Newsletter of the Centre for Genomic Regulation
Life @ CRG
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"JOVES I CIÈNCIA" PROGRAM: BIODIVERSITY RESEARCH TAKES TO THE MOUNTAINS

MónNatura Pirineus is a center founded with a mission to raise awareness of nature and landscape conservation. This inspiring location was the perfect setting to host the "Joves i Ciència" course on evolution and biodiversity taught by 3 CRG researchers. The CRG was selected to be one of the 5 institutions in Catalunya to teach in the 3-year program from the Fundació Catalunya La Pedrera. Selected from 800 applications, 9 students entering Batxillerat spent 12 intensive days learning theoretical and practical skills to study and understand life. Promoting scientific literacy, the core of the course combined theory with laboratory and fieldwork. By the close of the project, each student had contributed research data on biodiversity for use by the scientific community in the form of DNA barcodes and designed a research project based on their discoveries. The final day saw the students deliver a passionate presentation in defense of biodiversity and conservation that displayed their potential to contribute to what is one of the most pressing issues of modern times. <

THE EUROPEAN GENOME-PHENOME ARCHIVE

The European Genome-phenome Archive, the EGA, stores genome and phenome data on over 100,000 people, from 200 centres and research groups from all around the world, and is a fundamental resource for the advancement of personalised medicine.

This data, which totals around 1,000,000 Gigabytes, will be stored in the Barcelona Supercomputing Centre (BSC-CNS) facilities and subsequently analysed by the MareNostrum supercomputer. The EGA team is coordinated by Arcadi Navarro, who wrote the editorial for this issue of Life@CRG. The project is co-managed by the EMBL-European Bioinformatics Institute (EMBL-EBI) and the CRG. <

EDITORIAL

Arcadi Navarro
Head of EGA Team

On May 14, in one of Fundació La Caixa's most iconic buildings, Palau Macaya, the Secretary of State for R&D from the Spanish Ministry of Economy and Competitiveness, Carmen Vela; the Minister of Economy and Knowledge from the Government of Catalonia, **Andreu Mas-Colell**, and the director general of the "la Caixa" Foundation, **Jaime Lanaspa**, presented the iteration of the European Genome-Phenome Archive (EGA) that is run by the CRG. The EGA is a service for permanent archiving all types of personally identifiable genetic and phenotypic data resulting from biomedical research projects, and sharing this information in a carefully controlled manner. The EGA data was collected from individuals who consent to their data being released only for specific research purposes and to bona fide researchers. Strict protocols govern how the information is managed, stored and distributed by the EGA project.

The project began at the EMBL-European Bioinformatics Institute (EMBL-EBI) but since 2013 the CRG has being sharing responsibility for its management, including the creation of a fully functional copy of all the data, which will be stored at the Barcelona Supercomputing Centre (BSC-CNS).

The EGA Archive currently includes more than 800 studies on more than 50 diseases, such as cancer, diabetes, autoimmune and cardiovascular diseases, as well as neurological disorders. The archive comprises more than half a million files, with a combined volume of around 1PB. In total, over 200 international institutions have entrusted their data to it. The information is from around 100,000 people who have given their consent for this data to be used in scientific research. The amount of data generated by the projects will probably grow to 3-5PB, or even more, during next 12-18 months. And with the cost of genome sequencing down one million fold over the last decade not only will the volume of data keep growing, but the need for exhaustive analysis and interpretation will also increase to unforeseeable levels.

In this sense, the EGA is fundamental for ensuring that publicly funded *-omics* data is properly stored, quickly distributed and thoroughly analysed all over the world so research and transference can be accelerated. The purpose of EGA-CRG is to provide the project with greater resources and expand its functionality. The *-omics* knowledge available at the CRG and in Barcelona at large has been fundamental in the decision for including the CRG as a partner in the EGA project. <

SCIENCE@CRG

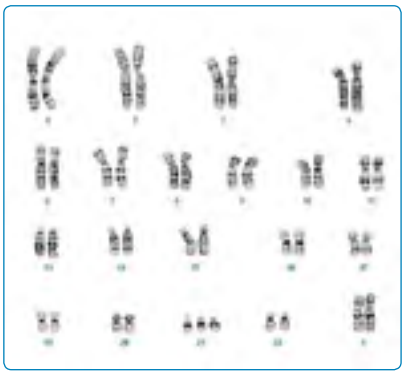
THE LITTLE BIG CHROMOSOME

According to a hypothesis called "gene dosage disequilibrium", the presence of a third chromosome 21 could influence the expression of all the other genes in the genome. Based on this hypothesis, several research groups have tried, so far without success, to identify changes in gene expression within trisomic cells and link them to symptoms seen in patients. However, as the level of most gene expression varies from one person to the next, it is extremely difficult to discriminate between changes exclusively linked to trisomy 21 and those due to natural variation between individuals.

The team of Stylianos Antonarakis at the University of Genève, who studies the genetic basis of phenotypic variation, mainly in humans, had the chance to study the differences between 2 identical twins, one with an extra 21 chromosome. The researchers worked with many specialists around the globe, including Roderic Guigó's lab at the CRG to perform the genome analyses using high-throughput sequencing technologies. And they found that the expression of the genes located on all the other chromosomes were disturbed in

trisomic cells. In the twin with Down's syndrome, the domains are sometimes over-expressed, and sometimes under-expressed when compared with the healthy twin. By comparing their results with data previously published by other researchers, this specific chromosomal organisation correlates with the position of the DNA in the cell nucleus. Therefore, domains over-expressed in the twin with Down's syndrome correspond to portions of DNA known to primarily interact with the periphery of the nucleus.

The study, published in *Nature*, therefore shows for the first time that the DNA's position in the nucleus or the biochemical characteristics of DNA-protein interactions in the trisomic cells is modified, leading to changes in the gene expression profile. More info at www.crg.eu/news <



UNDERSTANDING CELL REPROGRAMMING

From almost 8 years now researchers have been able to convert normal somatic cells into iPS cells, which have similar morphologies and growth properties to Embrionic Stem cells (ES cells) and express all their specific genes. And one way of doing this is by transmitting a signal to make cells reprogramme themselves. Maria Pia Cosma's lab is dedicated to understanding the "Wnt signalling pathway", a series of biochemical reactions produced in cells that are involved in many processes during embryonic development and cell fusion. In a paper published in *Stem Cell Reports* they explained how this route behaves during the process of reprogramming somatic cells into iPS. "It is a very dynamic process that produces oscillations from the pathway, which is not active all the time. We have seen that there are two phases and that in each of them, Wnt fulfils a different function. And we have shown that by inhibiting it at the beginning of the process and activating it at the end we can increase the efficiency of reprogramming and obtain a larger number of pluripotent cells", indicates Ilda Theka, a PhD student in Pia Cosma's group and a co-author of the article.

They have also seen that the exact moment when the Wnt pathway is activated is crucial. Doing it too early makes the cells begin to differentiate, for example into neurons or endodermal cells, and they are not reprogrammed. More info at www.crg.eu/news <

INSIDE

CELL AND DEVELOPMENTAL BIOLOGY PROGRAMME

Vivek Malhotra

Overall, we aim to address questions of fundamental importance with special focus on cell compartmentation, cytoskeleton, cell division, and tissue organization. An example of the kind of questions that are the focus of the labs in this department follows.

A question: The mechanism of cell compartmentation?

One of the most fundamental questions in cell biology has been how different proteins are correctly targeted to different compartments of the cell. About 40 years ago, George Palade and colleagues chose to take on the apparently simpler and more tractable question of defining the basic mechanism of protein secretion. Based on his painstaking analysis of the secretion of chymotrypsin by rat pancreatic acinar cells, Palade proposed that secretory cargo moved from the ER to the Golgi and then by large vesicles to the plasma membrane and eventually to the exterior of the cells.

Each of these 3 steps in the unraveling of the secretory pathway were awarded a Nobel Prize: Palade, De Duve and Claude (1974) for "their discoveries concerning the structural and functional organization of the cell; Günter Blobel (1999) for the discovery that "proteins have intrinsic signals that govern their transport and localization in the cell", and James Rothman, Randy Schekman and Thomas Südhof (2013) for their discoveries of "machinery regulating vesicle traffic, a major transport system in our cells."

This wonderful scheme is now known as the conventional secretory pathway and responsible for the trafficking and secretion of proteins that include

insulin, neurotransmitters, growth hormones, antibodies, opiates, and collagens (the most abundant of the secretory cargoes). These findings although motivated to understand the basic mechanism of secretion, in fact have provided a foundation for understanding the longstanding problem of cell compartmentation.

An old unanswered question

The vesicles identified to date are small 60-90 nm in average diameter and this cannot explain the trafficking of bulky secretory cargoes such as the collagens (necessary for virtually all cell to cell interactions and tissue organization) or even bulkier chylomicrons (necessary for the movement of fats and cholesterol in the blood). How are these molecules secreted?

New proteins and a new pathway

A protein called TANGO1 has been identified that packs collagen VII but not collagen I at the endoplasmic reticulum (ER). There are 28 different kinds of collagens in the humans and new findings reveal that collagens are sorted from each other in the lumen of the ER for their export by different pathways. Therefore, the choice of export routes from the ER is not based solely on the size of the cargoes. The new data also suggests that the target compartment (for example the Golgi) donates membranes necessary for generating a mega transport carrier from the ER. This suggests a novel method vesicle production for protein secretion (Nogueira C et al., *eLIFE* 2014).

In sum, a question that arose out of curiosity about a basic secretory mechanism has revealed insights to the more complex question of compartmentalization. The cycle of hypothesis-molecules-mechanism thus continues with more challenging questions arising, that will no doubt help reveal novel insights. And so we march forward in our quest to understand how a cell is compartmentalized and functions as a unit within a tissue. <

GENDER SUMMIT 2014: WHY INCORPORATING GENDER/SEX INTO SCIENCE IS IMPORTANT

Veronica A. Raker, Michela Bertero

The 4th Gender Summit (Brussels, 30/6-1/7; www.gender-summit.eu) focused mainly on gender in the upcoming EC funding scheme Horizon 2020, both on achieving gender equality among the participants and on incorporating the gender/sex dimension into research. Scientists have a strong external motivation for addressing these issues if they plan to apply for H2020 funding, as both will be considered during proposal evaluation. Women scientists are still underrepresented in EC funding; for instance, overall, only about one-fifth of the participants in the FP7 funding program were women scientists. Isabelle Vernos (CRG), who is the chair of the gender working group of the European Research Council, discussed the ERC situation, for which the success rate for women is lower than that for men (for instance, in life sciences, 30% of the applicants, but only 21% of the grantees, were women in the past 7 years; ERC Gender Statistics). Dr. Vernos mentioned the complexity of identifying the underlying reasons for this disparity and the measures that could be implemented to rectify it, such as training evaluators to avoid implicit bias and modifying that application procedure by restricting the number of publications that can be added (thereby focusing on quality rather than quantity and neutralizing effects due to time taken off, for instance for parenting duties).

While most scientists agree that reaching gender equality is important, fewer realize that gender and/or sex should be considered in the research directly—or how to do this. Londa Schiebinger (Stanford University) presented the "gendered innovations" website (genderedinnovations.stanford.edu; in collaboration with the EC), which provides scientists with in-depth case studies of how (and why) gender/sex should be taken into account in research. Several scientists also presented research exemplifying how results can differ once gender/sex is taken into account (for instance, some biomarkers of disease are predictive for only one sex but not for the other). Notably, scientists are getting pushes for incorporating gender/sex into their research not only from the funding agencies, but also soon from some of the top journals—Dr. Schiebinger mentioned that both *Nature* and *Science* will implement policies for this in the near future. <

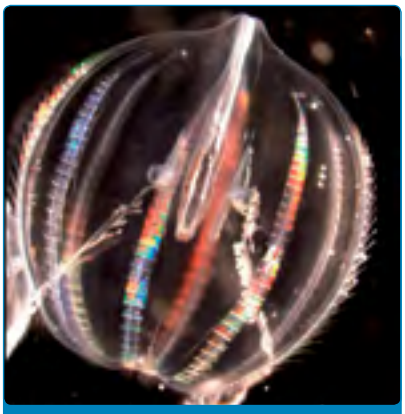
SCIENCE@CRG

THE SIMPLE BRAINS OF "COMB JELLIES" EVOLVED IN A COMPLETELY DIFFERENT WAY TO THAT OF THE REST OF NATURE

Simple organisms like the ctenophores can lead to impressive scientific discoveries. All organisms evolved from a single ancestor, and studying when a given organism branched off this tree is a way of understanding how a simple form of early animals evolved more complex systems. Ctenophores may represent the earliest lineage to split off from the common ancestor of all animals.

The neural development of the Pacific sea gooseberry (*Pleurobrachia bachei*) took a unique evolutionary path, not seen in any other animal's evolutionary history. They do not use serotonin, dopamine, acetylcholine or the majority of the other neural transmitters that control brain activity in most animals. Instead, they may use a unique array of peptides and glutamate neural signalling, genetic editing and a diverse array of electrical synapses. These findings have many consequences for research, including new ways for scientists to approach their study of neural diseases like Alzheimer's.

Lenoid Moroz, from the Whitney Laboratory for Marine Biosciences at the University of Florida, coordinated this 7 year study recently published in *Nature*, with the participation of several other institutes and researchers, including Fyodor Kondrashov's lab at the CRG. What they did was impressive, too: they took samples and set up a mobile sequencing unit on board of the boat "Copasetic". After 2 hours, the genomes were sequenced and the data sent via satellite to the university's supercomputer. More info at www.crg.eu/news <



Pleurobrachia bachei ©Leonid Moroz

STEROID HORMONES HAVE A DIFFERENT WAY OF MODULATING THE ACTIVITY OF TARGET GENES

Researchers from the Chromatin and Gene Expression lab at the CRG, coordinated by Miguel Beato, and the Institute of Biology and Experimental Medicine (IBYME) in Argentina, have recently published a study in *PLOS One* where they describe a new mechanism used by progesterone receptors to induce stromal cell proliferation at picomolar progestin concentrations. What they found is that progestin-induced proliferation of endometrial stromal cells is mediated by two kinases (ERK1-2 and AKT), dependent on the early regulation of USF1, which directly induces the cell cycle regulator Cdc2. The results in endometrial stromal cells are an example of the different ways used by steroid hormones, particularly progesterone, to modulate the activity of target genes. "To our knowledge, this is the first description of early target genes of progestin-activated classical PR via crosstalk with protein kinases and independently of hormone receptors binding to the genomic targets", says Patricia Saragüeta, co-author of the study and principal investigator at the IBYME-CONICET.

"These cells have very little progesterone receptor although it is enough to trigger cell proliferation through the route described in the paper. This finding highlights the importance of kinase signalling for genomic hormone effects", says Miguel Beato. "By clinical standards, the cells we used would have been considered negative for the progesterone receptor, and yet the cells respond to hormone stimulation. This could also apply to breast cancer cells with very low levels of hormone receptors", he adds. More info at www.crg.eu/news <

FEATURING CRG

2014 PhD RETREAT, VIENNA (AUSTRIA)

One of the most exciting events organized by the PhD community took place this June: the PhD international retreat. This year we met with our fellow PhD students from the CeMM (Research Center for Molecular Medicine of the Austrian Academy of Sciences). Additionally and for the first time, we invited one PhD representative from each EU life Institute to join.

The first day of the meeting, we visited the CeMM building in Vienna where their director, Giulio Superti-Furga, welcomed us with an original and inspiring talk followed by a lecture on competitive funding by Prof. Dr. Helga Nowotny, former presi-

FEATURING CRG

dent of the European Research Council. The rest of the meeting was held in Rax in the Northern Limestone Alps. Surrounded by this beautiful environment, keynotes lectures were held by Sebastian Maurer (Group Leader at CRG), Peter Rodgers (Features Editor of *eLife*) and Christoph Bock (Group Leader and Coordinator of the Biomedical Sequencing Facility at CeMM). Also, all PhD students presented their scientific interests in "elevator pitch" talks and participated in a workshop about negotiation skills and teamwork. Finally, the meeting was set out to be very interactive. We carried out games, a hiking activity and a farewell party, which gave us fantastic opportunities to get to know other students and establish valuable scientific connections between the CRG, the CeMM, the Curie Institute, the VIB, the IIT and the IEO. <

THE CRG IN NATURE JOBS CAREER EXPO

Following last years' experience, the CRG took part in the Nature Jobs Career Expo, organised by Nature and held at the John B. Hynes Veterans Memorial Convention Centre (Boston, USA) on May 20th. We participated in order to raise the CRG's international profile and attract talented junior researchers to our institute. There were more than 30 exhibitors, representing both international research institutes and

biotechnology/pharmaceutical companies. Most of the 300+ participants were from different states in the USA, but there were others from Canada and Europe. Everyone who visited the CRG booth was invited to fill in a questionnaire reflecting their current position and future interests. This was of great help in understanding that although the vast majority of participants were postdocs searching for PI positions, many were PhD students looking for a postdoc position for when they finished. In summary, it was a very important opportunity to show the world that despite the economical crisis, the CRG is still and will continue to be a place where excellent science is produced. <

4 RESEARCH INSTITUTIONS COLLABORATE TO COMMUNICATE SCIENCE TO SOCIETY

The CRG is a partner in the EU FP7 Communication Network CommHERE that attempts to effectively communicate the results of the research projects funded by the EU Health Directorate. The centre, in collaboration with the EMBL and the EUSJA, invited journalists from Poland, Russia, Germany, Belgium, Denmark, Italy, the Netherlands and Spain, to come to Barcelona and have an in-depth look at the health research performed by four top scientific institutes: the CRG, the Institute of Photonics Sciences (ICFO), the Barcelona Supercomputing Centre (BSC) and the Vall d'Hebron Institute of Oncology (VHIO).

The goal of the study trip was to showcase the cutting-edge research facilities based in Barcelona that join forces in many common projects to understand the complexity of life, from the genome to the cell to a whole organism, and the mechanisms that underlie genetic diseases. The journalists had the opportunity to visit the research facilities and also had the chance to speak directly to the researchers.

The participating research institutions valued the opportunity to meet with the journalists and show them their facilities. They were also interested in creating new activities among the 4 institutions to explain the science performed by their researchers. After this first-of-its-kind experience, they all want to continue developing more joint ventures to explain science to the society at local and international levels. <

FEATURING CRG

NEW SUSTAINABILITY AND ENERGY SAVINGS WORKING GROUP IN THE PRBB BUILDING

Many changes have already taken place as initiatives lead by individual centres at the PRBB to improve energy efficiency and promote more sustainable attitudes among a community that is already particularly sensitive to these issues. With the goal of moving forward with such initiatives globally, in a more coordinated and effective manner, a sustainability and energy savings working group has been appointed (http://bit.ly/1uiMR6G) comprising members from all PRRB centres. Such group will be responsible for planning and proposing common actions aimed at:

1. Implementing global energy-saving measures throughout the building as well as those that may be particular to each centre.
2. Reducing waste and promoting proper sorting using existing means.
3. Applying sustainability criteria in procurement and contracting activities.
4. Promoting environmentally friendly habits among PRRB residents.

The CRG already have launched the **2014 Sustainability & Environmental Management Campaign**, addressed to everyone in the centre. Thanks to your collaboration, during 2013 we reduce the energy consumption, the amounts of A4 sheets and the number of waste containers units. **The only thing to regret** is the water consumption, which we encourage you to help us reduce it during 2014. For further information on the campaign, visit the page: **www.crg.eu/intranet/sustainability_campaign** <

CRG & SOCIETY

PREVENTION OF HEALTH AND SAFETY RISKS IN THE CRG

From 21-23 May, the CRG took part in the International Conference on Occupational Risk Prevention (ORP2014), which was held in Zaragoza. The Health and Safety department presented two studies. The first was about how the general public is given information on risk prevention activities during the PRBB Open Day (each first Saturday in October). On this day, the CRG offers risk prevention activities in workshops designed for children. In these sessions the young people learn about how to protect researchers in a laboratory and they get to know the tools the researchers work with. The second presentation was about investigating lab accidents. In this study they looked at protocols in case of emergencies, periodic meetings with lab staff, periodic supervision, and so on. This particular work received a lot of attention due to the uniqueness of the working environment in a scientific institute, and proved the tremendous complexity of the work and the difficulty of maintaining high safety standards in this setting. <

AWARDS AND HONOURS

Mara Dierssen, group leader of the Cellular & Systems Neurobiology laboratory, has been awarded with the 2014 David and Hillie Mahoney Award for an Individual's Contribution to Outreach.

PEOPLE @ CRG

WELCOMES

We warmly welcome:

Manuel Irimia is the new Group Leader at the CRG. He holds a PhD from the Barcelona University (UB) and has had postdoc experience at the University of Toronto and Stanford University. He now coordinates the Transcriptomics of vertebrate development and evolution Group at the CRG.

Juan Laorden is the new Head of the Human Resources department at the CRG. He has had a long and successful career as director of HR departments acquired in different companies and sectors. Juan holds a degree in Industrial Psychology, an MBA by ESADE and a Management Development Programme (PDD) qualification from the IESE.

Salvatore Cappadona is the new Project Manager in the Tech Transfer department at the CRG. He holds a PhD. in Computational Proteomics from Politecnico di Milano and has had postdoc experience at Lund University, Utrecht University and the CRG. He also has an International Diploma in Science Management from the IE Business School in Madrid.

Mario Alberich (EGA); Sergio Aranda (Epigenetic Events in Cancer); Sharon Bel (Reception); Riccardo Delli Ponti (Gene Function and Evolution); Andre Faure and Jennifer Semple (Genetic Systems); Amargant Farnes (Microtubule function and cell division); Valentina Claudia Ferlito (Sensory Systems and Behaviour); Philip Germann (Multicellular Systems Biology); Marta Gómez (Cellular & Systems Neurobiology); Santiago Guerrero and Julien Villeneuve (Regulation of Protein Synthesis in Eukaryotes); Antonios Lloutas and Caroline Wiggers(Chromatin and Gene Expression); Jon Permanyer (Transcriptomics of vertebrate development and evolution).

FAREWELLS

Our best wishes to:

Federico Agostini (Gene Function and Evolution); Josep Burgés (Tech Transfer); Laia Campos (Secretariat); Felice Contaldi (Bioinformatics Unit); Pascale Crepieux (Design of Biological Systems); Marc Friedlander, Jacqueline Frost and Anna Houben (Genomics and Disease); Francesco Mancuso (Protemics Unit); Cristina Militti and Emilia Szostak (Regulation of Protein Synthesis in Eukaryotes); Kiashanee Moodley (Regulation of Alternative pre-mRNA Splicing during Cell Differentiation, Development and Disease); Barbara Negre (Comparative Analysis of Developmental Systems); Martina Niksic (Multicellular Systems Biology); Jean-François Popoff (Intracellular Compartmentation); Francesca Rapino (Hematopoietic stem cells, transdifferentiation and reprogramming); Zoe Barbara (Reception).

DIARY

01-05/09/2014 - CRG STAR Courses
1st CRG Bio-Business School
http://ibbs.crg.eu/

15-20/09/2014 - COURSES@CRG
Genome wide approaches to study functional protein/RNA interactions
http://www.crg.eu/events

25-26/09/14 -
1st Lightsheet Fluorescence Microscopy International Conference & 6th LSFM International workshop.
Casa Convalescència, Sant Antoni Maria Claret 171, 08041 Barcelona.
www.lsfm2014.com/

01-02/10/2014 - 50 Years of Histone Acetylation.
Barcelona Conference on Epigenetics and Cancer
www.crg.eu/en/event/2nd-bcec-50-years-histone-acetylation

06-07/11/14 - 13th CRG Symposium
Gene Regulation, Stem Cells and Cancer
http://2014symposium.crg.eu//

08-13/11/13
ESF-EMBO Conference on Flies, Worms and Robots: combining perspectives on minibrains and behaviour St.Feliu de Guixols
http://minibrains.esf.org/

CRG Centre for Genomic Regulation

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