CRG
Centre
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ANNUAL REPORT 2018

Executive Summary

CENTRE FOR GENOMIC REGULATION

EXCELENCIA
SEVERO
OCHOA

PRODUCED BY: Department of Communication & Public Relations
Centre for Genomic Regulation (CRG)
Dr. Aiguader, 88
08003 Barcelona, Spain
www.crg.eu

TEXT AND GRAPHICS: CRG scientists, CRG members of the administration and research support team, Kat Arney, Department of Communication & Public Relations

GRAPHIC DESIGN: Ondeuev Comunicació S.L.

PHOTOGRAPHY: Ivan Marti, CRG scientists

VIDEO: Adrià Sunyol

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CONTENTS

A LOOK BACK AT THE YEAR

The CRG Annual Report for 2018 describes the progress made by the Institute in its strategic priorities and in the science, people and technological facilities that make the CRG a unique and vibrant place for innovation and new scientific discoveries.

We continued to advance in our strategic priorities, notably in coordinating the Alliance of the Severo Ochoa Centres and María de Maeztu Units (SOMMa) to influence Spanish science policy and to further the visibility of science in Spain, in triggering innovation through the creation of a new spin-off company, Sequera Labs, and in fostering a culture of open science with numerous public engagement and education activities. Last, but not least, we set up a new dedicated training centre that boasts fully-equipped bioinformatics facilities, where we hosted international students and instructors from every continent. At the core of our strategy lies excellent science fuelled by renowned scientists and supported by cutting-edge technology, as well as by dedicated and effective administration and support services.

STRATEGIC OBJECTIVES

SOMMa was officially launched in October 2017. In 2018, the alliance's activities focused on influencing Spanish science policy to safeguard the competitiveness of Spanish science, promoting the visibility of centres and units of excellence, and reaching out to society through the organisation of the third edition of the 100xCiencia conference (Madrid, 15th November). In March 2018, the alliance presented the "SOMMa Report: actions required to safeguard the competitiveness of science" document, which called upon politicians in Spain to remove the bureaucratic shackles that hamper the country's research organisations and universities. The alliance has proven to be a very powerful tool in influencing science policy.

As part of our commitment to trigger innovation, we successfully launched a new spin-off company, Sequera Labs, to market the NextFlow Open Source Code software, support and services to ensure the reproducibility of data-intensive computation. Similarly, Microomics, a company incorporated at the end of 2017, offering microbiome consulting services, is developing successfully and is scheduled to reach break-even by mid-2019 thanks to the CRG's continued support in 2018.

We continue to strive to develop a culture and practice of Open Science. CRG Open Access publications amount to almost 70% and we have undertaken a policy for research open data management with other research institutes in Catalonia. We are actively fostering multiple initiatives to engage citizens in our research: the second edition of the "Saca la lengua" citizen-science project and the development of a collaborative board game with the results of this project, and the H2020 ORION Open Science project, including the launch of the new citizen science project GENIGMA. Gender equality is another key initiative. We have implemented a gender equality plan

in partnership with the EU LIBRA project coordinated by the CRG. As a result, in the last three processes for the recruitment of junior Group Leaders, three out of the five Group Leaders attracted to the CRG are excellent women scientists.

SCIENCE

This year, we are proud to say that CRG researchers have made important findings to further the concept of integrative biology, elucidating important genetic and cellular mechanisms underlining cellular reprogramming, embryonic stem cells and shedding light on the origins of vertebrate gene regulation. Some of the most significant advances are described in the Scientific Highlights section of this report. The CRG participates in several international collaborative projects, including the LifeTime Initiative (Marti-Renom, Heyn, Di Croce, Bertero, Lligadas). LifeTime is a partnership including a multidisciplinary consortium, distributed over 18 European countries, aiming to revolutionise healthcare by understanding and predicting how cells change as they age and progress towards disease. We also received funding from the Chan Zuckerberg Initiative to participate in the Human Cell Atlas (Heyn) and the prestigious ERC Synergy grant with €8.3 M to shed light on the origin and progression of leukaemia ('BCLLAtlas') under the leadership of Gut and Heyn and in collaboration with IDIBAPS. Other projects led by CRG scientists include a European interdisciplinary training network led by Di Croce to investigate how the genome is organised over time and its relationship with health and disease ('ChromDesign'); and two ERC Proof of Concept grants to explore potential clinical applications of their recent results on breast cancer and pneumonia, respectively (Beato and Serrano). It is also important to mention that a EU project coordinated by CRG, MycoSynVac, was short-listed with another 19 projects to be presented to the European Parliament. The CRG is co-hosting and developing the European Genome Phenome Archive (EGA) together with the European Bioinformatics Institute (EMBL-EBI). In 2018, the EGA established itself as a central repository for secure preservation and sharing of human genomics and phenotypic data, participating in several European-funded projects, notably in the European Open Science Cloud and several partnerships with Canada, and in the Global Alliance for Genomics and Health as driver project.

PEOPLE

Our faculty is truly international and highly multidisciplinary. In 2018, we welcomed three new Group Leaders: two junior Group Leaders, Eva Novoa, from the Garvan Institute of Medical Research in Sydney, Australia, working on gene regulation, and Donate Weghorn, from the Harvard Medical School, in the USA, focusing on cancer evolution; the senior Group Leader Jorge Ferrer from the Imperial College London, in UK, studying human diabetes. On the other hand, our best farewell wishes go to junior Group Leaders Stephan Ossowski and Eulàlia Martí, who have moved on to new positions as Group Leader at the University of Tübingen and Associate Professor at the Universitat de Barcelona, respectively.

TECHNOLOGY

The CRG's technological facilities are instrumental in serving our own scientists and the local and international scientific community, as well as in developing new methods and protocols. In 2018, the CRG-UPF Proteomics Unit was acknowledged as a new node of the Spanish Singular Research and Technological Infrastructure 'IOT', also comprised of the CNAG-CRG (Centro Nacional de Análisis Genómico) and the COS (Centre for Omics Sciences) in Reus. This infrastructure aims to become a technology hub for OMICS integrated analysis.

This year, significant efforts were made by the Direction and the Administration in actions geared towards improving and contending with the changing and growing regulatory framework in science, as well as with an uncertain and complex political context and the associated budget limitations. We make every effort to secure an adequate framework for public research institutes with specific regulations for science and progressively increasing budgets to support the ever-accelerating speed of our scientific environment.

2019 is already shaping up as a challenging but very promising year with exciting scientific discoveries, new faces, disruptive technologies and achievements for the CRG community and beyond. The CRG continues to be a unique and vibrant place.

Luis Serrano
Director

SCIENTIFIC HIGHLIGHTS

Real amphioxus, or lancelets. Credit: Vincent Moncorgé

EVOLUTION'S PLAYGROUND

A small sea creature is shedding light on the genetic changes that drive evolution.

Let's take a trip two hundred kilometres up the coast from Barcelona, skipping the beaches and amusement parks of the Costa Brave and heading over the French border to the small seaside town of Banyuls-sur-Mer. It's here, in the shallows of the Mediterranean, that we find our scientific subjects.

Dig into the sand and you'll pull out a handful of small, pointed animals known as lancelets (also called amphioxus, from the Greek for 'sharp at both ends'), which look similar to the slender, tasty anchovies that live around here too. But although it might share the same appearance as these bony little fish, amphioxus is a simpler type of organism.

Vertebrates like fish, birds and mammals have a bony spine that protects the long nerve cord running along their back. While they share the same basic body plan and have a central nerve (protected by a thick tube known as a notochord), amphioxus lacks this protective backbone, making it a sophisticated chordate rather than simple vertebrate. In fact, it is one of the closest living relative of back-boned animals, and thought to be the closest thing we have today to an ancient vertebrate ancestor.

Amphioxus' unusual characteristics and close relationship to more complex vertebrates have fascinated evolutionary biologists for more than 150 years, placing these unusual sea creatures at a pivotal point in the tree of life.

Amphioxus has now come firmly into the 21st century, thanks to a major study published in the journal Nature by CNRS researcher Héctor Escriva, José Luis Gómez-Skarmeta from the Centro Andaluz de Bio-logía del Desarrollo, and CRG group leader Manuel Irimia. They've been combining huge datasets from nearly 100 different samples of amphioxus tissues– including nine separate body parts and 16 developmental stages ranging from egg to adult – to create the most detailed molecular blueprint of the species to date, mapping out exactly how genes are switched on and off to create its needle-like body.

"The beauty of this paper is that we pulled together all kinds of different data – DNA, gene regulation and activity – as well as the different tissues, which really captures all the complexity," Irimia says. "The challenge has been that it's an enormous amount of information – it's certainly the biggest dataset I've ever had in my hands."

Once the team had gathered all the data together, they set to work comparing the patterns and control of gene activity in amphioxus with several species of vertebrates, including fish, frog, chicken, mouse and human, searching for clues about how things changed once the two groups split from each other back in the mists of evolutionary time.

At a genetic level, there are key differences between amphioxus and vertebrates. Somewhere back in time at the point the two groups split, the whole genome of early vertebrates got copied twice over. This created a large amount of genetic material for evolution to work with, generating the huge range of weird and wonderful evolutionary innovations found in species all over the world.

Meanwhile, the amphioxus genome has continued to evolve slowly and steadily, gradually accumulating small changes rather than dramatic doublings. As well as only having a single set of starting genes, amphioxus is also missing many of the complex genetic controls that are found in vertebrates.

The researchers discovered that while many of the basic 'control switches' that turn genes on and off are preserved between amphioxus and more complex animals, vertebrates have evolved many more layers of complicated regulatory circuits that enable much more precise activation of genes for a wider range of purposes.

It's like the difference between a simple light switch connected to just one bulb, which can only be turned on and off, and a complicated WiFi-connected home lighting system that can create all sorts of moods throughout the house.

Another of the study's key findings explains what happened after the early vertebrate genome was double-duplicated, producing four copies of every gene. For more than 50 years, researchers have suspected that this genetic bonanza led to individual copies of genes becoming more specialised in their roles in vertebrates – for example, only being active in the brain or at a certain point in the developing embryo.

For the first time, thanks to the huge dataset created by Irimia and his colleagues, we can now show that this is indeed the case. But, counterintuitively, they found that genes that are more restricted in their location of activity have evolved much more complex controls than those that are active more widely across the body.

"By creating these detailed genetic and molecular blueprints and comparing them across species, we've able to peel back the regulatory layers that have evolved over time and understand the unique genetic controls that emerged in vertebrates to give rise to their more complex body shapes," Irimia explains.

"We can think of the emergence of vertebrates as 'evolution without limits'. The genome doublings didn't just increase the number of genes these organisms can play with, but they have also evolved many more complex and specialised control switches – something that proved to be pivotal in the origin of these animals."

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SPIT PERSONALITY

A citizen science experiment maps out Spain's mouth microbes

There's more to your body than human cells. Each of us is home to trillions of bacteria, fungi and other microscopic organisms from more than 10,000 different species, collectively known as the 'microbiome', which grow in every possible location from the smooth expanses of our skin to the stinky, dark tube of the gut.

The microbiome is one of the hottest topics in biology right now, with researchers all over the world racing to understand the connections between the different populations of bacteria living within an individual person's body and their health. So when Toni Gabaldón and his team in the Comparative Genomics Group at the CRG sat down to devise an exciting national citizen science project for teenagers, collecting and analysing samples of bacteria from high school students across Spain seemed like a perfect plan.

Rather than asking teenagers to collect samples of fresh faeces or skin scrapings, Gabaldón's team hit upon the idea of analysing saliva, in order to build up a picture of the range of bacteria in the mouth. Very few researchers have studied the oral microbiome, offering the potential for revealing scientifically important new results, and so *Saca La Lengua* ('Stick Out Your Tongue') was born.

"This was an unorthodox way to do a research project, but we wanted to find something that would combine genomics, bioinformatics and public engagement as well as answering scientifically interesting and clinically relevant questions," Gabaldón explains. "Saliva samples are easy to collect and there is almost nothing known about the adolescent oral microbiome, so we saw a good niche."

The *Saca La Lengua* team hired a van, plastered it with brightly coloured bacteria-shaped stickers and set off on a three-month journey round Spain's high schools (even sleeping in the van some nights), delivering talks about genomic research, bioinformatics and scientific careers.

Most importantly, the researchers worked with the students to gather around 2,000 plastic tubes full of spit, teaching them how to spin the tubes in a centrifuge to collect the bacteria and keeping the bugs in cold storage until they could be sent back to the CRG for DNA extraction, sequencing and analysis.

As well as donating their saliva for science, the students were also asked to help develop the other part of the project – for example, in a questionnaire asking about diet, lifestyle and health – to find out if any of these factors had an influence on the types of bacteria living in their mouths.

"Of course, these were teenagers, so they had their own ideas about what was important to them. For example, they wanted to know if having a tongue piercing had an effect on their microbiome," says Gabaldón.

Back at the CRG, the researchers used a technique called 'barcoding' to identify the various families of microbes that were present in each saliva sample, focusing on the sequence of one single gene that is found in all types of bacteria. Overall, 1,555 of the samples were of high enough quality, to give a good result, providing a readout of the relative levels of hundreds of different groups of bacteria in each person's mouth.

Next, Gabaldón and his team cross-referenced these profiles against the data they had gathered from the student questionnaires and more general information about the populations in different parts of Spain. While they didn't find any significant differences between the oral microbiomes of teenagers living in cities compared with more rural areas, there were some intriguing correlations: for example, students with a kissing partner tended to have a larger number of bacterial species in their mouths, while people who used a lot of mouthwash tended to have a larger proportion of 'bad' bacteria. They also noticed that the microbiomes of teachers were very different from their students, which probably reflects differences in eating and drinking habits – teens eat more sweets, chew gum and drink soft drinks while their teachers prefer coffee and alcohol.

Taking a step back, the researchers spotted a bigger pattern emerging from their data. They noticed that the collections of bacteria fell into two distinct groups, analogous to two different types of 'ecosystem' in the mouth. More intriguingly, some bacterial groups showed geographical distributions that seemed to follow a map of Spain's various water systems, which are the source for the nation's tap water and contain different mixtures of salts and metals.

Could the chemical components of local tap water be having an effect on the types of bacteria growing in each student's mouth?

"We looked at the databases of water composition across Spain and found that the composition of tap water was one of the strongest links to the makeup of the oral microbiome," Gabaldón explains. "This makes a lot of sense - we drink water all the time, we cook with it and brush our teeth with it. Certain types of bacteria grow differently in response to particular salts, so it seems likely that tap water could have a long-term effect on the microbiome."

The team published the results from their initial study in the journal *Microbiome* and expanded the project into a second phase. Moving beyond teens, the researchers gathered saliva from another 2,000 people of all ages from the general public and worked with patient groups to include samples from people with certain health conditions such as cystic fibrosis, Down syndrome and coeliac disease.

Not only are there potential public benefits from understanding more about the microbes in our mouths and how they affect our health, these simple tubes of saliva have had a big impact on the researchers involved in the project too.

"It changed many things for me," Gabaldón says. "As a scientist, you are used to seeing things from one perspective, which is influenced by all the things you have learned before and all your ideas, but listening from the outside to what someone thinks – all the questions they have without any background – really opens your mind.

"These are the things that people are interested in and care about. Everyone worked extra hours on this project, from the PhD students to the technicians, but we are all so happy because it gives a greater purpose to our day by day work."

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POISED FOR ACTION

Genes are poised on the 'starting blocks', waiting to spring into action to build an embryo

It's the day of the Big Race. All the cars are lined up on the starting grid with their engines revving and tyres gripping the tarmac, waiting for the signal to start. The lights change and most of the cars go shooting down the track in a blur of smoke and squealing tyres, while a few unfortunate competitors have stalled and will have to withdraw from the race.

The adrenaline-fuelled world of motor racing may seem a long way from the complex molecular processes that turn a single fertilised egg cell into an embryo, but they are no less thrilling.

In the first few days of development, a mammalian embryo like a human or mouse is nothing more than a small ball of stem cells, each with the potential to become any of the hundreds of types of cells that make up the body.

At this stage, life moves fast. Cells are multiplying rapidly and having to make quick decisions about whether to follow one fate or another. These choices are made by a set of genes that are controlled by bivalent promoters – two-way genetic control switches that are poised either to turn on in early development and rapidly drive high levels of gene activity, or to switch off and shut down the gene completely.

Researchers had previously discovered that there are opposing types of chemical 'flags', known as histone modifications, that are present on these two-way switches – one telling the gene to GO (be switched on), and the other acting as a repressive STOP sign. The active tags are put in place by a molecule called MLL2, while the silencing marks are put on by Polycomb proteins.

At the start of development these STOP and GO signals are perfectly balanced, keeping the gene poised and ready to quickly flip into the correct pattern of gene activity, either on or off, like a racing car on the starting line.

To find out more about the interplay between the two type of signals on the switches, Luciano Di Croce, a group leader at the CRG, teamed up with Marc A. Marti-Renom at the CNAG-CRG and Ali Shilatifard at Northwestern University in Chicago, publishing their findings in the journal *Nature Genetics*.

It's obviously very difficult to study the first moments of development in the womb of a living animal, so the researchers turned to mouse embryonic stem cells growing in the lab. Under the right conditions, these cells will grow into tiny clumps known as embryoid bodies.

Although these clusters of cells aren't exactly the same as a real embryo growing from a fertilised egg - and would never be capable of growing into a baby mouse - they capture some of the early decisions and changes in gene activity that happen during development, which are driven by genes controlled by bivalent switches.

Using genetic engineering techniques, the scientists removed MLL2 from embryonic stem cells. This effectively wiped out all the activating GO signals from the bivalent gene switches and left only the STOP signals, tipping the balance strongly in favour of genes being switched off.

As might be expected, many important developmental genes weren't activated when they should have been, and the modified cells were no longer able to grow into embryoid bodies. Looking more closely at the location of these genes inside the nucleus, the researchers discovered that these genes had been relocated to regions that are usually associated with inactive genes.

"We found that changing the balance of histone modifications at these promoters had profound effects on gene activity and genome structure," explains Di Croce.

"Genes that should normally be active were packed away in areas containing silent genes that are not normally needed in these cells – it's the genetic equivalent of parking a car in the garage if you aren't driving it any more," adds Marti-Renom.

There was something else unusual about the genes with two-way switches in cells lacking MLL2, where the balance of signals had been tipped towards STOP. In normal embryonic stem cells, highly active genes form a loop so that their starts and ends are very close together. This means that the gene-reading machinery can quickly hop from the end back to the beginning to start again, like a racing car whizzing round and round a circuit.

But in cells without MLL2, the starts and ends of the genes were far apart, making it difficult to achieve very high levels of gene activity and revealing yet another way in which genes that should normally be poised for action are silenced.

Overall, the team's findings start to illuminate the complex interplay between histone modifications and three-dimensional gene organisation at the very earliest stages of development, when cells are quickly making decisions about what to do in order to build an embryo. There are also implications for understanding what might have gone wrong when development goes awry, leading to miscarriage or birth defects, and in diseases involving disrupted gene activity such as cancer.

"We now know more about the role of histone modifications at bivalent promoters and why they are important for proper activation of the genes," says Di Croce. "It's clear that there needs to be a balance between active and repressive marks in order to maintain the looped conformation for quick activation, and we now understand what happens when that balance changes."

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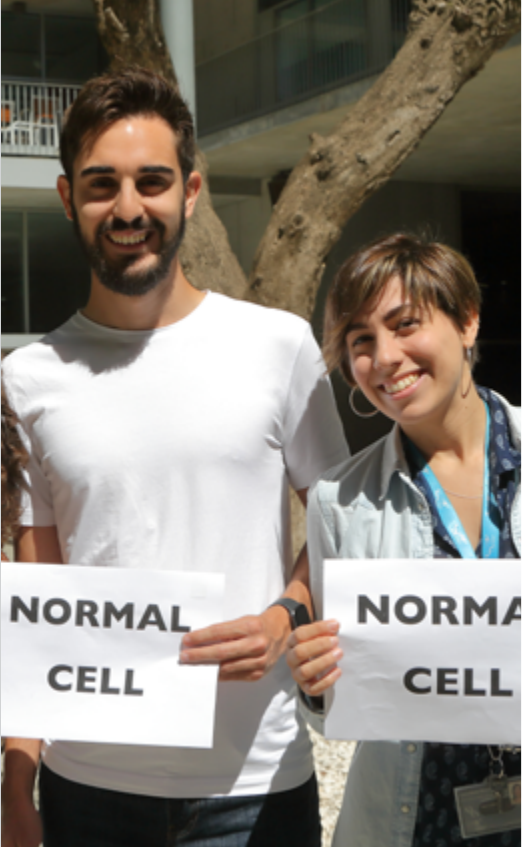

BAD BUDDIES

Overactive molecules team up to cause trouble

Pancreatic cancer is bad news. The disease is often detected late, because of a lack once it has spread aggressively through the body, and fewer than one in ten people will survive for five years after diagnosis – a figure that has barely changed over decades.

Now Susana de la Luna and her team in the Signalling and Gene Regulation group at the CRG may have discovered an important part of the puzzle of pancreatic cancer.

De la Luna's research focuses on a group of five related proteins called dual-specificity tyrosine-regulated kinases (known as DYRKs), which send signals inside cells by sticking tiny chemical tags onto other proteins, either triggering them into action or switching them off.

DYRKs seem to be multipurpose molecules with a wide range of cellular functions, such as switching genes on, controlling cell proliferation, or modifying other proteins important for cells to do specific jobs within the body.

One in particular – DYRK1A – seems to be very important for the development of nerve cells in the brain. So it was a big surprise when it turned up in pancreatic cancer cells too.

"De la Luna was approached by Cristina Fillat – a leading pancreatic cancer researcher at the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), next door to the Hospital Clinic in the heart of Barcelona, who had noticed that DYRK1A was present at high levels in pancreatic tumour samples and not in healthy tissue.

"This was surprising to us because DYRK1A overexpression stops cells from proliferating, so its presence in cancer cells was quite unexpected," de la Luna says. "So we really wanted to know what it was doing there."

To find out, de la Luna and her team reduced or removed DYRK1A from pancreatic cancer cells growing in the lab, either using genetic engineering or a drug called harmine. Intriguingly, both treatments dramatically slowed down the growth of the cells, and also reduced their ability to move around and spread.

Moving from Petri dish to real life, Fillat's group tested the same approach on mice with pancreatic cancer, significantly increasing survival time compared with untreated animals. Taking a closer look, the researchers discovered that the levels of two crucial cancer-driving signalling kinases – EGFR and MET – were also reduced along with DYRK1A.

Their findings, published in the journal *Gut*, suggest that the three proteins are teaming up inside cancer cells, forming a gang of 'bad guys' that take over the cellular controls and drive tumour growth.

"We realised that DYRK1A was joining together with these kinases, stabilising them so that they could send signals telling cancer cells to proliferate," she says. "Reducing DYRK1A also reduces both EGFR and MET together – you get two for the price of one!"

Although harmine isn't suitable for use in human patients, due to side effects, de la Luna and Fillat's findings have raised a lot of excitement that drugs designed to block DYRK1A could be a useful new treatment for pancreatic cancer, perhaps in combination with EGFR- or MET-blocking therapies.

However, DYRK-blocking drugs won't be suitable as a universal treatment for all types of cancer. Although DYRK1A drives the growth of pancreatic cancer and some other types of cancer, such as brain tumours, it might play a protective anti-cancer role in other types of cancer. This dual ability might seem confusing, but as de la Luna explains, it all depends on which other proteins have joined the team.

"We are working with the idea that this depends on the context and the proteins that DYRK1A is working with in that particular type of cell – sometimes this is good, and sometimes it's bad," she says.

"This highlights the importance of understanding the molecular makeup of a tumour before deciding on a treatment, so you know whether you're dealing with a 'good' team held together by DYRK1A that is preventing tumour cell growth or a 'bad' team that is promoting it."

The researchers are now studying pancreatic organoids – tiny 'mini-pancreases' grown in the lab from human tumour samples – to test out new drugs and combinations that might prove promising. There is a growing interest in DYRK inhibitors in academic labs and pharmaceutical companies, so de la Luna is hopeful that they will soon hit on some potential treatments to take forward into clinical trials.

Finally, there's a pleasing symmetry to the fact that the strong, positive team formed by de la Luna and Fillat's collaboration has helped to expose the bad team of proteins at work within pancreatic cancer cells.

"Neither of our labs could have done this on our own, and this joint study is much more than the sum of its parts," de la Luna says. "Our groups were very different – ours is molecular, while Cristina's has a focus on cancer therapies – but we have complementary perspectives on the problem. We've now applied for a shared grant to take forward our collaboration, so we're excited to see what we will discover together in the future."

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KEEPING IT TIGHT

How do you maintain shape and tension in the fast-changing fabric of a fruit fly embryo?

It may be less than a millimetre long and just a day old, but there's a lot going on in a fruit fly embryo as it tucks and folds itself into shape. Thin sheets of cells (epithelia) are on the move, wrapping themselves around the oval-shaped embryo and sealing together along its back.

This process, known as dorsal closure, works a bit like a suitcase being zippered shut. It's an essential step in the embryo's journey from fertilised egg to wriggling maggot and is a source of endless fascination to Jérôme Solon and his team at the CRG.

A few years ago, Solon made the important discovery that one of the driving factors of this biological zippering comes from the cells in the gap (known as the amnioserosa) that shrink down and die. The rest comes from cables of sturdy molecules known as actin and myosin – actomyosin – that connect the cells surrounding the gap on the embryo's surface and pull them together.

But although Solon and his team had figured out how forces could be generated by these cells, there was another mystery still waiting to be solved.

Although these epithelial sheets are moving around all the time as their cells change in size, shape and number, the surface always stays smooth and taut, with no baggy wrinkles, gaps appearing between cells or breaks in the cell borders due to being over-stretched. This suggests that the cell shape and the tension in the tissue sheet is somehow being adjusted so it always stays the same. So what's going on?

To find out, Solon's team did a very simple experiment that nobody had done before: they took some fruit fly embryos and squished them very, very carefully between thin pieces of glass. Pressing down on the embryos stretches their epithelial covering, while releasing the pressure causes the tissue sheets to temporarily ruffle up before becoming smooth again.

"We realised that the answer must lie in the connections between the individual cells," he says. These junctions are made from assemblies of the adhesive molecule cadherin, which form little chains suppor-

ted by actomyosin filaments. Importantly, the junctions can quickly be lengthened or shortened by adding or removing molecules as required.

"Our idea was to squeeze and stretch embryos to see what happens to the cell junctions as they are pushed together or pulled apart," says Solon. "This requires very careful precision, down to the level of a thousandth of a millimetre: squeeze too much and the embryo will burst, not enough and you don't see anything."

By carefully watching what was happening at the junctions as they squeezed or released the embryos, Solon and his team realised that the lengths of the cell connections were changing rapidly. Their results show that the tension between cells is maintained by quickly adjusting the junction length to accommodate the level of stretch.

"If the connection becomes too stretched then the cell brings in more actomyosin to pull everything back together again. And if it is too floppy and loose because the cells are bunching up, then some of the junction is removed so that the correct tension can be restored," he explains.

To understand how this works, imagine a chain of people holding hands across a shifting, stretchy ground, all trying to maintain a steady tension. If they drift too far apart and the chains risks being torn, they can call in some more friends and hold on tighter to keep the chain strong and sturdy. But if they start to bunch too closely together, then these extra people can drop out again.

"We were very excited to see the reaction of the cells – we weren't expecting it to be that dramatic for such a simple experiment, but it is amazing how quickly the cells adapt as the embryo changes shape," Solon says. "Our previous paper showed that cells shrink in size to help to close the embryo and now we have solved the mystery of how they make sure their shape and integrity is maintained while they do that, through constant readjustment of the junctions between them."

Published in *Developmental Cell*, this discovery sheds light on how tissues maintain their structure through the dynamic shifts and changes that happen during development. Other researchers have discovered similar processes at work in epithelia in other organisms such as developing frog tadpoles, suggesting that they are a fundamental part of the mechanics of life.

"Embryos are so dynamic – it is amazing the things that go on in a matter of minutes, and we are always finding something we weren't expecting about how cells are moving and responding to external pressures," Solon says. "It's an incredible self-organising system that can cope with all kinds of changes, yet still every embryo looks the same. I think that's really impressive."

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UNMIXING IT UP

Separating the subtle molecular flavours in a biological mixture

Stroll down *La Rambla* – the bustling boulevard that runs through the centre of Barcelona – and you might spot Escribà, a 100-year-old pâtisserie famous for its weird and wonderful creations.

Taking a bite of a delicious cake might tell you some information about the main components – flour, sugar, cream, and perhaps a strong flavour of fruit or chocolate. But you probably wouldn't be able to detect every single ingredient, especially the ones that are there in very small amounts.

Scientists have a similar challenge when trying to figure out the identities and proportions of all the thousands of components in a complex biological sample, such as blood or a tumour, which may contain thousands of different molecules.

One way to do this is with a technique called mass spectrometry, which identifies molecules according to their size. Firstly, all the components in the sample are heated up to the point where they turn into gas (vaporise), while capturing the electrical charges from the solvents. Finally, all the charged molecules are sent flying towards a detector that measures the size (mass) and charge of everything that hits it providing a detailed readout of the full ingredient list of a biological sample.

Mass spectrometry is quickly turning into a powerful tool for biomedical research, allowing researchers to precisely measure the levels of particular molecules in all sorts of cells and samples – for example, tracking the levels of certain proteins in the blood that act as an early warning sign of disease or reveal how well a patient is responding to treatment.

But there's a problem: many of the most medically useful molecules are only present in extremely small amounts. They can be easily missed using the most common mass spectrometry technique (data dependent acquisition), which looks at data by sampling subsets of all the molecules in a mixture.

To go back to the example of the delicious cake, this is the equivalent of trying to work out all the flavours and ingredients by taking a couple of small bites rather than eating the whole thing. Not only is it hard

to distinguish subtle flavours, there's also a chance of completely missing chocolate chunks, crystals of caramel or bits of fruit, which aren't evenly distributed.

When translated into patient samples, this means that it's possible to look at different samples from the same patient and get a slightly different list of the molecular 'ingredients' each time.

One alternative is to use an approach called data independent acquisition (DIA), which gathers information about every single molecule in a sample - the equivalent of eating the whole cake. However, this generates a huge amount of data that can be difficult to analyse, meaning that very rare molecules may still be overlooked.

Two researchers in the CRG/UPF Proteomics Unit – Eva Borràs and Eduard Sabidó – have now solved this problem with a new method called DIA+, which they describe in a paper in the journal *Analytical Chemistry*.

The key breakthrough came when they realised that they could take advantage from the fact that the mass spectrometer turns each molecule into two versions, each with a different electrical charge (either 2+ or 3+). These are interpreted as two separate chemicals, meaning that rare molecules appear to be even more scarce than they really are.

Simply combining the data from both the 2+ and 3+ versions of the same molecule together concentrates the 'flavour', boosting the signal to the point where it's possible to detect very low levels of rare chemicals in a reliable and repeatable way.

"Everybody in the field has this problem and most people are trying to solve it by improving the technology," Borràs says. "Instead, we decided to think differently, revisiting current methods and developing a new way to operate the mass spectrometer by measuring these particles together."

"The information is out there – every chemist knows these two things are the same, but nobody put them together," adds Sabidó. "It seems so obvious, but nobody had thought of doing it before."

He and his team are now working together with doctors in hospitals in Madrid and Barcelona to analyse samples from patients who have been treated for breast cancer and other diseases. They're hoping to find molecules in the blood that might indicate how well each patient is likely to respond to a particular treatment or flag up early warning signs that the cancer is coming back.

"The impact of mass spectrometry in biomedicine is huge," Sabidó says. "DIA allows us to look at all the proteins that are present in a sample in a consistent and reliable way, which is vital in clinical applications."

"When we started presenting our method at conferences people said it was very elegant, which was nice to hear," Borràs adds. "It isn't complicated and it's easy to apply, so we hope that it will be taken up by many researchers working in this field."

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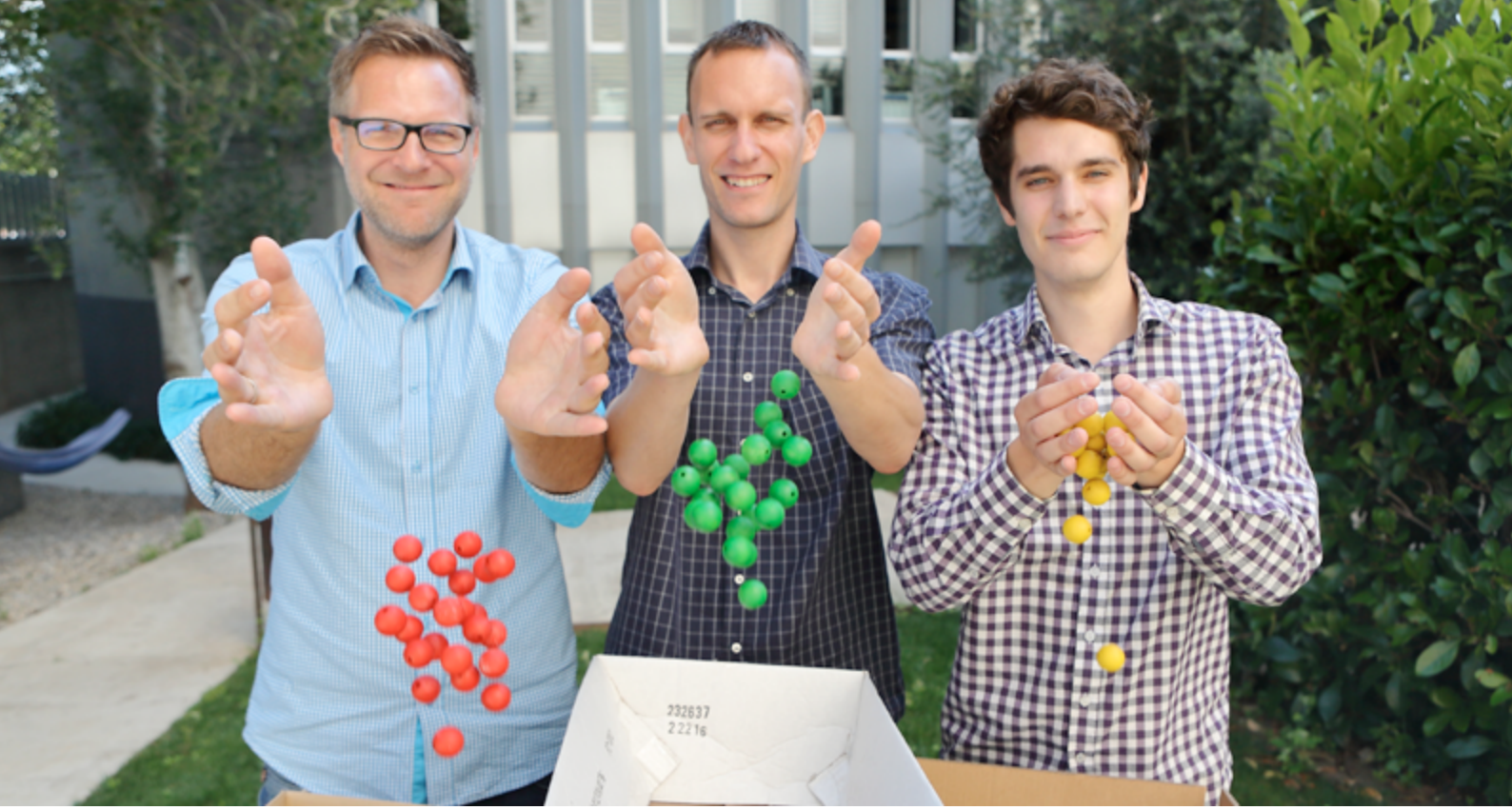

MAPPING THE MIND OF A MOUSE

A clever computer tool sifts through data from millions of cells at the same time

There are more than 200 different types of cells in an animal like a mouse or human, from bone and blood to skin, spleen, heart, hair and everything else in between.

Look more closely, and the picture becomes much more detailed. For example, there are at least 10,000 different types of nerve cells in the brain – adding up to many billions in total - each with its own particular characteristics and specialised job.

As an analogy, imagine a huge international company like a bank. There are broad groups of jobs within the organisation – managers, administrators, accountants, customer service representatives, communications specialists, receptionists, cleaners, and so on – and individual people or groups within each team may have an even more specialised role.

Simply saying that all of these people are 'bank workers' tells you nothing about how the company is structured or how it functions. Similarly, in order to understand how the brain works, we need to map out exactly what all these cells are like, where they are and what they're doing.

Recent advances in technology mean that researchers can measure the patterns of gene activity in single cells taken from anywhere in the body relatively quickly and easily, generating huge datasets from thousands or even millions of cells.

That's the easy bit. The hard part is sifting through all this information and distinguishing specific groups of cells that share the same profile, meaning that they are likely to have the same function in the body. One of the biggest problems is the fact that single cell gene activity is very noisy with lots of random fluctuations in activity levels between cells, making it hard to figure out whether any two cells are really alike or not.

One recent dataset contains gene activity profiles from about 1.3 million individual cells collected from the brain of a developing mouse fetus around three quarters of the way through pregnancy. Ten times bigger than any previous datasets, it was produced by the company 10x Genomics, who made it publicly available in the hope that someone might be able to come up with a way of analysing such a huge amount of information.

The challenge caught the attention of Holger Heyn, a team leader focusing on single cells genomics at the Centro Nacional de Análisis Genómico (CNAG-CRG), and his postdoctoral research fellow Giovanni Iacono.

"The falling cost and rising speed of single cell techniques mean that there is a tidal wave of data right now," says Heyn. "It may be one million cells now, but it could soon be ten million or more – we wanted to build a tool to analyse these huge datasets in a way that would scale up in the future."

Heyn and Iacono set about building a new computer tool known as bigScale, which would be capable of sifting through the data from all 1.3 million brain cells and identifying different types hidden within. One of the biggest challenges was figuring out how to handle such a large amount of biological data and load it into the computer's working memory for processing.

To solve the problem, the researchers worked out a trick for compressing the data by grouping data from cells that all seem to be the same to create index cells, or i-cells, then loading them into the computer. It's a bit like packing up to move house: putting every single item separately into the back of a van it would take a very long time and be chaotic and confusing, but the task becomes much more manageable if you put books in one box, plates and bowls in another and so on. And it's much easier to unpack and sort everything out again at the other end.

"Each i-cell represents a typical cell of a particular type, which enables us to reduce the dataset from more than a million cells to around 26,000," Heyn says. "We compress everything into i-cells and analyse the biologically relevant groups, then we can unpack it again later to see all the individual cells."

"It was the first time I had built such an ambitious tool but every time there was a challenge – whether it was in the size of the computer memory or data storage, the steps in the analysis – we just had to take things apart, solve the problem and put it all back together," adds Iacono.

Heyn and Iacono used this method to home in on elusive Cajal-Retzius cells, a small group of hard-to-find nerve cells named after the neuroscientists Santiago Ramón y Cajal and Gustaf Retzius, who first described them at the end of the 19th century. They exist for a short time during development, helping to control the organisation and growth of important parts of the brain, but die soon after birth.

Their rarity and brief existence make Cajal-Retzius cells hard to isolate and study, but the CNAG-CRG team discovered more than 15,000 in the whole 1.3 million cell mouse brain dataset – the largest group of these type of single cells ever analysed in this way.

"This huge dataset had just been sitting there for more than one year, full of super-interesting biological information that nobody could look at," Iacono explains. "Now we can find rare cells with properties that have never been seen before."

BigSCale has been quickly picked up by many researchers working on large-scale cell mapping projects, and Iacono has rewritten the software into a more user-friendly language to encourage as many people as possible to use it. One possible application is the Human Cell Atlas – an ambitious project aiming to map all the million-plus cell types in the human body, from early development in the womb through to adulthood and in diseases such as cancer.

Another opportunity is in clinical research, analysing single cells in blood or tissue samples to monitor the progression of diseases like cancer or even spot the early warning signs of illness before they become outwardly obvious.

"BigScale provides a glimpse into the future of what big data analysis can look like, and we're hoping it will be taken up by many people working in the field," says Heyn. "We're excited to see how it grows, and happy to be contributing to the research community."

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UP CLOSE AND PERSONAL

A powerful new data platform unlocks the possibility of personalised medicine

As you might expect from the name, rare diseases are rare. But the numbers soon start to stack up: while any one rare disease affects fewer than one in two thousand people, there are thousands of different conditions. This adds up to around 7 per cent of the population or one in 13, affecting an estimated 300 million people around the world.

Adding to the problem, most patients with rare diseases take up to five years to receive a diagnosis for their illness, during which time they and their family have to live with uncertainty and delays with starting treatment.

One of the key issues lies with the fact that a doctor might only see a handful of patients with rare diseases in any year and might only encounter a particular condition once in their entire career. Although clinicians may write case reports about individual patients, much of the information about the diagnosis and treatments of rare diseases remains locked away in confidential medical records and obscure scientific papers spread all around the world rather than being organised and shared in a way that could benefit patients.

“Around five years ago, we decided that this had to stop,” says Ivo Gut, director of the CNAG-CRG. “These patients are often young children, which puts a huge burden on their parents – caring for their child and running from doctor to doctor in search of answers takes a huge amount of time, money and emotional energy.”

“We realised the need to build an online system that would enable doctors to work faster and more effectively to deliver a diagnosis or potential treatment for rare diseases, and to find other similar cases elsewhere that might provide vital information and end this diagnostic odyssey.”

Gut teamed up with Sergi Beltran, head of the CNAG-CRG Bioinformatics Unit, to develop the Genome-Phenome Analysis Platform within the RD-Connect project, an international research collaboration for rare diseases. The cutting-edge global data platform allows doctors to store, analyse, and securely and ethically share all kinds of information about their patients with rare diseases.

Genomic data plays a significant role, as most rare diseases are caused by specific inherited genetic variations, but that's not all. Other types of information include the levels of various molecules in the blood, as well as physical symptoms and measurements. All of these datasets come together to provide a detailed picture of exactly how the changes in an individual patient's genes affect their body and cause their disease.

RD-Connect now contains information about more than 5,000 individuals and has led to the identification of hundreds of new genes that are implicated in rare diseases, slashing the time taken to diagnose most rare diseases to around a year. Importantly, it has also brought certainty for many families that have been desperately waiting for answers.

Having a specific diagnosis for a rare disease provides a name and a cause for a condition, unlocking access to financial help and other types of support. In some cases, although not all, a confirmed diagnosis may point towards a specific treatment, such as drugs, dietary changes or high-dose vitamin supplements. And it can provide a reason for something that was previously a frustrating mystery.

"Knowing what is wrong is very important for families," explains Gut. "They may worry that their child is sick because it's something they've done – they think it's their fault or they made a mistake. We can say, 'no, you were just unlucky,' which helps to calm their spirits."

Importantly, the RD-Connect platform provides a way to safely, securely and ethically share and search data, allowing clinicians to find information that might help their own patients.

"For diseases that are very are, it's hard to know how best to treat diseases that are extremely rare," says Gut. "Our platform effectively provides access to all the world's doctors. Clinicians can find information about what works – and what doesn't work – for similar patients by sharing details about best practice and treatments."

The platform's technology allows users in other locations to 'dial in' and search for similar cases – or even help to diagnose patients in other hospitals - without having to move data between institutions or across borders. It also provides a standardised way of gathering genetic and clinical information and reporting results back to doctors and genetic counsellors, ensuring that everyone is speaking the same 'data language' when it comes to diagnosing and treating patients.

Five years on, there are currently more than 400 doctors using the RD-Connect platform, inputting and analysing data to help diagnose and treat their patients with rare diseases. The CRG-CNAG team is also working with collaborators in Finland and other countries to establish the system as part of their national healthcare.

It is also being used in two major European projects on rare diseases, Solve-RD and the EJP-RD, connecting doctors and researchers across Europe to analyse, share and diagnose thousands of their most challenging unsolved rare disease cases.

In Spain, the CNAG-CRG is involved in several regional projects related to Personalised Medicine. URD-Cat (Undiagnosed Rare Disease Program of Catalonia), led by Luís Pérez-Jurado, is working to diagnose 1,000 patients with rare neurological diseases in seven Catalan hospitals, and the Navarra 1,000 Genomes Project, coordinated by Ángel Alonso, is a pilot project for diagnosing rare diseases and treating cancer within the health service, based on using genome sequencing as a front-line diagnostic test.

"The Navarra 1,000 Genomes Project is a genome-first approach, seeing how we can make this kind of genetic testing available to anyone in the healthcare system," explains Beltran. "We have customised the platform for them, collecting phenotypic and genomic information from 1,000 people with rare diseases or cancer, processing the data in a standard way and making it available through the platform, so doctors can work out what best to do for their patients."

However, the potential benefits of the tools that the CNAG-CRG team have built extend beyond rare diseases and into other health conditions, such as cancer.

The CNAG-CRG researchers have teamed up with Núria López-Bigas at the IRB Barcelona and David Torrens at the Barcelona Supercomputing Centre for the Bioinformatics developments in MedPerCan – a pilot project for personalised medicine in Cancer in Catalonia.

Run across three major hospitals in Barcelona, the project is using an adapted version of the underlying RD-Connect technology to set up a workflow for diagnosing and treating cancer patients in a more personalised way, cataloguing the underlying gene faults that are driving the disease and identifying potentially useful therapies.

All the DNA sequencing for URD-Cat, MedPerCan and the Navarra 1,000 Genomes project is being done at CNAG-CRG, highlighting the vital importance of the centre in supporting precision medicine within Spain.

Not only could this new platform help to diagnose rare diseases and treat cancer more effectively, it also looks at genetic variations that affect how people respond to and break down certain drugs (known as pharmacogenomics). And it can also provide information about the broader pattern of genetic changes that are present within an individual's genome, which could be relevant when planning a family.

"What is medicine for one person is poison for another, so what makes the difference?" Gut asks. "Is it genetics? Psychology? Food and lifestyle? Exercise? Sleep? Systems that can correlate all of this information and crunch it all together, including data from patients themselves, would really move us forward. That's the future of where this will go – collecting as much information about an individual's life and health as possible and figuring out what is best for them and why."

"The system is all about organising and interrogating data about genes and their effects on health, rather than focusing on any particular disease," Beltran points out. "We are now adapting the RD-Connect platform for providing insights about the best way to treat someone based on the genetic and molecular makeup of their disease – this is personalised or precision medicine."

For example, while there may be many patients affected by the same type of cancer, each case is an individual disease with its own biological quirks. Currently, patients are given treatments according to the physical and molecular characteristics of their tumour. But these are still relatively large groups, and some people's cancers respond well to therapy while others do not.

Understanding the complex interplay between the underlying genetic and molecular characteristics of the disease is likely to point towards therapies that are more likely to be effective – something that the underlying technology of RD-Connect is exactly designed to do. Yet despite the success of their system today, Beltran and Gut were convinced that they were lagging behind the field when they first came up with the idea to build RD-Connect.

"We thought we would be playing catch-up with other platforms that were already being built," Gut says. "But even now, although lots of people are talking about doing something like this, there is still nothing comparable out there."

"I'm extremely proud of our team," add Gut. "It's been a huge process and a lot of work for our engineers, and I'm also very grateful to the first users who helped us to improve and debug the system. Five years on from having started this project, it has turned out to be exactly the right thing to do and I'm delighted with what we have built."

RESEARCH AND SCIENTIFIC SERVICES

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

Roderic Guigó
Coordinator

The programme's scientific highlights in 2018 included the development of Pergola, a tool to visualise and analyse longitudinal data that uses the logical infrastructure built to display annotations along genome sequences; the investigation of the impact of the death of the organism in the transcriptional patterns in tissues and the corresponding development of a forensic tool to predict the time since death based on the gene expression values in a few selected tissues; the uncovering of evidence for the existence of an active sexual cycle in *Candida glabrata*, an opportunistic fungal pathogen, and the discovery of a number of proteins that regulate the expression of alpha-synuclein, which is linked to Parkinson's disease, through interactions with its 3' UTR.

Our programme also led the "Saca La Lengua" ("Stick Out your Tongue") citizen's science project (https://www.sacalalengua.org/stick-out-your-tongue/). The project aims to study the mouth's microbiome and its possible relationship with our environmental characteristics and lifestyle.

Several groups in the programme are participating in a number of large-scale genomic projects, such as ENCODE, GTEx, PanCancer, I5K, F1K, WebOfLife, IASIS, the Human Cell Atlas and others.

The programme has continued to deploy and support the European Genome-phenome Archive (EGA) in collaboration with the European Bioinformatics Institute (EBI). EGA is an ELIXIR Core Data Resource and an ELIXIR Recommended Deposition Database. It is one of the Global Alliance for Genomics and Health (GA4GH) Driver Projects. EGA is also one of the European Open Science Cloud (EOSC) Science pilot demonstrators.

Vivek Malhotra
Coordinator

CELL AND DEVELOPMENTAL BIOLOGY

The mission of the scientists in the Cell and Developmental Biology programme is to reveal the mechanisms of cell compartmentation, division and tissue organization. The department is staffed by Vivek Malhotra (mechanism of protein secretion), Isabelle Vernos (microtubule and spindle dynamics), Jerome Solon (tissue organization), Sebastian Maurer (cytoplasmic RNA localization), Verena Ruprecht (cell and tissue dynamics) and Elvan Boke (oocyte biology and cellular dormancy). Our former colleague Manuel Mendoza was recruited as a group leader to IGBMC, Strasbourg in 2017. Thomas Surrey, senior group leader from the Francis Crick Institute in London, is a leading figure in the mechanism of microtubule and spindle dynamics, who will join the CRG in October 2019.

A large number of outstanding papers were published by members of our department, although one in particular merits special note. This paper by Jerome Solon laboratory, Sumi et al. *Dev Cell* (2018), describes how the cytoskeleton and the removal of specific proteins from the cell junctions control tissue organization. These findings could help to understand how animals control a tissue's size, shape and the physiology of a tissue.

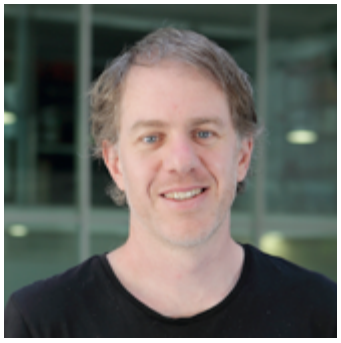
Vivek Malhotra is a fellow of the American Society for Cell Biology. Elvan Boke is funded by a European Research Council (ERC) Starting Grant. Isabelle Vernos is a member of the Scientific Council of the European Research Council (ERC) where she chairs the Gender Balance Committee.

Juan Valcárcel
Coordinator

GENE REGULATION, STEM CELLS AND CANCER

In 2018, we welcomed Eva Novoa and her group, coming from the Garvan Institute of Medical Research in Sydney, Australia. Eva's group studies the mechanisms and functions of the *epitranscriptome*, a large set of distinct chemical modifications that can be present in and regulate the function of RNA molecules.

Some highlights of this year's research include collaborative work involving up to five of the groups in the programme, revealing the roles of enhancer demethylation and of chromatin architecture in regulating cell fate decisions during cell reprogramming. The effects of genome conformation on transcription factor trafficking and of promoter bivalency in favouring the open genome architecture of stem cells constituted other exciting insights. Advances in RNA-based regulation include a role for Dicer-2 in mRNA activation by cytoplasmic polyadenylation and a patent application for the potential use of splicing-modifying antisense oligonucleotides in cancer therapeutics. Another important finding was the role of DYRK1A kinase in controlling the angiogenic responses of endothelial cells. Evidence of the mobilisation of endogenous bone-marrow cells to mouse retina to induce cell fusion-mediated reprogramming of Müller glia cells can pave the way for novel retinal degeneration therapies.



Ben Lehner
Coordinator

SYSTEMS BIOLOGY

The CRG Systems Biology Programme is a leading centre in Europe for quantitative biology. The programme's goal has always been to hire group leaders using a quantitative approach to fundamental biological problems rather than to target particular topics. The programme has therefore covered a broad range of questions: from genetics and dynamic gene regulatory networks to systems neuroscience. However, this diversity is underpinned by the common goal of combining systematic and quantitative data collection with computational models to acquire a deeper understanding of complex biological processes. Indeed, one of the programme's key characteristics is integration between computational and experimental approaches within the same labs and in which, somewhat unusually, all of the group leaders recruited are researchers who mixed wet and dry approaches when they were postdocs.

The programme was reviewed by the CRG SAB and an international panel in 2018, with the panel concluding that:

'The Systems Biology programme has been an outstanding success in every regard, numerous high-quality publications were produced and it was highly successful in attracting external grant income

from blue chip funding sources. The Panel applauded the manner in which all of the individual research programmes had so seamlessly combined wet and dry lab approaches, which is key to the success of quantitative biology projects. In broader terms, public outreach and the engagement and development of translational and commercial activities within the programme was exemplary. Furthermore, the Systems Biology Programme has served as a focus for a broader community, bringing together a number of non-CRG groups from inside the building, as reflected in an extensive portfolio of joint publications.'

We celebrate and congratulate all the group leaders and members of the programme for their achievements which have resulted in this extremely positive evaluation of the programme.

Finally, in 2019, Arnau Sebé-Pedrós will be joining the programme as a new junior group leader. Arnau was most recently a postdoctoral fellow at the Weizmann Institute in Israel. Arnau's lab will use single-cell genomics methods to study the origins and evolution of cell types. Welcome, Arnau!

CORE FACILITIES

Mònica Morales
Head

The core facilities programme currently comprises seven Core Facility Units: Genomics, Proteomics, Advanced Light Microscopy, Biomolecular Screening & Protein Technologies, Flow Cytometry, Bioinformatics and the Tissue Engineering Unit. The programme also includes the Histology Service and the Storage and Computing Unit that are only accessible to PRBB users or internal users, respectively.

All of the units work towards implementing new technologies and applications in response to both our user needs and future directions in their respective fields. The most prominent new technologies set up in 2018 include:

- Mass spectrometric application for the characterisation of protein-protein interactions and protein structural determination using chemical crosslinkers followed by LC-MS
- Identification and isolation of extracellular vesicles by flow cytometry for the study of vesicles' cargo
- CRISPR/Cas9 Gene editing directly in embryos
- PiggyBac transposon in mouse ES cells
- CRISPR/Cas9 Gene editing in human ES cells
- Derivation and culture of intestine organoids
- Generation and production of in-house Cas9 enzyme tagged with fluorescence
- NextFlow pipeline development for major workflows, community sharing and contribution to community development

In order to establish an integrated request management solution across all core facilities, we are working closely with the developers of the software Agendo to customise it and offer an integrated solution to all our users. Agendo will manage all bookings and requests across facilities, will become the communication channel and will offer tracking of samples and projects to our users.

In 2018, the Proteomics facility was acknowledged as a new node of the Scientific and Technological Singular (ICTS in Spanish), called Infrastructure for OMICS technologies (IOT), also comprised of the CNAG (Centro Nacional de Análisis Genómico) and the COS (Centre for OMICS Sciences) in Reus.

The CRG core facilities are not only well-established locally, with users coming from different institutions in Spain and abroad, but we are also acknowledged **partners in European initiatives.** The Proteomics facility is a partner in the recently-granted INFRAIA (H2020) consortium EPIC-XS. The Advanced Light Microscopy Unit is a partner in the ESFRI initiative EuroBioimaging (EuBI), and its head, Timo Zimmerman, is the national coordinator for biological imaging. The Genomics and Proteomics Units are members of MERIL, the European Research Infrastructure portal listing facilities with more-than-national relevance (CRG being the only Spanish Proteomics Facility).

The Core Facilities are member of the Core Facilities Excellence Alliance **"Core for Life"** (www.coreforlife.eu), which also includes EMBL (Heidelberg, Germany), VIB (Ghent/Leuven, Belgium), MPI-CBG (Dresden,

Germany), VBCF (Vienna, Austria), the FGCZ (Zurich, Switzerland), and the Institut Pasteur and Institut Curie (Paris, France). Core for Life aims at sharing and consolidating procedures, uniting efforts in personnel training and technology validation and sharing access to facilities across institutes.

Ivo Gut
Director

CNAG-CRG

In 2018, we refined our strategic priorities into five topics: Cancer, Rare Diseases, Personalised Medicine, Single-cell Analysis and the Genome in Action (epigenetics). High-throughput nucleic acid sequencing and data analysis are key to these topics. Our portfolio of sequencers has been diversified and extended by an Illumina NovaSeq6000, a 10x Genomics Chromium Controller, an Oxford Nanopore GridIon and ancillary instrumentation that all permit the streamlining of biological materials for sequencing. Instruments are now deployed according to the needs of the users of the CNAG-CRG Sequencing Unit and the CRG Genomics Unit. This guarantees sufficient capacity for all applications at both sites. We were renewed as an ICTS (Infraestructuras Científicas y Técnicas Singulares) and as of January 2019 this will include the CRG Genomics Unit and the CRG/UPF Proteomics Unit. Besides the re-certification and re-accreditation of ISO9001 and ISO17025, CNAG-CRG has become a BBMRI-Expert Center. Linking to biobanks across Europe facilitates academic and industrial research.

The EU-funded RD-Connect project that enabled us to establish the RD-Connect Genome-Phenome Analysis Platform (RD-Connect GPAP) ended in 2018. When the former scientific coordinator of RD-Connect, Hanns Lochmüller, moved, we took over the scientific leadership of this project for the final year and brought the project to a successful conclusion at the end of the year. The RD-Connect Genome-Phenome Analysis Platform is now an IRDiRC Recognized Resource, it is a key tool for the EU-funded Solve-RD project and is an important part in the upcoming European Joint Project on Rare Diseases (EJP-RD), due to commence in early 2019. The RD-Connect GPAP currently holds more than 4,000 patient entries and is used by more than 600 clinicians and researchers. In order to keep up the momentum generated by RD-Connect, we established the RD-Connect Community, which aims to maintain the connection between rare disease researchers and patients. The RD-Connect GPAP also lies at the heart of the two projects funded by the Catalan Ministry of Health (PERIS), URDCat and MedPerCan, that extend its utility to capture electronic health records and integrate genomic data from cancer patients.

CNAG-CRG researchers were also incredibly successful this year in attracting new funding, such as an ERC Synergy Project (BCLL@tlas) and several EU Horizon2020 projects (EUCanCan, which builds on the work of the ICGC-CLL project and EJP-RD). Our single-cell genomics activity brought funding from the Chan-Zuckerberg Initiative to partner up with the Human Cell Atlas project. We are taking on international leadership in genome analysis through the EU-funded EASI-Genomics Infrastructure Project, which we will be coordinating. Apart from many infrastructure activities that will be possible through this project, we will be able to establish the international standardisation of methods in genomics. Our first Innovative Medicines Initiative (IMI) project, focussed on immunotherapy for cancer, will commence in 2019. IMI projects are collaborative projects between academia and industry. A new Marie Skłodowska-Curie European Training Network, ChromDesign, will support PhD students working on nuclear structure projects. The European Commission is also supporting a Coordination and Support Action for LifeTime for the preparation of a Future and Emerging Technologies Flagship Project.

The development of computational tools for different types of analyses of genomic data are an important part of our activity. This year we released several new computational tools, namely GEM-BS, which was adopted as the standard pipeline for DNA methylation analysis by the International Human Epigenome Consortium, BigScale for single-cell analysis, and TADbit and TADkit, tools for analysing nuclear conformation.

Personalised medicine is a hot topic, and genomics has a major part to play in it. An EU member state initiative to share more that 1 million human genomes together with phenotype and clinical data across Europe in an interoperable and federated manner was launched in 2018. Several of our initiatives are putting us in an excellent position to play a major role in this project: the NAGEN1000, a pilot project

funded by the Servicio Navarro de Salud-Osasunbidea, and the two Catalan PERIS projects, MedPerCan and URDCat, on the integration of genomic information into the clinical system. These projects put us on a solid path towards the fully-fledged implementation of personalised medicine and will allow us to play a key role in the medicine of the future.

EUROPEAN GENOME-PHENOME ARCHIVE (EGA)

Jordi Rambla
Acting Team Leader

The EGA is a service for the permanent archiving and sharing of all types of personally identifiable genetic and phenotypic data resulting from biomedical research projects. The data at EGA were compiled from people whose consent agreements authorise data release only for specific research use or to bona fide researchers. Strict protocols govern how information is managed, stored and distributed by the EGA project.

Since its launch, researchers from around the world have deposited and accessed different types of data from more than 1,700 studies in the EGA. These studies vary from large-scale array-based genotyping experiments on thousands of samples in case-control designs or population-based studies to sequencing-based studies designed to understand changes in the genome, transcriptome or epigenome in both normal tissue and in various diseases such as cancer. As a result, the EGA has grown from about 50 TB to 5,800 TB over the last six years.

NEW HIRINGS

Two outstanding early-career scientists and one renowned senior scientist set up their new research groups at the CRG in 2018.

EVA MARÍA NOVOA

Eva María Novoa
Junior Group Leader

Eva is a Spanish scientist who studied her PhD at the Institute for Research in Biomedicine (IRB Barcelona), Spain, before taking up a three-year postdoc position at the Massachusetts Institute of Technology (MIT) and Broad Institute of MIT and Harvard in Boston, USA, first as an EMBO Fellow and then as a HSFP Fellow. Then she moved to the Garvan Institute of Medical Research in Sydney, Australia where she undertook a Senior Postdoctoral position, before becoming group leader in the same institute.

A current major challenge in biology is to understand how gene expression is regulated with surgical precision in a tissue-dependent, spatial and temporal dimension. Historically, genome-wide studies of gene expression have typically measured mRNA abundance rather than protein synthesis, in large part because such data are much easier to obtain. However, the correlation between mRNA levels and protein abundance are very low, suggesting that transcriptional regulation alone is not sufficient to unveil the complex orchestration of gene expression. In the last few decades, the scientific community has started to acknowledge the pivotal role that post-transcriptional regulatory mechanisms play in gene expression, however, scientists are still far from understanding how gene expression is finely tuned and regulated across tissues and conditions, suggesting that there are missing variables in the equation.

In Eva's lab, they are employing a combination of experimental and computational techniques, to unveil the secrets of three post-transcriptional regulatory layers: the epitranscriptome, RNA structure and ribosome specialization.

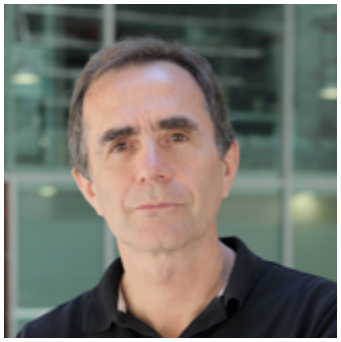
Donate Weghorn
Junior Group Leader

DONATE WEGHORN

Following a PhD in Theoretical Physics at the University of Cologne, in Germany, Donate took up a postdoc position at the Department of Medicine and Department of Biomedical Informatics, at Harvard Medical School, in Boston, USA.

Mutation, selection and stochasticity combine to leave their footprint in genetic data. With the proper tools and analyses, the resulting information can be leveraged to describe mutational processes, obtain estimates of selection, and reveal more intricate evolutionary dynamics.

Donate's lab is interested in a variety of topics in the field of genetics. A strong focus of the lab lies on cancer as an evolutionary system and selection as a readout. This involves investigating different modes of selection active during tumorigenesis, including negative selection, in both the coding as well as the non-coding part of the genome. They analyze sequencing and other datasets and develop mathematical and computational approaches to estimate selection. An important aspect of this effort is to account for the heterogeneity of mutation rate. Estimates of the strength of selection in cancer allow for a prioritization of genes and noncoding regions by their disease relevance, with the ultimate goal of promoting therapeutic advances. They extend some of the analyses to the level of human population genetics, which is another active area of research in her lab. The main goal of their work is the quantitative description of evolutionary processes through the development of new probabilistic models and computational methods.



Jorge Ferrer
Senior Group Leader

JORGE FERRER*

Jorge's impressive career took him through different positions at several hospitals and research institutes both in Spain and the USA, such as the Harvard Medical School and the Massachusetts General Hospital, in Boston, and the Hospital Clinic and IDIBAPS, in Barcelona, Spain. He arrived at the CRG after a six-year period in UK, where he took up a position of Professor and Section Head, at Imperial College London. Later he was also appointed Lead for Genetics and Genomics, at NIHR Imperial BRC.

Diabetes mellitus afflicts more than 400 million people. Current strategies to prevent and treat diabetes are limited by the scant knowledge of the molecular defects that cause diabetes.

Jorge's lab focusses on understanding changes in genome regulation that lead to monogenic and polygenic diabetes. They study the gene networks that are essential for insulin-producing beta cells to maintain glucose homeostasis, and develop strategies to manipulate these networks in human patients. They are also interested in how gene regulatory mechanisms can be harnessed for regenerative therapies in autoimmune diabetes. To achieve these goals, they combine regulatory genomics, human genetics, and genome engineering in model systems.

**Ferrer's lab is relocating from the Imperial College London and will be fully operational at the CRG by the end of 2020.*

AWARDS

National Research Prize 2018

Roderic Guigó

XII Prize Francisco Cobos Foundation

Luis Serrano

Committed Optimists Prize 2018

Mara Dierssen

Clover Prize to Solidarity 2018

DOWN ESPAÑA

Mara Dierssen

FEBS National Lecturer Award

Luis Serrano

Impulse 2018

UNIVERSIDAD DE ALICANTE

Microomics

Young Invest. Award

CATALAN SOCIETY OF BIOLOGY

Verónica Llorens and Ben Lehner

ERC RESEARCHERS AT CRG

STARTING GRANTS


Manuel Irimia


Elvan Boke

CONSOLIDATOR GRANTS


Ben Lehner


Toni Gabaldón

ADVANCED GRANTS


Jorge Ferrer


Luis Serrano


Juan Valcárcel

SYNERGY GRANTS


Miguel Beato


Thomas Graf


Guillaume Filion


Marc A. Marti-Renom (CNAG-CRG)


Ivo Gut (CNAG-CRG)


Holger Heyn (CNAG-CRG)

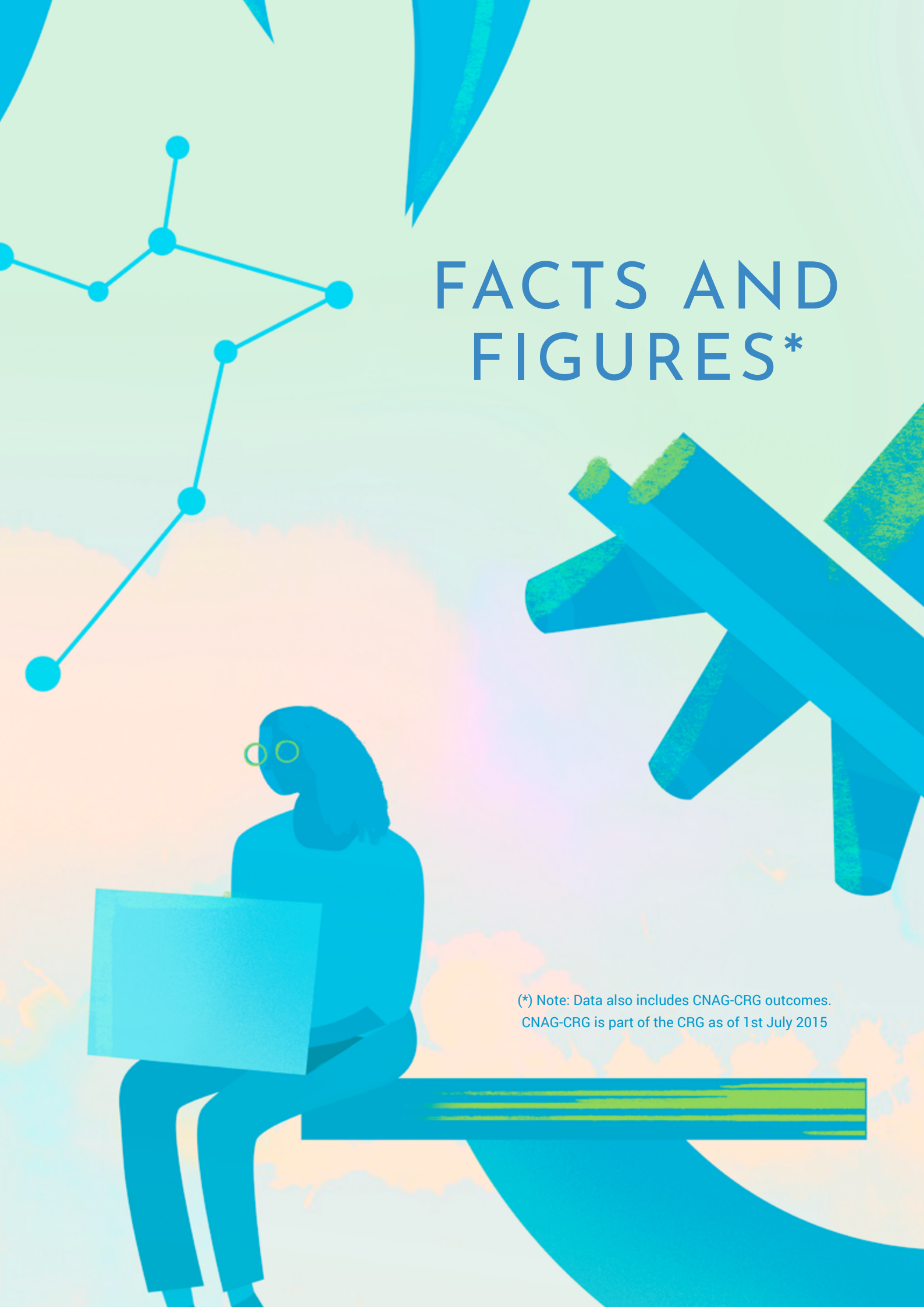
PROOF OF CONCEPT GRANTS


Juan Valcárcel


Miguel Beato


Luis Serrano

FACTS AND FIGURES*



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

PUBLICATIONS

243
Total Publications

68%
Open Access Publications

77%
1st Quartile Publications
187 publications

9
Average Impact Factor

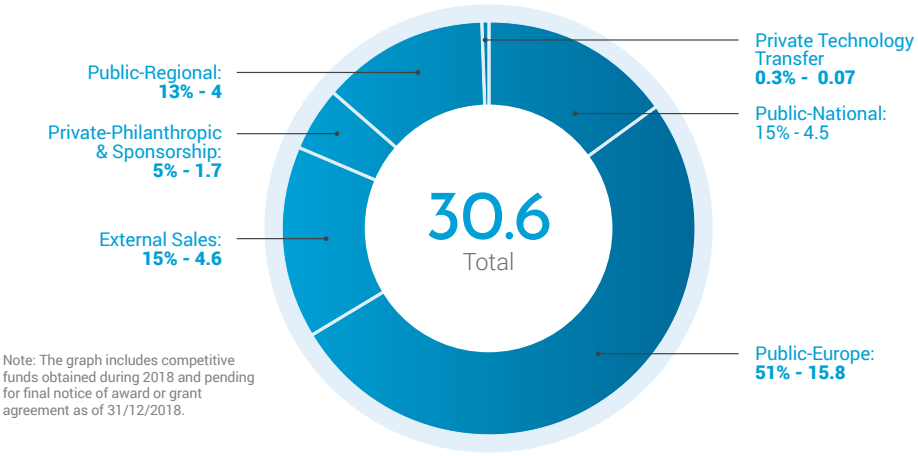
FUNDING (M€)

42.3
Total Funding

33.1
CRG

9.2
CNAG-CRG

External Funding awarded in 2018



Note: The graph includes competitive funds obtained during 2018 and pending for final notice of award or grant agreement as of 31/12/2018.

PROJECTS

129
Total Ongoing Research Projects and Networks

11
are Ongoing ERC Projects (16 ERC Grantees)

20
are Other Ongoing H2020 Research Projects and Networks

9
are Ongoing EU Coordinated Projects

11
are International Ongoing Research Projects (non-EC)

22
Total Ongoing Postdoctoral Fellowships

9
Total Ongoing EU Coordinated Projects

MYCOSYNVAC · miniCELL · Spathy · DivIDE · cell viewer · ORION open science · CHROMDESIGN

Hermes Super Resolution microscopy system

STAFF

TOTAL STAFF

486*
Total

(*FTE, full-time equivalent: 468.9)

408
CRG

78
CNAG-CRG

RESEARCH STAFF

309
Total

279
CRG

30
CNAG-CRG

SCIENTIFIC SERVICES

97
Total

53
CRG

44
CNAG-CRG

ADMINISTRATION & SCIENTIFIC SUPPORT

80
Total

76
CRG

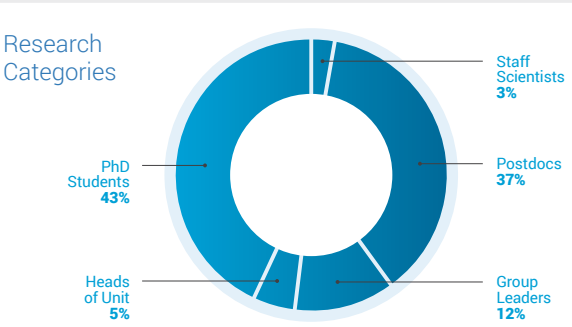
4
CNAG-CRG

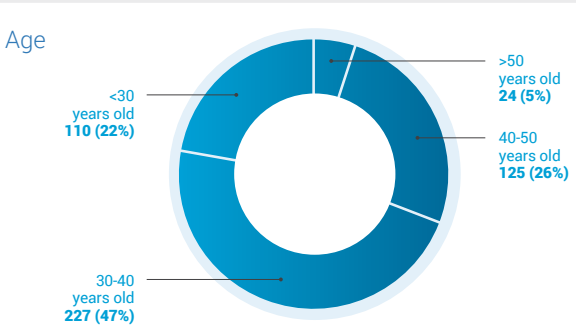
RESEARCH GROUPS
by 31st Dec 2018

31
Total

28
CRG

3
CNAG-CRG





INTERNATIONALITY

39
nationalities represented

56%
Group Leaders+Heads of Unit

64%
Postdoctoral Researchers

57%
PhD Students

59%
Total Research Staff

GENDER

FEMALE BY PROFESSIONAL CATEGORIES

APPLICANTS TO OUR SELECTION PROCESSES

Women	Men
1,062	792
57%	43%

SELECTED / HIRED CANDIDATES

Women	Men
31	29
52%	48%

FEMALE INVITED SPEAKERS

32%

EVENTS

8
International Events

151
High-profile Seminars

ADVANCED TRAINING

THESES

17

PhD Theses defended

SCIENTIFIC TRAININGS

35 Internal courses

277 Participants

6 External courses

168 Participants

COURSES@CRG

4 International courses

82 Participants*

*from 26 different countries

TRANSFERABLE SKILLS & CAREER DEVELOPMENT TRAININGS

5 Internal courses

77 Participants

INNOVATION COURSES

1 Courses (external)

3 Participants *from CRG

TECHNOLOGY & BUSINESS DEVELOPMENT

19

New Technologies Identified under Evaluation

PATENTS

2 Priority

1 PCT

2 National Phases

38

Agreements Signed with Industry & Investors

6

Projects Managed under Valorisation

seqeralabs

1

Spin-offs

COMMUNICATIONS, PUBLIC ENGAGEMENT & SCIENCE EDUCATION

Media Relations

2,197
Media Appearances

281
Written Media

1,692
Online Media

191
Blogs

22
Radio

11
TV

Social Media (by 31st Dec 2018)

TWITTER FOLLOWERS

10,940
@CRGenomica

2,115
@cnag_eu

FACEBOOK

3,753
Page likes

3,779
Followers

LINKEDIN FOLLOWERS

5,839
CRG

1,591
CNAG-CRG

YOUTUBE

163,952
Channel views

Public Engagement and Science Education

218
Activities Organised
(35 different categories of activities)

10,765
Audience Reached

7,621
Schools and Students

10
Social entities

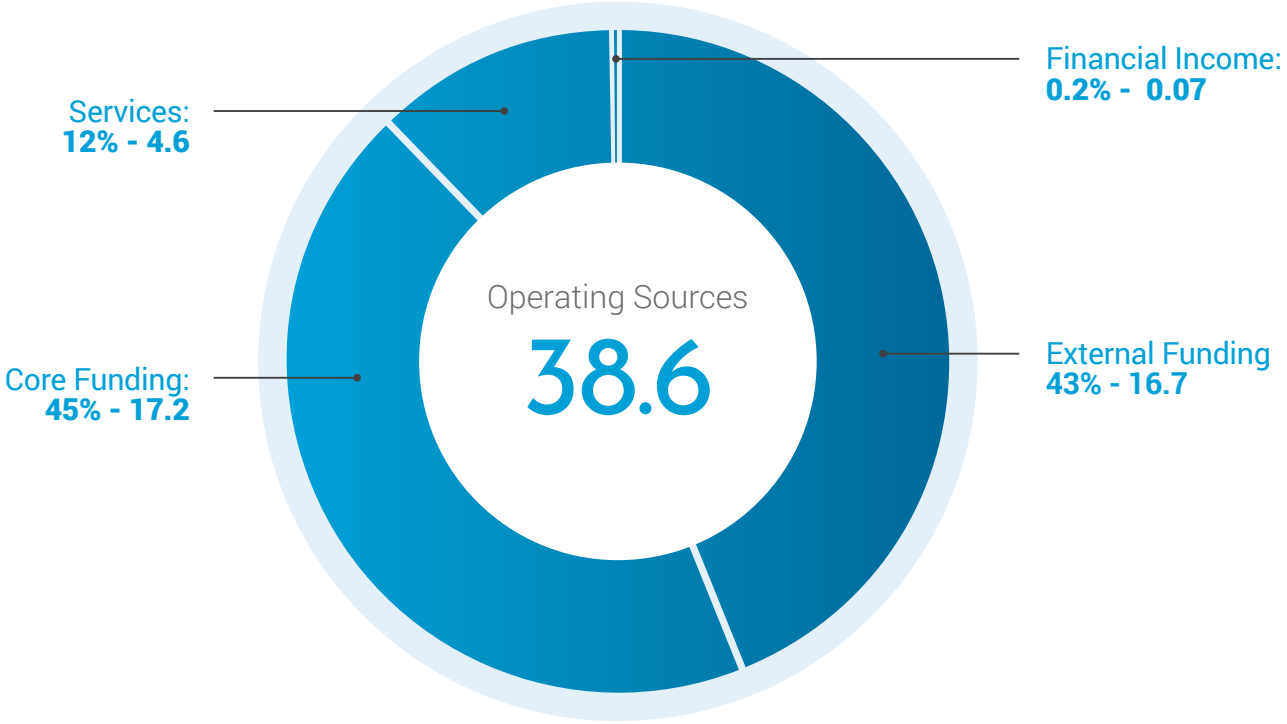
65
Teachers

3,069
General Public

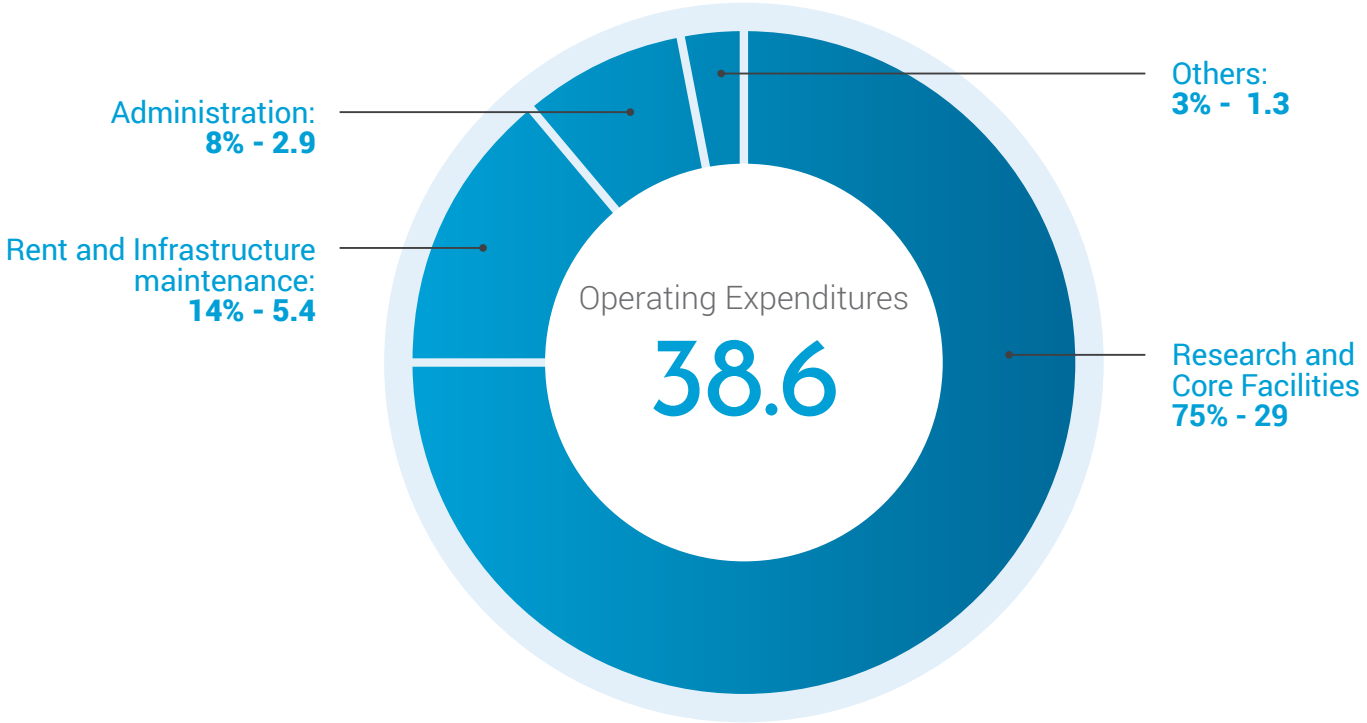
FINANCIAL REPORT

SOURCES & USES MANAGED

OPERATING SOURCES IN M€



OPERATING EXPENDITURES IN M€



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

PUBLIC FUNDERS

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. Further details on the projects co-funded by these funds can be found in the ERDF AND ESF FUNDS AT THE CRG section of the CRG website (http://www.crg.eu/en/content/erdf-and-esf-funds-crg).

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 run from October 2016 until the end of 2018. During this second edition, the project had its second tour of Spain, successfully tackling new challenges, reaching new target audiences and collecting samples from different populations and patients suffering from different diseases. In

2018, and thanks to different competitive calls, we were awarded one 'Caixa Impulse' award, 4 INPhiNIT PhD grants and 2 major grants from the 1st Health Research Call. The PIs Maria Pia Cosma and Fátima Gebauer received funding to develop their projects, which will explore new treatments for retinal degeneration and melanoma metastasis and progression, respectively.

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. In 2017, Dr. Bernhard Payer was appointed the second chair holder for a term of 3 years.

FUNDACIÓN RAMÓN ARECES

The Ramón Areces Foundation provided four-year funding for two highly-talented PhD Students to carry out their research at the CRG. The successful awarded candidates, selected from a competitive call, were Xavi Hernández (Luis Serrano lab) and María de las Mercedes Barrero (Bernhard Payer lab), that will do their PhD from September 2018 to September 2022.

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. Since 2016, the CRG has also been one of the institutes hosting students from the Barcelona International Youth Science Challenge (BIYSC), a two-week international excellence summer programme that seeks to stimulate scientific talent among young people from all over the world and to encourage their enthusiasm for pursuing scientific research and a career in science.

FUNDACIÓ MARATO TV3

The Fundació Marató TV3 funds several 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 Marti-Renom and Mara Dierssen), one project from the 2017 edition on '3D modelling of chromosomic structure in beta cells to identify genetic mechanisms of type 2 diabetes' (Jorge Ferrer).

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. In 2016, 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). More recently, in 2017, a new project was awarded to Mara Dierssen, entitled 'EpiGenetic Change Generator in Down Syndrome (2017-2019).

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 project that seeks to identify and "attack" stem cells involved in cancer, which will end in 2019. In 2018, Cátia Moutinho (in Holger Heyn's lab) was awarded a postdoctoral fellowship for her project about single cell analysis of non-small cells lung cancer, to understand their resistance to the therapy. The fellowship will run until September 2020.

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 every 3,500 individuals, who undergo progressive loss of vision and for which there is as yet 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. (October 2015-February 2019).

FUNDACIÓN ESPAÑOLA PARA EL FOMENTO DE LA INVESTIGACIÓN DE LA ESCLEROSIS LATERAL AMIOTRÓFICA (FUNDELA)

Our PI Luciano Di Croce was awarded a grant from FUNDELA on November 2017 to address the identification of new therapeutic targets for ALS treatment by using an epigenetic factors screening. The grant ended in December 2018.

GLENN FOUNDATION FOR MEDICAL RESEARCH

The Glenn Foundation is currently funding the project 'Temporal scaling in *C. elegans* aging', by our PI Nicholas Stroustrup until October 2018.

THE BARCELONA INSTITUTE OF SCIENCE AND TECHNOLOGY (BIST)

BIST is contributing to several ongoing initiatives at the CRG. First, it is co-funding 2 FI PhD Fellowships from AGAUR in the labs of our PIs Pia Cosma and Roderic Guigó for four years. On the other hand, 2 projects from Ignite Calls from BIST were awarded to CRG researchers. The first one is by Victoire Neguembor (Pia Cosma lab) and is entitled 'GenStorm: an integrated approach to visualize and model the spatial conformation of genes at the nanoscale level'. The second was awarded to Jofre Font (Miguel Beato lab), to the project 'Role of phase separation in gene regulation and chromatin architecture'.

CLÍNICA EUGIN

In March 2018, CRG and Eugin signed a collaboration agreement on molecular research applied to assisted reproduction. The project entails creation of four working groups that will focus their research on gaining insights into the aging of ovules, their sensitivity to the passage of time, and studying whether changes in vaginal microbiota have an impact on assisted reproduction. CRG groups involved are those of Isabelle Vernos, Toni Gabaldón, Bernhard Payer and Elvan Böke. This agreement consolidates a relationship already existing between the two organizations, through the group of Isabelle Vernos, with whom Eugin worked for four years to promote interdisciplinary research geared to patients and society.

THE NOVO NORDISK FOUNDATION CENTER FOR BASIC METABOLIC RESEARCH

Through an international research alliance with Jorge Ferrer, the project "Identification and functional characterization of novel genes and regulatory genomic regions associated with Maturity-Onset Diabetes of the Young (MODY)" is being developed. The main objective of this project is to identify and characterize novel molecular mechanisms causing early-onset autosomal dominantly inherited human hyperglycemia including novel subsets of MODY. The project started at IDIBAPS in June 2015, it was transferred to CRG in October 2018 and will end in December 2019.

CHAN ZUCKERBERG INITIATIVE (SILICON VALLEY COMMUNITY FOUNDATION)

The Chan Zuckerberg Initiative (CZI), an advised fund of Silicon Valley Community Foundation, awarded a grant to Holger Heyn, from CNAG-CRG, and to other 84 projects, to support the Human Cell Atlas (HCA), a global effort to map every type of cell in the healthy human body as a resource for studies of health and disease. The project awarded to Heyn is entitled "Benchmarking single-cell RNA sequencing methods" and will run from April 2018-March 2019.

SPONSORS

Read the full version here: annualreport2018.crg.eu

Centre for Genomic Regulation

Dr. Aiguader, 88
PRBB Building
08003 Barcelona, Spain

Tel.: +34 93 316 01 00
Fax +34 93 316 00 99

comunicacio@crg.eu
http://www.crg.eu

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annualreport2018.crg.eu

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