs were used to assess early progenitor and lysosomal phenotypes.

At day 30, organoids carrying the D416G and R405W mutations exhibited reduced PAX6 expression and smaller rosettes, with D416G organoids showing an approximately 40% decrease in rosette area, indicative of impaired neural progenitor expansion. MAP2 expression was also reduced, suggesting delayed early neuronal differentiation. By day 60, MAP2 levels increased in both mutant lines, while SATB2 was upregulated in D416G and KO organoids, with no significant changes in CTIP2 expression, pointing toward premature differentiation of upper-layer cortical neurons. Rosette size remained reduced across all mutant lines, and nearly half of the KO organoids failed to develop properly, highlighting the limited capacity of early compensatory mechanisms.

Lysosomal analyses showed reduced CLN3 and LAMP1 expression in mutant organoids, whereas smNPCs appeared unaffected at the protein level. Nevertheless, LysoTracker staining in smNPCs indicated mild lysosomal dysfunction, and Sudan Black staining demonstrated early lipofuscin accumulation, linking CLN3 mutations to early lysosomal stress.

Overall, these findings reveal mutation-specific neurodevelopmental defects and early lysosomal changes in Batten disease. The D416G mutation is associated with early progenitor loss and accelerated neuronal differentiation, consistent with its severe phenotype. R405W closely resembles WT. CLN3 KO display an initial compensatory phase that then fails during development. Altogether, this work underscores the contribution of early developmental defects to CLN3 pathology and demonstrates the utility of iPSC-derived cerebral organoids and neural progenitor models for exploring mutation-specific disease mechanisms.

SYStem

Poster number: 68

Mapping Genetic Dependencies in Human Naïve Pluripotency

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The transition from pre- to post-implantation epiblast represents one of the earliest and most critical cell fate decisions during human development. During this process, cells acquire the capacity to execute definitive lineage decisions while retaining the potential to differentiate into all embryonic lineages. Due to ethical and technical limitations in accessing human embryos, the molecular mechanisms driving this transition remain poorly characterized in humans. To bridge this knowledge gap, we adapted naïve human embryonic stem cells (hESCs), resembling the pre-implantation epiblast, to feeder-free culture and induced the transition to formative pluripotency — a state just prior to gastrulation at which cells are prepared for lineage differentiation but are not yet "primed" for a certain lineage. Transcriptomic analysis over time confirmed that our in vitro model faithfully recapitulates in vivo embryonic differentiation trajectories and indicates that the timing of the naïve-to-formative transition is governed predominantly by intrinsic factors rather than external cues, suggesting a cell-intrinsic pacemaker.

Building on this platform, we are now functionally interrogating the genetic architecture of naïve pluripotency maintenance. A systematic perturbation screen identifies essential regulators sustaining naïve pluripotency and reveals candidate targets for culture optimization. Together, this work integrates developmental modeling with functional genetics to refine our understanding of the molecular ground rules governing human pre-implantation pluripotency and provides a framework for improving stem cell-based systems to study early embryogenesis.

Poster number: 69

Establishing new models of organ-specific inter-species chimeras to study hindlimb growth regulation

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One of the unsolved mysteries in biology is how organ size is controlled during development, and how this process changes across evolution. Numerous studies on the vertebrate limb have led to a good molecular understanding of pattern formation and morphogenesis by the interaction of intrinsic and extrinsic factors, making it a powerful model to investigate this interaction in the determination of organ size. Classical transplantation studies of limb primordia between species of different sizes found a high degree of autonomy in limb development, suggesting limb size is determined by intrinsic factors. However, conventional grafting experiments are ill-suited to address the underlying question, as such experiments can only be done after fate specification has already begun and limb cells are less prone to being reprogrammed by extrinsic signals. Integration of the other species' cells in the host species before organogenesis, and in the absence of endogenous limb tissues, would bypass this roadblock. This approach will enable investigation of how diffusible factors emanating from the flank and the distal limb epithelium (aka apical ectodermal ridge, AER) interact with the intrinsic genetic programme of the limb mesenchyme. It has been found that the proximal patterning phase can be extended in avian embryos by prolonging RA signalling, slowing the pace of patterning while the limb bud continues to proliferate and grow. This leads to increased post-patterning limb size, mirroring the patterning duration and final post-patterning limb size of larger avian species. We speculate that the balance between proximal and distal diffusible factors varies across species, and is what determines final limb size. To test this hypothesis, we propose to use complementation of limbless murine blastocysts with rat embryonic stem cells (rESCs) to generate rat-to-mouse chimeras in which either the hindlimb mesenchyme or the hindlimb epithelium is of rat origin, while the remaining tissues stem from the host.

Characterisation of potential candidate mouse lines is underway. To replace the AER with rat cells, we are generating Msx2-Cre; Fgfr2flox/flox embryos, whereby the distal limb epithelium cannot proliferate and specialise in response to mesenchymal signals, so that rat cells will have an advantage to form the AER. To replace the limb mesenchyme, current work aims to generate a hindlimb-specific CRE line, which will be used to activate diphtheria toxin expression in the hindlimb field. These models provide two contrasting approaches to elucidate the mechanisms governing limb size determination in the developing hindlimb. In the future, we expect to identify gene regulatory networks differentially active between normal rat-limb cells and chimeric-limb cells. This knowledge would further our understanding of evolution and allow manipulation of organ size.

Poster number: 70

High-throughput neural connectivity mapping in organoids reveals wiring-defined neuronal subtypes and aberrant wiring in TSC

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The human brain is a complex network of ~80 billion neurons that changes with age, environment, and perturbations. To understand how and why these networks change, we need to integrate genetic perturbations, gene expression and connectivity data from individual cells, a gap current methods cannot bridge at scale.

We developed a 'connectomics-by-sequencing' method combining barcoded, rabies-based retrograde transsynaptic tracing with single-cell RNA sequencing. This approach allows mapping of thousands of synaptic networks and their transcriptomes simultaneously. To study both normal and pathological neural networks, we used IPS-based human cortical organoids, a scalable 3D disease model ideal for mapping connectivity.

Using this method, we identified connectivity patterns across different ages, cell lines, and disease conditions. We found that wiring of certain, but not all, cell types depend on tissue composition. We also demonstrated that upper layer excitatory neurons can be subtyped based on their connectivity, revealing differences in synapse organization genes.

In our Tuberous Sclerosis Complex (TSC) model, we identified disease-specific inversion of a network types ("motifs") together with replacement of within upper layer cell states. These changes led to increasingly unspecific synaptic connections, a known hallmark of TSC.

Altogether, our method uncovered connectivity rules in healthy and diseased networks and linked altered connectivity to transcriptional state.

SYStem

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