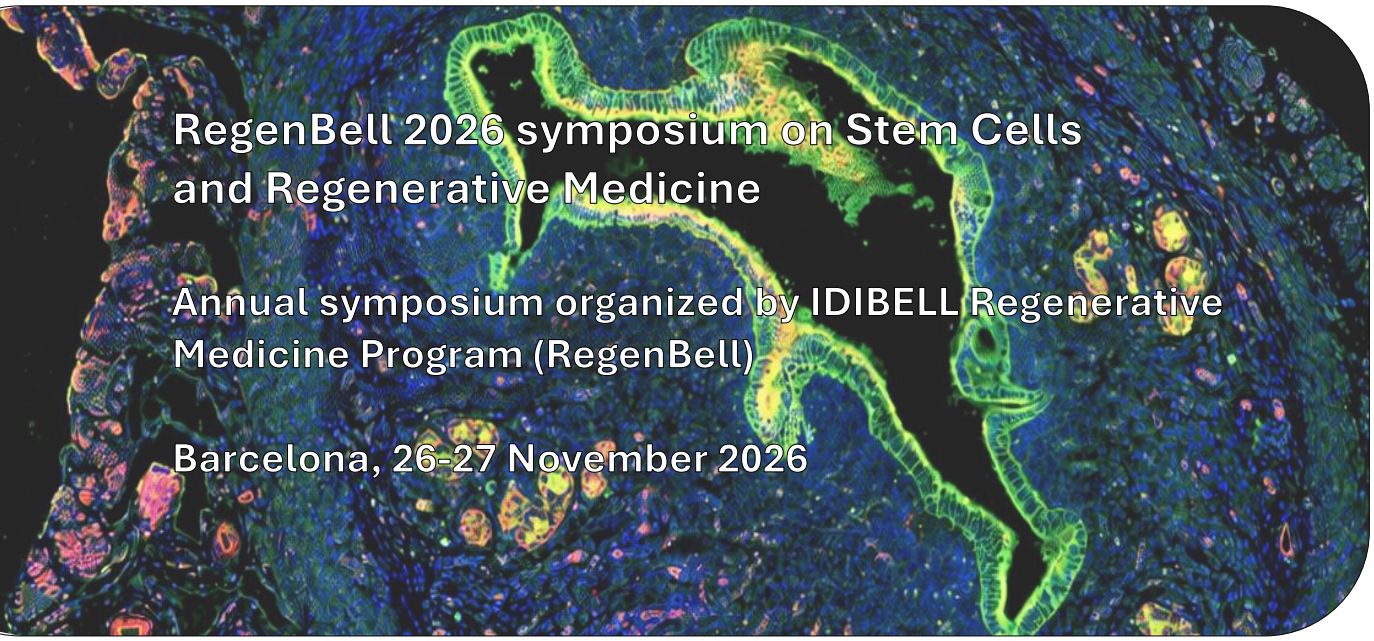


RegenBell 2026 symposium on Stem Cells and Regenerative Medicine

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MAIN SPEAKERS:

KEYNOTE SPEAKER: Ralf H. Adams

Max Planck Institute for Molecular Biomedicine, Department Tissue Morphogenesis, and University of Muenster, Faculty of Medicine, Muenster, Germany

Heterogeneity and functional specialization of the vasculature blood vessels in bone and marrow

Blood vessels in the skeletal system play a critical role in bone formation and homeostasis and are indispensable for regeneration. However, understanding the architecture and function of skeletal vasculature has been challenging due to the heavily calcified and matrix-rich nature of bone. By developing advanced protocols for bone immunostaining and imaging, we have surmounted many of these obstacles.

Our research has revealed that vascular growth in bone is mediated by a specialized form of angiogenesis distinct from other organs. We identified unique type of capillary, termed type H, characterized by high expression of the cell surface markers CD31/Pecam1 and Endomucin. These capillaries are closely associated with immature perivascular mesenchymal cells and osteoprogenitors and couple angiogenesis to osteogenesis.

Using single-cell RNA sequencing, we have systematically explored the heterogeneity of bone endothelial cells (ECs) in different age groups and conditions, providing deeper insights into the organization and functional specialization of bone vasculature. This has revealed significant age-related alterations in bone vasculature, including changes in arteries, blood flow, perivascular mesenchymal cells, and capillary EC subpopulations. Our work has also identified another vessel subtype, termed type R, that facilitates bone remodeling during adolescence, adulthood, aging, and in response to anti-osteoporosis treatments. Furthermore, we found that skull bone marrow is subjected to lifelong expansion, responds dynamically to physiological and pathological challenges, and exhibit substantial resilience during aging and in response to irradiation.

Ongoing studies address the role of blood vessels in bone fracture healing, regeneration post-irradiation, and fibrosis. This work is crucial for understanding and potentially manipulating the vascular contributions to bone health and disease.

Paul Bourgine

Lund Stem Cell Center, Lund, Sweden

Engineering human bone and bone marrow tissues; from regeneration to disease modeling

During development, our bones form through endochondral ossification, a tightly regulated process orchestrated by mesenchymal stem/stromal cells (MSCs). These cells form a cartilage intermediate that is progressively remodeled into bone and bone marrow. Following this process, MSCs persist in the marrow as adipocytes, osteoblasts, osteocytes, stromal cells, and perivascular cells, contributing to the establishment of a mesenchymal niche that supports hematopoiesis. Advances in stem cell biology and tissue engineering have enabled the development of models that recapitulate the stages of human endochondral ossification, from cartilage formation to bone and bone marrow development. These models provide an opportunity to investigate the role of MSCs in bone formation and regeneration, as well as their regulation of hematopoietic stem cells (HSCs) in health and disease. My talk will highlight existing models of human endochondral ossification and explore their applications in regenerative medicine and disease modeling.

Francesco Colucci, MD PhD

University of Cambridge Clinical School and King's College, Cambridge, UK

The Earliest Known Mother Died Pregnant: What Uterine Natural Killer Cells Teach us About Human Health

The Woman of Ostuni, discovered in southern Italy in 1991, is widely regarded as the earliest known human mother. Mother and child may have died from a severe pregnancy complication, highlighting the central importance of healthy placentation in human reproduction. This lecture will examine the role of uterine natural killer (uNK) cells in pregnancy, from trophoblast invasion and vascular remodelling to fetal growth and reproductive success and discuss what pregnancy can teach us about human health more broadly.

Helena Escobar[1,2]

[1]*Muscle Research Unit, Experimental and Clinical Research Center (ECRC), Charité – Universitätsmedizin Berlin and Max Delbrück Center for Molecular Medicine, Berlin, Germany*
[2]*Regenerative Medicine Program, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain*

Toward immune-compatible regenerative therapies for muscle wasting using gene-edited muscle stem cells

Skeletal muscle has a remarkable capacity for regeneration, largely mediated by resident muscle stem cells (MuSC). However, in inherited disorders such as muscular dystrophies, for which curative treatments remain unavailable, progressive muscle degeneration overwhelms this regenerative capacity, leading to muscle wasting and loss of function. Autologous transplantation of genetically corrected MuSC offers a promising therapeutic approach, combining the regenerative potential of stem cells with immunological compatibility. We developed methods for the isolation and propagation of primary human MuSC that preserve their regenerative properties, including cells obtained from patients with muscular dystrophy. Using transient delivery of CRISPR tools, we achieved highly efficient and precise correction of disease-causing mutations while maintaining the myogenic and proliferative properties of these cells. More recently, we established simultaneous and sequential multiplex-editing strategies to repair both pathogenic alleles in MuSC from patients carrying compound heterozygous mutations in *CAPN3* and *SGCA*. Dual repair resulted in substantially greater restoration of disease-associated proteins and contractile function in human 3D engineered skeletal muscle tissues than correction of either allele alone. Gene-edited human MuSC retain their capacity to engraft, regenerate muscle and repopulate the stem-cell niche following transplantation. Using humanized mouse models of limb-girdle muscular dystrophy, we have demonstrated proof of concept for disease rescue through autologous transplantation of gene-repaired MuSC. Together, these advances provide a foundation for the preparation of first-in-human trials of autologous transplantation of gene-edited MuSC in muscular dystrophy patients.

Pedro Sousa-Victor

Gulbenkian Institute for Molecular Medicine (GIMM)

The Interplay of Aging, Immune Signaling and Stem Cell Function

Adult stem cells (SCs) sustain tissue renewal and repair throughout life, and the decline in their function limits the regenerative capacity during aging. Age-associated SC decline results from cell-intrinsic defects and alterations in the extrinsic cues that regulate SC behavior. Among these, alterations in the tissue immune environment are emerging as important contributors to organ dysfunction in aging, but their role in SC impairments remains poorly understood. Using skeletal muscle as a paradigmatic model of age-related loss of repair capacity, our work has shown that changes in immune signaling are important drivers of SC regenerative decline in aging, and that immune modulation can improve tissue repair. We showed how aging remodels the immune environment of the injured tissue and identified specific immune populations and signals that shape the regenerative niche. Interestingly, we uncovered both protective and detrimental roles for age-associated immune populations. Understanding the interplay between immune aging and stem cell function may open new avenues for immune-based strategies to improve regenerative capacity in aging.

Nadia Mercader

Universität Bern, Switzerland

Paternal cardiac injury elicits an inflammatory signal relay to the gonads with intergenerational cardiac effects in vertebrates

The blood-gonadal barrier protects the germline from parental exposures. A phenomenon known as intergenerational inheritance suggests that, exceptionally, this barrier can be surpassed with consequences for the subsequent generation. Specific diet regimes and early traumatic experiences have been among the chronic stressors shown to be able to lead to intergenerational inheritance in mammals. Less is known about how acute stress can affect the germline.
Cardiac damage leads to several alterations in peripheral organs and, overall, affects blood flow, metabolism, and the immune response. Whether cardiac damage can also affect the reproductive system is not known and might offer new insights into the potential inheritance of cardiovascular disease.
Here, we used zebrafish and mouse models to explore the intergenerational role of cardiac damage and repair. In the first week after a cardiac cryolesion, male zebrafish gonads and gametes activated responses associated with inflammation. In sperm, chromatin accessibility was found altered in response to cardiac cryolesion. Offspring of cryoinjured zebrafish males revealed changes in cardiac function and cardiac gene expression. Induction of systemic sterile inflammation in the paternal generation mimicked cardiac injury effects in the following generation, while anti-inflammatory treatments in the injured paternal generation partially recovered F1 cardiac features. Similar features were found in mouse testis after a neonatal injury, and in the hearts of their offspring, suggesting a conserved role of sterile inflammation as a vector for intergenerational transmission of cardiac injury

Davide Leardini

Università di Bologna, Italy

Microbiota–Immunity Interactions and Microbiome-Based Therapeutic Strategies in Hematology

The intestinal microbiota is increasingly recognized as a key regulator of immune homeostasis and a relevant determinant of clinical outcomes in patients with hematological diseases. Profound alterations of the gut microbial ecosystem may occur during intensive chemotherapy, antibiotic exposure, hematopoietic stem cell transplantation, and other cellular and immune-based therapies. These perturbations can influence mucosal integrity, systemic inflammation, immune reconstitution, susceptibility to infections, and treatment-related complications. Growing evidence indicates that specific microbial communities and their metabolites interact closely with innate and adaptive immune responses, providing a biological framework for understanding the association between microbiome composition and outcomes in hematology. In the setting of allogeneic hematopoietic stem cell transplantation, reduced microbial diversity and the loss of beneficial commensal organisms have been associated with adverse outcomes, including graft-versus-host disease, infectious complications, and increased treatment-related mortality. At the same time, these observations have generated considerable interest in the microbiome as both a biomarker and a potentially modifiable therapeutic target. This presentation will discuss current knowledge on microbiota–immunity interactions in patients with hematological diseases, with particular attention to hematopoietic stem cell transplantation and the impact of treatment-related perturbations on the intestinal ecosystem. Emerging microbiome-directed approaches, including antimicrobial stewardship, nutritional interventions, prebiotics, probiotics, and fecal microbiota transplantation, are currently being investigated, with encouraging results, and will be discussed. Finally, ongoing challenges and future perspectives for translating microbiome research into safe, personalized therapeutic strategies in hematology will be addressed.

Francesco Neri

Università degli studi di Torino, Italy

Title: Loss of regeneration and epigenetic drift of the intestinal stem cells during aging

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2 *Molecular Biotechnology Center (MBC), University of Turin, Turin, Italy*
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Aging of the intestinal epithelium is associated with impaired stem cell function, reduced regenerative capacity and increased cancer risk. Epigenetic drift, particularly altered DNA methylation, is a hallmark of aging and is frequently observed in intestinal tumorigenesis. However, how age-associated inflammation, metabolic dysfunction and tissue regeneration converge to generate epigenetic drift in intestinal stem cells remains poorly understood. Across three studies, we combined transcriptomic, epigenomic, proteomic and metabolomic profiling of aged intestinal tissues with functional assays in mouse models and analyses of human colon datasets. We identified IFNγ-STAT1 signaling as a driver of age-related stem cell dysfunction, aberrant lineage priming and impaired regeneration. We further showed that aged epithelia develop proteostatic stress, while polyamine metabolism supports regenerative recovery. Finally, we demonstrated that intestinal DNA methylation drift originates in stem cells and expands through crypt clonality and fission, driven by inflammation, reduced Wnt signaling, altered iron metabolism and impaired TET activity. Together, these studies define a mechanistic link between inflammaging, regenerative decline and epigenetic drift, explaining how aging creates a molecular substrate for cancer-associated DNA methylation changes.

Joana F. Neves

King'sCollegeLondon, UK

Intestinal interactions of innate lymphoid cells in health and disease

Intestinal homeostasis relies on coordinated interactions among immune, mesenchymal, neural, epithelial, and microbial compartments. Disruption of these interactions contributes to the development of several diseases including Inflammatory Bowel Disease (IBD). Innate Lymphoid Cells (ILCs) are central regulators of these networks. In healthy intestine, type 3 ILCs (ILC3) predominate, whereas inflamed IBD tissue exhibits an accumulation of type 1 ILCs (ILC1) with a concomitant reduction of ILC3. Our work focus on dissecting the mechanisms that govern the interaction between ILCs and intestinal epithelial cells in health and in IBD.

Using human co-culture models of ILCs with intestinal organoids, we show that ILC1 drive epithelial and extracellular matrix remodelling, implicating them in the development of fibrosis and cancer—two major IBD sequelae.

Conversely, we show that ILC3 promote epithelial regeneration and induce regulatory FoxP3+ T cells via TGF-β1 production and activation. Importantly, TGF-β1 signalling remains intact in ILC3 from IBD tissue, suggesting this pathway is functional and therapeutically targetable.

Given the protective role of ILC3 and their depletion in IBD, we propose restoring ILC3 populations as a therapeutic strategy. To this end, we developed a protocol to generate large numbers of functional human intestinal ILC3 by co-culturing blood-derived ILC precursors with intestinal organoids.

In conclusion, ILCs are pivotal regulators of intestinal homeostasis whose dysregulation is linked to IBD pathology. Our findings support therapeutic approaches aimed at restoring ILC balance to reinstate intestinal homeostasis.

SHORT TALKS:

Manuel A. Fernández Rojo

The University of Queensland, Brisbane, Australia.

SHORT TALK 01_Methionine metabolism sustains liver regeneration under ketogenic diet feeding in male mice exhibiting paediatric chronic liver disease

Elevated mortality in liver transplantation-waiting list, clinical complications and scarcity of children liver-donors warrant alternatives to liver transplant in paediatric-chronic liver diseases (CLD). CLD hinders liver's unique intrinsic capacity to regenerate. We hypothesized that Ketogenic Diet (KD) could restore liver regeneration as a potential approach to treat CLD. Interestingly, KDfeeding impaired liver regeneration and increased mortality in hepatectomized juvenile CLD- and healthy-mice. Conversely, KD did not reduce the incidence and growth of DEN-induced hepatocarcinoma, suggesting that KD prevents cell proliferation in a regeneration-specific manner. Mechanistically, KD impaired one-carbon metabolism, signalling cascades for quiescence-exiting and proliferation, induced a liver progenitor-like transcriptional signature and altered the innate immune response. Consistent with KD methionine-deficiency underlying impaired liver regeneration, KD-supplementation with methionine, S-adenosylmethionine or spermidine restored liver regeneration and survival in young but not in adult mice. Altogether support that methioninedependent metabolism sustains liver regeneration under KD-feeding to emerge as an alternative against paediatric-CLD.

Eileen Gentleman

The University of Lausanne. Lausanne, Switzerland

SHORT TALK 02_ Tissue geometry and mechanics regulate patterning and morphogenesis in human neuroepithelial organoids

Human neuroepithelial organoids recapitulate key features of neural tube patterning and morphogenesis, providing a tractable system to ask how physical context interfaces with developmental signalling. Substrate stiffness alters FAK-actomyosin-dependent organoid fusion and thus organoid size, which controls ventral patterning. FOXA2, a marker of ventral identity, occupies a greater fraction of small organoids, which frequently become uniformly FOXA2+, whereas larger organoids more often form a single polarised FOXA2+ domain. Constraining organoid size in microwells removes the stiffness-dependent effect, while FAK or myosin inhibition reduces size and shifts patterning toward uniform FOXA2 expression. A mathematical model reproduces these size-dependent patterning behaviours through inhibitory feedback in which morphogen production per FOXA2+ cell decreases as the FOXA2+ domain grows, providing a mechanism for the transition from uniform ventral identity to spatially restricted patterning. Physical cues also regulate elongation and posteriorisation. Stiffer substrates enhance Wnt responsiveness, posterior neural identity and elongation, whereas FAK inhibition reduces nuclear β-catenin and elongation. During elongation, high-curvature tips are enriched for pERK and proliferative activity, suggesting that local tissue geometry focuses signalling and growth to drive anisotropic morphogenesis. Confinement in narrow grooves increases the spatial bias of posterior neural markers, indicating that geometry can reinforce the regionalisation associated with elongation. FGFR inhibition abolishes elongation and its stiffness dependence, supporting a requirement for FGF signalling in this mechanically regulated morphogenetic programme. Together, these findings show that tissue size, geometry and mechanics regulate where developmental identities emerge and where growth-factor signalling is focused, linking pattern formation to morphogenesis in human neuroepithelial organoids.

Isabel Martins

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SHORT TALK 03_A Biomimetic 3D Human Bone Marrow Niche Model to Rescue Stromal and Immune-Related Dysfunction in Aplastic Anemia

Acquired aplastic anemia (AA) is a bone marrow (BM) failure disorder marked by profound depletion of hematopoietic stem and progenitor cells (HSC/HPC). Immune-mediated destruction of HSC/HPC is central to its pathogenesis, yet dysfunction of the stromal microenvironment, in particular mesenchymal stromal cells (MSC), is increasingly recognized as a contributor to impaired hematopoietic support and aberrant immune regulation. Its mechanisms remain poorly defined, partly because conventional 2D cultures do not recapitulate the structural and biochemical complexity of the native niche.

We developed a biomimetic 3D platform based on detergent-free decellularized scaffolds from healthy human femoral bone, repopulated with patient-derived BM MSC to model the AA niche ex vivo. The protocol preserved bone architecture and matrix composition (histology, SEM).

Bulk RNA sequencing of AA MSC identified 306 differentially expressed genes linked to dysregulated adipogenic commitment, altered immune signaling and impaired hematopoietic support. Sustained JAK-STAT activation and aberrant Wnt/β-catenin and PI3K/AKT signaling emerged as candidate therapeutic axes.

AA MSC adhered efficiently to the healthy decellularized matrix and sustained metabolic activity, reconstructing a functional 3D stromal niche. Despite delayed early expansion relative to healthy controls, integration within the healthy matrix enhanced HSC/HPC expansion 8-fold compared with scaffold-only conditions.

These findings show that a physiologically relevant 3D microenvironment can partially restore stromal function and improve hematopoietic support in AA. This human ex vivo platform enables dissection of niche-driven and immune-related mechanisms of BM failure and testing of therapies targeting the BM microenvironment.

Maria Mercado-Gómez

Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 08036, Barcelona, Spain.

SHORT TALK 04_ Immature neutrophils contribute to chronic liver disease resolution

Ductular reaction–associated neutrophils (DRANs) have been shown to be highly plastic and to acquire pathogenic features that promote ductular reaction expansion during chronic liver injury. However, their role in the resolution of chronic liver disease remains largely unexplored.
Using a cholestatic DDC model, we observed that injury regression is accompanied by the loss of DRANs from periportal niches, hepatocyte proliferation and a marked reduction in fibrosis and ductular reaction. Neutrophil depletion during the recovery phase impaired these reparative processes, demonstrating that neutrophils actively contribute to hepatic regeneration.
Transcriptomic profiling revealed that liver neutrophils undergo transcriptional reprogramming during injury regression, acquiring a pro-resolutive state enriched in pathways related to tissue remodeling, leukocyte migration, glycolysis and wound-healing responses. Furthermore, single-cell RNA sequencing identified a distinct population of neutrophils with immature features and increased expression of granule-associated genes including Ngp, Ltf, Camp and Lcn2. This immature neutrophil cluster was selectively enriched during recovery and displayed regeneration-associated transcriptional programs. Notably, cells displaying immature neutrophil features were also detected by immunohistochemistry in liver samples from patients with different etiologies of chronic liver disease.
To functionally assess the contribution of immature neutrophils to tissue repair, mature neutrophil recruitment was selectively blocked during the recovery phase using the CXCR2 inhibitor SCH-527123. Under these conditions, liver regeneration and ductular reaction regression were preserved, whereas fibrosis was further reduced.
Overall, these findings identify CXCR2-/low immature neutrophils as a previously unrecognized component of the reparative response during chronic liver injury regression.

Jara Montero-Muñoz

Department of Pathology and Experimental Therapeutics, Bellvitge University Hospital-IDIBELL, Hospitalet de Llobregat, Spain; Institute of Biomedicine (IBUB), University of Barcelona

SHORT TALK 05_LRRK2-Dependent Astrocyte-Microglia Crosstalk Amplifies Dopaminergic Neurodegeneration

Parkinson's disease(PD) is a common neurodegenerative disorder characterized by progressive loss of dopaminergic neurons(DAn) in the substantia nigra and accumulation of misfolded α-synuclein. Neuroinflammation is increasingly recognized as a key contributor to disease progression, yet how disease-associated astrocytes and microglia cooperate to promote neuronal loss remains poorly understood. To address this, we developed a human iPSC-derived tri-culture system combining control DAn with LRRK2-G2019S mutant or isogenic-corrected astrocytes and microglia, enabling us to determine how LRRK2-G2019S in each glial population, alone or together, contributes to neurodegeneration. Using this system, we previously found that LRRK2-PD astrocytes induce degeneration of control DAn and increase the reactive state of isogenic-corrected microglia. Here, we asked whether LRRK2-PD microglia further amplify this phenotype.

Introducing LRRK2-G2019S into microglia in the presence of LRRK2-PD astrocytes further increased DAn degeneration compared with the astrocyte-only mutant condition, revealing a cooperative effect of mutant astrocytes and microglia on neuronal survival. Single-cell RNA sequencing identified CD14 as one of the most strongly upregulated gene in LRRK2-PD microglia in the double-mutant condition. Given the central role of CD14 in innate immune activation, we tested whether CD14 signaling contributes to the enhanced neurotoxic phenotype. Pharmacological blockade of CD14 prevented LRRK2-dependent DAn degeneration, implicating microglial CD14 signaling as a functional mediator of the amplified neurotoxic response. Together, these findings establish a human tri-culture platform for dissecting glial contributions to PD and reveal an LRRK2-dependent astrocyte-microglia cascade in which mutant microglia amplify astrocyte-mediated neurotoxicity through CD14 signaling. These findings identify CD14 as a potential target for limiting inflammation-driven neurodegeneration in PD.

Joji Marie Teves

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3 Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain

SHORT TALK 06_ Mapping the Uterine Remodelling from Pregnancy to a New Homeostatic State

Pregnancy drives uterine remodeling through rapid anatomical expansion and scar-free postpartum repair, yet how the organ reconstructs its cellular architecture after birth remains incompletely understood. Here, we present single-cell transcriptomic profiling of 698,631 cells derived from the whole mouse uterus across five distinct stages centered around parturition: Non-pregnant Control, late gestation (embryonic day 16.5), and postpartum days (PPD) 1, 7, and 30. We resolved 16 distinct cell lineages spanning epithelial, stromal, endothelial, and immune compartments. Although gross morphological involution occurs rapidly, with uterine horn length returning to baseline levels by PPD7, the underlying cellular architecture does not revert to its pre-pregnancy state. Tissue composition, transcriptional states, and intercellular signalling networks did not revert to their pre-pregnancy configurations. Instead, postpartum reconstruction proceeded through five sequential but overlapping transcriptional programs, with individual cells simultaneously extinguishing gestational programs and acquiring repair-associated states. By one month postpartum, the tissue adopts a reconfigured architecture that fails to fully reactivate the non-pregnant baseline, thus, establishing a novel homeostatic state. This work provides a foundation for delineating the specific organizational levels that fully recover following physiological injury versus those that establish new baseline set points.

Hafsa Zahid

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2 Max Planck Institute for Molecular Genetics, Ihnestrasse 73, 14195 Berlin, Germany
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SHORT TALK 07_ Fibro-adipogenic progenitors control the anti-inflammatory response of macrophages during skeletal muscle repair

Timely resolution of muscle tissue debris upon injury is essential for effective regeneration and requires a temporally regulated regeneration-specific niche supporting muscle stem cells. This niche is provided in part by fibroadipogenic progenitors (FAPs), and in part by macrophages, which activate upon muscle injury. More specifically, transition from pro-inflammatory (M1 macrophage) to anti-inflammatory (M2 macrophage) microenvironment is required for the complete restoration of muscle mass. Previously, an injury-activated FAPs sub-population expressing the transcription factor, Odd-skipped related 1 (Osr1), has been proposed to support myogenesis. Moreover, conditional knockout of Osr1 (Osr1cKO) in FAPs resulted in excessive fibrosis and a dysregulated macrophage polarization upon injury. This suggested a connection between atypical FAPs secretome and macrophage phenotypes, which remained elusive. The current study investigates how loss of Osr1 in FAPs regulates FAPs secretome and macrophage function upon injury. The results show that the depletion of Osr1 in FAPs impairs the population expansion of M2 macrophages in vivo. Moreover, Osr1cKO FAPs-derived conditioned media (CM) inhibits the M2 polarization of wild-type macrophages in vitro. Beyond signaling, Osr1cKO FAP's secretome profoundly disrupts the M2 macrophage immunometabolism and actin cytoskeletal organization both in vivo and in vitro. Characterization of the Osr1cKO FAP's secretome revealed a unique composition marked by altered extracellular matrix (ECM) turnover, alongside a reduced abundance of chemokines known for controlling M2 macrophage polarization, in CM derived from Osr1cKO FAPs. Furthermore, both the ECM and CM from Osr1cKO FAPs showed a higher abundance of fibrosis-related proteins, notably transforming growth factor-β (TGF-β). Collectively, these findings highlight a novel role of Osr1 expression in controlling FAPs secretome and the M2 polarization event during skeletal muscle repair.

Yiwen Zhang

German Cancer Research Center (DKFZ), Heidelberg, Germany

SHORT TALK 08_Heterogeneous hematopoietic aging is associated with distinct immune–niche communication programs

Hematopoietic stem cell (HSC) aging involves both cell-intrinsic and microenvironmental changes, but how immune–niche interactions shape heterogeneous aging trajectories remains poorly understood.
We generated a multi-layered hematopoietic dataset from a large cohort (>100) of young (2 months), middle-aged (18 months), and old (>24 months) inbred female C57BL/6 mice housed under specific pathogen-free conditions, characterizing aging across peripheral blood, bone marrow, spleen, and transplantation assays. Although the cohort recapitulated established age-associated traits, aged mice displayed pronounced phenotypic heterogeneity. Cohort-wide correlation analysis challenged previously proposed relationships between HSC functionality, HSC expansion, and myeloid bias, arguing against a single trajectory of hematopoietic aging.
To investigate its molecular basis, we derived cell type-specific aging scores from bone marrow scRNA-seq data, revealing substantial inter-individual variation across hematopoietic and niche populations. Intercellular communication analysis identified distinct inflammatory programs associated with specific aging phenotypes. Neutrophil-derived OSM signaling was associated with reduced B cell abundance in one subset, while neutrophil-to-AdipoCAR IL-1 signaling was associated with anemia in another. Neutrophil-to-AdipoCAR TNFα signaling was negatively associated with T cell abundance in blood, whereas T cell-to-AdipoCAR IFNγ signaling was associated with myeloid cell abundance in bone marrow. These non-overlapping associations indicate that inflammaging is not a single coherent inflammatory state.
Together, our findings suggest that hematopoietic aging follows heterogeneous phenotypic and molecular routes involving distinct immune–niche communication programs. This heterogeneity suggests that targeting a single inflammatory pathway may be insufficient to broadly prevent age-associated hematopoietic changes.

POSTERS:

Lucía Alonso Sánchez *et Al*

Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza, España.

POSTER 01_ Long-term human cervical and endometrial epithelioids for studying epithelial biology and HPV infection processes.

Background: Physiologically relevant models that preserve human epithelial architecture and cellular organisation are essential for studying tissue homeostasis and regeneration. Conventional 2D cultures often fail to reproduce the complexity of native tissues, highlighting the need for alternative long-term 3D culture systems.
Aim: To establish, optimise and characterise primary human 3D epithelioids derived from cervical and endometrial tissues as models for studying epithelial organisation and differentiation.
Methods: Epithelioids were generated from primary human tissue explants collected during surgeries. Culture conditions were optimised by evaluating hormonal supplementation with estradiol and progesterone. Tissue architecture, epithelial identity and cellular organization were characterised by immunofluorescence and confocal microscopy, assessing markers including cytokeratins, FOXA2, E-cadherin and integrin-α6. The feasibility of stable genetic manipulation was evaluated using third-generation lentiviral vectors expressing fluorescent reporters.
Results: Stable 3D epithelioid cultures were successfully established and maintained viability and organised epithelial architecture for up to six months without conventional passaging. Combined estradiol and progesterone supplementation appears to have improved the culture establishment and growth, reaching efficiencies of 73% in cervical and 47% in endometrial tissue. Immunofluorescence analysis confirmed the preservation of tissue-specific and epithelial organization markers, supporting the maintenance of cellular identity and epithelial hierarchy over extended culture periods. Lentiviral transduction with oncogenic viral proteins demonstrated the possibility of stable genetic manipulation, providing a proof-of-concept for future functional applications.
Conclusions: Human cervical and endometrial epithelioids provide a long-term 3D culture system for studying epithelial organisation and responses to genetic perturbations. Their susceptibility to lentiviral transduction offers a basis for investigating how viral oncogenes affect epithelial behaviour and contribute to disease.

Yolanda Andres-Lopez *et Al*

Institute of Molecular Biology of Barcelona (IBMB-CSIC)

POSTER 02_ Using CRISPR barcoding as a molecular clock to capture dynamic processes at single-cell resolution

Biological processes are fundamentally dynamic, yet existing methods for capturing these temporal changes are limited (1, 2, 3). We present scDynaBar, a novel approach that integrates CRISPR-Cas9 dynamic barcoding with single-cell sequencing to enable the recording of temporal cellular events. In this system, genetic barcodes accumulate mutations over a 4-week timeframe and then are sequenced together with the transcriptome of each single cell. We propose that this gradual accumulation of genetic diversity can be exploited to create a time-ordered record of cellular events. To demonstrate this, we apply the system to track the transition from a pluripotent state to a two-cell (2C)-like state in mouse embryonic stem cells (mESCs). The results provide compelling evidence for the transient nature of the 2C-like state. Additionally, our system shows consistent mutation rates across diverse cell types in a mouse gastruloid model, underscoring its robustness and versatility across various biological contexts. This technique not only improves our ability to study cellular dynamics but also creates exciting new opportunities for future applications based on recording temporal signals at the single-cell level, in other words, using dynamic barcoding as a molecular clock.

Joan M. Cabot (last Author)

Leitat Technological Center, Terrassa, Barcelona

POSTER 03_From Biofabrication to Functional Human Tissues: Organ-on-a-Chip Platforms for Regenerative Medicine

The development of regenerative therapies and advanced medicines is limited by the poor predictive value of conventional in vitro and animal models. Organ-on-a-chip (OoC) and microphysiological systems (MPS) offer promising alternatives to balance physiological relevance and reduce the use of animal models. Herein, we developed microfluidic platforms that integrate advanced biofabrication, biomimetic perfusion, and high-throughput screening to generate predictive human tissue models.

The first platform comprises a high-throughput microfluidic plate containing 56 independent OoC units. Its membrane-free vertical architecture enables direct communication between 2D cellular layers and 3D extracellular matrix compartments, recreating physiologically relevant tissue interfaces while maintaining scalability. The system has been successfully applied to joint-on-chip models incorporating human cartilage and synovial tissues, enabling the study of tissue crosstalk, inflammatory responses, and therapeutic interventions in controlled microenvironments.

To further enhance tissue functionality, a second platform was developed to support bioprinted tissues under dynamic perfusion. Using light bioprinting and GelMA-based bioinks, biomimetic liver constructs with hexagonal lobule-like architectures were generated and integrated into a microfluidic device designed to mimic hepatic portal circulation. Dynamic perfusion promoted homogeneous nutrient transport, sustained viability, and progressive functional maturation, evidenced by increased albumin production and structural integrity.

Together, these platforms provide physiologically relevant human tissue models. By integrating OoC engineering, bioprinting, and biomimetic perfusion, they offer powerful tools for regenerative medicine, disease modelling, drug discovery, and toxicology while supporting the reduction of animal experimentation.

Joan Casamitjana *et Al*

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POSTER 04_ Comprehensive characterization of pancreatic stromal heterogeneity to identify missing queues from embryonic mesenchyme to pancreatic pathologies

The stromal compartment of the pancreas plays major regulatory and supportive roles during development and progression of ductal adenocarcinoma (PDAC). In the developing pancreas, the mesenchyme is known to secrete important factors for ductal maturation and endocrine cell emergence. Furthermore, some of these factors such as FGF10 are used to grow pancreatic ductal organoids to model the organ and to generate de novo in vitro β cells. However, as the healthy adult remains undercharacterised, it is unknown which embryonic queues are maintained and the role and transition of the adult stroma in the development and progression of PDAC and other pathologies. Similarly, we are potentially losing important developmental queues that could prove key to unlocking the full potential of the pancreatic organoids.

Here, we have generated a comprehensive characterisation of mouse pancreatic stromal heterogeneity at a single cell resolution (over 15,000 stromal cells), including the endothelial (6,776 cells) and mesenchymal (8,266 cells) compartment. ScRNA-seq analysis unravelled 7 subpopulations of mesenchymal cells, including pericytes, smooth muscle cells, adventitial cells, stellate cells and 3 distinct types of fibroblasts. Cell chat analysis with our previously published scRNAseq data of the entire ductal tree compartment (Fernández, Casamitjana et al. 2024) revealed over a 100 distinct ductal-mesenchyme signalling networks active, including TGFβ, EGF, FGF and WNT pathways.

Simultaneously, we have isolated stromal cells from different murine embryonic stages (e12.5 to e18.5) and adult pancreata and cultured them in low serum conditions. Conditioned media was collected daily for 7 days, and by means of a cytokine array (640 cytokines), we have identified 61 proteins being differentially expressed.

Together, this data shows that the adult pancreatic mesenchyme may play an undiscovered role in tissue homeostasis that still needs to be studied in situ and in vitro.

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POSTER 05_ Inhibition of autophagy-related genes: detriments to stem cells

Regeneration requires coordinated stem cell activation, metabolic adaptation, and maintenance of tissue integrity, yet how stem cells sustain proliferation under nutrient-limited conditions remains unclear. The planarian Schmidtea mediterranea is a model for whole-body regeneration driven by neoblasts, adult pluripotent stem cells that remain active during prolonged starvation. Autophagy, a conserved degradation pathway induced by cellular stress and nutrient deprivation, is essential for cellular homeostasis, but its in vivo role in regeneration is not fully understood. Here, we investigate autophagy during regeneration using an RNA interference (RNAi) screen targeting canonical autophagy genes (atg). We demonstrate that atgs are essential for regeneration. Their inhibition impairs blastema formation, reduces regenerative capacity, induces tumor-like overgrowths, and leads to lethality. Together, our findings establish autophagy as a critical early regulator of regeneration, linking metabolic adaptation to stem cell function during tissue repair.

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POSTER 06_Spatiotemporal coordination of injury-induced cellular states durind planarian tail regeneration

Tail regeneration in bilaterian animals requires the coordinated re-establishment of body patterning and tissue growth. While key signaling pathways are well-studied, how injury-induced cellular states dynamically organize the regenerating tissue remains poorly understood.
We investigated the cellular dynamics of posterior blastema formation in Schmidtea mediterranea through single-cell sequencing of posterior wounds from 0 to 96 hours of post-amputation. We identified cell clusters corresponding to muscle, parenchymal, and phagocytic cells that adopt transient, regeneration-specific states. Functional study of genes expressed in these populations, such as fascin and the E3 ubiquitin ligase ARI2/3, demonstrates their requirement for proper tail regeneration. Our study provides evidence that the triggering of regeneration-specific transcriptomic signatures in specific cell types is required for mounting a successful regeneration response.

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POSTER 07_ Retinoid signalling regulates regenerative patterning in the planarian Schmidtea mediterranea.

Planarians are a powerful model for studying whole-body regeneration, as adult pluripotent stem cells enable the reconstruction of all tissues after injury. Retinoic acid (RA) is a conserved regulator of differentiation, axial patterning and neurogenesis, but its role in highly regenerative invertebrates remains poorly understood. Here, we characterize retinoid signalling in Schmidtea mediterranea and investigate its function during regeneration.

Genomic, phylogenetic and structural analyses identified most of the enzymatic machinery required for retinoid metabolism, two conserved RXR paralogues (RXR1 and RXR2), and a RERE-associated chromatin-regulatory module. In contrast, no canonical RAR or CYP26 orthologues were detected. Analysis of ATAC-seq datasets identified RXR-compatible motifs in accessible chromatin regions associated with retinoid- and regeneration-related genes, including rxr1, rxr2, bco1, aldh1, aldh2 and adh1, as well as candidate regulatory regions linking retinoid and Wnt-dependent programmes.

Functional perturbation further supported a role for this pathway during regeneration. Pharmacological inhibition of retinaldehyde dehydrogenase with DEAB and all-trans retinoic acid treatment produced dose-dependent regenerative defects. RNAi inhibition of RXR1/RXR2, RERE and retinoid-metabolism enzymes caused defects in eyes and posterior regeneration, left-right asymmetries, and abnormal nervous-system reconstruction. Alteration of the RA pathway also affected mitotic activity. Together, these results identify retinoid signalling as a component of the regulatory network coordinating proliferation, differentiation and positional information during whole-body regeneration.

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POSTER 08_ Metabolic context shapes the early regenerative response in planarians.

What commits a cell to a regenerative response after injury? The signalling pathways downstream of wounding are relatively well described, but what the tissue brings to that moment — its metabolic state, its nutritional history — has received far less attention. In stem cell-based regeneration, energy metabolism may determine which cascades get activated and in which cell types, acting as an early input rather than a passive backdrop. Planarians (Schmidtea mediterranea) let us test this directly: regeneration is driven by adult stem cells (neoblasts), animals remain regeneration-competent across very different nutritional states, and both gene function and dietary history can be controlled experimentally. We combine RNAi knockdown of metabolic candidates with single-cell transcriptomic analysis of early post-amputation time points to dissect the metabolic requirements for regeneration initiation. These approaches are being extended to animals under controlled dietary regimes combined with lipidomics and imaging-based methods.
RNAi knockdown reveals that disrupting pathways from both lipid metabolism and central carbon metabolism impairs blastema formation, demonstrating that the early regenerative response draws on multiple metabolic inputs. Single-cell transcriptomic data further identify metabolic programmes differentially activated after amputation. Lipid-related pathways emerge as particularly relevant, consistent with a role beyond classical energy provision. Together these findings challenge the glycolysis-versus-OXPHOS framing typically applied to proliferative stem cells and suggest that regeneration competence depends on a broader metabolic logic. Ongoing work integrating dietary conditions and lipidomics will determine whether pre-injury nutritional state gates these early transitions.

Anna Guixeras-Fontana *et Al*

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POSTER 09_ Smed-cbp-3 is essential for progenitor cells lineage progression and gene regulation in planarians

Characterizing how stem cells self-renew and differentiate in different organisms is pivotal to understand essential questions in evolution and developmental biology, such as tissue renewal and regeneration. Freshwater planarians are able to regenerate any part of their body based upon the presence of adult pluripotent stem cells. CBP (CREB-binding protein)/p300 proteins have an acetyltransferase activity and belong to a conserved gene family which functions as transcriptional co-activators regulating gene expression. Several CBP homologues have been identified in planarians and functional analyses have uncovered an important role for Smed-cbp-3 in stem cell differentiation. On-going bulk and single-cell RNA-sequencing analyses have identified specific biological processes and cell populations affected after silencing cbp-3. Thus, different gut and secretory cell populations, among others, are affected, many neural genes are downregulated and, remarkably, many genes expressed in parenchymal cells appear up-regulated after cbp-3 RNAi. Also, most of the identified transcription factors miss-regulated after silencing cbp-3 are expressed in neoblasts or progenitor cells. In addition, our recent work has shown that stem cells and progenitors accumulate in the absence of cbp-3 due to its inability to pursue differentiation, while mature differentiated cells of several cellular lineages are reduced, both under regeneration and homeostatic conditions. This inability might be caused by cell cycle alterations, as cycling cells were found to be accumulated. All this data should allow to better characterize the role of cbp-3 in the regulation of stem cell differentiation.

Gutiérrez-Franco A. *et AL*

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POSTER 10_ Single-cell transcriptomics reveal early RNA processing changes in iPSC-derived neurons and glial cells derived from Alzheimer's disease patients

We used iPSCs from multiple AD donors that were differentiated into neural fates alongside healthy controls. We used scRNA-seq to study their transcriptomes at multiple stages, revealing the expected cell types. Cell composition analysis revealed significant depletion of astrocyte populations in AD at multiple timepoints, in addition to an enrichment of excitatory neurons at day 70. Differential expression analysis showed significantly dysregulated RNA-binding proteins and known AD risk genes. It also described a significant upregulation of the lncRNA MEG3 across multiple clusters, previously shown to trigger necroptosis in AD neuron xenograft models. Gene set enrichment analysis showed AD-associated changes including apoptosis, metabolic pathways and RNA processing. Further investigation at the isoform-level with SCALPEL showed dysregulation of many genes, including known AD risk genes.
In summary, we found depletion of astrocytes and an excitatory-inhibitory imbalance in AD. We also identified alterations related to AD including known AD risk genes at the transcriptional and post-transcriptional level, including RNA processing, apoptosis and metabolic shifts. Importantly, capturing these changes in an in vitro human iPSC model, despite partial loss of epigenetic and aging signatures during reprogramming, allows for diverse approaches to investigate their underlying mechanisms and reveal novel targets to prevent or slow down neurodegeneration

Patricia Herrero-Molinero *et AL*

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POSTER 11_Dormancy emerges in a fetal hematopoietic stem cell subset with reduced Notch signaling

Hematopoietic stem cells (HSCs) arise from the embryonic aorta, migrate to the fetal liver (FL) for maturation and expansion, and later colonize the bone marrow (BM). In the adult BM, the most immature HSCs (about 30%) remain dormant, harbor the highest long-term reconstitution potential and are activated only under stress. However, when and how HSC dormancy is established remains unknown. The Notch signaling pathway is a key regulator of HSC generation but is dispensable in the adult BM. Moreover, Notch regulates dormancy in various stem cell types.
Hematopoietic deletion of the Notch effector RBPj after HSC generation using vav1-Cre results in increased quiescence with a dormancy signature in HSCs. However, both BM and FL RBPj-deficient HSCs show impaired competitive reconstitution capacity. Conversely, Notch1 overactivation (lox-stop-lox;NICDvav1:cre) induces increased proliferation and differentiation of FL HSCs, reducing their overall frequency. Transient Notch inhibition in HSCs using gamma-secretase inhibitors or Notch receptor blocking antibodies induces quiescence in FL HSCs in vitro but not in BM HSCs. This temporal inhibition preserves FL HSC numbers in vitro, and upon competitive transplantation, these cells exhibit enhanced reconstitution potential.
These results suggested the hypothesis that dormancy could be acquired during embryonic development in HSCs and that Notch activation would prevent HSCs from acquiring dormancy.
A previous study detected quiescent HSCs in the BM at 4 weeks after birth, with some of them acquiring dormancy. Our results using label retention assays (BrdU, TTA;H2B-GFP) revealed that a subset of HSCs acquires a dormant state during development and persists into adulthood.
In conclusion, dormancy is acquired during development, and Notch regulates this decision in fetal HSCs, thereby influencing their functionality in the adult BM.

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POSTER 12_Staufen2 modulates the temporal dynamics of human neurogenesis in vitro

RNA-binding proteins (RBPs) play a crucial role in post-transcriptional regulation during brain development, yet their precise contributions to human neurogenesis and neural fate commitment remain poorly understood. In this study, we investigated the role of the double-stranded RBP Staufen2 (STAU2) during human cortical neurogenesis using induced pluripotent stem cell (iPSC)-derived models. STAU2 has previously been implicated in asymmetric RNA distribution during mammalian corticogenesis. However, its function during the earliest stages of human neurogenesis remains largely unknown.

Using single-cell transcriptomics across a cortical time-course differentiation, we characterized STAU2 knockout (STAU2-KO) iPSC-derived neural cells and found that neuroepithelial cells (NECs), the earliest neural stem cells, show the strongest transcriptional response to STAU2 loss. STAU2-KO NECs show reduced expression and regulon activity of key developmental regulators, including ARID3A and CHD2, together with widespread alterations in miRNA-mediated regulatory programs. STAU2 loss also reduces the stability of a subset of transcripts involved in these regulatory networks, including CHD2 and the miRNA host genes MIR9-1HG and SLIT2. Moreover, the common targets of these affected transcriptional and miRNA-mediated regulatory mechanisms were found to be involved in cell proliferation and differentiation. These molecular alterations are accompanied by an earlier appearance of neuronal markers in two-dimensional cortical cultures and by disrupted neuroepithelial organization and reduced growth in cortical organoids. Together, our findings identify STAU2 as a regulator of early human cortical neurogenesis. By coordinating transcriptional and post-transcriptional programs, STAU2 helps maintain neuroepithelial identity and ensures the proper timing of neuronal differentiation.

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POSTER 13_ Identifying novel factors regulating hematopoietic stem cell specification

Pluripotent stem cells hold great therapeutical potential in hematological diseases but reliable protocols for HSC specification are required. The main obstacle remains to be the poor understanding of early commitment cues, which causes the process to appear unpredictable.
To identify the genes that are necessary and/or sufficient to induce HSC specification from embryonic stem cells (ESCs), we performed a whole mouse genome CRISPR activator screening. Genes were activated endogenously during mesoderm specification stage of embryoid body differentiation of mouse ESCs and the hemato-endothelial progenitors thus generated were serially transplanted. Sequencing engrafted cells consistently revealed seven genes that were previously not studied in hematopoietic context and we independently validated them for HSC induction potential. (Palma et al, Blood 2025; doi: https://doi.org/10.1182/blood.2024027742).
To interrogate how induction of these 7 genes led to HSPC specification, we compared scRNA-seq data from our embryoid bodies to murine embryos during ontogeny. Major observations include an intra-embryonic fate bias and differential activation of signaling pathways related to HSC homing in the induced cells. Exploring the expression of these genes individually revealed that while four of them were more widely expressed spatially and temporally, the remaining 3 display a significant upregulation in hematopoietic precursors during definitive hematopoiesis. Curious to know if a subset of the 7 is enough for HSC induction, we performed a combinatorial screen with the 7 genes. Although there was no consensus minimal cocktail that had similar HSPC inducing efficiency, 3 genes were consistently activated in all precursors analysed. We are currently characterizing the function of some of these genes in inducing HSPC fate from mouse and human ESCs.

Maria Magallon-Mosella *et Al*

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POSTER 14_CRISPRi screening identifies candidate chromosome 7 genes underlying monosomy 7-associated transformation in GATA2 deficiency

GATA2 deficiency is a common hereditary predisposition to pediatric MDS/AML, and over 75% of carriers develop monosomy 7 during leukemic progression. Which chr7 genes cooperate with GATA2 haploinsufficiency to drive this progression remains undefined, due to the lack of reliable human disease models. We aimed to identify chr7 genes cooperating with GATA2 deficiency using a doxycycline-inducible CRISPRi platform in hiPSC-derived HSCs.
A CRISPRi screening of 604 chr7 genes in K562 cells carrying GATA2 R396Q or GATA2 R398W mutations identified 15 candidates (including ACHE, AHR, CASP2, HOXA9, CDK13, KMT2E, RASA4B, IRF5). Knockdown restored proliferation of GATA2-mutant K562 cells, supporting a role in transformation. Candidates were validated in GATA2 R396Q hiPSC lines expressing dox-inducible dCas9-KRAB and a 15-sgRNA CRISPRi library. dCas9 induction and sgRNA presence were confirmed by RT-qPCR and DNA sequencing. Following differentiation and liquid culture, gene silencing increased the HSPC compartment, with higher monocyte and lower neutrophil output. CFU assays confirmed a role for chr7 candidates in progenitor maintenance and myeloid differentiation.
Bulk RNA sequencing of dox-induced versus non-induced GATA2 R396Q HSPCs confirmed downregulation of the candidate genes. Gene set enrichment analysis showed upregulated proliferative/growth-signaling programs (MTORC1, MYC, E2F targets, G2M checkpoint, mitotic spindle) and downregulated hypoxia, consistent with exit from quiescence. This mirrors the progenitor expansion and colony-forming capacity seen in vitro. WT and GATA2 R396Q iHSCs carrying the inducible system are being transplanted into NSGW41 mice to study long-term clonal evolution.
Altogether, we established a functionally and transcriptionally validated CRISPRi platform, showing that chr7 gene perturbation promotes progenitor expansion in a GATA2-mutant context and identifying proliferative and growth signaling as a potential mechanism of clonal expansion.

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POSTER 15_Functional and inflammatory characterization of menstrual-derived mesenchymal stem cells and macrophages in endometriosis

Background:
Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial-like tissue outside the uterine cavity, affecting approximately 10% of women of reproductive age and commonly associated with pelvic pain and infertility. Increasing evidence suggests that altered immune responses and dysfunctional endometrial cell populations contribute to disease pathophysiology. This study aims to characterize functional, molecular, and immunological alterations in menstrual blood-derived mesenchymal stem cells (MenSCs) and menstrual macrophages from women with endometriosis compared to healthy controls.
Materials and Methods:
A cross-sectional analytical study was designed including 40 women (20 diagnosed with endometriosis and 20 healthy controls) recruited at a tertiary hospital. MenSCs and macrophages isolated from menstrual blood and peripheral blood are being analyzed regarding proliferative capacity, inflammatory profile, and immunomodulatory properties. Intra-menstrual variability (days 1–5) in MenSC immunomodulatory capacity is also being assessed in a selected subcohort. Molecular findings will be further validated in endometrial and endometrioma tissues and correlated with clinical parameters.
Results:
The study is currently in the recruitment phase. Preliminary observations suggest differences in proliferation rates and inflammatory profiles between MenSCs from endometriosis patients and controls. In addition, intra-group variability associated with the day of menstrual collection has been observed.
Conclusions:
This study may contribute to a better understanding of the cellular and immunological mechanisms involved in endometriosis and support the identification of novel cellular phenotypes and potential therapeutic targets.

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POSTER 16_ Effect of Bile Acids on Hepatocyte Plasticity in Chronic Liver Disease

Background:
Hepatocyte plasticity is essential for liver regeneration but may become dysregulated during chronic liver disease. In alcohol-associated liver disease (ALD), hepatocytes can lose their mature identity and acquire progenitor-like features associated with disease progression. We investigated whether bile acids (BAs) contribute to this hepatocellular plasticity and whether patient-derived liver organoids can model these transitions.
Methods:
We integrated multi-omics approaches, including metabolomics, bulk and microdissection-based transcriptomics, and single-cell RNA sequencing, to characterize hepatocyte plasticity and its relationship with BA signaling across ALD progression. These analyses were complemented by a murine model of BA overload using a cholic acid-enriched diet. Primary mouse hepatocytes and biopsy-derived liver organoids from ALD patients (b-Orgs) were exposed to specific BAs and pharmacological modulation of FXR signaling. Hepatocyte identity and plasticity were assessed by qPCR and immunofluorescence.
Results:
Multi-omics analyses revealed a progressive loss of hepatocyte identity together with acquisition of progenitor-like features, including SOX9, KRT19 and EPCAM, associated with alterations in BA metabolism and signaling. BA overload in vivo similarly promoted hepatocellular dedifferentiation. Importantly, patient-derived b-Orgs recapitulated this plastic phenotype and responded to BA exposure with loss of mature hepatocyte markers and induction of progenitor-associated programs. These changes were modulated by FXR inhibition and accompanied by activation of YAP-related transcriptional programs, suggesting a mechanistic link between BA signaling and hepatocyte reprogramming.
Conclusion:
Our results identify BAs as modulators of hepatocyte plasticity in ALD and establish patient-derived liver organoids as a relevant model to study disease-associated hepatocellular reprogramming and its underlying mechanisms

Dr. Negar Nickkar

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POSTER 17_ iPSC-Derived Vascularized Organoids from Canine and Feline Sources: A Novel Approach to Veterinary Tissue Regeneration within a One Health Framework

Three-dimensional organoids have fundamentally expanded the toolkit of regenerative medicine, yet their clinical and preclinical utility remains constrained by a persistent limitation: the absence of a functional vascular supply. Without perfusion, diffusion-dependent nutrient and oxygen delivery becomes inadequate beyond a few hundred micrometers, producing central hypoxia, necrosis, and progressive loss of tissue-specific function. Over the past several years, strategies including endothelial co-culture, multilineage co-differentiation, and microfluidic perfusion systems have addressed parts of this problem in human iPSC-derived organoids, with recent work demonstrating that targeted transcription factor activation can accelerate vascular network formation with notable efficiency. Despite this progress, veterinary applications of vascularized organoid technology remain almost entirely undeveloped. Canine and feline induced pluripotent stem cells represent a scientifically compelling and practically underexplored substrate: companion animals share environmental exposures, metabolic profiles, and a range of spontaneous diseases with humans, creating a bidirectional translational logic that rodent models cannot replicate. Building on the recent demonstration of feeder-free canine iPSC generation and on documented calls for standardization within the veterinary organoid field, this review synthesizes current vascularization strategies from the human literature and evaluates their feasibility for adaptation to canine and feline systems. We identify a substantive gap — the absence of a validated, reproducible protocol for iPSC-derived vascularized organoids from companion animal sources — and propose a structured, stage-gated research path toward filling it. The resulting platform would serve tissue regeneration directly in veterinary medicine while contributing a rigorously characterized comparative model to the broader One Health agenda.

Virginia Nieto-Romero *et Al*

Stem Cell Potency Group, Regenerative Medicine Program, IDIBELL, Barcelona, Spain.

POSTER 18_ Patient-specific hiPSC-derived cardiomyocytes to investigate novel genetic drivers of hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disorder and a major cause of heart failure and sudden cardiac death. The main causes of HCM are pathogenic variants in genes encoding sarcomeric proteins. However, causative mutations remain unidentified in more than 50% of HCM patients. Traditionally, HCM has been considered a monogenic disorder with autosomal dominant inheritance. More recently, however, oligogenic inheritance involving non-sarcomeric pathogenic variants has been proposed in a substantial proportion of HCM patients.

We aim to investigate the contribution of non-sarcomeric gene variants to HCM pathogenesis using human induced pluripotent stem cell (hiPSC)-derived disease models.

Whole-genome sequencing was performed in thirteen HCM families negative for pathogenic variants in sarcomeric genes, leading to the identification of novel candidate genes associated with the disease. hiPSC lines were generated from affected and unaffected members of three selected HCM families carrying these newly identified variants. Patient-specific hiPSCs were subsequently differentiated into cardiomyocytes to establish in vitro models of HCM. Phenotypic and functional characterization is currently underway, including analysis of gene expression, cellular morphology, contractility, and calcium handling.

These patient-specific in vitro HCM models will enable the investigation of the pathogenic role of newly identified genetic variants. Furthermore, the generation of gene-corrected isogenic hiPSC controls will provide a powerful platform for establishing causal genotype-phenotype relationships.

Eleni Nikolopoulou *et Al*

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POSTER 19_ Vasculogenesis contributes to the regeneration of the adult bone marrow vasculature

Bone marrow (BM) vascular endothelial cells serve a critical role in regulating and supporting the function and regenerative capacity of hematopoietic stem and progenitor cells. Moreover, the BM vascular network has been shown to couple angiogenesis and osteogenesis. Despite its importance in several physiological and pathological conditions, the understanding of the underlying mechanisms of vascular regeneration in the BM is extremely limited. Recently, a cell population with vascular stem cell potential was identified in the liver tissue, termed vascular endothelial stem cells (VESCs). VESCs were characterized by the expression of CD157/BST1. Here, we employed an intra-femoral mechanical injury to model vascular endothelial regeneration in vivo and show that vasculogenesis possesses a crucial role in the regeneration process of the adult mouse BM vasculature. Combining lineage tracing approaches and functional assays we demonstrate that VegfR3+CD157+ BMECs exhibit progenitor-like properties and drive BM vascular regeneration in response to mechanical injury

Inés Ortiz-de-Solórzano *et Al*

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POSTER 20_ Title: Human skin 3D epithelioids as a model to study wound healing and tissue repair

Three-dimensional (3D) epithelioids are a recently developed (Fernandez-Antoran, et al., 2019; Ferreira, Pradilla-Dieste, Valverde-Lopez et al., 2026; Herms, Fernandez-Antoran, Alcolea et al., 2024) continuous long-term primary culture system that can be maintained without passaging for many months while preserving key features of epithelial architecture, homeostasis and clonal organisation. By sustaining continuous proliferation, differentiation and tissue turnover, epithelioids provide a tractable platform for studying dynamic epithelial processes over extended periods while minimising the perturbations associated with serial passaging.

Here, we have established human skin epithelioids from patient-derived foreskin explants to model reepithelization and wound closure. Following expansion into mature human epithelioid cultures, a wound was inflicted using a biopsy punch and repair was monitored longitudinally. Human skin epithelioids closed wounds within 7 days while retaining tissue architecture and cellular complexity, demonstrating that this system captures key features of epithelial repair in a human, tissue-like context.

Building on these findings, the model is being developed as an experimental platform to dissect molecular mechanisms governing wound resolution and inflammation. In particular, epithelioids will enable functional testing of ligands acting through G protein-coupled receptors (GPCRs), including pro-resolving signalling pathways, and assessment of their effects on epithelial migration, proliferation, differentiation and restoration of tissue integrity. Preliminary results suggest that the presence of specialized pro-resolving mediators (SPMs) at nanomolar concentrations may enhance wound closure capacity.

Our results establish human skin epithelioids as a physiologically relevant and scalable in vitro model for studying wound healing, inflammation resolution and candidate therapeutic interventions to increase tissue repair in patients.

Mireia Puig Tolosa *et Al*

Francesc Cebrià lab; Departament de Genètica, Microbiologia i Estadística

POSTER 21_ Title: Functional analysis of the transcription factor Smed-zfa3 in planarian regeneration and homeòstasis

Freshwater planarians are an exceptional model for studying whole-body regeneration due to their pluripotent stem cells, the neoblasts. This study focuses on the functional characterization of Smed-zfa3, a C2H2 zinc finger transcription factor identified as a potential downstream effector of the transcriptional co-activator cbp-3. Single-cell transcriptomic datasets and in situ hybridisation expression analyses revealed that Smed-zfa3 is enriched in the anterior region of the planarian and is predominantly expressed in neural lineages, particularly within neural progenitors.

Functional analysis using RNAi-mediated silencing demonstrated that Smed-zfa3 is essential for proper neuronal differentiation and tissue maintenance during both regeneration and homeostasis. In regenerating animals, Smed-zfa3(RNAi) led to significantly smaller eyes and blastemas, alongside a severe reduction in multiple neuronal populations, including cholinergic, dopaminergic, and GABAergic neurons. Furthermore, silenced animals developed a progressive late-onset phenotype characterized by body elongation, impaired locomotion, and a severe disruption of epidermal cilia. While the body-wall musculature remained largely unaffected, defects were also observed in non-neuronal lineages such as eye progenitors and basal gut cells. Interestingly, the role of Smed-zfa3 in neoblast proliferation appeared context-dependent, showing a reduction at late stages of regeneration but an increase during late homeostasis. In conclusion, these findings identify zfa3 as a key regulator that coordinates nervous system integrity with normal locomotion and body morphology in Schmidtea mediterranea

Taqwa Qasem *et Al*

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POSTER 22_ Modeling Hypertrophic Cardiomyopathy in 2D & in 3D Engineered System Utilizing iPSC-CM Edited by CRISPR-Cas9

Hypertrophic cardiomyopathy (HCM), the most common inherited cardiac disease, is frequently caused by pathogenic variants in sarcomeric genes, particularly MYBPC3 and MYH7. Here, we model HCM using CRISPR/Cas9-engineered induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) carrying clinically relevant mutations: P955fs and R502W in MYBPC3, and R403Q and R1712Q in MYH7. Edited iPSC lines were precisely genome-edited and differentiated into cardiomyocytes to assess mutation-specific effects on cardiac structure and function. Phenotypic characterization included assessment of sarcomere organization and length, cellular hypertrophy, contractility, calcium handling, and mitochondrial assessment (respiration, acidification rates, and overall mitochondrial function). By comparing distinct genotypes within an isogenic background, this platform enables dissection of divergent disease mechanisms and genotype–phenotype relationships. We further evaluate the therapeutic potential of cardiac myosin inhibitors, including Mavacamten and Aficamten, to assess their capacity to rescue disease-associated cellular phenotypes. These findings advance our understanding of HCM pathogenesis and establish a robust human-cell model for therapeutic development and precision medicine.

Marcel Schilling *et Al*

Regenerative Medicine Program, Bellvitge Institute for Biomedical Research (IDIBELL), Barcelona, Spain.

POSTER 23_ From Projects to Patterns: Reusable Workflows for Disease Modeling through Comparative Multi-Omics Analysis

Biological research programs investigate related processes through different experimental designs, data modalities, and analytical strategies. Despite these differences, they often share computational challenges, from quantifying molecular features to interpreting gene-level results at the pathway level. Independent pipelines can duplicate effort and limit opportunities to share improvements across projects.

In hematopoietic stem cell biology and disease modeling, we are developing a modular approach to bioinformatics analysis. Recurring analytical tasks are organized into reusable workflow components that can be combined and adapted to individual needs. Consistent implementation conventions and software environments support reproducibility, while interchangeable components enable methodological comparisons. This approach is particularly relevant to regenerative medicine, where disease models generated using patient-derived or genetically engineered stem cells can provide complementary systems to investigate disease mechanisms and compare molecular changes across experimental conditions.

We illustrate this approach using complementary RNA-sequencing studies: a CRISPR interference screen with multiple contrasts, a bulk RNA-seq study complicated by batch effects, and a complementary single-cell RNA-seq dataset. Analytical components can be repurposed for different questions, such as adapting a pathway-enrichment heatmap from comparing biological contrasts to comparing alternative batch-correction strategies. Modular workflows also allow analytical improvements to propagate across projects and alternative methods to be evaluated without rebuilding entire pipelines.

Connecting project-specific analyses through shared components can improve consistency without sacrificing flexibility, turning recurring computational challenges into shared resources and supporting more systematic interpretation of multi-omics data.

Aurora Scrivo *et Al*

Bellvitge University Hospital (IDIBELL)

POSTER 24_ LRRK2-G2019S shifts microglial cargo handling from lysosomal degradation toward extracellular secretion

Parkinson's disease (PD) is a neurodegenerative disorder characterized by dopaminergic neuron loss. Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common genetic cause of familial PD, with G2019S being a prevalent pathogenic variant linked to altered intracellular trafficking and lysosomal function. Microglia, the brain's resident immune cells, regulate neuroinflammation and maintain homeostasis by clearing neuronal debris through phagocytosis and lysosomal degradation. However, how LRRK2-G2019S affects the fate of phagocytosed neuronal material remains unclear. We hypothesized that LRRK2-G2019S impairs microglial degradation and redirects phagocytosed neuronal material toward extracellular secretion. We investigated induced pluripotent stem cell (iPSC)-derived microglia from two LRRK2-G2019S patient lines and their isogenic controls. Mutant microglia efficiently internalized synaptosomes and neuromelanin but showed impaired cargo degradation, reduced lysosomal acidity, and altered autophagy pathways . These defects were accompanied by increased endosomal abundance and redistribution of CD63-positive compartments toward the plasma membrane. Rab35, a LRRK2 substrate involved in plasma membrane docking, was upregulated and showed increased association with late endosomes. Under lysosomal inhibition, mutant microglia also showed enhanced extracellular release of internalized synaptosomes. These findings suggest that LRRK2-G2019S disrupts microglial endolysosomal homeostasis, shifting cargo handling from degradation toward extracellular disposal. This response may contribute to extracellular neuronal material accumulation and neuroinflammation in PD. Our study identifies microglial cargo fate as a disease-relevant pathway and the endolysosomal system as a potential therapeutic target

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POSTER 25_Macrophage Epithelial Crosstalk regulates intestinal homeostasis and drives aging

Aging is associated with a decline in intestinal regenerative capacity, resulting in structural and functional impairments that contribute to malnutrition and increased healthcare costs. Whether this decline originates in epithelial stem cells or in their supporting niche remains unresolved. We previously demonstrated that macrophages engage in crosstalk with the intestinal epithelium, being essential for homeostasis and regeneration after injury. We hypothesized that this cross-talk is impaired with age.

Using mouse models, intestinal organoids, and single cell transcriptomics, we discover that the aging phenotype is primarily driven by the niche. While scRNA seq of young and aged intestinal tissues reveals extensive transcriptomic alterations, these differences disappear in organoids derived from the same tissues and cultured in an identical niche. Moreover, aged intestinal organoids co cultured with young macrophages adopt the same fetal-like phenotype as young organoids exposed to young macrophages, demonstrating that aged epithelial cells retain the capacity to acquire again a youthful state once removed from the aged microenvironment.

In addition, scRNA seq of intestinal epithelial cells and macrophages revealed a previously unrecognized population of inflammatory macrophages that appears exclusively in aged mice. We believe that this cluster contains key regulators of the aging process and may hold the potential to rejuvenate the intestine.

Cristina Torres Torres *et Al*

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POSTER 26_ A Nano-theranostic tool to prevent mechanosensing-dependent pro-fibrotic evolution and failure of the heart

Heart failure (HF) is characterized by inflammation and progressive fibrosis, which reduce the pumping efficiency of the heart. Inflammatory cells (ICs) and cardiac fibroblasts (CFs) drive myocardial fibrosis through the biphasic secretion of pro/anti-inflammatory cytokines and differentiation into myofibroblasts, respectively. This leads to abundant collagen deposition, increased extracellular matrix (ECM) stiffness, and reduced contractility. The mechanosensitive YAP/TAZ pathway is a key driver of this fibrotic response, making it a promising therapeutic target. Crucially, while YAP/TAZ activation in cardiomyocytes (CMs) promotes proliferation, its activation in CFs drives fibrosis. Therefore, selectively targeting CFs over CMs is essential to mitigate fibrosis while preserving CM function. However, achieving cell-specific delivery within the myocardium remains a challenge. This study utilizes human induced pluripotent stem cell (hiPSC) models to evaluate a novel nanomedicine strategy using hyaluronic acid (HA)-coated nanoparticles (NPs) designed to selectively target the CD44 receptor in CFs. We characterized the internalization kinetics and specific endocytic pathways of these HA-decorated NPs in hiPSC-derived CFs (hiPSC-CFs) versus CMs (hiPSC-CMs). Our results demonstrated that HA-decorated NPs exhibit accelerated internalization kinetics and a significantly higher endocytic capacity in hiPSC-CFs compared to hiPSC-CMs, establishing a clear window for cell-selective targeting. Furthermore, the capacity of this targeted platform to deliver a YAP inhibitor and selectively disrupt mechanotransduction pathways in hiPSC-CFs versus hiPSC-CMs is currently being evaluated. In conclusion, HA-coated NPs successfully exploit CD44 expression for preferential uptake in hiPSC-CFs. This cell-specific kinetic advantage highlights the potential of this nanomedicine platform as a precise strategy to mitigate cardiac fibrosis.

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POSTER 27_ Clonal Dynamics of the Uterine Epithelium and Early Events in Mismatch Repair Deficiency

Lynch Syndrome is a hereditary cancer syndrome associated with an increased risk of endometrial carcinoma, yet early mechanisms underlying neoplastic transformation in the endometrium remain poorly understood. My study focuses on elucidating how stem cell fitness and early mutational events contribute to endometrial carcinoma initiation in the context of mismatch repair deficiency (MMRd), particularly MSH2 loss.

In this study, we perform fluorescent lineage tracing and 3D tissue imaging in mouse models, to examine the clonal dynamics and persistence of MMRd stem cell-derived clones in the endometrium over time. Spatial transcriptomics will help us identify possible early transcriptional programs and potential fitness advantages mediated by MMR deficiency.

To assess the conservation of these mechanisms in humans, we have generated patient-derived MMRd endometrial organoids to evaluate the impact of candidate early drivers on proliferation and apoptosis. We further labeled these organoids to track their fate over time in a clonal competition assay using self-sustained long-term 3D culture.

In conclusion, this work aims to uncover mechanisms by which MMR-deficient clones expand and initiate malignancy in Lynch Syndrome, and to propose novel biomarker-based surveillance strategies for personalized prevention of endometrial cancer.