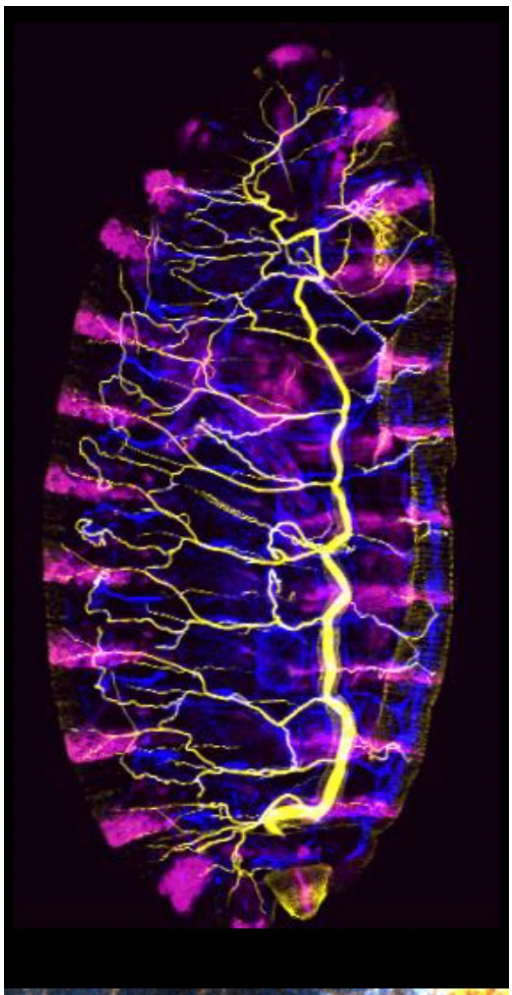

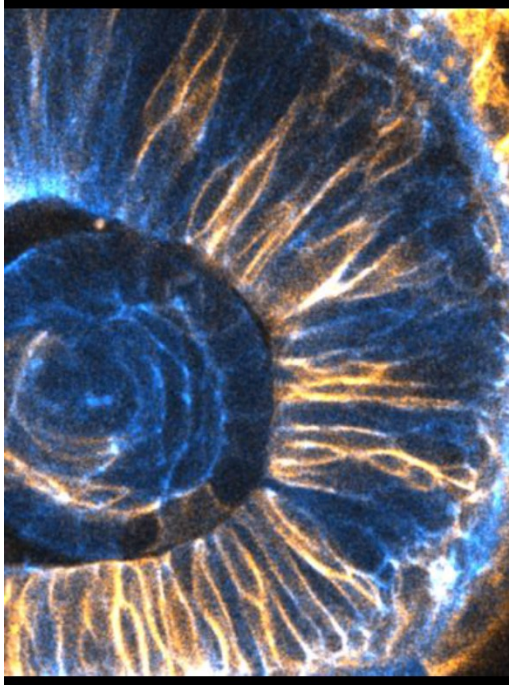

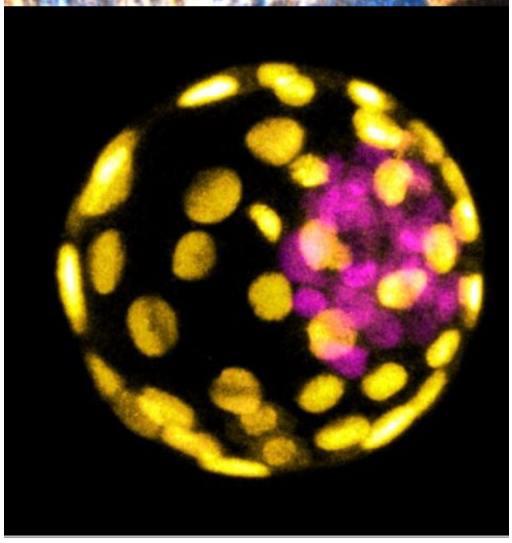

Institut d'Estudis Catalans

Societat Catalana de BIOLOGIA

XXXVI Jornada de Biologia del Desenvolupament

DevBioCat synergy meeting 2025

February 7th 2025

IEC, Sala Prat de la Riba

C/ del Carme 47

08001 Barcelona

Institut d'Estudis Catalans

Societat Catalana de BIOLOGIA

XXXVI Jornada de Biologia del Desenvolupament

DevBioCat synergy meeting 2025

Friday February 7th 2025

9:00	Registration
9:25	Welcome by the Organizing Committee
9:30-10:10	**Hervé Turlier** (Collège de France, CNRS-INSERM) **From microscopy images to mechanical models of tissues and back**
10:10-10:25	Daniel Moreno Cellular senescence contributes to regeneration in planarians
10:25-10:40	Joan Bertran Different cellular and molecular mechanisms of chitin deposition contribute to the specificity of the two chitin synthases in *D. melanogaster*
10:40-10:55	Xiao Wei Installing trophectoderm competence before the first developmental lineage bifurcation
10:55-11:10	Poster Flash Talks odd numbers
11:10-12:30	Coffee Break and ODD posters
12:30-12:45	Iván Sopena ROS-mediated Pten inactivation regulates Insulin signaling during tissue regeneration in *Drosophila* midgut
12:45-13:00	Núria Torres Uncovering the genetic toolkit against marine biotoxins in the zooplankton *Oikopleura dioica*
13:00-13:40	**EMBO Young Investigator Lecture** **Benjamin Towbin** (ICB, University of Bern) **Growth control from cells to organisms**
13:40-14:30	Lunch
14:30-14:45	Amelie Godeau Mechanics of human and mouse embryo implantation
14:45-15:00	Giannios Panagiotis Headcase proteins in *Drosophila* and humans: a novel family of RNP granule regulators
15:00-15:15	Isabel Turpin Assessing Dravet Syndrome pathological traits using brain organoids
15:15-15:30	Poster Flash Talks even numbers
15:30-16:30	EVEN Posters
16:30-17:10	**Berta Alsina** (Universitat Pompeu Fabra) **The path from a neuroepithelial cell to a sensory neuron**
17:10-17:25	Elena Fusari Depletion of aneuploid cells is shaped by cell-to-cell interactions
17:25-17:40	Ludovica Ciampi Deciphering the emergence of a novel olfactory neuron subpopulation via gene module co-option in mammals
17:40-18:00	Concluding remarks and awards.

Organizing Committee
Esteban Hoijman (IBMB-CSIC/IDIBELL)
Manuel Irimia (UPF/CRG)
Marta Llimargas (IBMB-CSIC)
Marta Morey (UB-IBUB)

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INVITED SPEAKERS

FROM MICROSCOPY IMAGES TO MECHANICAL MODELS OF TISSUES AND BACK

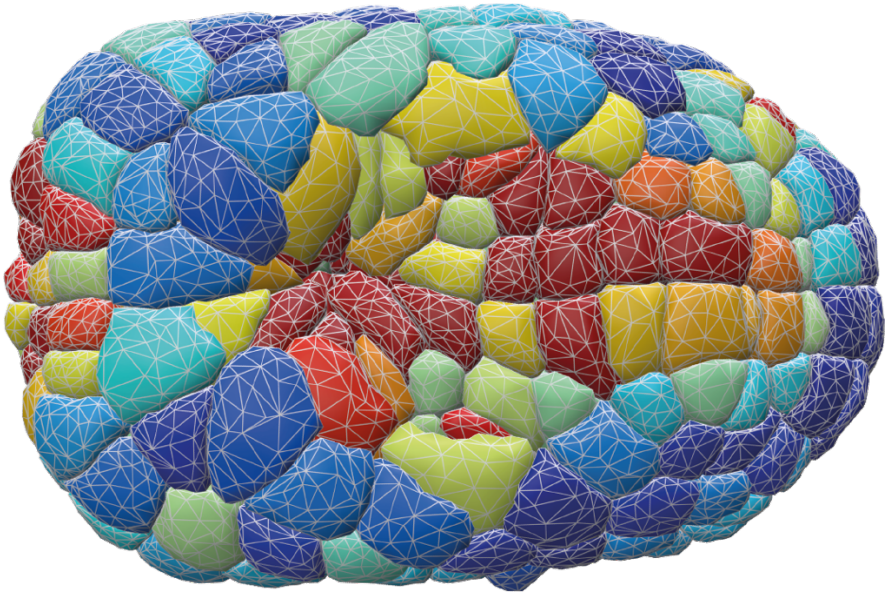
Hervé Turlier

Collège de France, CNRS-INSERM

Fluorescence microscopy is a widely used technique for quantifying biological systems, from the subcellular to the tissue scale. However, extracting meaningful physical information, especially in 3D, remains challenging. Meanwhile, physical and computational models of tissues are becoming increasingly realistic, yet their direct comparison, calibration, or initialization from biological images remains largely out of reach.

Here, I will present our recent efforts to bridge the gap between imaging and mechanical models of tissues. I will begin with a novel segmentation and 3D tension inference method that generates 3D mechanical atlases of embryos or tissues with up to a thousand cells from microscopy images. Next, I will introduce our cell-resolved computational model of 3D tissues, which is based on tensional forces, explicitly incorporates viscous dissipation at cell interfaces, handles cell divisions and topological events (T1, T2), and can be coupled to biochemical signaling networks to model multicellular mechanochemical feedbacks.

Finally, I will demonstrate how we close the loop between mechanical models and microscopy images with a generic pipeline that generates realistic fluorescence microscopy images from simulation results. This approach enables the design, training, and benchmarking of new image analysis methods and facilitates the seamless solution of inverse mechanical problems.



EMBO Young Investigator Lecture

GROWTH CONTROL FROM CELLS TO ORGANISMS

Benjamin Towbin

Institute of Cell Biology-University of Bern

Correctly sized body parts are crucial for organismal function. For example, small discrepancies in limb length severely obstruct motility, and overgrowth of cardiac muscle is a prevalent cause of heart failure. The growth of different cells and organs must therefore be tightly coordinated to prevent that even small differences in growth rates amplify to large differences in size during development. How growth signals are propagated from cell to cell, and how organs integrate combinatorial signals from different tissues is a fundamental, yet poorly addressed question of high biomedical relevance.

We approach these questions using the gastro-intestinal tract nematode *C. elegans* as a model system. By live imaging, we have tracked hundreds of individual animals at high time resolution to measure how the pharynx of individual animals reaches it appropriate size during development. We find that while total body growth is exponential, pharynxes grow by a near constant volume per larval stage that is independent of their initial size, such that undersized pharynxes catch-up in size during development. Tissue-specific depletion of RAGA-1, an activator of mTOR and growth, shows that maintaining correct pharynx-to-body size proportions involves a bi-directional coupling between pharynx size and body growth. In simulations, this coupling cannot be explained by limitation of food uptake alone, and genetic experiments reveal an involvement of the mechanotransducing transcriptional co-regulator *yap-1*. Our data suggests that mechanotransduction coordinates pharynx growth with other tissues, ensuring body plan uniformity among individuals.

THE PATH FROM A NEUROEPITHELIAL CELL TO A SENSORY NEURON

Berta Alsina, Aitor Bañon, Lucas Cunha, Mireia Rumbo

Universitat Pompeu Fabra-PRBB

The inner ear derives from the otic placode, a spherical neuroepithelial primordium that emerges adjacent to the posterior hindbrain. High spatiotemporal resolution imaging and 3D segmentation of the placode epithelialization process has allowed us to quantify the cell shape changes and track cell movements. We identify three main events, first an anteroposterior cell convergence, followed by an anisotropic cell elongation initiated at the ventromedial quadrant, ending by a folding of the epithelium and the formation of two rosettes. The plausible mechanisms for these key events will be discussed. After the neuroepithelium is defined, the neuronal progenitors delaminate out in an EMT manner to form the statoacoustic ganglion (SAG). Tracking of recently delaminated neuronal progenitors reveal their directed migration and coalescence around a small population of pioneer SAG neurons. These pioneer SAG neurons, not from otic placode origin, populate the coalescence region before otic neurogenesis begins and their ablation disrupts delaminated neuronal progenitors migratory pathways, consequentially affecting SAG shape. Very little is known on the mechanisms that regulate the establishment of proper connections in 3D of the SAG neurons to hair cells. We have found that the pioneer SAG neurons extend the first axons that innervate early-born hair cells, which are used as scaffolds for neuroblast migration and secondary axogenesis. Finally, we have discovered that the small chemokine cxcl14 is required for axon guidance to hair cells and proper separation of inner ear and lateral line axons. Altogether our work provides novel data on how the cellular behaviours underlying placodal epithelialization and the generation of the complex 3D SAG.

ORAL
PRESENTATIONS

CELLULAR SENESCENCE CONTRIBUTES TO REGENERATION IN PLANARIANS

Daniel Moreno-Blas, Daniel Font-Martín, Emili Saló, Cristina González-Estévez and Teresa Adell

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Senescent cells are being recently recognized for their participation in tissue repair and regeneration across diverse organisms, ranging from highly regenerative species such as salamanders and cnidarians to mammals with more restricted regenerative capacity. However, the precise contribution of cellular senescence to regenerative processes remains poorly understood, with numerous unresolved questions. In this context, planarians serve as an excellent model for investigating the role of cellular senescence in tissue repair and regeneration, due to their remarkable ability to regenerate any missing tissue. This regenerative capacity is driven by a population of self-renewing adult stem cells, known as neoblasts, which are abundantly distributed throughout the organism. Nevertheless, no studies to date have demonstrated the presence of senescent cells under normal physiological conditions in planarians or clarified whether they contribute to the regeneration process in these worms. Here, we explored the conservation of tissue injury-induced senescence in planarians and its participation in regeneration. Notably, amputation triggered the expression of senescence markers at the wound site in these animals. Furthermore, the clearance of senescent cells through treatment with the senolytic compounds quercetin and dasatinib significantly impaired tissue regeneration following amputation. These findings suggest a functional role for senescent cells in planarian regeneration and establish planarians as a valuable model for exploring the interplay between cellular senescence and regeneration.

DIFFERENT CELLULAR AND MOLECULAR MECHANISMS OF CHITIN DEPOSITION CONTRIBUTE TO THE SPECIFICITY OF THE TWO CHITIN SYNTHASES IN *D. MELANOGASTER*

Joan Bertran-Mas[1], Ettore De Giorgio[1,2], Nicolás Martín[1], and Marta Llimargas[1].

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Chitin, a key aminopolysaccharide, is a major component of arthropod extracellular matrices, such as the exoskeleton and midgut peritrophic matrix, playing essential roles in insect development, growth, and survival. Beyond its biological significance, chitin has also received a lot of attention in medicine and biotechnology due to its exceptional physicochemical and mechanical properties as a biopolymer. Chitin is synthesized and deposited extracellularly by chitin synthases. Most insects encode two types of chitin synthases, type A primarily associated with exoskeleton formation, and type B, linked to peritrophic matrix production. However, the factors controlling the specificity of these enzymes remain unclear. Using *Drosophila melanogaster* as a model system, we investigated the mechanisms and functional roles of Kkv (Chitin synthase A) and Chs2 (Chitin synthase B). We demonstrated that Chs2 is expressed and required in the larval proventriculus, a region responsible for producing chitin in the peritrophic matrix. Additionally, we explore whether these chitin synthases can substitute for each other, examine their subcellular localization in various tissues, and assess their ability to deposit chitin alongside auxiliary proteins. Our findings reveal that Kkv and Chs2 are not functionally interchangeable and employ distinct cellular and molecular mechanisms for chitin deposition. We propose that the specificity of insect chitin synthases underpins the production of chitin polymers with unique properties, which in turn confer diverse physiological functions to extracellular matrices.

INSTALLING TROPHECTODERM COMPETENCE BEFORE THE FIRST DEVELOPMENTAL LINEAGE BIFURCATION

X. Wei, I. Salvador-Martinez, M, Meglicki, M. Plana-Carmona, A. Klonizakis, B.Pernaute, M. Irimia, G. Stik, M. Popovic, G. Torcal Garcia, H.Heyn, M.Zernicka-Goetz, and T. Graf

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Mammalian embryogenesis begins with the division of the zygote into two blastomeres. As divisions progress, totipotency is gradually lost and at the 16-cell stage blastomeres begin to segregate into trophectoderm (future placenta) and ICM (inner cell mass, the embryo proper). A set of lineage-restricted transcription factors governs this process in a poorly understood manner. Here we identify the transcription factor CEBPa as a novel orchestrator of the murine trophectoderm-ICM bifurcation. CEBPa is expressed in 4- and 8-cell embryos and in the trophectoderm. Over-expression in embryonic stem cells drives their differentiation into trophectoderm-like cells, permitting to identify CEBPa regulated enhancers. Notably, enhancers of key trophectoderm-associated regulators are already accessible in 4-cell and 8-cell embryos and are either activated or primed, while others are still closed. CEBPa thus places early blastomeres in a state of alert, equipping them with the competence for trophectoderm differentiation before the first developmental lineage bifurcation.

ROS-MEDIATED PTEN INACTIVATION REGULATES INSULIN SIGNALING DURING TISSUE REGENERATION IN DROSOPHILA MIDGUT

Iván Sopena-Majós[1], José Esteban-Collado[1], Montserrat Corominas[1], Florenci Serras[1]

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Tissue regeneration after injury involves complex signaling cascades, with reactive oxygen species (ROS) playing a crucial role in initiating the repair process. Recent studies have highlighted the importance of the insulin signaling pathway in regeneration, but the mechanism by which ROS targets this pathway remains unclear. We investigated the role of Phosphatase and tensin homolog (Pten), an antagonist of Pi3K-Akt activity, in ROS-mediated regulation of insulin signaling during regeneration. Using the Drosophila midgut as a model system, we generated a Pten mutant ($Pten^{C79A}$) to explore the possibility of oxidation-dependent inactivation of Pten through disulfide bond formation. Ectopic activation of both wild-type Pten and $Pten^{C79A}$ reduced Akt and p38 activity, as well as intestinal stem cell (ISC) proliferation. However, dietary supplementation with H_2O_2 blocked the effects of wild-type Pten but not $Pten^{C79A}$, suggesting that Cys79 mediates the reversible inactivation of Pten by oxidative stress. Our findings indicate that ROS targets Pten in the insulin pathway during regeneration, providing new insights into the molecular mechanisms underlying tissue repair. This study contributes to our understanding of how early signals trigger the regenerative response and may have implications for developing targeted therapies to enhance tissue regeneration.

UNCOVERING THE GENETIC TOOLKIT AGAINST MARINE BIOTOXINS IN THE ZOOPLANKTON *OIKOPLEURA DIOICA*

Nuria P Torres-Aguila[1,2], Daniela Ascione[3], Vittoria Roncalli[3], Gaspar Sánchez-Serna[1,2], Biel Cassà[1], Johannes Nicolaus Wibisana[4], Charles Plessy[4], Michael Mansfield[4], Nicholas M Luscombe[4], Cristian Cañestro[1,2]

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Global warming and climate change are causing stress in natural environments and reducing biodiversity. Over recent decades, increasing reports of algae blooms highlight their potential to cause environmental damage through the release of natural toxins, such as polyunsaturated aldehydes (PUAs). These biotoxins are created during algae blooms upon cell damage and cell stress. Among other effects, PUAs have been reported to impair the embryonic development of marine animals. However, the molecular pathways underlying these lethal effects remain unclear.

Oikopleura dioica, a cosmopolitan zooplankton, has been shown to be affected by these toxins but in a less severe manner. The unique characteristics of *O. dioica*—such as genome plasticity and extensive gene losses—make it the perfect animal model to study potential genetic adaptabilities to those toxins as well as compromised developmental pathways conserved among marine animals.

In this study, we conducted RNA-seq analysis on embryos exposed to PUAs compared to non-exposed embryos. This approach identified 23 differentially expressed genes at the 8-cell stage, including 4 down-regulated and 19 up-regulated genes, highlighting potential early PUAs-response pathways. To further investigate these findings, we will integrate ATAC-seq data to identify regulatory regions associated with PUAs-response genes and perform qRT-PCR experiments to validate RNA-seq results across additional developmental stages. These findings provide a foundation for understanding the impact of environmental stressors on marine embryogenesis and offer insights into potential adaptive gene regulatory networks.

MECHANICS OF HUMAN AND MOUSE EMBRYO IMPLANTATION

Amélie L. Godeau[1], Anna Seriola[1], Oren Tchaicheeyan[2], Marc Casals[1], Denitza Denkova[1], Ester Aroca[1], Ot Massafret[1], Albert Parra[1], Maria Demestre[1], Anna Ferrer-Vaquer[1], Shahar Goren[2], Anna Veiga[4], Miquel Solé[5], Montse Boada[5], Jordi Comelles[1,6], Elena Martínez[1,6,7], Julien Colombelli[8], Ayelet Lesman[2,3], Samuel Ojosnegros[1]

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During implantation, the mammalian embryo establishes attachment to the endometrium, the lining of the maternal uterus, followed by invasion into the underlying tissue. To understand how embryos penetrate the collagen-rich endometrial stroma, we have developed an innovative hydrogel-based ex-vivo platform supporting traction force microscopy. We reveal the forces applied by human and mouse embryos and recapitulate implantation specificities of both species in our platform. Mouse embryos exhibit limited penetration depth whereas human embryos integrate into the matrix. Nevertheless, both types of embryos apply forces during implantation resulting in the remodelling of the collagen matrix. Interestingly, the applied forces lead to distinct displacement patterns: Isotropic radial displacement for human and anisotropic with main displacement axes for mouse embryos.
Blocking force transmission through integrins, specifically β5 and β3 integrins with a cyclic pentapeptide or Src kinase with dasatinib, reduces the size of mouse embryos and their matrix displacement. Notably, when placed pairwise, embryos form tension-bearing mechanical bridges between them, leading to collagen densification and directed matrix displacement along the connecting axis.
Furthermore, both human and mouse embryos exhibit mechanosensitive responses to an external mechanical stimulus: The mouse embryo either orients its growth direction or aligns its axis relative to the external force cue. The human embryo recruits phosphorylated myosin basally and forms a cellular protrusion towards the external force cue.
In conclusion, our findings highlight the intricate mechanical interactions between embryos and their environments and mechanosensitive capacity of embryos during implantation. We suggest that mechanical forces may play an important role in guiding the invasion of the extracellular matrix during implantation.

HEADCASE PROTEINS IN *DROSOPHILA* AND HUMANS: A NOVEL FAMILY OF RNP GRANULE REGULATORS

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Cells adapt to environmental stresses, such as temperature changes, toxins, and nutrient fluctuations, through dynamic stress responses. These responses extend beyond transcriptional regulation and include post-transcriptional mechanisms that enable rapid modulation of protein synthesis. Previous studies identified *headcase* as a critical gene for stress responses and the survival of Drosophila Adult Progenitor Cells (APCs). However, its molecular function has remained unclear. We present evidence identifying Headcase as a component of Ribonucleoprotein (RNP) granules. Our findings reveal that Headcase is essential for proper RNP granule formation and remodeling under stress conditions, playing a pivotal role in translational control. Moreover, we show that the human homolog of Headcase (HECA) similarly localizes to RNP granules, where it contributes to translational regulation and stress protection. These results position Headcase proteins as a novel family with specific roles in the heterogeneous RNP network, highlighting their evolutionary conservation in stress response mechanisms.

ASSESSING THE DRAVET SYNDROME PATHOLOGICAL TRAITS USING BRAIN ORGANOIDS

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Brain organoids (BOs) have risen as a reliable model for neurodevelopmental disorders, reproducing human brain development milestones. In this study, we have approached Dravet Syndrome (DS) pathological phenotype, an infantile epilepsy, using BOs at multiple maturation stages. Compared to control-derived BOs, DS-derived BOs show an imbalance in the synaptic circuitry both at transcriptomic and functional levels in mature BOs. This synaptic DS-associated phenotype involves channels and receptors implicated in the GABA metabolism and its synaptic inhibitory role. These differences in neural circuitry can be identified and automatized by combining live imaging and DL techniques. Although DS is a developmental epileptic encephalopathy, patients' symptoms appear at post-natal stages. Correlating with this temporal disease onset, immature control and DS BO are morphologically and molecularly indistinguishable, suggesting that the phenotype rises in more mature neurons also in vitro. Altogether, these findings highlight the use of BO as a model for studying DS pathology and its potential implementation in therapeutic strategies.

DEPLETION OF ANEUPLOID CELLS IS SHAPED BY CELL-TO-CELL INTERACTIONS

Elena Fusari [1], Mariana Muzzopappa[1], Juliette Gracia[1] and Marco Milán[1,2]

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In all animals analyzed to date, aneuploidy—the condition of having an imbalanced number of chromosomes or parts of them—has dramatic consequences at the cellular and organismal levels. Aneuploidy, systemically or in mosaics, is the major cause of miscarriages in humans and is associated with many pathological conditions, including growth retardation, developmental disorders, aging, and cancer. Surprisingly, however, chromosomal instability is highly prevalent in early human embryos, and more than 80% of human blastocyst-stage embryos present mosaic aneuploidy. Aneuploid cells are depleted from embryonic germ layers to give rise to healthy births. Later in life, the emergence of aneuploidy in somatic tissues has been associated with pathological conditions such as cancer, with 90% of human solid tumor reported to be aneuploid. Unfortunately, a mechanistic understanding of the identification and elimination of these aneuploid cells both in development and disease remains elusive. Whether the detrimental effects of aneuploid cells result from changes in the expression of specific dosage-sensitive genes or, additionally, from the gene expression imbalance of all genes present in the affected chromosome remains to be fully elucidated Moreover, the potential impact of mosaicism and cell interactions in mediating or exacerbating the detrimental effects of aneuploid cells and their elimination is unknown. Unraveling these questions could unlock the appealing potential to specifically target aneuploid cells, offering groundbreaking therapeutic avenues for a variety of diseases. We have used Drosophila to generate cells carrying molecularly defined segmental monosomies and trisomies and characterize their immediate impact on cellular behavior. Our data reveal signs of out-competition of cells carrying monosomies in genomic regions devoid of previously known haploinsufficient genes. By simultaneously inducing cells carrying monosomies and trisomies of the same genomic location, we present evidence that segmental trisomies potentiate or alleviate the negative effects of the monosomy on growth. Our results reveal a key role of cell interactions in defining the in vivo elimination of aneuploid cells.

DECIPHERING THE EMERGENCE OF A NOVEL OLFACTORY NEURON SUBPOPULATION VIA GENE MODULE CO-OPTION IN MAMMALS

Ludovica Ciampi[1,2], Luis Pedro Iñiguez[1,2], Marta Miret[1,2], Miquel Anglada-Girotto[2], Mohammad Zardbani[4] and Manuel Irimia[1,2,3]

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In vertebrates, neurons involved in sensory perception possess specialized ciliated structures whose molecular determinants remain poorly understood. A multi-omics factor analysis of sensory cilia revealed that olfactory sensory neurons (OSNs) uniquely express motile cilia genes, whose specific expression is shared with spermatozoa/testes. Given that OSN cilia are non-motile, the function of this gene module is a mystery. By performing transcription factor binding motif and ChIP-seq analyses, we identified Rfx3 as the key factor behind the regulation of the module. In-house single-cell RNA-seq of mouse olfactory epithelium uncovered an atypical cell cluster highly expressing *Rfx3* and its targets, and we further localized it in a subset of OSNs by immunohistochemistry. Additionally, expression analyses of *Rfx3* and its paralogs in testes revealed a *Rfx*3 expression dominance in vertebrates but a shift to *Rfx2* dominance in mammals. This transition coexists with an opposite one in OSNs, suggesting an evolutionary scenario in which *Rfx3* has been co-opted to OSNs in mammals to drive motile cilia gene expression.
Currently, we are exploring the evolutionary origin of Rfx3 and its regulated module through comparative single-cell transcriptomics of the olfactory epithelium between mammalian and non-mammalian vertebrates. Finally, by generating a conditional *Rfx3* KO in mouse OSNs, we aim to determine the functional significance of Rfx3-driven co-option in OSN physiology.

POSTERS

P1. DYRK1A KINASE REGULATES THE APICAL DOMAIN SIZE OF RADIAL GLIA PROGENITORS DURING CORTICAL NEUROGENESIS

María Jesús García-Reina[1,2,3], María José Barallobre[1,3], Borja Barbastre[2,3], Susana de la Luna[2,3,4], Mariona Arbonés[1,3]

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DYRK1A is a dose-dependent protein kinase encoded on chromosome 21, implicated in Down syndrome and in a recently identified syndromic form of intellectual disability and autism caused by *de novo* loss-of-function (LoF) mutations in the *DYRK1A* gene. Our previous studies demonstrated that cortical expansion and neurogenesis are impaired in *Dyrk1a* LoF and gain-of-function (GoF) mutant mice. In this study, we investigated the role of DYRK1A in the apical end-foot of radial glia (RG) progenitors during neurogenesis. Analysis of the dorsal telencephalon in *Dyrk1a* LoF and GoF embryos using open-book preparations revealed a direct correlation between *Dyrk1a* gene dosage and the apical domain size of RG progenitors. Overexpression of DYRK1A in the embryonic chick spinal cord *via in ovo* electroporation increased the apical domain size of RG progenitors, whereas overexpression of an enzymatically inactive DYRK1A had no effect. The kinase-dependent effect of DYRK1A on the apical domain size in chick RG progenitors was further confirmed using the DYRK1A inhibitor Harmine. Among the putative DYRK1A targets, we focused on Leucine Zipper Tumour Suppressor 1 (LZTS1) due to its role in apical constriction and neuronal delamination. Our results demonstrate that DYRK1A interacts with and phosphorylates LZTS1. Furthermore, LZTS1 overexpression in the chick neural tube reduced the apical domain size of RG progenitors. Notably, co-overexpression of DYRK1A and LZTS1 partially rescued the apical constriction induced by LZTS1. These findings indicate that DYRK1A regulates the apical domain size of neurogenic RG progenitors in a dose-dependent manner and restrains apical constriction through a mechanism involving LZTS1 phosphorylation. This regulation by DYRK1A may contribute to the microcephaly observed in humans and mice with reduced DYRK1A dosage.

P2. DECIPHERING THE ROLE OF PDE4DIP IN NEURAL DEVELOPMENT AND 1Q21-ASSOCIATED DISORDERS

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During Central Nervous System (CNS) development in vertebrates, the neural tube, comprising neural progenitor cells (NPCs), serves as the primordium of the brain and spinal cord. Precise regulation of NPCs proliferation within the neural tube is crucial for proper CNS growth. Genetic mutations impacting NPCs proliferation often manifest as microcephaly, characterized by a diminished brain size. Despite extensive efforts to elucidate genes involved in CNS development, most instances of microcephaly remain genetically uncharacterized. The 1q21 neurodevelopmental disorder (NDD) presents a distinctive genetic signature- a 1q21 copy number alteration- associated strongly with both micro- and macrocephaly phenotypes and developmental delay. The 1q21 chromosomal region is extremely repetitive and enriched in human-specific genes. Some of these genes have been linked to the evolutionary expansion of the brain size. However, the list of affected genes remains elusive, and the function of most genes still unclear. Our study focuses on unravelling the pathogenic mechanisms underlying 1q21 copy number variations in NDDs and elucidating the role of one associated gene, *PDE4DIP* in CNS development. Preliminary findings suggest that PDE4DIP could be affected in patient-derived induced pluripotent stem cells (iPSCs) with 1q21 alterations. Furthermore, PDE4DIP encoding proteins localise to the centrosome in NPCs of the chick neural tube, suggesting potential isoform-specific functions in NPCs proliferation. In summary, our study sheds light on the role of PDE4DIP in CNS development and provides insights into the pathogenic mechanisms underlying 1q21 NDDs.

P3. ECHOES OF POLLUTION: IMPACT OF NOISE ON THE GENETIC RESPONSE OF MARINE INVERTEBRATE EMBRYOS.

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Noise pollution from human activities is a growing threat to marine life and ocean health. While research on vertebrates (e.g., cetaceans, fish) is extensive, studies on invertebrates remain scarce, limiting our understanding of how noise impacts marine trophic webs.
The DeuteroNoise JPI-Oceans is a consortium investigating the effects of noise pollution on invertebrates across European basins, with a Barcelona hub characterizing noise sources and modeling soundscapes along the Barcelona coast while studying the effects of noise on marine food webs. Using the zooplanktonic tunicate Oikopleura dioica as a model organism, we are examining the effect of noise on behavioral, morphological, and reproductive parameters in both adults and embryos, with a primary focus identifying noise-responsive genes— the "noisesome". Noise sources, defined by frequency, amplitude, and duration, are recorded in the field and reproduced in controlled lab conditions.
To test if marine noise can physically influence gene expression, we have conducted differential gene expression analyses of bulk RNAseq data from after noise exposure of early tailbud embryos, stage at which no mechanoreceptors have developed yet. Our preliminary results reveal numerous differentially expressed genes, including the downregulation of key developmental genes, and the upregulation of genes involved in energetic metabolism, nucleoside synthesis and proteasome function. We are currently exploring how this genetic response is translated to the mechanisms of embryo development to try to identify the function of the noisesome, with special interest in identifying the first genes that respond to noise. Additionally, these results will be compared with those obtained in other invertebrate species within the consortium to identify a conserved core of "noisesome" genes that could serve as a panmarker for noise stress across marine organisms. Our results will deepen our understanding of how noise pollution affects marine species development, and therefore on food webs and ocean health, providing a tool for monitoring and mitigating its impact on marine ecosystems.

P4. CRISPR-ING *USP48* IN hiPSCs TO STUDY ITS ROLE IN RETINAL DEVELOPMENT

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Proper cilia function is critical for tissue morphogenesis, and its disruption often leads to syndromic disorders associated with severe developmental defects. Ciliopathies, characterized by extensive phenotypic and genetic heterogeneity, are associated with mutations in more than a hundredth genes, with emerging evidence highlighting the role of deubiquitinating enzymes (DUBs) in cilia biogenesis. Building on prior observations of *USP48* expression in the mouse retina, we investigated its regulatory role in cell ciliogenesis and retinal development. *USP48* knockout lines were generated via CRISPR/Cas9, and the ciliary and cytoskeletal phenotypes were assessed in *USP48*$^{+/-}$ human induced pluripotent stem cells (iPSCs) and hiPSC-derived retinal pigment epithelium (RPE) cells. Our analyses reveal that heterozygous knockout of *USP48* results in ciliary and cytoskeletal defects, as well as delayed RPE differentiation, due to haploinsufficiency. These findings support a critical role for USP48 in the regulation of ciliary dynamics and development, as well as cytoskeletal integrity in the retina and other organs.

P5. LOSS OF CENTRIOLES DURING EMBRYONIC DEVELOPMENT LEADS TO AXONAL MISROUTING AND MUSCLE ABNORMALITIES

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During development, the central nervous system (CNS) establishes multiple stereotyped neuronal networks. At the leading edge of growing axons, the growth cone navigates toward target cells by interpreting extracellular cues that influence membrane dynamics and the cytoskeleton, including actin filaments and microtubules. The dynamic behavior of microtubules plays a crucial role in the formation, stabilization, and remodeling of neuronal axons. Centrosomes, as primary microtubule-organizing centers (MTOCs), are essential for diverse cellular functions such as cell shape maintenance, division, and migration. While centrosomal roles in mitosis are well-characterized, their functions in differentiated cells remain poorly understood. Moreover, the relationship between centrosome activity and axon pathfinding is not fully defined. Using the centrosome-deficient mutant *Sas-4*^{S2214}, we observed multiple structural defects in intersegmental and sensory nerves and of the CNS and peripheral nervous system (PNS), respectively. In most embryos, these abnormalities were spatially correlated with disruptions in muscle development. Specific downregulation of *Sas-4* in the pioneer neurons aCC, pCC and RP2 induced axon guidance errors, suggesting at least a partially autonomous role for centrosomes in axonal navigation. Notably, gamma-tubulin and acetylated tubulin colocalized with centrioles in aCC and RP2 neurons, confirming the presence of functional centrosomes. Although some *Sas-4* mutants survived to adulthood, they exhibited post-eclosion lethality. Similar phenotypes were observed in embryos with mutations in *Sas-6*, another gene essential for centrosome function. These findings underscore the critical role of centrosomes in axon guidance during embryonic development and provide new insights into their functional contributions beyond cell division.

P6. IDENTIFICATION OF REGENERATION-SPECIFIC ELEMENTS REQUIRED FOR POSTERIOR SPECIFICATION IN PLANARIANS

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Regeneration is the process through which missing tissue is generated, restoring both the structure and function of an organism. Planarians are well-known for their ability to regenerate their entire bodies, making them an ideal model for studying the molecular and cellular mechanisms that govern regeneration. In our lab, we focus on understanding the mechanisms that control the specification of the proper anterior-posterior identity after amputation at any level of the planarian body, that is, how a planarian fragments decides to regenerate a head or a tail in the proper end. Previous studies demonstrate that the Wnt/beta-catenin pathway is the key intercellular signaling pathway controlling this process. However, the early events that trigger the appropriate response of the pathway remain unknown. To investigate this, we previously conducted bulk and SC-RNA seq as well as genomic analyses comparing anterior versus posterior wounds. These studies led to the identification of key factors required for the specification of the posterior identity, such as the secreted peptide Smed-Tuck, which disruption results in Two-headed or Tailless animals. In this study, we aim to further investigate the mechanism of action of Smed-Tuck by functionally studying its putative interactors. Additionally, we will perform a RNAi screen to identify regeneration-specific elements involved in posterior specification, focusing on candidates identified in our SC-RNAseq analysis. The results of this research will provide deeper insights into the molecular mechanisms that trigger the proper identity during a complex regeneration process, such as those occurring in planarians in nature.

P7. 4D-STUDY OF NEURONAL CELL LINEAGES AND THE GENERATION OF NEURONAL DIVERSITY IN THE ZEBRAFISH HINDBRAIN

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Understanding how the brain is built and its cell diversity established is key to understand its function. Brain development requires a balance between cell proliferation and cell differentiation of the distinct progenitor populations to generate the correct number of neurons, at the right place and time. This can be assessed by studying cell lineages and the implicated molecular pathways.

The hindbrain is the embryonic primordium of the brainstem, which is responsible for vital roles, such as respiration, circulation or motor coordination. It is also an excellent model for studying how cell lineages contribute to organ growth in space and time, since it undergoes profound morphogenetic changes as development proceeds.

We perform high-resolution 4D live imaging of the zebrafish hindbrain using lineage tracing to unravel how specific proneural gene-expressing progenitor populations contribute to hindbrain growth. For that we have developed a customized algorithm to automatically detect nuclear centers in 3D, in a highly compact tissue, where nuclear fluorescent signals from adjacent nuclei highly overlap with one another. Finally, we have tracked these nuclei in time (4D) to determine the mode of division of cells. In parallel, we are using the multicolor clonal analysis technique *Zebrabow* to assess the stochastic or deterministic nature in the neuronal output (number of neurons) of individual progenitors.

We are likewise interested in understanding how cells can regulate division mode and differentiation. We are exploring the potential repurposing of cellular waste or detrimental cargoes in the regulation of cell division mode and the generation of cell fate.

Finally, we have used already published zebrafish hindbrain single-cell RNA seq data to assess the molecular differences of the distinct proneural-expressing populations and their contribution to neuronal diversity.

P8. CELLULAR IMBALANCE IN DRAVET SYNDROME: A SINGLE-CELL RNA SEQUENCING APPROACH IN DRAVET SYNDROME-DERIVED HUMAN BRAIN ORGANOIDS

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Dravet Syndrome (DS) is a severe developmental epileptic encephalopathy that begins in early in early childhood. DS is associated with heterozygous mutations in the Sodium Voltage-Gated Channel Alpha Subunit 1 (NaV1.1), encoded in humans by the SCN1A gene. In this study, we have generated brain organoids from induced pluripotent stem cells (iPSCs) carrying a missense mutation in SCN1A (p.A371V:GCT>GTT) and compared them with control healthy organoids by single-nuclei RNA sequencing (snRNAseq). Differential gene expression analysis revealed an upregulation of synaptic transmission genes occurring in the excitatory populations of DS-derived organoids at 3 months of culture, when the neural network is still under development. Additionally, Calcium signalling analysis performed in vivo at the same timepoint showed an increase in the number of active neurons and network efficiency. These defects led to increased excitation and synchronization of the neural network at later timepoints of organoid maturation. Our findings provide insights into the underlying mechanisms of the epileptic phenotype observed in the Dravet pathology.

P9. SEX-DEPENDENT NEURAL PLASTICITY IN RESPONSE TO DAMAGE

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Neural plasticity mediates recovery of neural circuits after damage. Plasticity of intact neural tissue in the vicinity of neural damage serves to restoring functionality. Much remains to be learned about the mechanisms regulating this process and the reported sex differences in recovery outcomes. Here we present the fly gut and its innervation as simplified model to address these questions. We have developed an automated morphometric analysis pipeline that allows us to quantify the amount of neural tissue and the complexity of the neural network in whole mount preparations. We show that gut damage caused by ingestion of toxic agents resulted in plasticity of the enteric neuronal network, manifested as an increase in neural tissue, which was induced by gut-derived reactive oxygen species (ROS). Neural growth was reversible, with neural tissue retracting after a recovery period through a caspase-independent mechanism. Interestingly, males did not display neural plasticity and masculinization of neurons in females suppressed the damage-dependent neural growth. While this plasticity response to damage has, so far, an unclear functional role, it positions the fly gut as a system to investigate the cellular, molecular and sex-specific underpinnings of neural plasticity, with implications for therapeutic advancements in neural circuit recovery.

P10. APICAL CELL SURFACE: CAN WE USE IT AS A PROXY TO PREDICT CELL DIVISION MODE IN THE ZEBRAFISH HINDBRAIN?

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Understanding how coordination between cell proliferation and cell differentiation is balanced remains a major challenge during organ morphogenesis. A precise orchestration of molecular and cellular events allows progenitors to generate the neuronal diversity of the adult brain, with proper location and number of cells. However, how this is regulated has only been partially revealed, and alterations in these processes can lead to brain perturbations. Untimely differentiation may result in microcephaly and a loss of later-born cell types, whereas excessive proliferation can lead to brain tumours. The research proposed here aims at investigating the cellular processes involved in progenitor cell specification and how they are coordinated in the construction of the functional brain. We will address these questions in the embryonic brainstem, the hindbrain, the structure at the origin of mastication, eye movement, locomotion and respiration. Thus, the central questions of this proposal are: i) Can we foresee cell division modes by quantifying cell dynamics? ii) Can we predict tissue growth and morphogenesis by understanding how changes in cell dynamics are integrated in time and space? To tackle these questions, we propose to study the cell morphology features as a readout of the mode of cell division. Combining high-throughput analysis of time-lapse imaging data and semi-automated image quantification we aim to assess the role of cell and tissue architecture in cell fate acquisition during brain morphogenesis.

P11. FROM TRANSPOSONS TO NEUROPLASTICITY: CONVERGENT EXAPTATION OF GYPSY CAPSID IN FLIES AND TETRAPODS

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Neuroplasticity-related processes are fundamental during the last stages of nervous system development. Activity-Regulated Cytoskeleton associated (ARC) genes are essential for neuroplasticity-related functions in both tetrapods and dipterans, (including neuromuscular junction development, long-term potentiation or dendritic spine formation). Surprisingly, despite their shared roles, the ARC genes of tetrapods (tARC) and dipterans (dARC) originated independently by co-option of two different retroviral capsid-derived gene families.

Here, we investigate which properties of capsids could have favored their convergent integration into neuroplasticity networks. To that end, we have characterized the evolution and gene expression of the two ARC families. We have reconstructed putative ancestral transposons of ARCs, revealing two markedly different exaptation routes.

We are also characterizing an Arc2-KO line in D. melanogaster, which exhibits a decrease of viability at larval stages and eye patterning alterations, a phenotype that we can observe at morphologic and transcriptomic level. We are now generating lines expressing non-domesticated retroviral capsids to rescue the WT phenotype.

Finally, we established two zebrafish lines that express exogenous tARC and a non-domesticated Latimeria chalumnae capsid, which will allow us to determine if ARC proteins can interact with the neuroplasticity networks. Our preliminary data shows slight functional and transcriptomic alterations, which is compatible with an evolutionary scenario in which the expression of an exogenous capsid into a neural environment can drive new physiological proteins without a highly deleterious phenotype. In summary, by a phylogenetic and synthetic approach, we describe key changes and functional properties leading to the domestication of TE capsids.

P12. MOSAIC VARIEGATED ANEUPLOIDY: A PIVOTAL ROLE OF PROTEOSTASIS FAILURE AND MITOCHONDRIA DYSFUNCTION

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Mosaic variegated aneuploidy, a human congenital disorder characterized by extensive abnormalities in chromosome number, can cause microcephaly, and is induced in half of the patients by mutations in genes involved in accurate mitotic chromosome segregation, including those of the spindle assembly checkpoint (SAC) (1). Drosophila has proven to be a valuable model system to demonstrate a causal relationship between chromosome segregation errors and microcephaly (2-4). These studies have shown that by combining changes in centrosome number (amplification or loss) with SAC mutations or by acute targeting of chromosome cohesion the resulting brains present extensive abnormalities in chromosome number, a drastic reduction of the neural stem cell (NSC) population and small size. However, the underlying molecular and cellular mechanisms leading to NSCs loss and microcephaly are so far unidentified and the contribution of the different types of aneuploidy and DNA damage to the observed phenotypes remain to be carefully studied. Here we have generated a fly model of microcephaly caused by the depletion of a single SAC gene, as it occurs in human patients, in NSC compartment. We present evidence that DNA damage or simple aneuploidies have a minor contribution to the reduction in brain size. By contrast, complex aneuploidies consisting of gains of more than one chromosome compromise the viability, proliferative capacity and stemness of NSCs. Our data unravel a central role of mitochondria in the resistance of NSCs to aneuploidy and indicate that proteostasis failure, most probably as a consequence of gene dosage imbalance, and mitochondria dysfunction are major contributors to the deleterious effects of complex aneuploidies in NSCs. Most interestingly, enhancing autophagy or increasing mitochondria homeostasis dampen the deleterious effects of aneuploidy in NSCs and ameliorate SAC-depletion-driven microcephaly. These findings bring new insights into the fundamental mechanisms of microcephaly and open up promising avenues for therapeutic intervention in aneuploidy-related neurodevelopmental disorders.

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P13. DISSECTING THE TEMPORAL PLASTICITY OF NEURAL PROGENITORS

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During brain development, progenitor cells generate an enormous diversity of neurons in the correct numbers and proportions. Proneural transcription factors (TFs) trigger the specification of neuronal lineages and commit progenitors by activating downstream differentiation genes. Yet, how the transition from stem cells to mature neurons is controlled and how plastic this process is over time remains largely unexplored.

Our objective is to dissect the determinants of progenitor's capacity to give rise to inhibitory and excitatory neuronal subtypes. For this, we aim to combine cell lineage analyses of spatially and temporally segregated progenitors with chromatin profiling of proneural TFs. We will focus in glutamatergic and GABAergic circuits of the zebrafish embryonic brainstem – the hindbrain– which controls life-sustaining functions and is extremely conserved in vertebrates.

To express reprogramming factors in specific progenitor populations and at the desired temporal window, we will use TEMPO, a Cre-dependent system that simultaneously permits i) genetic cell labelling with a cascade of fluorophores and ii) time-restricted ectopic gene expression. This method will allow us to follow sequential windows of neurogenesis while assessing the versatility of cell fate restriction. We will also analyze the impact of progenitor modulation on resulting glutamatergic and GABAergic populations and on proneural TF expression. Overall, these experiments will provide important insights on how progenitor competence varies in time and space.

P14. HOW MUCH GENOME SCRAMBLING CAN OCCUR WITHOUT AFFECTING EMBRYO DEVELOPMENT?

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In the field of EvoDevo, the tunicate *Oikopleura dioica* is emerging as an attractive model to study the impact of gene losses and genome rearrangements on the evolution of mechanisms of development in chordates. This tiny organism is a filter-feeder part of the marine meso-zooplankton and it is widely distributed around the globe. O. dioica has a highly compact genome (<70 Mb and 18,000 genes), which exhibits a high degree of plasticity, with elevated rates of mutations and frequent losses and duplications.Interestingly, recent studies of our group demonstrated the presence of an unprecedented amount of genome scrambling when different populations from different geographical regions (e.g. Barcelona, Osaka and Okinawa) were compared, suggesting the presence of cryptic species despite identical morphological features. How the massive genome reorganizations affect the evolution of the regulation of developmental gene networks remains unknown, specially considering how it might affect the potential regulation linked to chromosomal architectural domains.
To address this question, we aim to identify chromosome re-arrangements within populations using de novo assembled genomes obtained with PacBio long-reads. Preliminary results showed breakpoints on the different haplotypes of the *de novo* assemblies. We are currently generating a gold-standard annotation using long-read RNAseq to identify the developmental genes surrounding those break points, potential gene losses, and any possible changes to their regulation. Additionally, we will perform ATAC-seq to determine chromatin accessibility regions and remodelling linked to the break points. In the future, we will evaluate the extent of genome rearrangements among different cryptic species with special focus on breakpoints that have differentially affected developmental genes.
This comparative analysis will provide critical insights into how genome rearrangements can influence the mechanisms of embryo development and the robustness of regulatory networks.

P15. DECIPHERING SCAN-1: THE ROLE OF *gkt* IN *DROSOPHILA* ORGANOGENESIS

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Spinocerebellar ataxia with axonal neuropathy type 1 (SCAN-1) is a debilitating peripheral neuropathy characterized by slowly progressive cerebellar ataxia and atrophy. All SCAN-1 patients identified to date carry the same mutation in tyrosyl-DNA phosphodiesterase 1(TDP1). Like in humans, the homologue of TDP1 in Drosophila, a gene named glaikit (gkt) encodes a tyrosyl-DNA phosphodiesterase 1.
Previously, Glaikit was found to be essential for the formation of epithelial polarity and nervous system development. The fact that the Drosophila ortholog appears to have different functions, may help clarifying the complex aetiology of SCAN1.
Preliminary results from the laboratory indicate that *gkt* is expressed in tracheal cells and is important for tracheal formation in *Drosophila melanogaster* embryos.
Our aim is to elucidate the function of gkt in the nervous and tracheal system of Drosophila melanogaster and to further explore the connection between gkt and other components in the pathway. So, we are using the Drosophila tracheal and nervous system as a model to study Gkt function in organogenesis. Furthermore, we intend to reintroduce a functional TDP-1 allele into a gkt G85 genetic background in an attempt to restore the normal wild-type tracheal phenotype.

P16. FUNCTIONAL AND EXPRESSION CHARACTERIZATION OF DARC2, A TRANSPOSON-DERIVED GENE IN DROSOPHILA DEVELOPMENT

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The dArc (Activity-Regulated Cytoskeleton protein) gene family comprises two Drosophila genes, dArc1 and dArc2, which originated from the duplication of a domesticated retrotransposon capsid gene. This evolutionary transition repurposed viral properties for neural development and plasticity. While dArc1 regulates neuromuscular junction formation and neural remodeling, dArc2 contributes to synaptic changes following spaced learning. This functional divergence suggests specialization after duplication, but the regulatory mechanisms and evolutionary significance of dArc genes remain poorly understood. To address this, we investigated dArc2 using reporter and knockout (KO) lines.

We found that dArc2 is expressed not only in the adult brain but throughout development, with robust expression in the larval central nervous system and enrichment in the adult retina and optic lobe. These patterns suggest a role in visual system development and activity-regulated processes. Contrary to earlier reports, dArc2 mutants are viable under standard conditions but show reduced fitness in competitive environments. Morphological analyses revealed subtle eye defects, including irregular ommatidial arrangement and rhabdomere abnormalities, which likely underlie the viability reduction.

To further investigate the role of dArc2, we are performing ultrafine retinal cuts to study structural abnormalities in detail. Transcriptomic analysis of dArc2 KO flies revealed dysregulation of genes involved in eye development and rhabdomere membrane formation, supporting its link to visual system morphogenesis.

We hypothesize that capsid genes like dArc1/2 are predisposed to domestication in neural systems due to their ability to interact with neural structures. Ongoing rescue experiments using capsid genes from other species aim to uncover the molecular and evolutionary mechanisms underlying this unique family of domesticated genes. These studies provide insights into how transposable elements drive neural innovation.

P17. CRISPR AND CHILL. A LOW TEMPERATURE APPROACH TO GENETIC EDITION IN THE CHORDATE *OIKOPLEURA DIOICA.*

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In our laboratory we use *Oikopleura dioica*, a planktonic tunicate, as a model to study the impact of gene loss on the evolution of developmental mechanisms in chordates. Our results have already revealed that many developmental signaling pathways have been affected by gene loss, including the drastic dismantling of the Wnt and FGF pathways, and the total disappearance of the retinoic acid pathway. These massive gene losses make this species a unique evolutionary knockout of many developmental genes, whose study has revealed, for instance, how the deconstruction of the cardiopharyngeal gene regulatory network facilitated the innovation of the fully free-living style of appendicularians. The development of molecular tools for gene manipulation in *O. dioica* is key for future progress. The fast development, rapid cell divisions and DNAi system of this animal are great obstacles for the CRISPR-Cas9 genetic edition technique. In our laboratory we have already obtained knocked-out embryos for selected genes via CRISPR, and we are making progress towards the knocking-in of reporter genes. The efficiency and reliability of both methods are still low, that's why we present here some new promising approach that may help us overcome some of the challenges of this model. *O. dioica* thrives through a wide range of temperatures in the wild, so we tested egg viability, embryonic development and *in vitro* Cas9 efficiency at low temperatures (4 to 13°C) to perform CRISPR in these colder conditions, which in theory can slow down the developmental rate, extending the time window for the Cas9 nuclease to access the target DNA, and facilitating the insertion of reporter gene constructions. These new resources will be applied to the study of heart and muscle development and evolution, and the embryonic response to environmental stress (biotoxins and noise), which are our current main research lines.

P18. EFFECTS OF rRNA PROCESSING PROTEINS Kkz AND Clw IN *DROSOPHILA* TRACHEAL MORPHOGENESIS

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The tracheal system of *Drosophila melanogaster* is formed by a complex airway network that transfers oxygen to tissues. Aimed at finding novel genes involved in subcellular lumen formation and branching, we focused on the tracheal terminal cells (TCs), which are specialized cells that form unicellular branches with a cytoplasmatic seamless tube called subcellular lumen. From an EMS screen we selected mutant phenotypes in tracheal terminal cell (TC) development. One mutant showed extra TC branching at embryonic stages. We mapped the mutation to a region of chromosome 2 and identified a previously unidentified gene in *Drosophila*, which we named *kid kazoom* (*kkz*). The human ortholog of *kkz* is part of a complex involved in ribosomal RNA (rRNA) processing. By homology, we have identified one of KKz's partners in this complex and named the gene *clowny (clw)*.

Here we characterize the role of *kkz* and *clw* during tracheal organogenesis. We establish that *kkz* and *clw* are essential for larval tracheal development. In *kkz* and *clw* tracheal knockdown experiments we observe tracheal defects in L3, which cause the death of the animal at this stage. L3 knockdown larvae have defects in TC branching and an aberrant dorsal trunk, which has also collapsed chitin. Together, these results provide the first characterization of the ribosomal Kkz-Clw complex in *Drosophila;* as well as the first evidence of a direct link between ribosomal genes and the development and *Drosophila* tracheal system growth.

P19. *Smed-nlk-1* REGULATES EYE SIZE IN PLANARIANS

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During embryonic development and regeneration, the growth of any organ must be tightly regulated in order to achieve their optimal final size and become fully functional. While numerous factors influencing growth have been reported, most of them function as growth activators. Freshwater planarians, with their remarkable ability to regenerate any part of their body based upon the presence of adult pluripotent stem cells, provide an ideal model to study how the final organ size is regulated, in a regeneration context. Here, we investigate the role of *nlk-1*, a nemo-like kinase, known to play a role in eye development in other organisms. Planarian photoreceptors consist in two cell types: sensory photoreceptors and a pigmented eye-cup. Functional analyses show that *Smed-nlk-1* silencing results in bigger eyes both in intact and regenerating planarians. This increase in eye size is associated to an increase of the number of both progenitor and differentiated eye cell types. In addition, the absence of *nlk-1* disrupts the normal proportions of the cephalic ganglia. Phototaxis behavioral assays have revealed that *nlk-1* RNAi planarians exhibit an increased sensitivity to light. Overall, these findings highlight *Smed-nlk-1* as a key regulator of eye size in planarians.

P20. DECIPHERING THE ROLE OF THE CHEMOKINE CXCL14 IN PIONEER AXON GUIDANCE IN THE STATOACOUSTIC GANGLION

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Proper morphogenesis and circuitry establishment of the statoacoustic ganglion (SAG) is essential for the correct connection between the hair cells and the brain. We have recently shown that SAG morphogenesis relies on pioneer neurons that get specified outside the otic vesicle. Pioneer neurons project pioneer axons that target newborn hair cells in anterior and posterior sensory domains of the otic vesicle. We have identified the chemokine Cxcl14, which is expressed in otic hair cells from 24hpf onwards, with a possible role in pioneer axon guidance and/or fasciculation. Pioneer axons serve as a scaffold for axonophilic crawling of the otic neuroblasts, allowing the formation of the posterior lobe of the SAG. A lack of Cxcl14 due to a CRISPR/Cas9 KO results in defasciculation of pioneer axons, incorrect targeting of these and malformation of posterior lobe. SAG development occurs in close contact with anterior and posterior lateral line ganglia, which progressively become separated from SAG and send axons towards cranial neuromasts and the hindbrain. In situ hybridization of Cxcl14 shows no expression in neuromasts, indicating that this chemokine is otic-specific and might play a role in regulating the correct targeting of SAG towards otic hair cells and lateral line axons towards neuromast hair cells but not viceversa. Also, cxcl14 is expressed in anterior and posterior hindbrain entry points at 36hpf, possibly regulating the correct targeting and fasciculation of both SAG and lateral line neurons towards the hindbrain.

P21. EVOLUTIONARY INSIGHTS INTO FAM72 GENE FUNCTION IN NEURAL DEVELOPMENT

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Enlargement of the brain is one of the most notable features of human evolution. Brain size is determined in embryonic development by the proliferative activity of neural progenitor cells (NPCs), which give rise to virtually all cells in the brain, including neurons and glia. This suggests that human NPCs possess features that support a higher proliferative activity, as can be the expression of human-specific genes. One such gene is the poorly characterized FAM72. In humans, the FAM72(A-D) gene family consists of four paralog genes which originated in the hominid lineage by duplication of the ancestral FAM72A. The duplicated segment also contains, in the opposite strand, the gene SRGAP2, involved in neuron synaptogenesis.

Here, we investigate the localisation and function of FAM72 in embryonic neural development. We find that FAM72 expression in NPCs fluctuates in concert with the cell cycle. In chick embryonic NPCs, FAM72 localizes at the base of the cilia in interphase cells, and it is enriched in the spindle pole of mitotic cells. In addition, we show that the regulation of FAM72A transcription is highly conserved, as expression of a human FAM72A promoter reporter construct in chick embryonic NPCs occurs in a cell-cycle regulated manner. Moreover, we demonstrate that the FAM72A promoter region, located between FAM72A and SRGAP2, is a bidirectional promoter region with differential directionality in NPCs and neurons.

Our experiments shed light on the function of FAM72 paralogs in NPC biology, and on the tight regulation of the expression of the proliferative FAM72 and synaptogenic SRGAP2.

P22. UNRAVELING NEURONAL MIGRATION: DRAVET VS. CONTROL ORGANOIDS – INTRINSIC AND NICHE INFLUENCES ON NEURONAL MIGRATION

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Dravet syndrome (DS) is one of the most common developmental epileptic encephalopathies (DEEs). This severe disorder, caused by mutations in the *SCN1A* gene encoding Nav1.1 sodium channel subunit in approximately 80% of cases, serves as an important model for understanding neurodevelopmental disorders. Brain organoids enable the recapitulation of developmental processes, molecular mechanisms underlying cell differentiation and also mimic the spatial organization and structural architecture of the developing human brain. Furthermore, assembloids, created by integrating different types of organoids, allow us to study interactions driven by distinct genotypes or brain regions, offering a more comprehensive model of brain development and disease mechanisms. In this project, we aim to understand potential defects in excitatory/inhibitory imbalance and neuronal migration in Dravet syndrome compared to control organoid models. To achieve this, we developed assembloids and mosaic organoids at different time points using Lancaster (2014) unguided protocols to explore how the cell environment influences migration dynamics, such as migration speed. We generated a mCherry reporter Dravet cell line by using PiggyBac transposase system carrying an mCherry gene under the control of an ubiquitous promoter, ensuring that all cells expressed the reporter. Using this cell line, we created assembloids and mosaic organoids composed of Dravet (mCherry +) and control cell lines. Live imaging over 6 weeks revealed migration of Dravet mCherry+ astrocytes (GFAP+) and neurons (NFM+) into control organoids. Additionally, mosaic organoids from DS (mCherry +) in 1% proportion and Dravet showed similar differentiation capacity to individual organoids, with the presence of neural cell types such as neurons (MAP2+ and NeuN+), upper-layer neurons (SATB2+) and astrocytes (GFAP+). The minority mCherry+ cell population within the mosaic organoids was capable of differentiating into all expected cell types. Interestingly, while long-term live imaging (62 hours) of mosaic organoids did not capture cell migration events, our observations suggest that progenitors are actively migrating within the model. These findings provide insight into the cellular integration mechanisms of DS in a healthy context, highlighting the potential of assembloids and mosaic organoids for studying neurodevelopmental diseases.