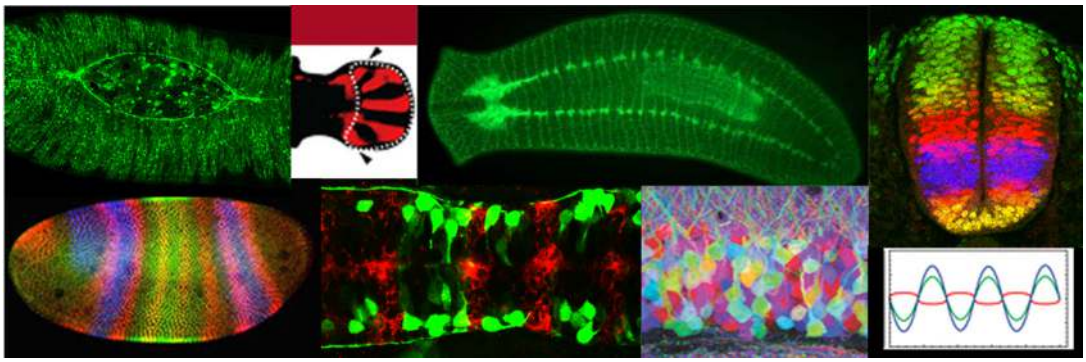

XXIX DEVELOPMENTAL BIOLOGY MEETING

Date: November 24th 2017

Location: Sala Prat de la Riba, Institut d'Estudis Catalans,
C/ Carme 47, Barcelona

Organized by the Section of Developmental Biology of the SCB

Coordinator:
Francesc Cebrià (UB)

Collaborators:
Teresa Adell (UB)
Berta Alsina (UPF)

Secretariat of the SCB:
Mariàngels Gallego
Maite Sánchez

Sponsored by:

Institut d'Estudis Catalans

Societat Catalana de BIOLOGIA

XIX JORNADA DE BIOLOGIA DEL DESENVOLUPAMENT
SOCIETAT CATALANA DE BIOLOGIA

Friday November 24th 2017

8:30-9.00 Arrival and Registration at Sala Prat de la Riba
9:00 Welcome by the Coordinator of the Section of Developmental Biology

9.10-10.00 **Invited speaker: Cristina Pujades (Universitat Pompeu Fabra)**
"Decoding the hindbrain boundaries: from the genomic landscape to the cellular function"

Selected talks
10.00-10.15 Sheila Cárcel "*Smed-cbp* regulates neoblast differentiation during planarian regeneration"
10.15-10.30 Maria Rosselló "Cross-talk between mitochondrial activity and the Hippo pathway in planarians"
10.30-10.45 Elena Vizcaya "The regulome of *Drosophila* regeneration"
10.45-11.15 Coffee break

Selected talks
11.15-11.30 Alejandra Fernández "Molecular mechanisms regulating wiring specificity"
11.30-11.45 Laura Taberner "Neurovascular interaction in the vertebrate inner ear"
11.45-12.00 Josefa Cruz "EGF signaling pathway regulates ecdysone biosynthesis"
12.00-12.15 Silvia Chafino "A size-assessment checkpoint that regulates metamorphosis in *Tribolium castaneum*"
12.15-13.05 **Invited speaker: James Sharpe (EMBL-Barcelona)**
"Dynamic computer modeling to span the scales: from molecular circuits to organogenesis"
13.15-14.45 Lunch

Selected talks
14.45-15.00 Aina Pi-Roig "*tbx5a* role in left/right asymmetry in zebrafish"
15.00-15.15 Giovanni Dalmasso "Four-dimensional growing mouse limb bud: reconstruction and analysis"
15.15-15.30 Carlos Herrera "A promising example of deep lincRNA conservation in *B. lanceolatum*"
15.30-15.45 Miquel Marín-Riera "Evo-devo of epithelial mesenchymal organs. Modelling morphogenesis and tissue mechanics at the interface between epithelium and mesenchyme"

15.45-16.15 Present your Poster

16.15-17.45 Coffee break and Poster session

17.45-18.40 **Invited speaker: Marta Llimargas (Institut de Biologia Molecular de Barcelona, CSIC)**
"Mechanisms of morphogenesis of branched tubular structures: the case of the respiratory system of *Drosophila*"

18.40 Concluding remarks and awards

Use the hashtag #DevBioSCB2017 @ Facebook and Twitter

INVITED TALKS

Cristina Pujades (ICREA Academia, Universitat Pompeu Fabra)

Decoding the hindbrain boundaries: from the genomic landscape to the celular function

The hindbrain is subdivided into seven segments called rhombomeres. At the interface between rhombomeres arises a specialized cell population displaying specific features, the rhombomere boundary cell population (BCP), which serves to distinct functions as development proceeds. First, when morphological segments arise boundary cells work as an elastic mesh, preventing cell intermingling between adjacent compartments. We have previously shown that, in zebrafish, this is due to the enrichment of actomyosin cable-like structures in their apical side, whose formation requires Eph/Ephrin signaling and downstream small GTPase effectors. During neurogenesis, hindbrain boundaries behave as a node for signaling pathways instructing the differentiation and organization of neurons in the neighboring rhombomeres. Later, hindbrain boundaries provide proliferating progenitors and differentiating neurons to the hindbrain. Therefore, a fundamental question is how these cells coordinately unfold their distinct functional properties over the entire program of hindbrain morphogenesis. I will discuss how we have identified the regulatory modules underlying the specific activation of morphogenetic genes in the boundary domain, identifying hindbrain boundaries-specific *cis*-regulatory elements. In addition, we have explored the contribution of the BCP to hindbrain cell diversity by cell lineage studies and addressed the potential role of Yap/Taz-TEAD activity in maintaining neuronal progenitor capacity within these territories.

James Sharpe (EMBL-Barcelona)

Dynamic computer modeling to span the scales: from molecular circuits to organogensis

The predominant emphasis of genomics, bioinformatics and computational biology is at the molecular scale, however many of the things we wish to understand occur at the macroscopic scale of organs and organisms: the development of a phenotype, the spread of a cancer, the regeneration of an organ. At the molecular scale, regulation of genes and proteins creates complex networks, which control cell activities (division, migration, cell fate decisions, differentiation, and many others), with both an intracellular part (circuits of transcription factors) and an extracellular part (secreted ligands which move between cells allowing cell-cell communication, such as FGFs, WNTs, etc). The coordination of thousands of cells by this extended molecular network, leads to large-scale morphogenesis at the scale of tissues and organs. However, these large-scale tissue movements also feedback to the molecular scale: the movement of tissue regions relative to each other causes cells to receive dynamically changing concentrations of signaling molecules, and this in turn changes the activation or repression of genes and proteins.

A full understanding of this large-scale feedback between genes, cells and tissues will require multi-scale computer modeling, and we have chosen vertebrate limb development as a model system to explore this problem. Crucially, the data on gene expression and tissue movements should be both dynamic and spatial. Traditional high-throughput "omics" technologies do not preserve spatial information, and we therefore develop novel 3D imaging technologies (OPT and SPIM) to generate geometric and spatial data for the models. I will present results of this interdisciplinary modeling approach, which is gradually allowing us to tackle this complex problem.

Marta Llimargas (Institut de Biologia Molecular de Barcelona-CSIC)

Mechanisms of morphogenesis of branched tubular structures: the case of the respiratory system of *Drosophila*

One of the main goals of development biology is to understand the genetic, cellular and molecular basis of organogenesis and morphogenesis. The branched tubular structure is the most common structural design for organ formation found in nature. Many essential organs present in most organisms, such as the lungs, kidneys or vascular system, consist of complex branched tubular structures that develop basic functions such as the transport of gases and liquids. Available bibliographic data currently indicate that the cellular, genetic and molecular mechanisms of tubulogenesis (morphogenesis of branched tubular structures) have been highly conserved throughout evolution. The respiratory system of Drosophila melanogaster, the trachea, consists of a network of branched epithelial tubes that emerges as an ideal and amenable model system for the study of tubulogenesis. The aim in our lab is to analyse the cellular mechanisms that underlie tracheal morphogenesis and to understand how these cellular mechanisms are genetically controlled at the molecular level. We ask how these genetically controlled changes in morphology and behaviour at single cell resolution contribute to the formation of tissues and organs. In addition we ask how the epithelial features of tracheal cells are remodelled during the dynamic process of tracheal morphogenesis and how they contribute to specific steps of tracheal formation. In this talk I will analyze some of the mechanisms of tracheal morphogenesis we investigate in the lab and discuss how they have contributed to widen our knowledge about the formation of organisms.

SELECTED TALKS

ST1

Smed-cbp regulates neoblast differentiation during planarian regeneration

Sheila Cárcel[1], Susanna Fraguas[1], Thileepan Sekaran[2], Kerstin Bartscherer[2] and Francesc Cebrià[1]

[1]Departament de Genètica, Microbiologia i Estadística, Universitat de Barcelona
[2]Max Planck Institute for Molecular Biomedicine, Münster, Germany

Planarians have astonishing regenerative abilities, including whole-body regeneration from tiny pieces, thanks to neoblast (adult pluripotent stem cells), which are responsible for blastema formation after amputation. However, the molecular mechanisms regulating neoblast differentiation into multiple specific lineages are poorly understood. Previous studies have shown the role of the epidermal growth factor receptor (EGFR) signaling pathway in the differentiation of the progenitors of the digestive lineage, as well as in neuronal differentiation. More recently, *egr*-4, a transcription factor of the family of the "early growth response", has been identified as a "downstream" gene of the EGFR pathway. The silencing of *egr-4* results in the inhibition of regeneration together with the incapability of differentiating proper brain primordia. In order to search for putative targets of *egr-4,* RNAseq experiments have been carried out. These analyses have lead to the identification of *Smed-cbp*, a homologue of the p300/CBP (CREB-binding protein) conserved gene that functions as transcriptional co-activator and histone acetyl transferase. In other organisms, CBP plays an important role in wide range of cellular processes, including cell proliferation and differentiation, but the cellular and molecular mechanisms underlying CBP function, is still not clear. Here, we show that silencing of the planarian *Smed-cbp* by RNA interference (RNAi) results in proper blastema formation. However, over time blastemas remain unpigmented and no sign of eye regeneration is observed. In fact, analyses with molecular markers for different cell types indicate that cell differentiation is largely blocked, suggesting that *Smed-cbp* could have a function in regulating overall neoblast differentiation.

ST2

Cross-talk between mitochondrial activity and the Hippo pathway in planarians

Maria Rosselló, Nídia da Sousa, Emili Saló and Teresa Adell

Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Spain

The Hippo pathway is a master regulatory network that regulates cell proliferation, cell death and cell differentiation in response to the environment. Its deregulation throughout development and in adult organisms leads to the unbalance of these processes and to the establishment of a variety of diseases including neurodegeneration and cancer. Its targeting appears as a powerful medical tool to improve regeneration and to prevent tumoral transformation. However, its precise molecular out and inputs remain poorly understood. With the aim to further understand the role of Hippo in adult animals, we studied the result of inhibiting *hippo* in planarians, flatworms that continuously change their size according to nutrients, thanks to the presence of a unique population of adult pluripotent stem cells. Our results showed that inhibition of *hippo* in planarians leads to overgrowths that are caused by the inability of *hippo* knockdown cells to maintain the differentiated fate. Interestingly, the transcriptomic analysis of those *hippo* knockdown animals revealed that changes in the mitochondrial activity could be directly linked to the formation of the overgrowths. The RNAi inhibition of those genes with mitochondrial function caused a similar phenotype to the one observed after *hippo* inhibition, which is also deregulating apoptosis, proliferation and stem cell maintenance. These evidences support a cross-talk between mitochondrial activity and the Hippo pathway in planarians, which is essential in controlling cell fate and tissue homeostasis in planarians.

ST3

The regulome of *Drosophila* regeneration

Elena Vizcaya[1], Cecilia C. Klein[2], Florenci Serras[1], Rakesh Mishra[3], Roderic Guigó[2] and Montserrat Corominas[1]

[1]Departament de Genètica, Microbiologia i Estadística, Facultat de Biologia and Institut de Biomedicina (IBUB), Universitat de Barcelona. Barcelona, Catalonia, Spain
[2]Centre for Genomic Regulation (CRG), Universitat Pompeu Fabra, Barcelona, Catalonia, Spain
[3]The Centre for Cellular and Molecular Biology (CCMB), Hyderabad, India

The ability to regenerate varies greatly not only between species but also between tissues and organs or developmental stages of the same species. Differential activation of the genome, determined by a complex interplay of regulatory elements functioning at the level of chromatin, must be the initial mechanism behind these different regenerative capabilities. Resetting gene expression patterns during injury responses is, thus, shaped by the coordinated action of genomic regions that integrate the activity of multiple sequence specific DNA binding proteins. *Drosophila* imaginal discs, which show a high regenerative capacity after genetically induced cell death, are a great model to interrogate chromatin function trough the regeneration process. Using genome- wide approaches (RNA-seq and ATAC-seq) at different tissue time points after injury we have identified the regulatory elements and the expression profile dynamics governing the process. Our findings point to a global co-regulation of gene expression and provide evidence for a regeneration program driven by different types of Damage Responsive Regulatory Elements (DRRE). Among them, novel-DRRE are found acting exclusively in the damaged tissue, and cooperating with DRRE co-opted from other tissues and developmental stages. Altogether, our results decipher the regulome of regeneration and suggest the existence of a specific toolkit to drive the regenerative capacity.

ST4

Molecular mechanisms regulating wiring specificity

Alejandra Fernández Pineda, Martí Monge Asensio and Marta Morey

Deparment of Genetics, Microbiology and Statistics, Faculty of Biology, and Institute of Biomedicine of the University of Barcelona (IBUB)

A fundamental requirement in the assembly of neural circuits is that neurons establish synaptic connections with their appropriate partners. In many systems, this involves extension into a particular synaptic layer, and selection of the appropriate partner among all the cells in the layer. Virtually nothing is known about the mechanisms governing the establishment of specific connections in any system. Our hypothesis is that the molecular differences that exist between neuronal subtypes, with similar developmental origin and function, contribute to their distinct connectivity. We study the differential layer selection of the closely related R7 and R8 photoreceptors. Each eye contains 750 R7 and 750 R8 cells, and the entire population of each subtype proceeds synchronously to their respective final synaptic layer during pupal development. Taking advantage of such precise coordination, we have profiled the R7 and R8 transcriptomes right before this final extension. Our bioinformatic analysis has identified differentially expressed genes between the R7 and the R8. We have focused on 229 R8 enriched genes and performed an RNAi screen. Out of 175 genes analyzed we have identified 43 candidate genes showing layer selection defects. We are currently confirming our findings using mutant alleles. One of the validated genes is *espinas (esn)*. This cytoplasmic LIM domain protein has been shown to physically interact with the atypical cadherin Flamingo (Fmi) to promote self-avoidance in dendritic neurons. Given that Fmi plays a role in R8 layer selection we are addressing whether Esn also works in concert with Fmi in this context. We expect that characterization of *esn* and other identified genes contribute to the understanding of the molecular mechanisms regulating R7 and R8 differential layer selection.

ST5

Neurovascular Interaction in the Vertebrate Inner Ear

Laura Taberner and Berta Alsina

Laboratory of Developmental Biology, Faculty of Health and Life Sciences, Universitat Pompeu Fabra-PRBB, Dr. Aiguader 88, 08003 Barcelona

The Statoacoustic ganglion (SAG) of the inner ear is composed by bipolar afferent neurons that transmit acoustic and vestibular information to their corresponding nuclei in the hindbrain. Until now, efforts have focused on the signals produced by the inner ear and the SAG itself to regulate SAG´s development [1-3]. However, the influence of the vascular system surrounding the inner ear in neuronal development has not been studied. These two systems are found in close proximity in the inner ear, besides, there is a growing evidence of vessels to neurons signalling phenomenon in other systems' development [4-6]. Our working hypothesis is that signals for the neuronal growth, differentiation, proliferation and migration could come from the adjacent vascular network. First, we have used different transgenic lines reporting the expression of markers for neurons (Tg[neurog1:dsRed] and Tg[Neurod:GFP]) and vessels (Tg[Kdrl:ras-mCherry] and Tg[Kdrl:GFP]) to generate a precise 3D anatomical map of the neurovascular system of the inner ear at various stages. Secondly, when comparing the size of progenitors and differentiated pools in wild-type and avascular (cloche mutant) embryos we have found an increase in cell number of 106,27% in the transit amplifying progenitors pool, while there is a statistically significant reduction of 40% in the number of post-mitotic differentiated neurons, at 72hpf. Together with a role of vasculature in SAG maturation, defects in axonal patterning to the sensory patches are also present. In conclusion, our results highlight for the first time the role of the vascular system in sensory neural differentiation and axon guidance in the otic system.

ST6

EGF Signaling pathway regulates ecdysone biosynthesis

Josefa Cruz, Silvia Chafino-Aixa, Elena Casacuberta, David Martín and Xavier Franch-Marro

Institute of Evolutionary Biology (IBE; CSIC-Universitat Pompeu Fabra), Barcelona (Spain)

During metamorphosis, insects undergo dramatic morphological and physiological changes to reach adulthood. The processes involved in this metamorphic reorganization are under the coordination of the steroid hormone ecdysone. Given the relevance of this hormone, the control of ecdysone synthesis during development is finely regulated by a number of circulating factors such as the prothoracicotropic hormone and Insulins. Here we investigate the role of the Epidermal Growth Factor (EGF) signaling pathway in ecdysone biosynthesis using *Drosophila* and *Tribolium* as model organisms. In *Drosophila,* EGF Receptor (EFGR) is expressed in the PG and activated by the ligands *spitz (spz)* and *vein (vn)*, which are synthesized from the *corpora allata* and the *corpora cardiaca*, respectively. In addition, depletion of either *egfr* or *pointed*, a transcription factor downstream of EGFR, specifically in the PG blocks development at the last larval stage, thus impairing pupariation. This phenotype is due to a deficit in ecdysone synthesis as inactivation of EGFR signaling abolishes the expression of the Halloween genes an effect that can be rescued by exogenous ecdysone administration. On the contrary, over-activation of the pathway by overexpression of either the ligand *spz* or a constitutively activated form of EGFR induces premature pupariation. Interestingly, this effect is evolutionary conserved as depletion of Tc-*egfr* or both ligands *Tc-vn* and *Tc-spz,* in the penultimate larva stage impairs pupa formation in the coleopteran *Tribolium*. Altogether, these results strongly suggest that EGF signaling controls ecdysone biosynthesis in insects by activation of the Halloween genes expression trough the transcription factor Pnt.

ST7

A size-assessment checkpoint that regulates metamorphosis in *Tribolium castaneum*

Silvia Chafino, Enric Ureña, Elena Casacuberta, Xavier Franch-Marro and David Martin

Institute of Evolutionary Biology (CSIC-Universitat Pompeu Fabra), Passeig Marítim de la Barceloneta 37-49, 08003 Barcelona, Spain

Holometabolous insects grow during successive juvenile stages to reach an appropriate species-specific size before undergoing metamorphosis. As larvae progress through juvenile development, a critical size-assessment checkpoint called *Threshold Size* (TS) must be surpassed to ensure that enough reserves are attained before initiating the metamorphic process. Despite the relevance of this checkpoint, however, the molecular mechanism underlying it is not fully understood. Here, by using the holometabolous insect *Tribolium castaneum*, we show that TS is attained at the onset of the last larval stage, and triggers critical changes in the expression of three key metamorphic transcription factor genes: *(i) Krüppel-homolog 1* (*Kr-h1*), a JH-dependent factor that prevents metamorphosis; *(ii)* the pupal-specifier *Broad-complex* (*Br-C*); and *(iii) E93*, which we have recently identified as a factor promoting adult differentiation. We show that reaching the TS triggers the critical down-regulation of *Kr-h1*, which, in turn, results in the up-regulation of *E93* and *Br-C*. Finally, we determine the minimal level of *E93* expression required to promote the exit of larval development and the onset of metamorphosis. In summary, our findings indicate that larvae need to reach the TS checkpoint, which is associated with the critical up-regulation of *E93,* to initiate metamorphosis.

ST8

tbx5a role in left/right asymmetry in zebrafish

Aina Pi-Roig[1], Carolina Minguillón[2] and Jordi Garcia-Fernàndez[1]

[1]University of Barcelona, Biology Faculty: Genetics, Microbiology and Statistics Dpt
[2]Pasqual Maragall Foundation

Tbx5 is a transcription factor expressed in the developing heart, eyes and anterior appendages. Mutations in human TBX5 cause Holt-Oram syndrome, a condition characterized by heart and upper limb malformations. In our lab, we identified a novel *tbx5* gene in zebrafish (*tbx5b*) that is co-expressed with its paralogue (*tbx5a*). *tbx5* paralogues downregulation in zebrafish revealed that *tbx5* genes have essential roles in the establishment of cardiac laterality, dorsoventral retina axis organization and pectoral fin development. Our data show that distinct relationships between *tbx5* paralogues are required in a tissue-specific manner to ensure the proper morphogenesis of the three organs in which they are expressed. Additionally, we uncover a novel role for *tbx5* in the establishment of heart asymmetry in zebrafish embryos. Further analysis of *tbx5a* role during left-right (LR) asymmetry establishment show that the expression of left-side markers expressed in the lateral plate mesoderm (LPM) is also randomized. We also detected a randomization of *lefty1* expression in the dorsal diencephalon in *tbx5a* morphant embryos and that the display of the endodermal structures of the liver, pancreas and gut is also affected after *tbx5a* morpholino knock-down. To our surprise when we specifically knocked-down *tbx5a* in the DFCs/KV (dorsal forerunner cells / Kupffer's vesicle) lineage, responsible for LR asymmetry generation, cardiac jogging was randomized. Interestingly, we observed a stronger phenotype with this DFC-targeted injection. Furthermore, we detected by ISH and RT-PCR early *tbx5a* expression during gastrulation. In addition, we observed a reduction on BMP signalling levels in DFC-targeted morphants and one putative binding site for *tbx5* binding site in the *bmp4* regulatory region after an in silico analysis, pointing towards a regulatory mechanism that would at least partially rely on BMP signalling as a downstream effector.

ST9

Four-dimensional growing mouse limb bud: reconstruction and analysis

Giovanni Dalmasso[1,2], Marco Musy[1,2] and James Sharpe[1,2,3]

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[2]Universitat Pompeu Fabra (UPF)
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The use of computer modeling to facilitate the understanding in organogenesis has slowly but constantly increased in recent years. All these models, however, need to rely on empirical quantitative data in order to faithfully predict biological results. The availability of 3D data in the case of the limb bud is extensive and detailed, but it provides only a characterization of development at discrete moments in time, through single snapshots. In order to provide a dynamic characterization in space and time, we present a comprehensive four-dimensional (4D) reconstruction of growing mouse limb buds. Using the embryonic Mouse Ontogenetic Staging System (eMOSS), we are able to stage embryos from optical projection tomography (OPT) of their lib buds. Subsequently, by aligning and averaging over several lib bud shapes for each time point and morphing over time, we are able to reconstruct the development of a whole limb. Specifically, we are recreating the growing process starting from E10 (i.e. 10 days after conception) when the limb bud is just a small bump of tissue and finishing at E12.5 when the limb bud already shows a distinctive “paddle” shape. Our reconstruction also provides a precise characterization of the dynamically changing angle of the limb bud with respect to the flank of the embryo. The spatial and temporal reproduction and characterization for the first time of the dynamic growth of a limb bud provides the framework towards new insight in organogenesis. Additionally, it represents the definitive reference for any computational models of limb development.

ST10

A promising example of deep lincRNA conservation in *B. lanceolatum*

Carlos Herrera[1], Beatriz Albuixech-Crespo[1], Ariadna Rossell-Espier[1], Demian Burguera[1], Manuel Irimia[2] and Jordi Garcia-Fernàndez[1]

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Among the numerous classes of RNAs, long non-coding RNAs (lncRNAs) are similar in terms of expression and gene structure to the mRNAs but lack the potential to encode proteins. Over the last years, lncRNAs have been proven to play important roles in gene regulation, and to be involved in many key developmental processes. However, the low sequence conservation of lncRNAs has hindered the identification of deep orthologs among distantly related species. Thus, the evolutionary dynamics of lncRNAs have been scarcely studied and few data exist at evolutionary key-nodes of animal evolution. We aim to identify the lncRNA complement in the cephalocordate amphioxus, the best proxy to the key evolutionary node of the origin of chordates and vertebrates. For this, we used RNA-seq data from several adult tissues and developmental stages of *Branchiostoma lanceolatum*. After being processed by a filtering pipeline, around 1700 putative long non-coding transcripts were classified according to their relative position among coding genes into intergenic, antisense, intragenic or overlapping. Using the intergenic portion (lincRNAs) we developed the scripts for finding conserved mycrosinteny between *Branchiostoma lanceolatum* and *Homo sapiens*. We made an attempt to characterize the putatively conserved lincRNAs, and we found at least one of them to be present in almost all the vertebrates analyzed and in amphioxus, making it seemingly the first example of a deeply conserved lncRNA among chordates.

ST11

Evo-devo of epithelial-mesenchymal organs. Modelling morphogenesis and tissue mechanics at the interface between epithelium and mesenchyme

Miquel Marín-Riera

EMBL-Barcelona, C/Dr. Aiguader 88, 08003 Barcelona, Spain

One of the main challenges of evolutionary biology is to understand how morphological variation is originated in populations, and for that it is necessary to understand how morphology arises through development. We are mainly interested in the morphogenesis of the vertebrate organs that arise from the interaction between epithelium and mesenchyme, or epithelial-mesenchymal organs (e.g. tooth, hair, feather, limb, etc.). This group of organs shows great morphological and functional diversification and yet they have a high degree of conservation at the level of gene expression and signalling pathways, which has been extensively studied. However, less is known about the morphogenetic processes (i.e. cell movements and tissue deformations) and mechanical interactions between epithelium and mesenchyme that ultimately lead to organ-specific morphologies. These consist of highly dynamic cell behaviours coordinated at the tissue scale by morphogen gradients, tissue-level mechanical interactions and other spatial cues. We combine computational modelling and experiments to understand the conserved morphogenetic mechanisms that lead to diverse three-dimensional morphologies. We used a cell-based model to explore how differential growth and cell adhesion between epithelium and mesenchyme drive early tooth morphogenesis. We found that the combination of these two processes is enough to explain the complex tissue deformations observed in the early tooth germ. In addition, our model predicted the directionality of mechanical stresses in the tooth tissues, which were later confirmed experimentally. Currently we are working on a cell-based, data-driven model of limb morphogenesis that accounts for early limb bud elongation by means of cell proliferation and convergent extension.

POSTERS

P1

Muscle development and tail elongation in the chordate *Oikopleura dioica*

Alba Almazán-Almazán, Enya Durán, Marcos Plana-Carmona, Alfonso Ferrández-Roldán, Anna Moncusí, Josep Martí-Solans, Ricard Albalat and Cristian Cañestro

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A characteristic feature of vertebrates and cephalochordates is an obvious segmented body plan made of repetitive muscular units that are developed by a complex process of somitogenesis. In urochordates, however, tail muscle consists of an array of muscle cells, but no obvious structural somites are observed. The evolutionary origin of somitogenesis remains unknown, and whether the formation of the array of muscle cells of urochordates shares some of the signalling pathways that underlie somitogenesis remains unclear. To address this issue, our group investigates the mechanisms of development of the tail muscle in *Oikopleura dioica*, a larvacean urochordate species that does not suffer a drastic metamorphosis as ascidians and preserves its tail throughout their entire life. We have performed an exhaustive *in silico* survey to identify several muscular gene markers (e.g. *Act*, *TnnT* and *Myo*), many of which have suffered extensive gene duplications during larvacean evolution. Comprehensive analyses of their expression patterns revealed an unexpected anterior-posterior molecular regionalization that correlated with their cell lineage origin. We have characterized the expression patterns of members of the *Wnt*, *Fgf* and *Notch* signalling pathways as well as myogenic transcription factors such as *Tbx* and *Hairy* to understand muscle development and tail elongation in the absence of *RA*, a signaling pathway that has been lost during *O. dioica* evolution due to the high propensity of this species to lose genes.

P2

Cellular Events leading to otic neuroblast delamination

Aitor Bañón, Laura Fargas and Berta Alsina

Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra-PRBB, Barcelona

The generation of the otic sensory neurons during devleopment is a fascinating process in which distinct events such as neuronal specification, epithelial-mesenchymal transitions (EMT), cell migration and cell proliferation are tighly coordinated at the molecular and cellular level. After the activation of the proneural gene, *neurod*, the otic neuroblasts exit the epithelium by EMT. This process has mostly been studied in neural crest development but the exact sequential events leading to the exit of cells from the neuroepithelium is not well understood. By high spatiotemporal imaging of single cell labelled neuroblast and intracellular proteins in the zebrafish embryo, we have been able to investigate the dynamics of cell shapes during EMT. We have reconstructed in 3D delaminating cells with their membranes labelled and the polarity marker pard3. Our results indicate that first, the cytoplasm and nuclei concentrates basally, then the basal membrane begins blebbing and progressively the apical side contracts into a thin and elongated extension still attached to the apical membrane with pard3. 3D reconstructions suggest that the attachment and pard3 is lost prior to full delamination. Interestingly, we have also observed dynamic filopodia extending between predelaminating neuroblasts and between delaminated neuroblasts, suggesting that could be involved in their delamiantion or migration. Currently, we are investigating the role of these filopodia in signalling the possible localization of FGF5 in neuroblast filopodia.

This work is supported by MINECO BFU2014-53203 to B.A.

P3

Intrauterine growth restriction effects on the hippocampus development and brain neurotransmitter profile in a pig model

Natalia Yeste[1], Daniel Valent[1], Laura Arroyo[1], Consolación García[2], Marta Vázquez[2], Antonio González-Bulnes[2] and Anna Bassols[1]

[1]Departament de Bioquímica i Biologia Molecular, Facultat de Veterinaria, Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), ES
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Intrauterine growth restriction (IUGR) refers to poor growth of a fetus during pregnancy due to several causes like poor maternal nutrition or lack of adequate oxygen supply to the fetus. IUGR is typically asymmetric due to the "brain sparing" effect, by which the brain is protected from the adverse effects of malnutrition to ensure vital functions like respiration, suckling, etc. Nevertheless, this does not warrant the normal development of the brain and the risk exists of neurological and cognitive deficits at short or long term. We have used a porcine model for IUGR to study the effects of IUGR on monoaminergic neurotransmitters (catecholamines and indoleamines) in several brain areas, and to study the hippocampus morphology by using immunohistochemical methods. In our model, porcine fetuses are classified as NBW (normal birth weight) or LBW (low birth weight, consequence of IUGR).
Our results show specific effects in the hippocampus, where an increase in the serotonin (5-HT) pathway is observed only in male LBW fetuses. Neuronal markers were studied by immunohistochemical, allowing to observe a decrease in the number of mature neurons in the CA1 and the gyrus dentatus regions of the hippocampus of LBW fetuses. Furthermore, morphological changes are also observed in LBW hippocampus, like alterations in neuronal morphology, a decrease in the number of dendrites and axons, decreased neuronal connectivity and higher number of immature neurons. These results are consistent with a deleterious effect of IUGR on the brain development in pig fetuses.

P4

Study of gliogenic progenitors within the hindbrain

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The hindbrain is the most posterior embryonic brain vesicle of the Central Nervous System (CNS) and one of the most highly conserved structures in vertebrates. Its derivatives control numerous physiological processes (Aldinger et al., 2009). During embryonic development, it is transiently subdivided in seven bulges called rhombomeres, whose molecular identity prefigures cell specification. Within the hindbrain, neurogenesis is initiated by proneural genes, regionalized over time, and restricted in space (Glez-Quevedo et al 2010). Little is known, however, about how gliogenesis takes place and how these different capacities are allocated. Recent studies in zebrafish show *sox9* is expressed in the center of the rhombomeres, an area devoid of neurogenesis (Esain et al., 2010). Nevertheless, *sox9* appears to play a key role in activating glial specification in mice spinal cord (Stolt et al., 2003) but not in initiating gliogenesis in cerebellum (Vong et al., 2015). These observations suggest gliogenesis may be context dependent rather than a general mechanism in the central nervous system.

We aimed to understand how glial progenitors are specified and regulated within the embryonic hindbrain. We analyzed the spatiotemporal expression of sox9 genes within the hindbrain and showed that their onset of expression is preceded by the onset of neurogenesis. Moreover, our preliminary results show that neurogenic and gliogenic domains are spatially and temporally segregated during cell specification, suggesting that neurons and glial cells originate from different progenitor pools. We are also investigating the role of the Notch pathway during gliogenesis to understand how both populations are established. Coupling these studies with glial cell lineage tracing we hope to determine how gliogenic progenitors behave over time and to shed light on the poorly explored gliogenic process during development.

P5

Uncovering the clonal dynamics of the hindbrain progenitors: the cellular contribution to hindbrain growth

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During embryonic development, a vast diversity of cellular types is generated within the central nervous system (CNS). These neural cells derive from multipotent progenitors, which follow patterning cues before proneural genes specify the distinct neuronal populations. Proneural genes commit neural progenitors to a given fate and initiate neurogenesis by promoting cell cycle exit and activating a downstream cascade of differentiation genes. Neuronal subtype identity is defined by the expression of neuronal homeodomain proteins, which are critical for determining the neurotransmitter phenotype of the mature neuron, as well as its axonal connectivity and circuit assembly. It has been proposed that proneural genes also play a role in specifying the neuronal subtype that the committed progenitors will acquire during differentiation. Our main goal is to **understand how spatiotemporally controlled cell specification and differentiation occur alongside morphogenesis in the construction of the functional hindbrain**, whose neuronal populations regulate a wide range of processes vital for the organism. The orchestrated division of neural progenitors and patterning of lineages leads to the assembly of a well organized hindbrain, where progenitors end up located in the ventricular zone, whereas differentiated neurons move to the mantle zone where they will project their axons out of the neural tube.

We have characterized the spatiotemporal relationship between the different proneural domains and the putative neuronal subtypes arising from them. Preliminary results on loss-of-function experiments suggest context-dependent mechanisms in which cell specification occurs in different proneural domains: some neuronal populations rely in a single proneural gene for fate acquisition, whereas others seem unaffected by the loss of a single proneural gene -where redundant and regulatory relationships between overlapping and neighboring proneural clusters are expected-. To understand the structural divergence, and how this beautifully organized architecture is maintained over extensive cell proliferation and organ morphogenesis, we combined life-monitoring of specific mosaic and clonal lineage tracing, and compare it with specific neuronal progenitor pools. Thus, our findings provide information about how morphogenesis impacts cell allocation, by tracing the lineage of a given progenitor population and assess its mode of growth, proliferative potential and neurogenic capacity while cell specification and differentiation is occurring simultaneously.

This work was funded with BFU2015-67400P (MINECO) to CP. IB is a recipient of a predoctoral FI fellowship (AGAUR, Generalitat de Catalunya). CP is awardee of ICREA Academia (Generalitat de Catalunya).

P6

Dismantling of the FGF-signaling pathway in *Oikopleura dioica*, a retinoic acid evolutionary knockout in chordates

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The Urochordate *Oikopleura dioica* is an emergent model for studies in the field of Evolution and Development -Evo-Devo-. Its extreme genome compaction accompanied by massive gene losses entail *O. dioica* as an "evolutionary knockout" for many genes, even for essential genes that play conserved roles in all chordates such those involved in the Retinoic Acid (RA) pathway. Several studies have demonstrated the antagonistic roles between the FGF and RA pathway during embryo development, for instance to regulate anterior-posterior axial patterning. In this study, we focus on how the FGF signaling pathway has evolved after the loss of the RA pathway in *O. dioica*. To address this problem, we have identified nineteen characteristic genes of the three downstream signaling cascades activated by FGF signaling. Our results reveal that *O. dioica* FGF pathway has suffered an extensive dismantling by loosing six of the nineteen analyzed FGF components. The pathway that has suffered the deepest modification is the Ras/MAPK. Our genomic survey reveals that despite the many gene losses, the FGFR family has been expanded up to three paralogs, whose structure suggests different ligand responses. Expression analysis of three *FGFR* and one *ERK* reveals potential roles of these genes during development of *O. dioica*. Finally, we have demonstrated that the FGFR inhibitor (SU5402) is effective in *O. dioica*, providing the first step to future functional analyses.

P7

Can Heavy Metals impact on the development of *Oikopleura dioica*?

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Heavy metal exposure alters embryo development of different animal species by affecting important physiological process such as meiosis progression, oocyte maturation, morphogenesis and hatching. Human activities are increasing the levels of heavy metals in aquatic environments thereby affecting marine ecosystems. Our objective is to study the effect of heavy metals during the embryo development of the chordate *Oikopleura dioica* (urochordate subphylum, larvacean class) because the ecological key role of larvaceans as the second most abundant group of animals among the mesoplancton in marine trophic networks. Preliminary results indicate that heavy metals affect *O. dioica* development causing embryo malformations and development arrest. In order to understand the genetic mechanisms behind the response of *O. dioica* to metal exposure, we have searched for metallothionein genes (MTs) in this urochordate species. Metallothionein genes encode cysteine-rich, low molecular weight proteins that bind and protect against heavy metals. Our genomic survey have identified two MT genes, one of them being the longest MT so far described, that might responsible for detoxification against heavy metals in polluted waters.

P8

Cabut and D-GADD45 as putative modulators of the JNK pathway in regeneration

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Drosophila imaginal discs are a well established model system to study regeneration, both after physical damage or cell-death induction. Although little is known about the early signals driving the regenerative process, the activation of the Jun N-terminal kinase (JNK) pathway is likely to play a decisive role. Studies on the gene expression profiles of imaginal discs at different time points after cell death reveal several genes showing an expression burst right after damage and returning to normal levels early in the process. We focus on two of these genes, the transcription factor Cabut *(cbt or dTIEG or TGF-b inducible early gene)* and the *Drosophila* Growth arrest and DNA damage-inducible gene 45 (D-GADD45). Cabut is a crucial downstream mediator of the JNK signalling required during wing disc regeneration. D-GADD45 is a stress sensor involved in DNA repair, apoptosis and cell cycle control. Downregulation of D-GADD45 after cell death blocks the activation of the JNK pathway and severely compromises the regeneration process. Our results confirm Cabut and D- GADD45 as putative modulators of the JNK pathway during regeneration.

P9

Clearing tools for mesoscopic imaging

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Generally in science but especially in developmental processes, an image or movie is worth a thousand words. In order to fully understand morphogenesis we need 3D and 4D images of whole specimens, but there is the constraint that most biological samples are opaque to light. To overcome this limitation, a growing list of tissue clearing protocols has been reported over the last years. We have been exploring different methods for chemically clearing mesoscopic samples, investigating the trade-offs between photon scattering, fluorescence preservation, and changes in sample morphological properties. There are three main groups of clearing techniques: the ones based on aqueous solutions, the organic solvent-based methods and the protocols that combine those with embedding of the tissues in polymers. We have seen that CUBIC (aqueous method) clears whole organs like adult mouse brain well and preserves the endogenous fluorescence. On the other side, it is a slow process and the tissue swells as a result. TDE is a water-soluble clearing agent suitable for small volumes (approximately up to 1 mm thickness) which is fast and also preserves fluorescence. Amongst the organic solvent-based methods, BABB is the most popular: it produces high transparency, but inconveniently quenches the endogenous fluorescent proteins. Finally, it has been demonstrated that CLARITY (a polymer-based technique) provides good clearing results, but its methodological complexity might not make it the ideal method for many samples. The combination of the appropiate clearing protocol with one of the two advanced optical imaging techniques developed in the lab, Optical Projection Tomography (OPT) and Selective Plane Ilumination Microscopy (SPIM) gives a range of possibilities to explore developmental issues, such as mapping the 3D distribution of gene expression patterns and cell populations in whole specimens or study the tissue arrangements between several time points. I will give examples of samples cleared using these techniques, and illustrate the parameters to be considered when selecting the appropriate protocol.

P10

ASK1 senses tissue damage by oxidative stress during regeneration

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Apoptotic cells result in a burst of reactive oxygen species (ROS) that can propagate to neighboring cells. These ROS are known to activate JNK and p38 kinases for regenerative growth. In this work we investigate the link between ROS and p38 and JNK signals. The Apoptotic Signal-Regulating Kinase 1 (ASK1), a MAPKKK upstream of JNK and p38, forms a complex that is sensitive to oxidative stress. Our results reveal that Ask1 senses ROS differently in apoptotic cells and living surrounding cells. High levels of ROS are produced in apoptotic cells, which in turn generates high activity of Ask1 that turns on JNK, which is known to enhance apoptosis. Neighboring undamaged cells show low ROS levels, which are beneficial for the regenerating tissue. In these, Ask1 is activated but its activity is attenuated by Pi3K dependent Akt1 phosphorylation, as a survival signal that results in beneficial levels of p38 and JNK. These results point to ROS as a true signaling mechanism for regeneration and compensatory proliferation. Our data reveal a non-autonomously activated ROS sensing mechanism that includes Ask1 and Akt to drive regeneration in the neighboring unstressed cells. We present a molecular mechanism of communication between dying and living cells required for regeneration and compensatory proliferation.

P11

Oikopleura dioica braveheart: a cardiogenic loser, but not a heartless chordate

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Recent increase in genomic data reveals that gene losses are abundant in metazoans. Little is known, however, about how gene loss can impact the evolution of the mechanisms of development. As a case study, we investigate how gene losses affected the cardiogenetic toolkit in the chordate *Oikopleura dioica*. After the first description of the heart in 1903 by Saliensky, our work provides the first modern atlas of its development and describes the cell lineage fate map of all cardiac progenitors up to tailbud stage. Our data reveals that cardiac precursor cells derive from the most anterior muscular cells and migrate from the tail into the trunk, very similar as in ascidians. In *O. dioica*, however, precursor cells finally migrate and fuse to form the heart primordium in the left side of the animal, rather than in the midline as in ascidians. Our exhaustive *in silico* survey for all cardiogenic factors conserved in other chordates reveals important differences in *O. dioica* regarding its early signaling pathways as well as cardiac transcription factors involved in migration, differentiation and cardiogenesis. Thus, our work reveals that despite the highly similar process of early heart development between *O. dioica* and ascidians, the former is a braveheart by pushing its developmental mechanisms to their functional limits, deconstructing its cardiac genetic toolkit with several gene losses, absence of cardiac expression and lack of action of developmental signaling pathways that are fundamental to make a heart in other chordates.

P12

CRISPR/Cas9-mediated Knock-in in zebrafish to uncover the fate and function of the hindbrain boundary cell population

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During early stages of vertebrate development, the hindbrain -the most posterior brain vesicle- is transiently subdivided into seven segments, named rhombomeres. This process of compartmentalization is followed by the specification of a population of cells at the interface between rhombomeres, called boundary cell population (BCP). The BCP plays an important role in restricting cell intermingling between adjacent rhombomeres, and as a source of signalling molecules. However, little is known about the cell fate and behaviour of this cell population. Therefore, a fundamental question is how these cells coordinately unfold their distinct functional properties over the morphogenetic program and to what kind of cells they give rise to. In order to address these questions, we need to be able to specifically trace these cells. For this we use the CRISPR/Cas9 gene edition technology in zebrafish, which is an excellent vertebrate model for studying cellular dynamics and morphogenetic processes using live imaging. We have generated a Gal4 knock-in transgenic line targeting *sgca*, a gene endogenously expressed in the BCP. This Gal4-driver in combination with different UAS-lines provides a highly versatile tool to manipulate gene expression in this domain. We want to address two questions: i) the dynamic behaviour and fate of the BCP, by following its derivatives over time by KAEDE photoconversion; and ii) the functional requirements of this population within the hindbrain, by analysing the impact of genetically ablating these cells [5]. Our findings will contribute to decipher the importance of rhombomeric boundaries during early stages of brain development.

P13

Understanding the anterior and the posterior signaling centers in planarian

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A signaling center is a region that instructs the fate of the surrounding cells, and thus directs a patterned growth. The activity of signaling centers relies in the secretion of signaling molecules, or morphogens, which are received and interpreted by the surrounding cells. Signaling centers are well studied in embryonic models. However, their requirement in adult tissues during their normal homeostasis or in regenerative processes is poorly understood. In planarians, flatworms that are able to regenerate any missing body part, it is assumed that the anterior and the posterior tips behave as signaling centers. It is also known that the secreted molecules Wnt1 and Notum provide posterior and anterior specificity to each center, respectively. Thus, inhibition of *wnt1* generates heads in posterior and inhibition of *notum* generates tails in anterior. However, the molecular networks and the cellular interactions that enable the formation of the proper signaling centers during the regenerative process remain unknown. To board this question we are performing ATAC-seq analysis of anterior and posterior regenerating blastemas of wild-type, *wnt1* RNAi and *notum* RNAi animals to identify Cis-regulatory (CREs) specific of anterior and posterior regeneration. The transcription factors related to the CREs found as well as the target genes regulated by them will be also identified and functionally analyzed. Preliminary results show the existence of several specific CREs of anterior and posterior blastemas. Furthermore, with the aim to understand the cellular behavior that underlies the establishment of the posterior signaling center, we are performing a single cell sequencing (SCS) of posterior blastemas. Current results show the existence of 11 different cell populations which analysis is in process.

P14

Glial ionic homeostasis in brain development

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Glia-neuron interactions are crucial during development and the correct function of the adult nervous system. The mammalian CLCN2 chloride channel is widely expressed in the brain. While its expression in oligodendrocytes and astrocytes is related to K+ buffering in myelinated processes, its physiological role in other glial types is unknown. We turned to the Drosophila visual system as a convenient structure to address glial cell biology and glia-neuron interactions. We have detected expression of the CLCN2 Drosophila homolog gene *ClC-a* in cortex glia and several other glial types in the developing brain. Mutations in *ClC-a* result in brain compartimentalization defects due to cortex glia impaired ionic function. We focused on the *ClC-a* expressing glial barrier, which acts a landmark for photoreceptor axon guidance. The glia-photoreceptor interaction in early development of the visual system is mediated by Slit/Robo signaling. Slit secretion from glial cells is necessary for the correct guidance of photoreceptors. Similar to optic lobe specific *slit* mutations, *ClC-a* mutant animals showed defects in photoreceptor axon guidance. Through detailed developmental analysis we have characterized the formation of the barrier, the glial types contributing to the barrier and their Slit expression in wild type and mutant animals. Our findings indicate that ClC-a is required during development for the correct assembly of the glial barrier and Slit signaling. We propose that, in addition to its relevance in adult brain physiology, glial ionic homeostasis is an important aspect of brain development.

P15

Aquaporins as a mechanism for ROS propagation in *Drosophila* wing disc regeneration

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Drosophila wing imaginal discs are able to regenerate following different types of injury, which leads to the reconstruction of normal adult wings. Recent studies pointed out the importance of oxidative stress in driving the cellular response for wound repair and regeneration. Upon apoptotic stimuli or physical injuries, a burst of reactive oxygen species (ROS) is generated in the wing disc epithelium. This results in the activation of different signalling pathways (like JNK and p38) that are required for regeneration. A key issue is to unveil how reactive oxygen species (H_2O_2 in particular) spread from cells that are committed to die to the surrounding ones, however the mechanism of ROS propagation is poorly understood. In this study, we focus on two different *Drosophila* aquaporins: AQP and Drip as putative mechanisms of oxidative stress propagation. Our results indicate that, in stressing conditions, AQP is a key element of cell-to-cell communication facilitating ROS diffusion across membranes, thus allowing the onset of the regenerative stimulus. Interestingly, while AQP loss of function impairs the regenerative process, no significant defects were observed with Drip, suggesting that the function in regeneration is not shared among all aquaporins.

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