Contents

FOREWORD 4

SCIENTIFIC HIGHLIGHTS 6
Mapping the ‘fitness landscape’ 7
Unpacking a packaging problem 9
Nuclear power 11
Breaking the law 13
Down syndrome treatment is shaping up 15
Let’s get together 17
Collecting fingerprints 19
ERC Researchers at CRG 21
Research 22

FACTS AND FIGURES 26

FINANCIAL REPORT 32

ACKNOWLEDGEMENTS 34
Executive Summary 2016

Integrative Biology will be the CRG’s cornerstone of its scientific programme in the coming five years, according to its new strategic plan approved in 2016. Addressing the complexity of biological systems, and more specifically of humans, now more than ever requires consensus-based and integrated approaches and biomedical interdisciplinary science. To foster Interdisciplinary Biology, the CRG Strategic Plan (2017-2021) will open up new scientific horizons, provide novel translational opportunities for CRG’s scientific activities and help to bring its triple mission of generating knowledge, training the next generation of scientists and adding value to society.

In the course of the year, we underwent four different evaluations by external panels: a) the European Genome-phenome Archive (EGA), a database run jointly with the EMBL-EBI and the Barcelona Supercomputing Center-Centro Nacional de Supercomputación (BSC-CNS) (13-14 June 2016); b) Core Facilities (15-16 December 2016); c) Evaluation of the Administration (28-29 November 2016); and d) An overall evaluation of the CRG by the CERCA Institution, of the Catalan Government (15 December 2016). The feedback was highly positive in all cases and provided us with useful insights for improving the CRG. Particular mention should be made of the first-ever evaluation of our Administration by a panel of international experts. In the future, all of the CRG’s scientific and administration departments will be periodically evaluated.

In 2016, three of our young PIs found senior positions in other institutes. Pedro Carvalho moved to the University of Oxford, in the United Kingdom, as EP Abraham Professor of Cell Biology. Bill Keyes became Team Leader at the Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC) in Strasbourg, France, and Matthieu Louis moved to the University of California in Santa Barbara, in the United States, as Assistant Professor in Molecular, Cellular and Developmental Biology. We are extremely pleased that all of them have found excellent positions, thus attesting to the CRG’s success in training and promoting young scientists.

Moreover, in the course of the year we hired three new young PIs. Verena Ruprecht arrived in September from the Institute of Science and Technology (IST) in Austria; Elvan Boke, previously employed at the Harvard Medical School in the United States, will be joining us in February 2017. Both Verena and Elvan will be joining the Cell & Developmental Biology Department. Nicholas Stroustrup, also from the Harvard Medical School in the United States, will join the Systems Biology Programme in February 2017.

Foreword
It is important to highlight the fact that two of these new young PIs are women. We trust that thanks to both our strategic plan and our cooperation with other EU-LIFE institutes in the framework of the LIBRA project (led by Isabelle Vernos) we will be able to attract more top women scientists to the CRG in the coming years in order to improve gender equality. In this regard, we are very proud of the activities implemented by the CRG Gender Balance Committee, including the Women Scientists Support Grant (WOSS). By providing extra financial support, which can be used, for example, for extra day-care and child-care hours, the CRG seeks to enable excellent women scientists to follow their passion in research and go on to become future leaders in their respective fields.

Mention must also be award of the distinguished awards that recognised the scientific commitment and merit of Ben Lehner, who received the EMBO Gold Medal and the Liliane Bettencourt Prize in Life Sciences 2016.

We continued to foster multiple innovative activities to engage with society and are proud of the successful closing event and the results of the "Stick out your Tongue" citizen science project. The second edition of the project, which started in September 2016, received funding once again from the "la Caixa" Bank Foundation. Moreover, the Summer School of Molecular and Theoretical Biology was held for the first time in Barcelona and successfully organised by Fyodor Kondrashov from 2 to 8 August for 80 international students.

In the realm of funding, the CRG continues to attract competitive funds by securing two new coordinated European projects under the H2020 scheme: Divide (coordinated by Isabelle Vernos), and CellView (coordinated by Pia Cosma). Moreover, Toni Gabaldón was awarded his second ERC Consolidator Grant (CoG). In this regard, the CRG is among the top 10 beneficiaries of EC financial contribution granted in H2020 in Spain and holds fifth place in the ranking of ERC-funded projects in Spain per host institution and scheme.

At international level, EU-LIFE, an alliance of 13 European research institutes in life sciences, co-founded by the CRG, now has a strong voice on the European scientific policy scene. During the year, Michela Bertero, Head of the International & Scientific Affairs office at the CRG, was appointed member of the European Open Science Policy Platform to advise Commissioner Moedas on Open Science policies and reaching out to stakeholders.

Another important aspect that deserves mention is the CRG’s ongoing and steadfast commitment to activities of the newly-founded Barcelona Institute of Science and Technology (BIST), which brings together six world-leading institutes in photonics, chemistry, life sciences, high-energy physics, nanoscience and nanotechnologies. Highlights here include the recruitment of new PhD students, joint training activities and a joint school with the ESADE business school.

We are excited and enthusiastic about starting to work on the new ideas underlying Integrative Biology, described in the plans that will drive the CRG’s future in the coming years. I firmly believe that these new ideas, coupled with the CRG’s excellent people, will enable us to continue to produce frontier science.

Luis Serrano
Director
Scientific Highlights
Mapping the ‘fitness landscape’

A fluorescent jellyfish gene is shedding light on how DNA changes affect a gene’s function.

Genes are genetic recipes that our cells use to make proteins – the biological building blocks of life. Changes in genes affect the characteristics of an organism. For example, variations in pigmentation genes affect eye or hair colour in humans and other animals, while different genetic changes can cause diseases such as cystic fibrosis or cancer. On a longer time-scale, genetic changes are the fuel for natural selection, leading to the evolution of new species.

DNA is made up of four chemicals called bases, known by their initials: A (adenine), C (cytosine), G (guanine) and T (thymine). Like a four-letter alphabet, the order of the DNA ‘letters’ in a gene spell out the recipe within it. Until now, researchers have tended to only study single letter changes in a particular gene at any one time, observing the effect of the alteration on the resulting protein. But in real life, organisms have many DNA changes and variations scattered throughout each of their genes, which can all interact to affect the outcome.

To work out how multiple genetic changes work together, Fyodor Kondrashov and his team in the Evolutionary Genomics laboratory at the Centre for Genomic Regulation (CRG) have sifted through more than 50,000 altered jellyfish genes. This work was done in collaboration with scientists in Russia, Israel and the USA, and published in the journal *Nature*.

The gene in question encodes Green Fluorescent Protein (GFP), which was originally taken from a North American species of jellyfish, *Aequorea victoria*. GFP is widely used by scientists as a tool for labelling other proteins inside cells so they can be seen down a microscope, and glows bright green when exposed to certain colours of light. The CRG team scanned through thousands of different versions of the GFP gene, analysing the effect of one, two or multiple genetic changes (mutations) on the fluorescence levels of the resulting proteins.

Rather than having to examine thousands of jellyfish, the researchers made mutations in a version of the GFP gene that had been transferred into harmless lab bacteria called E. coli, which produce the altered fluorescent protein as they grow. Some changes don’t affect the level of fluorescence of the protein, while others make it dimmer or get rid of the glow altogether.
Thanks to advances in DNA sequencing – the technology that allows scientists to ‘read’ the genetic information – Fyodor and his team were able to find out exactly what changes had been made within every altered version of the GFP gene and link that back to any changes in fluorescence of the protein. Surprisingly, they found that some combinations of mutations had a more pronounced effect on the fluorescence than might have been predicted from the effect of each single change by itself – like a tower of stacked blocks suddenly collapsing when a couple of key pieces are removed.

Finally, using computer modelling, the researchers were able to construct a ‘fitness landscape’, mapping how multiple combinations of changes in the GFP gene interact to affect the brightness of the resulting protein. The genetic changes in the ‘peak’ still produce brightly fluorescent GFP, while those around the edges do not, with a sharp drop-off between the two states. To use our stacking bricks analogy, either the tower stands tall with several bricks missing or it suddenly collapses into a heap.

“It is the combination of mutations that is important,” explains Karen Sarkisyans, co-lead author of the research paper along with Dmitry Bolotin from the Institute of Bioorganic Chemistry in Moscow. “They don’t act independently of each other, and in some cases the outcome is more than the sum of its genetic parts.”

“The fitness landscape is an abstract concept that simplifies our thinking of how the characteristics of an organism come from its underlying genetic makeup,” Fyodor says. “This is the first time anyone has been able to generate real data to graphically represent this concept, looking at combinations of genetic changes rather than just single mutations.”

He believes this work a first step towards understanding how changes in the DNA (genotype) of an organism combine together to affect its traits, characteristics and even diseases (phenotype). “Our research takes us some way towards being able to predict the effects of different combinations of mutations. If we can understand and draw fitness landscapes for genes, cells and even one day for whole organisms, we would know so much more about biology – what combination of mutations causes cancer or other diseases, or the evolutionary changes that make a characteristic like the trunk of an elephant.”

REFERENCE WORK:
“Local fitness landscape of the green fluorescent protein.”
Unpacking a packaging problem

Researchers have figured out how cells manage to stash large molecules into biological bags.

All the cells of your body are made up from proteins and fats, encoded by the genetic instructions within DNA. Most of these proteins are manufactured in a kind of molecular ‘factory’ known as the endoplasmic reticulum – a sprawling network of membranes found inside every cell. They are then packaged into biological ‘bags’ called vesicles, ready to be shipped around inside and outside the cell, depending on their function.

Vesicles are created from a combination of the fat and protein-containing membrane of endoplasmic reticulum, along with specialised coating proteins. The coats surround the protein cargo and pinches it off into a little bag – a bit like picking up a lump of wet sand from a beach with your hand. There’s been a huge amount of interest in studying the components and formation of these bags or vesicles over the years, and they’ve been the subject of several Nobel prizes.

Much of this ground-breaking work has been done on the packaging and transportation of small proteins. However, bigger molecules are also packaged into vesicles, and include long rods of collagen that make up the skin, bones and other structures, or big blobs of fat and protein called chylomicrons. So how do cells change the size of the bags based on the size of the cargo?

In theory, these components – such as collagens and chylomicrons – should be too large to fit into the standard sized vesicles that are usually pinched off from the endoplasmic reticulum, and it was a mystery as to how this feat of biological packing is achieved. Now Vivek Malhotra, leader of the Intracellular Compartmentation group at the Centre for Genomic Regulation (CRG), has found out, publishing his discovery in the Journal of Cell Biology.

He and his team focused on a protein called TANGO1, which they first discovered around ten years ago. They recently found that TANGO1 plays a very important role in packing long collagen rods into vesicles, a bit like someone holding open a big bag with one hand and piling sticks inside. Importantly, this bigger vesicle grows by adding in smaller vesicles that fuse together to generate a larger space, rather than by
grabbing more membrane from the endoplasmic reticulum itself.

Next, Vivek turned his attention to the fatty chylomicrons. He discovered that TANGO1 couldn’t pack them alone – imagine just one person trying to put very large balloons into bag all by themselves. Instead, TANGO1 needs help from another molecule called TALI (TANGO1-like). Similar to the production of collagen-containing vesicles, this pair grab the fat and protein cargo and package it up, pulling in extra little vesicles and joining them together to grow a big enough bag to contain it all.

This finding is more important than just solving a biological packing problem. Scientists have revealed that changes in the TANGO1 protein affect the release of fatty, cholesterol-packed chylomicrons into the bloodstream. Once there, they can clog up the arteries and cause heart disease. Furthermore, too much production of collagen creates a condition called fibrosis, which can cause serious health problems. Vivek believes that his discovery could lead to important new treatments for these diseases.

“We’re excited about this discovery because it helps us to not only understand the basic principles of biology and secretion, but also has the potential for providing a tool to control diseases,” he says. “If we can come up with a compound that reduces TANGO1 in cells, this would control the amounts of collagen that is secreted so you could treat fibrosis in the skin, liver, or even lungs. Similarly, we could block TANGO1 and TALI together, which would control the secretion of chylomicrons to control the levels of fat in the blood.”

He’s also thrilled because his lab has answered one of the major challenges in the field of vesicle formation research. But the hard work is only just starting. “Our findings have started a brand-new challenge, so it’s going to keep many people occupied for many years finding out exactly how TALI and TANGO1 are working together.”

REFERENCE WORK:
Nuclear power

A newly-discovered energy-generating process inside cancer cells provides the fuel for growth.

It’s hard work being a cancer cell, constantly growing and dividing. This takes a lot of energy, not just in terms of building new molecular components but also for switching on important genes that drive cell growth.

DNA, which encodes our genes, is housed inside a kind of ‘control centre’ within the cell called the nucleus. The DNA itself is coiled into ball-shaped structures called nucleosomes that themselves are folded into the chromatin fibre, which keep them tightly packed up. In order to switch a gene on, the chromatin has to be “opened” and the nucleosomes need to be shuffled around so the DNA can be easily accessed by the cell’s gene-reading machinery.

All of this shifting and shuffling uses a lot of energy, especially for highly active cancer cells. Until now, the way in which cancer cells generate all this energy has been a mystery. But it’s finally been solved by Miguel Beato and his post-doctoral fellow Roni Wright in the Chromatin and Gene Expression group at the Centre for Genomic regulation in Barcelona, who published their work in the journal Science.

First, they had to develop a technique for measuring the levels of ATP (adenosine triphosphate) in the nucleus – this is the chemical ‘fuel’ that is used for energy inside cells. They discovered that levels of ATP shot up in the nucleus of breast cancer cells in response to the female sex hormone progesterone, which strongly stimulates gene activity. This suggests that the hormone is triggering a lot of nucleosome remodelling, using up a lot of fuel.

Normally, ATP is created by cellular ‘power stations’ known as mitochondria. However, when Roni used a drug to shut down the mitochondria, the fuel surge in the nucleus still happened – but only as long as the mitochondria provided a little initial burst of ATP to get things started. Clearly, there must be another source of energy inside the nucleus itself.

While searching for possible fuel sources, Miguel and Roni hit upon a chemical known as PAR (short for poly-ADP-ribose), which exists as long chains of a smaller chemical called ADP-ribose that are strung together by a protein called PARP (poly-ADP-ribose polymerase). PARP uses NAD (nicotinamide adenine...
dinucleotide, the exchange energy currency) synthesized in the nucleus from mitochondrial ATP.

When an energy hit is required, PAR is generated leading to opening of the chromatin and strings of PAR are chopped up to release lots of ADP-ribose molecules. A protein called NUDIX5 uses pyrophosphate to turn them into a very similar molecule: adenosine triphosphate – the highly desirable ATP fuel. Thus, making PAR serves a double function, opening the chromatin and recovering part of the ATP for shuffling nucleosomes.

In fact, this isn’t a new idea. US scientist Vincent Allfrey had suggested that there might be a source of energy inside the nucleus around 50 years ago. But researchers lacked the technical tools required to find it at the time. It’s only now that technology has improved that Roni and Miguel have been able to pin down the fuel. It wasn’t easy convincing the rest of the scientific world that they had found the elusive energy source after so long, though.

“The scientific establishment resisted this idea because it was too new,” says Miguel, even though it’s half a century old. “People forgot these things and thought that if the mitochondria are making energy, why do you need another source of ATP? But because we were newcomers to this field, we were not so loaded with knowledge, bias or prejudice. This is what science is about. You have to destroy prejudices and over.”

The discovery has big implications for the development of new treatments for cancer. Drugs that can block the activity of PARP have recently been approved for treating some types of ovarian cancer. Combining them with a treatment that also switches off the ATP-generating capabilities of NUDIX could be an effective way to ‘power down’ cancer cells, shutting off the source of the fuel they rely on to switch on the genes that keep them growing.

It’s hugely exciting for Miguel and his team that they have made a finding with such big implications. “This is the first time that anyone has found this, and even though I am in my 70s now it is probably the most important discovery I have made in my life!” he laughs.

REFERENCE WORK:
Breaking the law

A rogue molecule leads others astray, causing cancer cells to spread around the body.

Imagine a town situated in beautiful countryside. Although property developers might want to build as many houses as possible, spreading buildings out across the land, it would be a bad idea to completely destroy the environment. So the government passes laws limiting how many houses can be built and where they can go. In this way, the town grows at a controlled rate without spoiling the landscape.

This is a useful metaphor for the cells within our body. We need to make new cells as we grow, and to replace damaged or dead ones. But this process has to be tightly controlled to prevent cancer – a disease caused by cells multiplying out of control, forming tumours that grow and spread.

In the case of melanoma skin cancer, small tumours at an early stage can be easily treated with surgery, removing the overgrown cells and curing the cancer completely. But if the melanoma cells have started to spread through the body (a process known as metastasis) the outlook is much worse. Although new treatments that activate the immune system have started to show promise against metastatic melanoma, the chances of survival are currently still very poor.

It’s currently a mystery why some melanoma tumours just stay in one place, while others start to spread aggressively around the body. But Fátima Gebauer, head of the Regulation of Protein Synthesis in Eukaryotes group at the Centre for Genomic Regulation in Barcelona, is starting to figure out the answer.

Her lab focuses on RNA binding proteins in tiny Drosophila fruit flies – molecules that stick to the molecular ‘message’ that is produced when genes are activated. One of these, called UNR, is also found in human cells, where it’s known as CSDE1. Fátima and her team were intrigued to notice that Drosophila UNR was sticking to many messages that have been implicated in cancer progression in humans, so they decided to take a closer look.

Working with collaborators in Spain and Germany, Fátima and her team discovered that removing UNR from melanoma cells meant that they could no longer spread when they were transplanted into
a mouse. In contrast, making extra UNR in a non-metastatic cell could transform it into the dangerous spreading type. To find out exactly what was going on, they took a closer look at the RNA messages that UNR was interacting with inside the cancer cells.

Using large-scale gene analysis techniques, Fátima found that UNR was stuck to the RNA messages made from a number of genes that were known to be important in melanoma. In some cases, it helped to ‘stimulate’ these messages, effectively making the genes more active, while it suppressed the messages from others.

Importantly, the genes that were activated by UNR are cellular ‘builders’, including two genes called VIM and RAC1. These are like the enthusiastic property developers in our analogy, wanting to build as many cells as possible all over the beautiful countryside. Normally, they are kept in check by tumour suppressor genes such as PTEN. This has the same effect as the government does on the aggressive builders, keeping cancer cells in check so they can’t start spreading out around the body. But UNR deactivates PTEN, so it can’t carry out this vital protective role.

Publishing her discovery in the journal Cancer Cell, Fátima thinks that the combined activities of UNR – activating the ‘builders’ and removing the ‘law’ that stops them from spreading – could be an important trigger for melanoma cells to start spreading aggressively through the body. “Many other proteins have been show to stimulate the growth of cancer cells,” she explains, “but the important thing here is that UNR is one of the few RNA binding proteins that has been shown to play a dedicated role in metastasis – this is not about tumour growth, but about how it spreads.”

Although it’s exciting to think that this discovery might pave the way for treatments that stop melanoma from spreading, this is a very long way off. In the nearer future, Fátima hopes to use this knowledge to develop markers that would enable doctors to predict whether an individual person’s melanoma is likely to spread around the body, so they can design the most effective approach for treating it.

To test this idea, she is now collecting samples from melanoma patients and measuring the amount of UNR in their tumours. She wants to see whether those with high UNR levels go on to spread aggressively around the body, while those with low levels would be predicted to stay put. She is also investigating whether UNR is involved in encouraging other types of cancer to spread, such as ovarian or breast tumours.

Finally, for someone who has spent her life working on fruit flies, Fátima is very pleased to discover that her work has direct implications for human health. “It’s not the first time that Drosophila has relevance for human disease,” she says. “Flies have been used as a model of many diseases and are now being used as a model for cancer. It seems far-fetched, but we are all very similar in terms of how we function at the molecular level.”

REFERENCE WORK:
Down syndrome treatment is shaping up

Brain training and green tea extract could improve life for people with Down syndrome.

Down syndrome is a complex condition with a range of characteristic symptoms, including intellectual disability. Although most women who discover they are carrying a fetus with Down syndrome decide not to go through with their pregnancy, hundreds of babies with the condition are born every year across Europe. And while there is no cure for it, scientists are searching for ways to improve the quality of life for children and adults with Down syndrome.

It’s caused by having an extra copy of chromosome 21 – one of the genetic ‘recipe books’ inside all our cells. The additional dose of genes leads to problems as a fetus develops in the womb, especially with the delicate, spidery nerve cells within the brain. In unaffected people, spiny ‘antennae’ (dendrites) on the nerve cells spread out and make contact with other cells, forming a rich network within the brain that transmit thoughts and information. But in people with Down syndrome, there are fewer, smaller dendrites, and fewer contacts between nerve cells. In turn, this leads to a less active neural network, causing problems with behavior and learning.

To find a solution, Mara Dierssen and her team in the Cellular and Systems Neurobiology group at the Centre for Genomic Regulation (CRG) decided to try to normalize the extra dosage of one gene on chromosome 21, known as DYRK1A. This encodes a protein that adds specific molecular ‘tags’ onto other proteins in nerve cells, switching them on.

Genetically engineered mice with an extra copy of DYRK1A have fewer dendrites on their nerve cells, similar to other animal models and humans with Down syndrome, along with the typical learning problems, suggesting that the protein somehow was sufficient to inhibit the growth and maturation of these connections. So Mara wondered if using a drug that blocks the activity of the DYRK1A protein in the nerve cells of people with Down syndrome might recover their neuronal connectivity, enhancing their brain function.

The unexpected source of this wonder-drug turned out to be green tea, which contains a chemical called EGCg (epigallocatechin-3-gallate) that partly but not completely shuts down DYRK1A activity. Importantly, this drug can be given in tablet form, making it easy to administer, and it also crosses easily from the blood into the brain.
When Mara and her colleagues tested it on animals with overactive DYRK1A, which have the same characteristic changes in their nerve cells as people with Down syndrome, the results were astonishing. After just one month there were many more connections between the nerve cells, and the mice were showing improvements in their learning. The next step was to see if these effects could be achieved in humans too.

To test whether people with Down syndrome could benefit from EGCG, Mara and her team designed a double-blind, placebo-controlled clinical trial – the ‘gold standard’ for investigating medical treatments. They recruited almost 90 adults with Down syndrome living in Catalonia, Spain, and randomly allocated them into two groups. Initially, both received a placebo (inactive) treatment for a month, then one half were switched to EGCG pills, while the others continued to receive the placebo.

At the same time, the participants were given regular ‘brain training’ exercises, designed to boost their thinking and learning powers. Neither the scientists nor the trial participants and their families knew who was getting each type of pill over the 12-month course of the study, and the answers were only revealed at the end of the trial.

After the trial was over, Mara and her team carried out detailed assessments of the participants’ brain structure and mental abilities, comparing them to identical tests carried out at the start. Impressively, they saw a significant improvement in certain aspects of memory and behavior in the participants who received EGCG compared with those on the placebo pills, publishing the results in the journal *Lancet Neurology*. These advantages persisted for several months afterwards, suggesting there might be long-term benefit from the treatment.

“Until now there were no trials for Down syndrome that had a solid scientific hypothesis behind them,” Mara says. “This is the only one that has shown changes supported by brain imaging and neurophysiology. When we opened the envelope to reveal the treatment groups and saw the results, we had a really big party.”

The participants in this trial were adults, but Mara believes that her treatment approach might have even more benefits if it starts at a younger age, when the brain is still developing and making connections. As a next step, she and her team are about to start a new trial of EGCG and brain training focusing on 6 to 12-year old children with Down syndrome.

However, she warns against parents deciding to medicate their children with EGCG before there is evidence from further clinical trials. The green tea supplement she and her team use is highly purified and the dose has been carefully calculated. And although inactivating DYRK1A a little bit can be beneficial for people with Down syndrome, blocking it too much can also have serious negative impacts on vital brain cells.

But with larger studies planned, new drugs in development, and more researchers around the world taking notice of these remarkable findings, there’s a lot of potential to help children and adults with Down syndrome in the very near future.

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**REFERENCE WORK:**


"Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down’s syndrome (TESDAD): a double-blind, randomised, placebo-controlled, phase 2 trial.”

Let’s get together

The unusual lifestyle of a microscopic organism is shedding light on the origins of multicellularity.

An incredible diversity of life has evolved on earth, from tiny, delicate mosses and giant redwood trees to bizarre, boggle-eyed deep-sea creatures and our own human species, *Homo sapiens*. But it’s easy to forget that although life first arose around 3.8 billion years ago, for hundreds of millions of years it only existed as single-celled organisms such as bacteria. Multicellular life – creatures made of groups of cells working together – are a relatively new evolutionary invention.

Caught somewhere in between these two states is an unusual organism called *Capsaspora*. It can exist in three different forms: as separate single cells encapsulated in little cysts; as a slug-like amoeba, made up from many cells coming together; or as a loose collective of cells bound together by a kind of molecular ‘glue’. Exactly what triggers this biological get-together is unknown, but Eduard Sabidó, head of proteomics at the Centre for Genomic Regulation (CRG) – working in close collaboration with Iñaki Ruiz-Trillo at the Institute of Biological Evolution and Toni Gabaldón, CRG – is finding out.

It all started when Eduard got talking to Iñaki, who is based in the same place on the Barcelona sea-front as the CRG. Iñaki and his team are focused on understanding the origins of multicellular life, using *Capsaspora* as a simple model system. Intrigued by the strange lifestyle of these tiny cells, Eduard’s team decided to take a closer look at the proteins inside them.

Although Iñaki’s team had studied *Capsaspora*’s genes in depth – effectively the genetic ‘recipe book’ that tells cells to make all the different proteins that they need – they hadn’t looked in detail at the proteins produced by them. What’s more, proteins can be chemically modified in several different ways, effectively switching them ‘on’ or ‘off’ and altering their activity.

Using high-throughput proteomics techniques that enable the study of many thousands of proteins at the same time, as well as their modifications, Eduard and his team discovered crucial differences in the amounts of certain proteins and their associated modifications between single-celled *Capsaspora* and the collectivist collaborators. In particular, they spotted important changes in a modification known as phosphorylation, which acts as a molecular ‘flag’ to send signals inside cells that affect their behaviour.
Intriguingly, Eduard and Iñaki found that as *Capsaspora* changed between different lifestyles, the pattern of phosphorylation signals on key proteins changed inside the cells. Looking more closely, they noticed that these changes particularly affected proteins encoded by genes that are known to be important in multicellular organisms, as they grow and develop from one single fertilised egg into a complex arrangement of different specialised cells. What’s more, many of these genes appeared relatively recently in evolutionary history, suggesting that they are key players in the evolution of multicellular life.

Publishing the findings in the journal *Developmental Cell*, Eduard thinks that the protein signals that *Capsaspora* uses to switch between its different forms – from one cell to many – have somehow been ‘hard wired’ into multicellular organisms. But while it has been beneficial for *Capsaspora* to keep its options open, switching between single or collective forms as its situation changes, multicellular organisms have found it better to stick together.

Eduard’s team now plans to investigate protein modifications in other simple organisms that exist in single and multicellular forms, to identify further signals of gene regulation that might be vital for multicellularity. There is also a pleasing parallel in the fact that this project arose from a collaboration between individual researchers in different labs, coming together to form a single scientific ‘organism’.

“This collaboration arose from our curiosity – I wondered why Iñaki was working on these strange organisms,” Eduard says. “Although his group was very good at gene sequencing and evolutionary research, they had no experience working with proteomics technologies. We were able to overcome this limitation and answer questions from a molecular biology point of view that they could not have addressed before.”

**REFERENCE WORK:**
Collecting fingerprints

A systematic collection of molecular ‘fingerprints’ could provide new clues for treating blood cancers.

We’re all familiar with blood – just prick your finger and a drop of the red stuff will seep out – and we learn at school that it contains red oxygen-carrying cells and white immune cells. But you may not know that this vital fluid actually contains around forty different types of cells, from the earliest stem cells to highly-specialised infection fighters and antibody manufacturers.

The process of blood development is well known. Stem cells divide to produce more specialised cells, which mature and specialise further to form the huge variety of blood cells that we need to stay healthy. All these different cell types share the same genetic instructions encoded within their DNA, with a few bits of chopping and changing in cells that make infection-fighting antibodies. However, each of them uses a slightly different set of genes. These are labelled with the equivalent of molecular ‘sticky notes’ known as epigenetic marks, which help to tell cells whether certain genes should be switched on or off.

Each blood cell type will have a unique pattern of marks, creating a kind of epigenetic ‘fingerprint’. Together with his collaborators, Ivo Gut, Director of the Centro Nacional de Análisis Genómico (CNAG) within the Centre for Genomic Regulation (CRG), set out to make a detailed catalogue of them all. This was done as part of the EU-funded Blueprint programme – an ambitious collaborative project aiming to map out epigenetic marks across the whole family of blood cell types.

Perhaps the most challenging part of the project was tracking down samples of all the different types of cells. Researchers gathered umbilical cord blood packed with fetal stem cells, collected stem cells from the bone marrow, sorted various cells from the blood running through adult volunteers’ veins, and even pulled out immune cells from surgically-removed tonsils. While some types of cells are very common and easy to purify – such as immune cells in the blood – others, like the earliest stem cells in the bone marrow, are extremely rare and hard to find. Eventually, they ended up with more than 100 samples in total, covering a few different examples of each the forty or so cell types as well as samples from five different blood cancers.

For their fingerprinting study, Ivo and his team focused on an epigenetic mark known as DNA methylation. This is a small chemical tag put onto DNA, changing the chemical cytosine (the letter ‘C’ in the
genetic code) into methyl-cytosine (meC). The team used the latest techniques to scan through all the DNA in each cell type, carefully noting the distribution of C and meC across the whole genome.

Comparing all these epigenetic fingerprints revealed some intriguing patterns. For a start, immune cells are broadly divided into two ‘families’ (lineages): lymphoid and myeloid cells. Ivo and his team found highly characteristic and almost ‘opposite’ arrangements of epigenetic marks in lymphoid and myeloid cells. Because DNA methylation is closely linked to the way in which DNA is packaged up – which affects how accessible it is to the cell’s gene-reading machinery – this discovery suggests that genes may be packed up in distinctive ways in each of these lineages. They also noticed that DNA methylation levels in lymphoid cells (lymphocytes) tended to reduce as they specialised and matured, which reflects underlying changes in patterns of gene activity.

Furthermore, meC is usually found in special places in the genome known as CpG dinucleotides, where the chemicals cytosine (C) and guanine (G) occur next to each other, often in long repeated strings. Ivo spotted specific patterns of meC popping up in other locations in certain cell types, not just at CpG sites. This might also reflect changes in gene activity and/or DNA packing as cells mature from one type into another.

Finally, understanding the detailed differences in epigenetic marks between cell types is crucial when it comes to leukaemia and lymphoma – cancers affecting the blood. Each type of cell can give rise to a different sort of cancer with its own characteristics, which will need treating in a particular way. To see if they could figure out the culprit responsible for an individual patient’s cancer, Ivo and his team looked at samples from five different blood cancers – three from lymphoid cells and two from myeloid cells – and compared them with the fingerprints from healthy cells.

Although the DNA and methylation patterns in the cancer cells are pretty messed up (as we would expect), although they still followed the broad trends seen in the epigenetic fingerprints from their healthy counterparts. In the future, this could lead to the development of molecular tests (known as biomarkers) that could help doctors diagnose an individual patient’s blood cancer type more accurately and help them select the best treatment. And given that there are new drugs available that can alter DNA methylation patterns, this information could also reveal whether such a treatment might be beneficial.

Publishing their findings about blood cells in the journal Cell Reports, Ivo and his team are now planning to draw up catalogues of epigenetic fingerprints from other families of related tissues. One idea is to compare healthy bowel cells with those from patients with a variety of inflammatory bowel diseases including Crohn’s disease and ulcerative colitis.

Importantly, this kind of research is much more than mere data collection. “To me, the big thing is that there is a connection to something that has a benefit for patients,” says Ivo. “If I can see there is a biomarker that informs us whether a patient is suffering from this disease and not that one, then it is very satisfying. There needs to be a purpose at the end, and that purpose has to be to improve people’s quality of life.”
ERC Researchers at CRG

STARTING GRANTS

Pedro Carvalho
Toni Gabaldón
Manuel Irimia
Fyodor Kondrashov

Manuel Mendoza
Gian Gaetano Tartaglia

CONSOLIDATOR GRANTS

Ben Lehner
Toni Gabaldón

ADVANCED GRANTS

Roderic Guigó
Vivek Malhotra
Luis Serrano
James Sharpe

Juan Valcárcel

SYNERGY GRANT

Miguel Beato
Thomas Graf
Guillaume Filion
Marc Martí-Renom (CNAG-CRG)
Research

The breadth of topics, approaches and technologies at the CRG allows us to ask a wide range of fundamental questions in life sciences and biomedicine. Research at the CRG falls into four main areas: gene regulation, stem cells and cancer; cell and developmental biology; bioinformatics and genomics; and systems biology. As of July 1, 2015, the National Centre for Genome Analysis (CNAG-CRG) is also part of this research structure.

BIOINFORMATICS AND GENOMICS

The programme’s scientific highlights in 2016 include the discovery that the symbiotic event that leads to the emergence of mitochondria occurred later in the evolution of eukaryotic cells than was previously thought, the systematic exploration of the fitness landscape of the green fluorescent protein from Aequorea victoria (avGFP) by measuring the fluorescence of tens of thousands of derivative genotypes, the development of methods to predict interactions between proteins and long non-coding RNAs, and the discovery of a novel approach to reduce the toxic activity of trinucleotide repeat expansions in polyglutamine diseases.

Several groups in the programme participated in a number of genome projects, including the olive tree, the lynx and the bean, in which we shared the leadership, as well as in the first Arabidopsis genome assembled to complete chromosomes using PacBio.

The programme has continued to deploy and support the European Genome-phenome Archive (EGA) in collaboration with the European Bioinformatics Institute (EMBL-EBI) and the Barcelona Supercomputing Center-Centro Nacional de Supercomputación (BSC-CNS).

Xavier Estivill has been leading the personal genomics initiative in Qatar.

Roderic Guigó
Coordinator
CELL AND DEVELOPMENTAL BIOLOGY

The mission of the scientists in the Cell and Developmental Biology department is to reveal the mechanisms of cell compartmentation, division and tissue organisation. The department is staffed by Vivek Malhotra (mechanism of protein secretion), Isabelle Vernos (microtubule and spindle dynamics), Manuel Mendoza (cytokinesis, chromosomal segregation, and cell cycle check points), Pedro Carvalho (organelle biogenesis and homeostasis), Jerome Solon (tissue organisation), and Sebastian Maurer (cytoplasmic RNA localisation). Vivek Malhotra, Manuel Mendoza and Pedro Carvalho are funded by grants from the European Research Council (ERC). Pedro Carvalho is also a recipient of the international early career scientist award from HHMI and in 2013 was elected EMBO Young Investigator. Isabelle Vernos is a member of the Scientific Council of the ERC and is also a member of the Advisory Council for Science, Technology and Innovation of the Spanish Secretariat for Research, Development and Innovation. In the year 2016, Pedro Carvalho was recruited as the EP Abraham Professor at Oxford University’s Dunn School of Pathology. The department recruited two new group leaders: Verena Ruprecht (from IST Vienna) who is interested in cell and tissue dynamics, and Elvan Boke (from Harvard University) who works on the mechanism oocyte biology and cellular dormancy. The department published a number of highly important papers in 2016. But the publication of Santos and colleagues, merits special attention (Santos et al., J. Cell Biol. 2016). In this paper, the authors describe the identification of a protein, TALI, that is required for the export of ApoB-containing lipoprotein particles at the endoplasmic reticulum. ApoB-lipoproteins are necessary for transferring dietary lipids from small intestine and liver to other tissues of the body. The identification of TALI is therefore important for understanding the mechanism controlling homeostasis of cholesterol and dietary lipids in circulation.

GENE REGULATION, STEM CELLS AND CANCER

The year 2016 witnessed the departure of Bill Keyes and his group, which has taken up a senior scientific position at the Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC) in Strasbourg. During their time at the CRG, Bill and his team made headline news with the discovery that the process of cellular senescence, previously considered to be a mechanism related to aging and defence against oncogene activation, is important both during normal development and in facilitating cellular plasticity and tissue regeneration. We will miss Bill and his group and wish them all the best in their new lives in France.

Research in the Programme yielded other important findings in a wide variety of fields in 2016. Miguel Beato’s group proved that the NUDIXS enzyme generates ATP in the nucleus of breast cancer cells from pyrophosphate and ADP-ribose, the latter derived from the hydrolysis of poly(ADP-ribose) stored in PARylated proteins. This is important in meeting the high energy requirements of remodelling chromatin following hormone stimulation. It is now becoming clear that the three-dimensional organisation of chromatin establishes a footprint for gene regulation and cell identity, and work in Thomas Graf’s group revealed that this landscape is indeed progressively altered during cell reprogramming, accompanied by the expression of transcription and epigenetic factors that generate elite cells that are particularly apt for the acquisition of pluripotency. The balance between gene activation and repression is key to the homeostasis of pluripotent cells, and Luciano Di Croce’s group discovered that an interaction between the proteins EPOP and Elongin BC at genomic locations that can be either active or repressed in stem cells is crucial in maintaining this balance. Also illustrating the importance of genomic context, work in Guillaume Filion’s lab elegantly established that the reactivation of the HIV1 virus, integrated in the genome of host cells in latent state, can be accounted for by the proximity of the viral integration site from cellular transcriptional enhancers. Post-transcriptional gene regulation is emerging as a key contributor to cancer progression, and work in Fátima Gebauer’s lab identified the RNA-binding protein UNR as a regulator of mRNA translation of genes essential for the metastasis of melanoma cancer cells, thus revealing a novel potential target for therapeutic intervention. Finally, advances in
The research groups in the Systems Biology program cover a wide range of topics: from dynamic gene regulatory networks to systems neuroscience, and employ a wide range of model systems to address these issues, including prokaryotes, cell lines, *C. elegans*, *Drosophila* and mice. Underlying this diversity, however, are the common goals of combining systematic and quantitative data collection, using computational models, going beyond molecular descriptions and arriving at a deeper dynamic understanding of complex biological processes. To achieve these goals the program is strongly interdisciplinary, comprising a high proportion of physicists, mathematicians and computer scientists, in addition to biologists. In this way the program tackles topics such as: signal transduction, gene regulatory networks, multicellular patterning, chemotaxis, systems neuroscience, the evolution of networks, and the impact of stochastic noise at the whole organism level. We contribute to the training efforts of the CRG with an annual Systems Biology Summer School, which in 2016 taught the theory and practice of “whole-cell modeling” to a group of internationally-selected young researchers.

As usual, scientific highlights of the program covered a diverse variety of projects. The group of Matthieu Louis used high-resolution electron-microscopy imaging to achieve the first complete wiring diagram of the primary neural circuit (the antennal lobe) that processes signals sent by olfactory sensory neurons in the larva’s brain, while Mara Dierssen’s group discovered new mechanisms of learning and memory in mice, and achieved the first successful attempt at treating cognitive impairment in patients with intellectual disability. Ben Lehner’s group found that increased protein expression can cause cellular toxicity through a concentration-dependent liquid phase separation, and also elucidated the rules and impact of nonsense-mediated mRNA decay in human cancers, while Luis Serrano’s team generated preliminary evidence for the potential use of mycoplasma pneumoniae as a vehicle for vaccination and treating infectious diseases. The group of Manuel Irimia showed that a regulatory switch controlling alternative splicing lies at the core of animal pluripotent cells, and finally, through a combination of experimental embryology in catsharks and dynamic computer simulations, the group of James Sharpe revealed that the WNT-BMP Turing system which patterns the digits in mammals, also controls skeletal patterning in cartilaginous fish – thus demonstrating a deep genetic homology conserved across the evolutionary transition from fins to limbs.
2016 was another productive and successful year for CNAG-CRG. We continued on our strategic path to deliver the best possible support to our collaborators in their research projects. Particular focus areas are patient-near research, such as in rare diseases and cancer. From the application standpoint, we have furthered our expertise in single-cell analysis, epigenomics, translational techniques and the integration of population information.

The year witnessed many highlights. We took our quality system to the next level through our ISO17025:2005 accreditation with the scope of DNA/RNA analysis by high throughput sequencing (NGS) by the Spanish national accreditation body ENAC. Our ISO17025:2005 accreditation covers the laboratory and data analysis. This puts us in the unique position of having achieved this with such a wide scope. We are one of very few NGS operations to be accredited and to be able to offer it both for academic research projects and clinical application. We are now working with the clinical services of several hospitals for personalised medicine.

In 2016, we began to upgrade our sequencer park. The first Illumina HiSeq4000 was received and commissioned. Our work on the Oxford Nanopore sequencer has reached a level where we can now offer this to our collaborators. Nanopore sequencers provide an orthogonal type of sequence to the Illumina short-read sequencing. Sequences from the nanopore can reach read lengths of several 10s kb. This datatype can be applied perfectly in combination with Illumina short-reads in de novo assembly projects. We are investigating its use in projects in which genomes are heavily rearranged, such as in cancer and other exciting projects.

The EU-funded BLUEPRINT project concluded in 2016 with the publication of a series of 41 scientific papers within the IHEC framework in journals of the Cell Press group and other high-impact journals. These papers report on the relationship of complete epigenetic descriptions of immune system cells and place them in the context of different diseases. They also describe the tools that have been developed to capture the entire content of epigenetic profiles. CNAG-CRG played a key role in this effort by sequencing and analysing almost 200 whole genome methylomes. The RD-Connect database, developed at the CNAG-CRG, was made available to the European International Rare Disease Research Consortium investigators for beta-testing this year. The database was highly praised by the beta testers. The RD-Connect server was installed towards the year-end.

Several of our de novo assembly and annotation projects were published this year, notably the Iberian lynx, the turbot and the olive tree. The Iberian lynx is a critically endangered felid. The annotated genome sequence permits the fine-tuning of conservation efforts of this species, of which less than 200 animals remain. Supported by funding from the Emilio Botín Foundation, we sequenced an olive tree that is more than 1000 years old, the oldest living organism ever sequenced. This genetic information will help olive trees in their development and in the protection against infection. Researchers from CNAG-CRG and CRG have collaborated on several of the large initiative projects; projects involving eight different CRG PIs continued or were initiated in 2016.

Personalised medicine is almost with us, and genome analysis is its major tool, as it provides unprecedented resolution for diagnosing patients. Moving forward, it is clear that CNAG-CRG will play a key role in the implementation of personalised medicine into healthcare. Our sequencing platform, sophistication in data analysis and databases for making genomic data more user-friendly place us in a prime position to support this monumental task.
Facts and Figures *

(*) Note: Data also includes CNAG-CRG outcomes. CNAG-CRG is part of the CRG as of 1st July 2015
### Publications

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total publications</td>
<td>279</td>
</tr>
<tr>
<td>Average Impact Factor</td>
<td>8.9</td>
</tr>
<tr>
<td>1st Quartile publications</td>
<td>83%</td>
</tr>
<tr>
<td>Impact factor above 10</td>
<td>69</td>
</tr>
</tbody>
</table>

### Funding (M€)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total budget</td>
<td>44</td>
</tr>
<tr>
<td>CRG budget</td>
<td>35.7M€</td>
</tr>
<tr>
<td>CNAG-CRG budget</td>
<td>8.3M€</td>
</tr>
</tbody>
</table>

#### External Funding awarded in 2016
- Public-Europe: 24% - 4.3M€
- Public-International: 3% - 0.6M€
- External Sales: 21% - 3.8M€
- Private-Philanthropic: 9% - 1.7M€
- Private-Technology Transfer: 2% - 0.3M€
- Public-Regional: 5% - 0.8M€
- Public-National: 35% - 6.6M€

**TOTAL**: 18.1M€

Note: The above graph includes competitive funds obtained during 2016 and pending for final notice of award or grant agreement as of 31/12/2016.

### Projects

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing Research Projects and Networks</td>
<td>148</td>
</tr>
<tr>
<td>Ongoing ERC Grants</td>
<td>15</td>
</tr>
<tr>
<td>Ongoing Postdoctoral Fellowships</td>
<td>33</td>
</tr>
</tbody>
</table>

#### Ongoing EU Coordinated Projects*
- 8

#### Total budget (8 projects)
- 36.4M€

#### Total CRG budget (8 projects)
- 8.8M€

#### Participating institutions (including 15 industrial partners)
- 49

* Swarm Organ; 4DCellFate; Mycosynvac; Libra; Opathy; Mini Cell; DivIDE (awarded in 2016); Cell Viewer (awarded in 2016)
**Staff**

Total

519

* FTE, full-time equivalent: 500.7

Research Programmes

332

Core Facilities

35

Administration & Scientific Support

77

CNAG-CRG Staff

75

Research Groups

29

Scientific Services

9

+ 1

affiliated group from CNAG-CRG

CORE FACILITIES

9

TECHNOLOGICAL PLATFORMS

2

European Genome-phenome Archive (EGA) and Centro Nacional de Análisis Genómico (CNAG-CRG)

Research Categories

PhD Students 38%

Staff Scientists 4%

Heads of Unit 5%

Postdocs 43%

Group Leaders 10%

Age

<30 years old 115 (22%)

30-40 years old 236 (46%)

40-50 years old 118 (23%)

>50 years old 23 (4%)

Internationality

43

nationalities represented

60%

Group Leaders+Heads of Unit

58%

PhD Students

74%

Postdoctoral Researchers

63%

Total Research Staff
Gender

Female invited speakers

32%

an improvement of almost 10% compared to 2015

Female by Professional Categories

21% Group Leaders
31% Head of Units
50% Staff Scientists
43% Postdocs
46% PhD Students

Selection processes for scientific positions

APPLICANTS

Male 53%
Female 47%

PRE-SELECTED CANDIDATES

Male 48%
Female 52%

SELECTED CANDIDATES

Male 37%
Female 63%

Selection processes for group leaders positions

APPLICANTS

Male 65%
Female 35%

PRE-SELECTED CANDIDATES

Male 47%
Female 53%

SELECTED CANDIDATES

Male 33%
Female 67%

Advanced Training

PhD Theses defended
31

Courses@CRG
8

(international courses)
Participants: 155

Career Development
13

(internal)
Participants: 210

Innovation Courses
2

Participants: 23
**Executive Summary 2016**

**New Technologies Identified under Evaluation**

- 35

**Agreements Signed with Companies (during 2016)**

- 18

**Patent Portfolio Projects managed under valorisation**

- 7

**Junior PIs holding senior positions in academia**

- 100%

**Postdoctoral Researchers that became PIs after leaving the CRG**

- 11%

and

- 23%

when looking at their current positions

**Alumni working in Spain, Europe and US (%)**

- Spain 34%
- Europe 38%
- US 18%
- Others 7%
- Unknown 10%

**Alumni working in academia, industry and other (%)**

- Current Job
  - Academia 79%
  - Unknown 8%
  - Industry 13%

- After leaving the CRG
  - Academia 76%
  - Unknown 21%
  - Industry 5%

* data includes research staff only
Communications, Public Engagement & Science Education

MEDIA RELATIONS

Media Appearances

3,718

452
Written Media
2,776
Online Media
428
Blogs
27
Radio
35
TV

Value of Media Appearances

24,835,432.78€
(value provided by our press clipping supplier Acceso)

SOCIAL MEDIA

Twitter followers
6,796
@CRGenomica
1,285
@cnag_eu

Facebook page likes
2,851

LinkedIn followers
2,162
CRG
1,268
CNAG-CRG

YouTube channel views
119,003

PUBLIC ENGAGEMENT AND SCIENCE EDUCATION

Activities Organised
185

Categories of activities organised
39

Audience Reached
11,898

8,554
Schools and Students
40
Teachers
100
Librarians
3,204
General Public
Financial Report
**Sources & Uses**

**Operating Sources in Thousand Euros**

- **Financial Income**: 0%
- **External Funding**: 48%
- **Core Funding ***: 42%
- **Services**: 10%
- **Others**: 3%

Total Operating Sources: **39,965**

* Core Funding includes:
  - Government of Catalonia
  - Spanish Ministry of Economy, Industry and Competitiveness
  - Instituto de Salud Carlos III

**Operating Uses in Thousand Euros**

- **Administration**: 8%
- **Rent and Infrastructure maintenance**: 10%
- **Technology platform CNAG**: 18%
- **Research and Core Facilities**: 61%
- **Others**: 3%

Total Operating Uses: **39,965**
Acknowledgements
Support from our trustees, public and private funders and sponsors is key to accomplishing the CRG’s mission of discovering and driving knowledge for the benefit of society, public health and economic prosperity.

**Trustees**

![Trustee Logos]

**Public Funders**

![Public Funder Logos]

Note: ERDF and ESF funds have been instrumental over the years through different funding schemes and in a variety of activities in supporting our research and keeping our infrastructures state-of-the-art.

**Private Funders**

**OBRA SOCIAL “LA CAIXA”**

The “la Caixa” Bank Foundation has supported several key initiatives at the CRG, such as its International PhD Programme since 2008 and additional scientific and outreach activities since 2014: the partnership between the CRG and the European Bioinformatics Institute (EMBL-EBI) to run the European Genome-phenome Archive (EGA) jointly, and the CRG’s first citizen science initiative ‘Saca la Lengua’ (Stick out your tongue). In the first half of 2016, the Foundation generously decided to fund the second edition of ‘Saca la Lengua’, which started in October 2016 and aims to tackle new challenges, reach target audiences and collect samples from different populations.

**AXA RESEARCH FUND**

The ‘AXA Chair in risk prediction in age-related diseases’ was created in 2014 for a 15-year period with a 1-million euro endowment. Dr. Ben Lehner was appointed first chair holder to further his work in the development of personalised medicine to provide people with better protection from the unique risks they face in diseases such as cancer.
**FUNDACIÓN BOTÍN**

The Fundación Botín, through its Science area, and in collaboration with the CRG’s Technology and Business Development office, promotes the translation of research results produced in the labs of Dr. Juan Valcárcel (until 2016) and Dr. Luis Serrano (2007-2013) into the market. They accomplish this by providing economic and management resources to identify promising ideas and results at an early stage, assessing their potential and the best form of protection through intellectual and industrial property rights, while also sourcing the necessary technology and industry partners or investors to help technologies or products to enter the market to the ultimate benefit of society.

**FUNDACIÓN RAMÓN ARECES**

The Ramón Areces foundation provides three-year funding for a highly-talented young postdoctoral student to carry out research at the CRG. The successful postdoc, selected from a competitive call, is currently Xianghua Li, who works in Dr. Ben Lehner’s lab.

**FUNDACIÓN BANC SABADELL**

The Banc Sabadell Foundation provides support to the CRG’s travelling scientific picture exhibition launched in 2013 “TREE OF LIFE. The complexity of life: from the cell to a living organism”. It was first exhibited in Alella, near Barcelona, and subsequently in Alicante and Barcelona (Palau Robert) in 2014 and on the premises of the Government of Catalonia Delegate’s Office of Girona in 2015. The exhibition was also part of the celebration of “Researcher’s Night” in Barcelona (CCCB) and of the Open Day at the Barcelona Biomedical Research Park. The exhibit has attracted over 20,000 visitors. In November 2016 it was exhibited at the Urgell Community Centre in Barcelona.

**FUNDACIÓ CATALUNYA-LA PEDRERA**

The Fundació Catalunya-La Pedrera supports vocational training activities for young and talented students to nurture their interest in science and to pursue a scientific career. Key activities include scientific summer stays at MónNatura Pirineus and at the CRG, where students take part in sessions and events focused on scientific topics with the aim of eventually proposing and developing their own project idea.

**FUNDACIÓ MARATO TV3**

The Fundació Marató TV3 funds six research projects led by CRG investigators related to different editions of the telethon: three projects from the 2012 edition on ‘Cancer’ (Thomas Graf, Pia Cosma and Susana de la Luna), two projects from the 2013 edition on ‘Neurodegenerative diseases’ (Fátima Gebauer and Luciano Di Croce), one project from the 2014 edition on ‘Heart disease’ (Gian G. Tartaglia) and two projects from the 2016 edition on ‘Strokes and traumatic spinal cord and brain injury’ (Marc Martí-Renom and Mara Dierssen).
WORLDWIDE CANCER RESEARCH (formerly AICR)

Worldwide Cancer Research is a charity that funds research into any type of cancer anywhere in the world. WWCR is currently supporting Bill Keyes’ initiative to investigate the role of the chromatin remodeler Lsh in skin cancer (2015-2018).

BANCO SANTANDER

The Banco Santander is funding a joint project by the CSIC, the Royal Botanical Garden in Madrid and the CRG (Toni Gabaldón), aiming to sequence the DNA of the olive tree for the first time. The project was successfully completed in the course of 2016.

FONDATION JEROME LEJEUNE

The relationship between the CRG and the Jerome Lejeune Foundation began many years ago. They provided support to several of Mara Dierssen’s research initiatives linked to the identification of molecular and genetic bases in several pathologies accompanied by mental retardation: Rett Syndrome, Fragile-X Syndrome, William-Beuren Syndrome and Down Syndrome. Dierssen also received the first international Sisley-Jerome Lejeune Award in 2010. More recently, they awarded a grant to Eduard Sabidó’s project on the elucidation of the mechanism of action of epigallocatechin-3-gallate as a therapeutic agent on the cognitive phenotype in Down Syndrome mice models (2015-2017).

AECC

The Spanish Association Against Cancer (AECC) has supported a number of research projects and initiatives by CRG scientists over the years. In 2015, Pedro Vizán (in Luciano Di Croce’s lab) was awarded the AECC Oncologic Research fellowship for a 3-year project that seeks to identify and “attack” stem cells involved in cancer.

ZIMIN FOUNDATION

Thanks to the Zimin Foundation, the School of Molecular and Theoretical Biology (SMTB), organised by our researcher, Fyodor Kondrashov, was held in Barcelona for the first time. The SMTB brought together 80 intellectually inquisitive and talented secondary school students and outstanding scientists from all over the world for three weeks in August, all of them working together on real scientific experiments that might yield novel results. They spent the first three days simply discovering the different labs participating in the summer school so that they could subsequently choose the scientific project they were interested in. As a closing event, the students prepared a poster session to present the outcomes of the projects developed over the previous weeks.

FUNDACIÓN BBVA

In the 2016 call of the BBVA Foundation Grants to Researchers and Cultural Creators, Neus Martínez, from James Sharpe’s group, was awarded a grant for her research project titled ‘Non-Invasive Facial Biomarkers of Mental Diseases’. The aim of the project was to create a facial analysis and modelling application with diagnostic and prognostic value for mental diseases related to genetic alterations of DYRK1A and also translatable to other disorders.

FUNDACIÓN OLGA TORRES

In 2014, the FOT awarded a 60,000 euro grant to the project by Holger Heyn (CNAG-CRG) titled ‘Systems Colorectal Cancer Genomics’, to be conducted between 2015 and 2016. The aim of the project is to conduct a multidimensional genome-wide study and the systematic data integration of mutational, epigenetic, transcriptional and clinical data of primary colorectal cancer samples to identify cancer-driving mutations in non-coding contexts with regulatory impact of cancer gene activity.
THE VELUX FOUNDATIONS
The Velux Foundations are funding the research project titled ‘Regenerating Photoreceptors in Retinitis Pigmentosa’, by our PI Pia Cosma. Retinitis pigmentosa (RP) is a severe disease that affects 1 in 3,500 individuals, who undergo progressive loss of vision and for which currently there is no cure. We intend to test cell fusion-mediated reprogramming as therapy in rd10 mice, an RP mouse model, with the ultimate goal of regenerating photoreceptors and achieving functional rescue of vision.

SWISS NATIONAL SCIENCE FOUNDATION
The SNSF is currently funding a research project by our PI, James Sharpe, entitled ‘Reaction-diffusion networks underlying pattern formation of lymphoid tissue’. The project explores the various possible scenarios of pattern formation in lymphoid tissue.

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