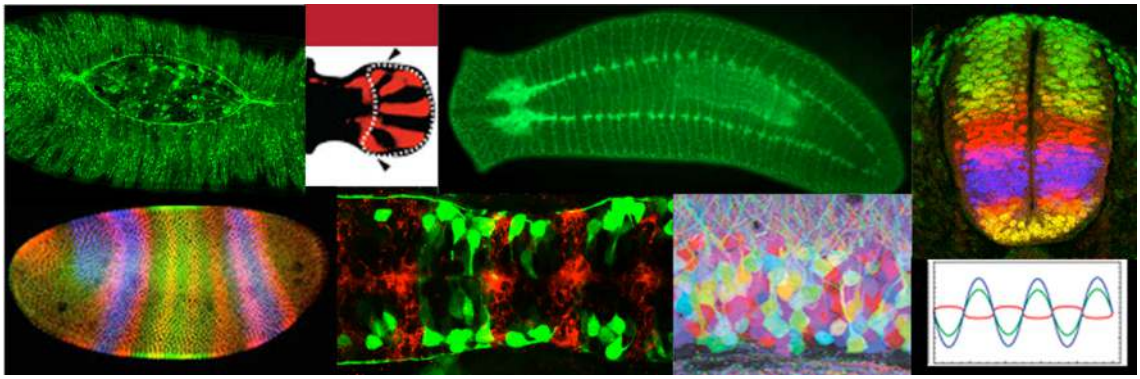
SCB DEVELOPMENTAL BIOLOGY JOINT RETREAT 2015



Eden Roc Hotel
Sant Feliu de Guíxols, Girona
19-20 March 2015

Meeting Organizers

Eva Jiménez-Guri, Center for Regulative Genomics (CRG), eva.jimenez@crg.eu
Francesc Cebrià, Dept. of Genetics, University of Barcelona, fcebrias@ub.edu
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Coordinator of the SCB Section of Developmental Biology: Jordi Garcia-Fernàndez

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SOCIETAT CATALANA BIOLOGIA : I. E. C. :

BCN DEVELOPMENTAL BIOLOGY JOINT RETREAT 2015
Eden Roc Hotel, Sant Feliu de Guixols, Girona - Spain
19th and 20th March 2015

PROGRAMME

Thursday 19th March 2015

10:00-11:30 Arrival and Registration at Eden Roc Hotel

11:30-12:30 **WELCOME AND OPENING LECTURE**

Manuel Irimia: *Transcriptome remodeling through alternative splicing during vertebrate nervous system development*

12:30-13:30 **SESSION 1A** *MORPHOGENESIS*

12:30-12:50 – H. Gálvez *Overcoming the repression of Atoh1: How to delay Hair Cell formation*
12:50-13:10 – K. Wotton *Quantitative changes in regulatory dynamics compensates for altered inputs to the gap gene network*
13:10-13:30 – S. Barberán *Smed-egfr-1 controls planarian gut regeneration and homeostasis by modulating neoblast differentiation*

13:30-15.30 **LUNCH**

15:30-16:50 **SESSION 1B** *MORPHOGENESIS*

15:30-15:50 – S. Dyballa *Building the inner ear: progenitor dynamics in neurosensory organ development*
15:50-16:10 – J.J. Fraire-Zamora *Comparative tissue dynamics in dipteran embryos*
16:10-16:30 – K. Onimaru *Transformation from fins into limbs through a mode change of Turing mechanism*
16:30-16:50 – M. Sureda-Gómez *Beta-catenin specifies posterior identity through a protein gradient and it is required for anterior patterning in planarians*

17:00-17:30 **COFFEE BREAK**

17:30-19:30 **SESSION 2** *STEM CELL & DISEASE*

17:30-17:50 – A. González-Sastre *The pioneer factors of the GATA456 family are required for gut regeneration and anterior mediolateral patterning in the planarian Schmidtea mediterranea*
17:50-18:10 – A. Terriente-Félix *Interplay between p38 MAPK and JAK signalling in normal haematopoiesis and leukaemia*
18:10-18:30 – P. Santabárbara-Ruiz *Tissue Repair in Drosophila Imaginal Discs: From Oxidative Stress to Cytokines*
18:30-18:50 – E. Pascual *Smed-Blitzschnell is a novel gene which modulates proliferation in planarians*
18:50-19:10 – M. Pardo *Study of gene expression profile during striatal development*
19:10-19:30 – N. de Sousa *The Hippo signaling controls cell turnover and differentiation in planarians*

20:00-21:30 **DINNER**

21:30-23.30 **POSTER SESSION**

Friday 20th March 2015

8.00-10.00 **BREAKFAST**

10:00-11:20 **SESSION 3** *NEUROGENESIS*

10:00-10:20 – H. Plazaola *Cl homeostasis in brain development and disease*
10:20-10:40 – I. Guardia *New insights in development: Zfp521, a key factor involved in mouse and human medium spiny neuron differentiation*
10:40-11:00 – J.L. Ferrán *Comparative analysis of PAX7 expression across amniota development highlights size differences in specific derivatives under conserved genoarchitectures*
11:00-11:20 – J.I. Rojo-Laguna *Wnt5-Ror and Slit-Robo signaling generates a mutually dependent system to establish a corridor for nervous system regeneration and medio-lateral specification*

11:20-11:50 **COFFEE BREAK**

11:50-12:300 **SESSION 4** *EVO-DEVO*

11:50-12:10 – J. Martí-Solans *Dismantling the Retinoic Acid Developmental Pathway in the Chordate Oikopleura dioica*
12-10-12:30 – E. Navas *Origins and regulation of an eutherian novelty: The BGW cluster*

12:30-13:30 **CLOSING LECTURE**

Christen Mirth: *Regulating body size: integrating environmental conditions with developmental processes*

13:30-13:45 **POSTER AWARD AND CONCLUDING REMARKS**

13:45-15.30 **LUNCH**

INVITED SPEAKERS

Manuel Irimia

TRANSCRIPTOMICS OF VERTEBRATE DEVELOPMENT AND EVOLUTION
SYSTEMS BIOLOGY UNIT
CENTER FOR GENOMIC REGULATION, BARCELONA, SPAIN

We are interested in understanding the roles that alternative splicing and other mechanisms of transcriptomic diversification play in vertebrate embryonic development, and how novel transcript variants have contributed to shape the unique vertebrate development and body plan during evolution.

Christen Mirth

DEVELOPMENT, EVOLUTION AND THE ENVIRONMENT
INSTITUTO GULBENKIAN DE CIÊNCIA, LISBOA, PORTUGAL

Our research focuses on the developmental regulation and evolution of environmentally dependent traits in species of the genus *Drosophila*. In particular, we explore how nutritional cues affect body size and determine larval foraging behaviour.

ORAL PRESENTATIONS

Overcoming the repression of Atoh1: How to delay Hair Cell formation

Héctor Gálvez, Fernando Giráldez, Gina Abelló
Universitat Pompeu Fabra Department of Experimental and Health Science, Barcelona, Spain

Hair Cells (HC) are the sensory receptors for sound and balance in the inner ear. Their production is tightly regulated during development. In amniotes, multipotential progenitors generate first neurons and, later on, HCs. Neuronal and HC development is driven by proneural factors Neurog1 and Atoh1, respectively. The proneural factor Neurogenin1 (Neurog1) is crucial for the specification of otic neurons and several experiments indicate that it counteracts Atoh1 function. Mammals cannot restore HCs after damage but inhibition of Notch signalling does improve their ability to regenerate. This indicates that HC development and regeneration relies strongly on the release of repressor factors.

Atoh1 is a basic helix-loop-helix factor (bHLH) that is necessary and sufficient for HC formation. Its expression during development is mostly recapitulated by a 3'-enhancer located 3,5Kb downstream from its coding region and formed by two regions, blocks A and B. The block B contains several putative binding domains for other bHLH factors that are likely to be important for the repression of Atoh1. The aim of this work is at understanding the molecular mechanisms of bHLH repression of Atoh1.

We first characterized a 3'Atoh1 reporter showing its activation by Atoh1 and repression by bHLH factors Neurog1, Hes5, Hey1 and Id3. Those experiments were carried out in chick embryos and in several cell lines, from which P19 and N2A reproduced the in vivo results. We then fractioned blocks A and B into different reporters to show that both, the activation and repression reside in block B, block A behaving as a poor regulator but essential for spatial restriction during development. Neurog1 and Hey1 were dominant over Atoh1, repressing enhancer activity in the presence of Atoh1. We analysed also the behaviour of the two E-boxes present in block A and B and showed that they were both weakly activated by Atoh1 and more strongly by Neurog1, even in the presence of Atoh1, while Hey1 and Hes5 prevented this activation. Therefore, the E-box alone cannot account for the activation by Atoh1 or the repression by Neurog1, implying that regions flanking the E-box are essential for normal regulation. Further, when confronted Atoh1 with a Neurog1-null lacking the DNA binding domain, it was still able to inhibit Atoh1 activation, suggesting strongly that the mechanism is other than competition for DNA binding. We are

currently exploring possible mechanisms for this interaction. Besides, we are mapping the genomic landscape of Atoh1 by using the ATAC-seq technique and performing ChIP-seq techniques to get a view of Neurog1 binding sites.

This work has been sponsored by Ministerio de Economía y Competitividad, MINECO (BFU-2011-24057) and Fundació La Marató TV3 (122730 / 31), Spain.

Quantitative changes in regulatory dynamics compensates for altered inputs to the gap gene network

Karl R Wotton, Eva Jimenez-Guri, Johannes Jaeger
Centre de Regulaciò Genómica (CRG), Systems Biology Program, Barcelona, Spain

The segmentation gene network in insects can produce equivalent phenotypic outputs despite differences in upstream regulatory inputs between species. We investigate the mechanistic basis of this phenomenon through a systems-level analysis of the gap gene network in the scuttle fly *Megaselia abdita* (Phoridae). It combines quantification of gene expression at high spatio-temporal resolution with systematic knock-downs by RNA interference (RNAi). Initiation and dynamics of gap gene expression differ markedly between *M. abdita* and *Drosophila melanogaster*, while the output of the system converges to equivalent patterns at the end of the blastoderm stage. Although the qualitative structure of the gap gene network is conserved, there are differences in the strength of regulatory interactions between species. We term such network rewiring 'quantitative system drift'. It provides a mechanistic explanation for the developmental hourglass model in the dipteran lineage. Quantitative system drift is likely to be a widespread mechanism for developmental evolution.

Smed-egfr-1 controls planarian gut regeneration and homeostasis by modulating neoblast differentiation

Sara Barberán, Francesc Cebrià
Department of Genetics, Institute of Biomedicine of the University of Barcelona (IBUB), University of Barcelona

The activation of differentiation programs in stem cells is a fundamental process during animal development and regeneration, required for proper tissue and organ formation and maintenance. The EGFR signalling pathway has been shown to play an important role during key steps of stem cell commitment and organogenesis in all studied model systems. In the planarian *Schmidtea mediterranea,* the EGFR pathway includes six EGF receptors (EGFR) and eight ligands. Previous studies showed that the receptors *egfr-3* and *egfr-5* are required for proper blastema and excretory system differentiation, respectively; also *egfr-1*, which is expressed in the digestive system, is required for pharynx and eye pigment cells regeneration and maintenance. Here we show that *egfr-1* is additionally essential for correct gut morphogenesis during planarian regeneration and homeostasis, as *egfr-1 (RNAi)* animals fail to regenerate new gut branches and dramatically reduce the existing ones during homeostasis. Moreover, their gut has a very reduced lumen, aberrant tissue organization, and significantly less gastrodermal cells. Importantly, the loss of gut cells in *egfr-1 (RNAi)* animals is not due to an increase of apoptotic levels in the gastrodermis, suggesting that the gut-associated phenotype is likely caused by defects in gut cell differentiation. In this regard, *egfr-1 (RNAi)* animals show greater number of *piwi* positive cells, and we are currently analysing the expression of gut-progeny markers, such as *gata4/5/6*, *hnf*4 and *nkx*2.2. Altogether, our data supports a model in which *egfr-1* may be modulating the differentiation of neoblasts into gastrodermal cells, strengthening the general function of the EGFR pathway in controlling organ morphogenesis and neoblast dynamics in adult planarians.

Building the inner ear: progenitor dynamics in neurosensory organ development

Sylvia Dyballa[1], Thierry Savy[2], Philipp Germann[3], Róbert Špir, Karol Mikula, Nadine Peyriéras[2], Cristina Pujades[1]

[1]Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, [2]BioEmergences CNRS, Gif-sur-Yvette France, [3]Centre for Genomic Regulation, Barcelona, [4]Slovak University of Technology, Bratislava

The inner ear is the sensory organ for hearing and balance. Two main cell types mediate the function of this organ: sensory hair cells and sensory neurons, which arise concomitantly during early embryonic development from a common structure, the otic placode that also undergoes extensive morphogenesis. While neuroblasts delaminate from the structure and accumulate in the underlying stato-acoustic ganglion (SAG), hair cell progenitors remain within the otic epithelium to form the sensory patches. The neurogenic region partially overlaps with the sites where sensory patches will develop, raising the question of whether neurons and hair cells arise from a common progenitor cell. We have recently shown that the otic neurosensory precursors may be composed of three populations: i) unipotent neuronal precursors, ii) sensory precursors that form only hair cells, and iii) bipotent precursors that give rise to both cell types.

In order to reveal the lineage of these cell types and to understand the dynamics of progenitors in giving rise to these fates we applied an in vivo imaging approach: we imaged fluorescently labelled zebrafish embryos and processed the 3D+time data with the methodologies and tools of the BioEmergences platform to achieve cell detection, cell tracking and cell lineage analysis.

We show how the first hair cells, called tether cells, set the polarity of the patches and how later forming hair cells are added to the patches. Differentiated hair cells never divide, supporting the hypothesis that the final number of hair cell is under the control of the progenitor pool. We also reveal the heterogeneity of the developing inner ear in terms of tissue architecture and cell behaviour by comparing the prosensory-domain to the non-sensory domain.

We are now analyzing the dynamics of otic neurogenesis and delamination of neuroblasts, which initiates in the antero-lateral aspect of the otic placode and only later extends medio-laterally. We are working to determine how time and place of birth affect neuroblast behaviour within the nascent statoacoustic ganglion (SAG) and how these cells organise within the SAG according to their function.

Comparative tissue dynamics in dipteran embryos

Juan J. Fraire-Zamora, Johannes Jäger, Jerome Solon
Centre de Regulaciò Genómica (CRG), Barcelona, Spain
Cell and Developmental Biology and Systems Biology Programs

Development can be viewed as spatial reorganization events that follow established genetic patterns. A recent renaissance of the mechanical view of development has pointed out the action of mechanical forces (such as pulling, twisting, buckling and/or bending) on tissue remodeling and their tight interplay with the genetic processes that orchestrate morphogenesis. This view motivates exciting questions on whether physical constraints play a role in the evolution of developmental processes or if the evolution of gene network results in specific physical properties of tissues. Our research project focuses on the comparative study of tissue dynamics and cellular forces that shape dipteran embryos of *Megaselia abdita* and *Drosophila melanogaster*. We aim to establish an interdisciplinary experimental approach to obtain comparative maps of embryonic mechanical forces that can be linked to gene expression. For the SCBDB retreat we will present our current methodologies that allow us to obtain time-lapse sequences of dorsal closure in the scuttle fly *Megaselia abdita* and traditional immunostaining and *In situ* hybridization techniques to understand the genetic and phenotypic differences of contractile structures (i.e. actin cables and extraembryonic tissues) with respect to *Drosophila melanogaster*. We envision that our experimental approach will reveal new insights in the interplay of mechanics and genetics during the evolution of development.

Transformation from fins into limbs through a mode change of Turing mechanism

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Turing mechanism is increasingly recognised to underlie digit patterning in mouse limb buds. Because it flexibly creates a variety of patterns with slight modifications of its parameters, Turing mechanism may contribute to morphological diversity of vertebrate limbs. Here we provided evidences that a spot mode of Turing mechanism may underlie pectoral fin development of a catshark, *Scyliorhinus canicula*. We observed that *Sox9* expression formed periodic spot patterns in *S. canicula* pectoral fin buds in contrast to mouse limbs, in which *Sox9* forms only stripe patterns. By building a realistic computational model, we successfully reproduced the *Sox9* spot pattern in silico. Furthermore, we showed that the computational model could predict *Sox9* expression patterns of experimentally perturbed fins. Together, our study suggests that Turing type mechanism drives morphological evolution of skeletal patterns of fins and limbs.

Beta-catenin specifies posterior identity through a protein gradient and it is required for anterior patterning in planarians

Miquel Sureda-Gómez, José María Martín-Durán, Teresa Adell
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Re-establishment of the axial identities is a main challenge during regeneration. Whole-body regenerating animals, as planarians, are an ideal system to study the molecular signals underlying axial re-specification. The canonical or beta-catenin-dependent Wnt signaling is an evolutionary conserved mechanism to specify posterior identity during embryogenesis. Through RNAi silencing we and others have demonstrated that in adult planarians beta-catenin is necessary for posterior specification, both during regeneration and during its normal homeostasis. We hypothesized a model in which a gradient of beta-catenin activity underlies planarian antero-posterior identities. To test this hypothesis we have generated an antibody against planarian beta-catenin1 protein (BCAT1) to analyze its subcellular expression along planarians AP axis. Our results show that it exist a parenchymatic gradient of nuclear BCAT1 along the animal, from the pharynx to the tip of the tail. During regeneration, B-CAT1 is highly activated in every blastema, but it is higher expressed in posterior ones. Moreover, we demonstrate that planarian Wnt1 is the responsible of the accumulation of BCAT-1 in posterior blastemas. Finally we show that B-CAT1 is also expressed in specific organs and tissues, as the testis, the pharynx and the brain, and that it exerts an essential function during anterior regeneration, especially for brain patterning. In conclusion, we demonstrate the existence of a gradient of nuclear BCAT1 protein which drives posterior specification and we show a novel function of BCAT1 during anterior regeneration in planarians

The pioneer factors of the GATA456 family are required for gut regeneration and anterior mediolateral patterning in the planarian *Schmidtea mediterranea*

Alejandro González-Sastre, Emili Saló
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The great plasticity of freshwater planarians have made them a classical model for regeneration. Its extraordinary regeneration capacity relies on the presence of neoblasts, the only proliferative cell type of the animal, which can differentiate into any cell lineage of the organism. Among them, *Schmidtea mediterranea* is one of the most used for regeneration studies. One of the main remaining open questions is how neoblasts are driven into differentiation. Pioneer factors, which are among the first elements that contribute to stem cell differentiation in other models, also play a role in *Schmidtea mediterranea*. Here we aim to characterize the function of two pioneer factors of the GATA456 family of transcription factors, evolutionary conserved key regulators of the endoderm, which are characterized by the presence of two GATA-type Zn fingers. On the one hand, *Smed-gata456-1* is expressed in the gut as well as in neoblasts around the digestive system, presumably its precursors. RNA interference experiments reveal that *gata456-1* is important for the maintenance and regeneration of the planarian gut. Thus, although a tail fragment is able to regenerate an apparently normal brain and a pharynx, it fails to regenerate a functional intestine. Furthermore, both regenerating and non-regenerating animals die 7-12 days after *Smed-gata456* knockdown due to general lesions in the parenchyma, suggesting that this gene may also have a role in the general homeostasis of the animal other than the maintenance and regeneration of the intestine. On the other hand, *Smed-gata456-2* is expressed mainly around the gut. RNA interference experiments reveal that *gata456-2* is necessary for the correct mediolateral patterning of the anterior structures. Thus, regenerated animals present a fused brain and a central cyclopic eye.

In summary, here we present the functional analysis of two transcription factors of the GATA4/5/6 family, which play an important role in the regeneration of different organs. *Gata456-1* is required for proper gut homeostasis and regeneration, while *gata456-2* is necessary for the correct mediolateral patterning of the anterior structures. In whole, these results open a way to explore the role of the GATA456 family of pioneer factors in planarians.

Interplay between p38 MAPK and JAK signalling in normal haematopoiesis and leukaemia

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Drosophila haematopoietic organ, the lymph gland (LG), is the main supply of cells to pupae and adults's inmune system. It progressively acquires a pattern and differentiates during larval development. In normal conditions, the LG develops in two defined phases. During the first phase, progenitors are clustered in a structure named the Medulary Zone (MZ), where they proliferate and their differentiation is prevented by the activation of signalling pathways whose ligands are secreted by the so-called "niche" of the gland. The second phase starts when progenitors switch off these pathways and gain expression of the early-differentiating marker Peroxidaxin (Pxn) to become Cortical Zone (CZ). In this stage, progenitors continue proliferating and some of them differentiate into crystal cells or plasmatocytes. Simultaneously, cells that remain at the MZ continue dividing.

JAK signaling is necessary to both prevent premature differentiation in the MZ and induce the final differentiation of two cell types: plasmatocytes and lamellocytes, the first cell type in healthy larvae, and the later only upon infection of parasite eggs. However, gof mutants for JAK block the normal developmental program and induce a tumorigenic one, consisting in an increase of cell proliferation, and ectopic differentiation of lamellocytes without infection. More interestingly, gof mutations in human JAK2 signalling members are driver mutations of Primary Myelofibrosis, a type of leukaemia that affects the myeloid lineage.

We have found that p38 mapk signalling in gof conditions produces a similar response to JAK signalling. We have also found that p38 mapk is downstream of JAK signalling and we have demonstrated that by two means. These are epistatic assays and p38 phosphorilation. In healthy larvae however, p38 mapk is not necessary to block differentiation as JAK signalling does in the MZ, nor to prevent cells from entering the CZ. On the contrary, lof of p38 mapk signalling results in opposite phenotypes. Many questions remain to be solved, such as which are the mechanisms that induce p38 signalling downstream of JAK signalling, whether or not p38 mapk acquires a new function downstream of JAK signalling in JAK gof conditions, and whether loss of p38 reduces the growth advantage of JAK gof clones but it does not prevent cells to be capable of inducing more aggressive tumours. We would like to discuss all these questions during the retreat.

Tissue Repair in *Drosophila* Imaginal Discs: From Oxidative Stress to Cytokines

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Tissues and organs need to function reliably regardless of adverse environmental conditions, which may cause cell damage that can be repaired as part of the homeostatic machinery. *Drosophila* imaginal discs are a suitable model to analyze the molecular nature of that response because damage can be induced by cell death or mechanical injury and in both cases recovery occurs. In this work we aim to uncover the nature of the signals that drive tissue repair. As oxidative stress can trigger pro- inflammatory responses to protect epithelia from environmental aggressions, we first checked whether Reactive Oxygen Species (ROS) are present after cell death or mechanical injury. We found that, after both aggressions, a burst of ROS propagates from the dying to the nearby surviving cells as well as from the edge of the injury to rest of the epithelium. High ROS levels in dead cells resulted in high JNK activity, which enhances apoptosis. However, low ROS levels propagated to the living nearby cells to activate non-deleterious JNK and p38 MAPK pathways. In those cells JNK activates the downstream phosphatase *puckered* (*puc*), which in turn inhibits JNK. We found that low levels of JNK are necessary for the tissue involved in repair. These are achieved by p38 inhibition of *puc*. Our results also show that the presence of tolerable levels of JNK in living cells is required to activate the cytokines *unpaired* (*upd*), which will activate JAK/STAT signaling. We propose a stress responsive module based on JNK-p38 activation and repression of *puc* to achieve beneficial levels of JNK, essential to activate JAK/STAT pathway to restore tissue homeostasis.

Smed-Blitzschnell is a novel gene which modulates proliferation in planarians

Eudald Pascual, Marta Marín, Kay Eckelt, Teresa Adell, Emili Saló

Department of Genetics, Universitat de Barcelona (UB) & Institute of Biomedicine of Universitat de Barcelona (IBUB)

Activation of proliferation is a key step during regeneration, and several cell cycle entry signals are known to be activated after wounding. Planarians are flatworms which are able to regenerate their whole body, due to the presence of pluripotent adult stem cells, the neoblasts. Several genes required for neoblast proliferation have been described, whose inhibition through RNA interference (RNAi) delays or impairs normal regeneration. Here we report the first example of a gene, Smed-Blitzschnell (Smed-Bs), whose role could be to attenuate proliferation and differentiation during regeneration, since its inhibition produces an acceleration of this process.

Smed-Bs encodes for a secreted peptide which has no homologues in other organisms. Smed-Bs is secreted by a specific subset of cells, which are located in the dorsal prepharyngeal region of the animal, as well as by some marginal cells. Loss-of-function analyses reveal that at 3 days of regeneration, Smed-Bs (RNAi) animals show a faster regeneration regarding brain, eyes and sensory cells, presenting an early appearance of the progenitor cells of these organs. These organisms also present a significant increase in the mitotic rates during anterior regeneration, and after any kind of injury. Long term Smed-Bs (RNAi) inhibition during homeostasis (up to 9 weeks) showed a significant increase of the basal mitotic activity through the body as well as a higher mitotic response after feeding.

Our hypothesis is that Smed-BS is a species specific small secreted peptide which is required for the refined control of cell cycle progression of neoblasts. We are investigating the role of Smed-BS in the different cell cycle stages.

Study of gene expression profile during striatal development

M. Pardo[1], AG. García Díaz-Barriga[1], NN. Vinh[2], J. Alberch[1], R. Martín–Ibáñez[1], AE. Rosser[2], JM. Canals[1]

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The striatum plays a key role controlling motor coordination and its impairment results in several neurodegenerative disorders. For this reason, a better understanding of striatal development is required to further reproduce *in vitro* the striatal characteristics we observe *in vivo*. To achieve this goal, we used laser microdissection to extract mRNA from the mouse striatal Germinal and Mantle Zones (GZ, MZ) during different developmental stages (E12.5, E14.5, E16.5 and E18.5) and subsequently performed 32 microarrays to analyze the gene expression profile of striatal progenitor and postmitotic cells during the striatal development. From the whole mouse genome, using a linear fit algorithm analysis, 3,636 DEGs (Differentially expressed genes) were obtained. Gene ontology analyses showed that upregulated genes in the MZ were mainly involved in ion transport, synaptic transmission and neuron differentiation processes, while genes in the GZ were mainly participating in progenitors'cell cycle.

To go deeper into the study of genes involved in the generation of striatal neurons, we used clustering techniques (hierarchical and k-means) to classify DEGs into different patterns of expression. We could group the 3,636 DEGs into 6 categories (LGE progenitors, Late GZ progenitors, Fate Specification, Neuronal differentiation, Maturation and Reorganization) to generate a Model to explain the striatal development and, more interestingly, to find out which genes are putative candidates to be involved in each process. In addition, using the MIDAS software to predict alternative splicing, we also could detect genes with alternative splicing events depending on the region or stage; supporting the idea that there are other mechanisms a part of mRNA levels controlling striatal differentiation.

Finally, considering the necessity to extrapolate mouse results into human, we compared mouse DEG's with human striatal samples from Brain Span. The hierarchical cluster between mouse and human samples indicate that a high amount of genes share a similar gene expression profile between species, suggesting the proposed striatal model can be applied also to explain human striatal development.

In conclusion, these results demonstrate that the microarray study provides us with huge information about striatal development that, precisely analyzed, is transformed in an integrative model that includes mRNA gene levels and alternative splicing events to explain how striatal development proceeds.

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The Hippo signaling controls cell turnover and differentiation in planarians

Nídia de Sousa, Teresa Adell, Emili Saló
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Control of cell number is crucial in tissue homeostasis and regeneration, since its deregulation results in tumors or degeneration. The Hippo signaling is an essential mechanism to control cell turnover through sensing cell-cell contacts. However, whether the pathway is active in stem or differentiated cells, and its input signals and output effects in the context of a whole organ/organism remain unknown. To deeper insight these questions we are studying the role of the Hippo signal in Planarians, flatworms with an unlimited ability to regenerate and to change their body size.

Planarian striking plasticity is based in the presence of totipotent adult stem cells (Neoblasts) and the continuous activation of intercellular signals that enable the refined control of cell turnover, size and proportions. The expression pattern of the core elements of the Hippo pathway (*Hippo, Warts, Salvador, Yki*) in the planarian *Schmidtea mediterranea* showed that the Hippo signaling could be active in Neoblasts but mainly in terminal differentiated cells. Activation of the Hippo pathway through RNAi inhibition of Yorkie, produce a 'blotted' phenotype, showing an increase of apoptosis and in the proportion of differentiated cells. The levels of proliferation also increase in homeostatic conditions but not during regeneration. Interestingly, RNAi inhibition of the *Hippo* cassette (*Hippo/Warts/Salvador* RNAi) during homeostasis leads to the formation of overgrowths throughout the animal, characterized by the accumulation of undifferentiated cells and a decrease in cell junctions. Those overgrowths could be a consequence of the unbalanced cell turnover caused by the increase in proliferation and the decrease in apoptosis observed. Simultaneous inhibition of *Smed-Hippo* and *Smed-JNK*, that alone never induces tumoral growths, increases the rate of overgrowths. Remarkably, Smed-Hippo silencing during regeneration results in several tissue defects but never produces overgrowths.

Our results suggest that in a stem cell-based organism Hippo signaling controls proliferation, apoptosis and differentiation primarily in differentiated or differentiating cells rather than in stem cells. Future work will focus on the specific role of Hippo in neoblasts and the role of cell junctions and cell polarity elements as upstream regulators of the pathway in planarians.

Cl homeostasis in brain development and disease

Haritz Plazaola Sasieta[1], Raul Estevez Povedano[2], Marta Morey Ramonell[1]

1. Departament de Genética, Facultat de Biologia, Universitat de Barcelona
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Normal development depends on the maintenance of proper intra- and extracellular ionic concentrations, as well as control of ionic flow between tissues. Cl, which is regulated by the ClC family of chloride channels, is one of the most abundant ions used by cells. Thus, it is not surprising that many inherited human disorders involve Clc genes. *Clcn2* has been linked to the white matter disorder megalencephalic leukoencephalopathy with subcortical cysts (MLC), which causes vacuolization and edema of the brain. Mice lacking *Clcn2* experience early onset loss of photoreceptors and germ cells, and progressive swelling of the brain.

In order to understand the role of this channel in this disease we sought to identify and characterize mutations in the *Drosophila* homolog gene *Clc-a*. Mutant animals show defects in different brain structures, which vary according to the severity of distinct allelic combinations. We are focusing on the defects observed in optic lobe, a region involved in the processing of visual information and the best characterized region of the fly brain, to understand how these defects arise during development. We have detected Clc-a expression in glial cells abutting the neuroepitheliums that give rise to precursos of the medulla and lobula plate /lobula neuropils. Our preliminary results and analysis of developmental phenotypes suggest that Cl homeostasis could play an important role in both the differentiation of precursors and axon guidance in this system. Since Clcn2 expression in mice has been detected as well in astroglia, the fly presents it self as an excellent model to unravel the role of this channel in MLC.

New insights in development: Zfp521, a key factor involved in mouse and human medium spiny neuron differentiation

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Many factors involved in striatal development remain uncharacterized. The mouse protein Zfp521 (ZNF521 in human) is a transcription factor that is expressed in the striatum during development, however its role in striatal development has not been investigated. Here we have characterized Zfp521 expression in the mouse telencephalon and striatum. During mouse development Zfp521 is expressed in several brain regions, including the Lateral and Medial Ganglionic Eminences (LGE and MGE respectively), olfactory bulb, septum, thalamus, cortex and cerebellum. Within the LGE, the area that gives rise to the striatum, Zfp521 levels of protein and mRNA tended to increase in the postmitotic mantle zone (MZ) from E14.5 until early postnatal stages, although its expression is maintained during adulthood. Zfp521 was not detected in proliferative Ki67-positive progenitors, but expression was detected in medium spiny neurons (MSNs) of the striatonigral pathway.

Other critical transcription factors are implicated in the development of MSNs of the striatonigral pathway such as Ebf1. We found a large reduction of Zfp521 expression in Ebf1 KO mice, suggesting an interesting relationship between Ebf1 and Zfp521 during differentiation of the striatonigral MSNs. Thus we next characterized the relationship of Zfp521 with Ebf1. We overexpressed Ebf1 in HEK923T cells and observed induction of Zfp521 protein expression in the Ebf1 positive cells, while the overexpression of Zfp521 did not induce Ebf1 expression. This result suggests that Ebf1 may regulate expression of Zfp521.

We also characterized ZNF521 expression in human fetal tissue. Similar to the mouse expression data, ZNF521 expression was observed in the LGE/striatum, internal capsule, choroid plexus, and septum. In the basal ganglia ZNF521 was expressed in the MZ with a lateral pattern of expression from 8 weeks post conception onwards. Most of the ZNF521 positive cells were found in the MZ and did not colocalize with Ki67, although a few ZNF521 positive cells also expressing Ki67 were detected in the SVZ. We also demonstrated that ZNF521 is expressed by

human MSNs during development since it colocalized with Ctip2 and FoxP1 positive cells.

To verify these results in human, we studied the expression of both transcription factors during the differentiation of human embryonic stem cells (ESCs) and human induced pluripotent stem cells (iPSCs) to striatal neurons. The mRNA levels of ZNF521 switched on early at day 4 of the differentiation followed by the expression of Ebf1 at day 8. We observe an opposite profile for Ebf1 expression, switching on when ZNF521 expression droped off. These data reinforce the relationship between Ebf1 and ZNF521 during human neuralization.

Taken together our findings indicate that that Zfp521/ZNF521 in conjunction with Ebf1 has a role during MSN differentiation.

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Comparative analysis of PAX7 expression across amniota development highlights size differences in specific derivatives under conserved genoarchitectures

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During development and regionalization of the central nervous system of vertebrates a set of transverse subdivisions, known as prosomeres, are established. All prosomeres along the forebrain are dorsoventrally regionalized to establish the basic structural plan brain or bauplan shared among vertebrates. Genoarchitectonic studies have given strong support for these partitions and shown that patterns analyzed with the prosomeric model can be compared in a topologically precise ¨point to point way" between different vertebrates. In this work we compare PAX7-Pax7 expression during late development in the central nervous system between three representative amniote species: crocodiles, chicken and mice.

We obtained Nile crocodile embryos from a South African farm between 70 and 85 days of development; the chicken embryos came from a local farm and ranged between stages HH28 and HH45, and mouse embryos from our animal facility ranged between E11.5 and E18.5. Crocodile and chicken brains were analyzed using PAX7 immunohistochemistry; mice brains were examined using in situ hybridization.

We found that PAX7 was detected in the same prosomeres in the three species analyzed; the expression pattern includes mainly a basal domain at the hypothalamic mamillary region and prosomere 3 basal plate, as well as alar plate domains in prosomere 2 (habenular and pineal expression) prosomere 1 (caudal pretectum), and mesencephalon, and we observed labeled alar and basal plate regions at the most rostral rhombomeres. A detailed analysis at selected stages of nuclei and cell layers derived from each mentioned region showed that specific derivatives are absent in some species (e.g. paraphysis expression is only observed in crocodile and chicken brains), or there are differences in the size of homologous nuclei that express this transcription factor (e.g. the principal pretectal nucleus has a different relative size in the compared species).

Wnt5-Ror and Slit-Robo signaling generates a mutually dependent system to establish a corridor for nervous system regeneration and medio-lateral specification

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Regeneration of adult neural tissues after damage or amputation requires polarization and regionalization of the missing structures. How neuronal migration and targeted axon growth are controlled to integrate new and preexisting tissues and to rebuild the neural circuitry remains largely unknown. Planarian flatworms stand out as a model to approach these questions, since they can regenerate a complete and functional nervous system in a few days after amputation. Such amazing plasticity is due to the presence of an adult pluripotent stem cell population and the ability to maintain constitutively active all the signaling pathways involved in positional identity. During nervous system development, the integration of a conserved set of diffusible molecules, such as Netrins, Slits and Wnts will define neuronal migration and axonal paths. In planarian, Slit and Wnt5 show complementary domains of expression along the ML axis, and their silencing through RNAi produces the displacement of the CNS with respect to the ML axis in opposite directions. By generation of ectopic sources of active human/mouse Wnt5a, we provide conclusive evidences that Wnt5 is restricting the path of nervous system regeneration. Interestingly, non neural tissues, as the digestive system, appear also displaced. We have identified a Ror and a Robo receptor as mediators of the Wnt5- and Slit- depending process, respectively. Interestingly, we have found that a subset of cells in the midline co-express the Ror receptor and Slit. We hypothesize that Wnt5 and Slit act together to establish their expression boundaries and thus, to generate a corridor for CNS regeneration and ML axis specification.

Dismantling the Retinoic Acid Developmental Pathway in the Chordate *Oikopleura dioica*.

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Gene losses affecting developmental signaling pathways can lead to drastic changes in embryonic patterning with important consequences in the evolution and diversification of species. To understand the impact of a gene loss on the evolution of mechanisms of development, we need to analyze, first, whether the biological function of the lost gene might be rerouted through an alternative pathway, and secondly, how the loss of a gene in a signaling pathway affects to other genes in the same or in different signaling pathways. To conduct this kind of analyses, we have chosen as a case study the retinoic acid (RA) signaling, a major morphogenetic pathway conserved in all chordates except in the urochordate larvacean *Oikopleura dioica,* a chordate species prone to lose genes. *O. dioica* has lost the two main enzymes of RA metabolism, as well as the RAR nuclear receptor. After performing a comparative genomic analysis, we found that most of the main components of the RA genetic machinery are not present in *O. dioica*. However, 3 families of enzymes related with the RA metabolism have survived the dismantling of the RA gene network. To assess if those RA survivors genes could provide an alternative pathway to synthesize RA, we have analyzed the retinoid content in *O. dioica*, and we have characterized their expression patterns and some of their biochemical activities. Our results provide clear evidence that there is no an alternative RA synthesis in *O. dioica*, and suggests that the retention of the surviving genes is compatible with complex pleiotropic roles related to metabolism of alternative compounds, as well as a response to environmental offenses such as the release of toxic aldehydes secreted during microalgal blooms. Initial analyses of the FGF and WNT signaling pathways in *O. dioca* point as well to a major remodeling affected by gene losses with significant consequences for the molecular patterning of embryo development.

Origins and regulation of an eutherian novelty: The BGW cluster

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Two related gene subfamilies known as *BEX* and *TCEAL* (also known as *WEX*) map to a genomic region specific to Eutheria (placental mammals), located on the X chromosome. These families are part of a gene cluster, named "BGW cluster", together with the *ARMCX* family and *HNRNPH2*. Some of the *BEX*/*TCEAL* genes have been related to control the balance between proliferation and differentiation, while others promote apoptosis in a p75-dependent manner, but most of them remain poorly studied.

The *ARMCX* family and *HNRNPH2* are derived from retrocopies of the *ARMC10* and *HNRNPH1* genes respectively –conserved across bilateria, and located in autosomal chromosomes–, whereas no orthologs have been found for the *BEX*/*TCEAL* family outside of Eutheria. However, all these genes share an intriguing feature: a sequence motif in their proximal promoter region that appears to be crucial for their expression, the BGW motif. To further understand the evolution of this gene cluster, we investigated the origin of the *BEX*/*TCEAL* genes and traced it to an atypical formation in the ancestor of eutherians. Furthermore, novel features associated with *BEX*/*TCEAL* suggest a more complete scenario for the origin of the cluster: the BGW motif was already present at the *HNRNPH2* locus in the ancestor of therian mammals, being subsequently duplicated and coopted in the eutherian lineage by the *BEX*/*TCEAL* ancestor and, posteriorly, by the *ARMCX* ancestral gene. Finally, we also studied the expression of the *BEX*/*TCEAL* genes during mouse development using in situ hybridization. We found that they are highly expressed in the brain and placenta, which are structures that require a well-tuned control of cell cycle during their development in eutherian mammals.

Here we propose a scenario for the origin of the *BEX*/*TCEAL* family and for the formation of the BGW cluster where they belong. Their uncommon origin, their pattern of expression, and their putative biological function during development makes these genes an interesting subject of study to understand how lineage-specific genes could contribute to mammalian evolution.

POSTER PRESENTATIONS

Individual cell properties and supracellular organization during trachea organogenesis in *Drosophila*

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The *Drosophila* tracheal system consists of a network of epithelial tubes formed after several morphogenetic events, that requiere cellular mechanisms of collective cell migration, cell shape changes and cell rearrangements. These cellular mechanisms are finely regulated by a complex genetic program. A particular type of rearrangement is the process of intercalation, by which cells reorganise their position and there is an exchange of intercellular AJs by autocellular ones. Intercalation occurs in most primary branches, except in the DT, and has been proposed to depend on intracellular trafficking and cell shape changes. On other hand, major changes in the tracheal architecture, such as the control of tube size or diameter, have been linked to the organisation/secretion of components into the luminal space and to the roles of GTPases in intracellular trafficking, rather than in changes in cell number. In this scenario, our present work aims to elucidate 1) how cell number impinges on the morphogenesis of the overall trachea and in particular on cell rearrangement and 2) the role of the actin-cytoskeleton in tracheal cell shape changes and how these processes are regulated during trachea organogenesis.

Nejire contributes to regulate food intake, growth and ecdysis in the premetamorphic nymphal stage of *Blattella germanica*

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Nejire (Nej) (a term was coined for *Drosophila melanogaster*) is a CREB-binding protein, or CBP, that acts as a transcriptional coactivator, interacting with a large number of developmentally important transcription factors. CBP is recruited to DNA by several transcription factors, including CREB and cFos.

In our model insect, the cockroach *Blattella germanica*, Nej (BgNej) appeared as a differentially expressed transcript at the beginning of the last, pre-metamorphic nymphal instar. After characterizing the structure and establishing the expression patterns during the penultimate and the last nymphal instars, we approached the functional characterization of BgNej by RNAi. We injected a single 1-ug dose of dsRNA targeting BgNej in freshly emerged last instar male nymphs. Transcript decrease measured in tergites 4 and 5, 6 days after the treatment was moderate (46%), but statistically significant.

With respect to controls, BgNej-depleted specimens showed diminished food intake, grew more slowly and had problems of ecdysis in the adult molt, as they were not able to correctly shake off the exuvium. Concerning food intake, BgNej-depleted specimens showed higher mRNA levels of sulfakinin (SFK), which is a food intake inhibitor, and lower mRNA levels of taquikinin (TQK), a food intake stimulator. This suggests that BgNej regulates food intake by enhancing the expression of orexigenic peptides, like TQK, and repressing the expression of antifeeding peptides, like SFK.

Concerning molting to the adult stage, the mRNA levels of E75A and E75B, which are transcription factors belonging to the ecdysone signaling pathway, were lower in BgNej-depleted specimens, which accounts for the molting problems observed in these specimens. Moreover, mRNA levels of eclosion hormone, which is specifically involved in the ecdysis process, were also lower in BgNej-depleted specimens, which can explain the problems to shake off the exuvium observed in them. BgNej, thus, appears to be contribute to the performance of ecdysone signaling and to the correct execution of the ecdysis program.

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Pushing the genetic limits of heart development

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A complex genetic toolkit for heart development is conserved among vertebrates, and even with some urochordates, their closest sister relatives. Retinoic acid (RA), WNT, FGF and BMP signaling pathways regulate the expression of key cardiac transcription factors, such as *Mesp, Ets, Gata-4/5/6, Nkx-2.5*, and *Hand*. Understanding the genetic interactions of these factors, however, is difficult due to the extensive gene duplications occurred during early vertebrate evolution. To circumvent this genetic redundancy, we have launched an analysis of heart development in the basal chordate *Oikopleura dioica*. This urochordate species is an emerging EvoDevo model animal that conserves the typical chordate body plan despite it has suffered an extreme genome compaction accompanied of massive gene losses. These gene losses entail *O. dioica* as an '*Evolutionary Knockout*' for many genes, which allows us to explore the minimal genetic toolkit for the development of different chordate organs such as the heart. To understand how signaling pathways and regulatory factors that drive chordate cardiac development have evolved in *O. dioica*, we have performed an in silico survey of the *O. dioica* genome looking for orthologous genes for the main signaling pathways as well as a dozen cardiac developmental factors. Our results revealed that *O. dioica* has totally dismantled the RA signaling, has lost many FGF and WNT genes, and has lost at least three of these extremely conserved heart developmental factors. We have tested whether the nine surviving cardiac orthologs were still involved in heart development in *O. dioica*, and when the ortholog was gone, we tested whether the closest paralog could have regained a cardiac function. So far, our results are somewhat surprising, suggesting that *O. dioica* has either reinvented the genetic machinery for developing a novel chordate heart, or it has shrunk the cardiac genetic toolkit, pushing it to its functional limit.

The nervous system of Xenacoelomorpha: a genomic perspective

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Most phylogenetic studies maintain that acoelomorph flatworms (acoels and nemertodermatids) constitute a sister group of Xenoturbellida, forming the monophyletic phylum Xenacoelomorpha. Even though some molecular analysis placed Xenacoelomorpha as the most basally branching group of the Bilateria, other authors included it in the Deuterostomia, as a sister group of the Ambulacraria. Due to this controversy, the interest in Xenacoelomorpha has been renewed within the area of phylogenetic analysis. However, what it seems to be clear is its condition of monophyletic group. Given the relative phylogenetic positions of its constituent three clades, with Xenoturbella as the earliest branch followed by the split of Nemertodermatida and Acoela, Xenacoelomorpha has becomes an interesting animal group for studying evolutionary trends (whether genomic or morphological).
Over the last few years, different research groups have studied the microscopic anatomy of these animals, focusing on organs such the nervous system (and others), traditionally considered an important character for phylogenetic inference. How nervous systems are assembled over evolutionary time has been, over the last century, a controversial issue. The major aim of our research group is to understand the structure, evolution and development of nervous systems. Since the members of the clade Xenacoelomorpha present different degrees of "cephalization", analyzing the nervous system development inside this phylum could provide us with insights about the early organization of the bilaterian nervous system and the origin and formation of 'cephalized' nervous systems (brains).

Recently, the involvement of several research groups (included ours) in sequencing several xenacoelomorph genomes has allowed us to initiate molecular evolutionary studies of some specific gene families. We present here the characterization of three gene families involved in several aspects of the nervous system's formation: the basic helix-loop-helix (bHLHs), G protein-coupled receptors (GPCRs) and Wnts. We have focused our analysis in the acoel *Symsagittifera*

roscoffensis and the xenoturbellid *Xenoturbella bocki* (the most complete genomes we have). How their evolutionary history is reflected in the progressive degree of 'cephalization' seen in the phylum constitutes the target of our study. In parallel, several new techniques have been developed in the lab to better map the detailed structures of the nervous tissue in these organisms. Here we show some detailed morphology, revealed by inmuno-histochemistry, of the nervous system of the adult *S. roscoffensis*.

A comprehensive pipeline for identifiying lincRNAs on the basal-branching chordate Amphioxus

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Among the numerous classes of RNAs, long intergenic non coding RNAs (lincRNAs) are similar in terms of expression and gene structure to the mRNAs but lacking the potential to encode proteins. Over the last years, lincRNAs have been proven to play important roles in gene regulation, and shown to be involved in many key developmental processes. However, the evolutionary dynamics of lincRNAs has been scarcely studied, and few data are known at evolutionary key-nodes of animal evolution, as the origin of chordates and vertebrates. The cephalocordate amphioxus is recognized as the best proxy to these nodes. Very little is known about the conservation of these developmental functions due to the low sequence conservation of lincRNAs, which has hindered the identification of deep orthologs among distantly related species. We aim to identify the lincRNA complement of the amphioxus genome, in order to approach the complement and evolution of this regulatory fraction of the genome at the origin of chordates and early evolution of vertebrates. For this, we used RNA-seq data from several adult tissues and developmental stages of Branchiostoma lanceolatum in order to identify its lincRNAs. First, we used CPAT software and blastx searches to eliminate transcripts with coding potential and/or with similarity to conserved protein domains upon 6-frame translation. Next, we selected only those with multiexonic gene structures (at least 2 exons) and a minimum length of 500 nucleotides. This pipeline yielded around 2000 putative lincRNAs and we will show the preliminary analyses of these Bl-lincRNAs, regarding their experimental validation, their conservation among amphioxus species and to other invertebrate and vertebrates, and their expression profile during development and in adult tissues.

Non-canonical dorsoventral patterning in the moth midge *Clogmia albipunctata*.

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Étienne Geoffroy Saint-Hilaire famously proposed that invertebrates and vertebrates had very similar body patterns but with an inversion in the dorsoventral (DV) axis. This idea is nowadays supported by molecular evidence showing that key factors for DV patterning (such as BMP morphogens) are expressed with opposite polarity in these two groups of animals. We have recently reported surprising evidence that the situation may not be quite as clear-cut. The insect BMP homologue dpp is expressed ventrally, around the anterior and posterior poles, in the blastoderm of the nematoceran moth midge *Clogmia albipunctata*. How this arrangement of gene expression patterns in *C. albipunctata* is able to function as a dorsal morphogen gradient is unknown. We are currently systematically characterising other components of the DV patterning pathway to elucidate the mechanism of Dpp gradient formation in this fly. Our analysis suggests that a shuttling mechanism like that proposed for *Drosophila* is improbable in *Clogmia*. We are using RNAi injection, previously unavailable in this species, to elucidate the interactions between these genes.

Investigating the roles and mechanisms of EGFR during tracheal development.

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The EGFR signalling pathway plays critical roles during development by regulating important cellular activities like proliferation, cell survival, differentiation or cell migration. During Drosophila tracheal development the EGFR pathway has been shown to participate in tracheal cell invagination and in maintaining the epithelial integrity during branching. Previous results in our lab indicated that the activity of EGFR in regulating tracheal tissue integrity correlates with a differential accumulation of markers for cell-cell adhesion, like E-Cadherin. We are investigating the mechanisms of regulation of E-Cadherin by EGFR. Our data indicate that this regulation is posttrancriptional, and we are using different tools to assess different mechanisms by which E-Cadherin levels may be controlled by EGFR during tracheal formation (like endocytosis, cytoskeleton regulation, modifying other Adherens Junctions components, etc...). We are also investigating the possible effectors of EGFR in this activity. Furthermore, we have observed that the modulation of EGFR activity, besides controlling invagination and tissue integrity, also impinges on tube size regulation. Therefore, we are currently investigating the mechanisms and effectors of EGFR in tube size control.

TBX5 genes tissue-specific requirements during heart, retina and pectoral fin development in zebrafish

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The transcription factor Tbx5 is 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. Tbx5-knockout mouse embryos have severely impaired forelimb and heart morphogenesis from the earliest stages of their development. However, zebrafish embryos with compromised tbx5 function show a complete absence of pectoral fins, while heart development is disturbed at significantly later developmental stages and eye development remains to be thoroughly analysed. We identified a novel tbx5 gene in zebrafish--tbx5b--that is co-expressed with its paralogue, tbx5a, in the developing eye and heart and hypothesized that functional redundancy could be occurring in these organs in embryos with impaired tbx5a function. We have now investigated the consequences of tbx5a and/or tbx5b downregulation in zebrafish to reveal 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. Furthermore, we uncover a novel role for tbx5 genes in the establishment of correct heart asymmetry in zebrafish embryos.

The expression of Pipe in Blattella germanica ovaries is essential for embryo development.

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The formation of dorsoventral (DV) axis in *D. melanogaster* requires a localized activation of a serine protease cascade, formed by Gastrulation Defective, Snake, and Easter, in the perivitelline space surrounding the developing embryo. The activation of this protease cascade causes ventral to dorsal gradient of Toll receptor activation in the embryonic membrane, which regulates the DV patterning of the embryo. The ventral restriction of the activation of the protease cascade relies on signals in the vitelline membrane which is the first chorion layer secreted by the follicular cells. It has been reported that Pipe, that encodes for a sulfotransferase, modifies some structural components of the vitelline membrane becoming the responsible of this restriction.

Pipe has been well studied in the meroistic ovaries of *Drosophila melanogaster*, where it is expressed in the follicular cells placed in the ventral part of the egg chamber playing a pivotal role in dorsal-ventral polarity of the embryo, activating the protease cascade triggering Toll pathway, and restricting its area of action.

We report the function of Pipe in hemimetabolan insect, the cockroach *Blattella germanica*, which has panoistic ovaries and an embryo that is of short germ band type. The depletion of BgPipe expression in newly adult females leads to embryos with dorsal-ventral defects. While the depletion of Pipe, in sixth nymphal instar females or at the end of adult stage leads to oviposit normal embryos. These findings indicate that BgPipe has a maternal effect and play a pivotal role in the process that defines the embryonic dorsal-ventral axis.

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Retinoic acid is essential for inner ear and lateral line hair cell regeneration

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Hair cell damage, as result of several causes such as aging, increased acoustic aggressions and the use of ototoxic drugs, provokes hearing loss in humans, the major problem in the actual society. In mammals damaged hair cells cannot regenerate, whereas lower vertebrates have retained the ability to replace damaged hair cells by inducing cell proliferation of supporting cells and/or their transdifferentiation. Retinoic Acid (RA) has been implicated in limb, heart, spinal cord and peripheral nervous system regeneration. Although little is known about its role in the inner ear, a combination of gene expression profiling, functional assays and cell lineage tracing allows us to highlight the essential role of the RA pathway in hair cell regeneration in zebrafish. In the inner ear, *aldh1a3* (*raldh3* in mouse) is expressed in the sensory patch surrounding hair cells. In addition *RARgammaa* and *cyp26b1* show specific expression patterns further confirming that RA pathway is active in the inner ear. After laser-ablation of hair cells of the lateral crista, regeneration is impaired upon blockade of the RA pathway (by blocking either the synthesis or the activity of RA). In the lateral line, regeneration of neuromast hair cell after neomycin treatment is also inhibited after RA blockade due to a reduction of supporting cell proliferation. Moreover, expression of *aldh1a3*, *RARalphab* and *cyp26a1* is induced during neuromast hair cell regeneration, confirming the activation of this pathway, while in the inner ear the levels of RA upon regeneration are modulated at the level of *cyp26b1* expression. Interestingly, *p27* cell cycle inhibitor, normally expressed in lateral line supporting cell, is down-regulated upon hair cell damage, but remain strongly expressed in RA depleted larvae. This observation suggests a possible link between RA pathway activation and supporting cell proliferation. Altogether, we uncover a new role of retinoic acid in the regeneration of hair cells that could be useful in future therapeutic strategies.

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Early growth response (EGR) genes are required for planarian anterior regeneration

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Mammalian early growth response (EGR) proteins are zinc-finger transcription factors that play a key role in the control of cell growth, differentiation and apoptosis. They are immediate-early genes, since they are synthesized in a very quick manner after many different stimuli. EGR proteins transduce extracellular signals into a rapid transcriptional response, process that is controlled through different signalling pathways, including the EGFR and MAPK/ERK. Even though this family may be functionally redundant since they are usually coexpressed, the knock-out of different members has revealed specific roles for individual EGR proteins.

The planarian *Schmidtea mediterranea* is an emerging model system that has amazing regenerative abilities and the RNAi technique is well established to perform functional studies on them. Some members of the *Smed-egr* family have been already described. Recently, we have identified *egr-4* as a key gene required for the formation of the brain primordia and head regeneration in planarians. Here, we describe a new *Smed-egr* zinc finger protein (EGR-6). *Smed-egr-6* is expressed in the CNS and throughout the parenchyme. During regeneration, it appears downregulated in anterior blastemas during the first 24h, but strongly upregulated after 48h. Similarly to *Smed-egr-4,* the inhibition of *Smed-egr-6* by RNAi blocks anterior regeneration without affecting anterior polarity, showing impaired anterior blastema formation. Strikingly, the percentage of animals in which the anterior regeneration is severely disturbed increases significantly after the double knock-down of *Smed-egr-6* and *Smed-egr-4*. Therefore, these results may indicate that these two genes could act synergistically to regulate anterior regeneration.

Finally, we performed RNAseq of the *Smed-egr-4* RNAi animals. In order to better understand this signalling pathway, we are characterizing its upstream and downstream targets.

Decoding boundaries: From genomic landscape to cellular function

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The existence of compartments in the vertebrate Central Nervous System was first demonstrated in the hindbrain, which is subdivided into segments called rhombomeres. At the interface between rhombomeres arises a specialized cell population – the rhombomere boundary cell population (rBCP) – that has specific cellular behavior in terms of gene expression profile, differentiation state, morphology and function. In previous works, we have described how the rBCP acts as a signalling center for patterning neurogenesis in the hindbrain and, thanks to the assembly of actomyosin cables at every boundary, as a physical barrier necessary for keeping rhombomere cells segregated during development. To further understand the specification of the rBCP and its specific cell behavior and cell fate, we have taken a genomic approach. We have dissected the possible non-coding regulatory elements that drive the expression of a set of genes to the rBCP. Particularly, in zebrafish we have found a genomic region that hosts a given number of genes, whose expression is specifically enriched at the rBCP; these genes are located in synteny in several species (from medaka to mice). These findings suggest the existence of a common regulatory element responsible for gene expression at the rBCP. With this hypothesis in mind, we combined data from gene expression studies in different species, “open chromatin” Chip-Seq analysis, functional enhancer activity and 4C analysis, and isolated a region of 2.5 kb displaying the features of a *bona fide* rBCP enhancer. These results provide a very novel example of genetic coregulation with interesting evolutionary implications. In addition, they shed light into the cis-regulatory logic of the rBCP fate and opens the opportunity to develop new tools for assessing the rBCP behavior and lineage.

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Are Mechanisms of Development prepared for Global Climate Change? Vulnerability of *O. dioica* embryo development to diatom-bloom derived aldehydes, a case study

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Changes in Ocean temperature, pH and salinity are undeniable facts due to the Global Climate Change. Alterations of these variables are inducing algal blooms associated with the release of toxic metabolites harmful for the marine food web. The release of polyunsaturated aldehydes (PUAs; e.g. trans,trans-2,4-decadienal, DD) during diatom blooms is one of the examples described to affect the development of marine species, including copepods, sea urchins and ascidians. Although the genetic mechanisms altered by PUAs are mostly unknown, recent data suggest that retinoic acid (RA) signaling could be distorted. Our objective is to investigate these mechanisms by revealing the effects of DD treatments in the development of the chordate *O. dioica*, an emerging model animal with a fully sequenced genome, a short life cycle, established laboratory cultures, and a well-characterized embryonic development, which in addition is an evolutionary knockout of RA-signaling. Our results show that DD arrests *O. dioica* development mostly after neurulation in a dosage-dependent manner. Using molecular markers we reveal that, despite initial embryonic polarity and cell fate establishment is not affected, the development of mesodermal derivatives is interrupted. Our results, therefore, reveal that PUAs can alter developmental pathways other than RA-signaling. Moreover, our results provide a paradigmatic example of how consequences derived from Global Climate Change can affect developmental programs, and thus can alarmingly alter marine food webs, since *O. dioica* is one of the most abundant zooplankton species in oceans, playing a central role in fish larva survival, and therefore with potential impact on fishery production.

Epigenetic control of regeneration in *Drosophila*

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Regeneration is the ability to restore damaged or lost body parts and tissues. This process is highly regulated and requires a combination of signaling and chromatin events to promote gene expression changes and tissue reprogramming. However, the mechanisms underlying transcriptional regulation during regeneration remain unclear. Chromatin modifying enzymes are crucial modulators in transcriptional regulation and cell memory. Thus, epigenetic modifications are important players in the activation and silencing of genes underlying the ability for a cell to rebuild the lost part. Here we study the role of histone methylation and acethylation in *Drosophila* imaginal disc regeneration. *Drosophila* is an excellent model to approach this question as imaginal discs have the intrinsic competence to restore itself after injury giving rise to normal adult structures. The levels of chromatin modifications have been analyzed in regenerating wing discs through Western blots and immunostaining. Moreover, experiments using heterozygous mutant backgrounds for chromatin modifying enzymes, such as histone methyltransferases (HMTs), acetyltransferases (HATs), histone demethylases (HDMTs), and deacetylases (HDACs), demonstrate that these enzymes are essential during wing disc regeneration.

Hindbrain boundary cell population: from cell cycle dynamics to tissue components

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The rombencephalon or hindbrain is the third and posterior-most vesicle of the brain. During embryogenesis, the hindbrain is transiently metamerized into 7 or 8 segments known as rhombomeres, at the interfaces of which physical barriers appear as actomyosin cables in parallel to the specification of a particular cell population, the so-called rhombomeric boundary cell population (rBCP). The rBCP is a non-neurogenic population relevant to the building up of hindbrain architecture since i) it is a signaling centre that contributes to hindbrain patterning and ii) it acts as a cell mesh that avoids cell intermingling between adjacent rhombomeres, keeping them as lineage-restriction compartments.

The analysis in time of boundary markers shows that the rBCP is kept as a transient two-cell layer at rhombomeric interfaces, indicating that the rBCP displays a neutral growth. Nevertheless, BrdU incorporation analysis and live-imaging show that it is indeed a proliferating population. In order to understand how growth and cell behaviour are linked in the rBCP, in this work we address cell cycle and mode of cell division analyses in the hindbrain by way of in vivo single-cell tracking and PCNA-GFP nuclei distribution. Interestingly, such analyses revealed that different sub-populations according to their cell cycle behaviour build up the rBCP. Aiming to unravel the origin and the fate of the different rBCP cell pools, in vivo cell-tracking of neuroD-GFP+ neuronal precursors and distribution of HuC+ differentiated neurons in the hindbrain were carried out.

Since preliminary results show that there is TEAD-dependent transcription in the boundary tissue, ongoing and future work is focused on sorting out the potential implication of Hippo pathway in rBCP neutral growth. In addition, we also aim to unravel rBCP cell lineage. Shedding light to the proposed questions would allow us to better define how this cell population contributes to the spatio-temporal organization of hindbrain architecture, and hence, to unravel how growth control of a signalling centre contributes to the patterning of the posterior brain.

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