ANNUAL REPORT

Executive Summary

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CRG
Centre
for Genomic
Regulation

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A LOOK BACK AT THE YEAR

Luis Serrano
DIRECTOR

2019 has been a memorable year at the Centre for Genomic Regulation. We continued our track record in pursuing research excellence and technological advances, welcoming new talent to our faculty, hosting high-profile international meetings, delivering world-class training and renewing our commitment to open science through creative public engagement and science education activities. Here we describe our most recent successes and achievements, highlighting the most salient aspects of our research that make the CRG worthy of pursuing the biggest ideas in science.

STRATEGIC PRIORITIES

Through our leadership of SOMMa, we continue to influence science policy and safeguard Spanish science competitiveness, promoting the visibility of research centres and units of excellence across the country. SOMMa has become one of the most important actors in Spanish science policy, recognised officially by the government and other relevant agents within the national research ecosystem. SOMMa Chairs have been invited to join high-level meetings on the R&D strategy for 2021-2027 and the Spanish forum on Open Science chaired by FECYT. In November, SOMMa ran the 100xCiencia.4 conference to reach out to society in San Sebastián, and other relevant events on open science and gender equality to exchange good practices among the members.

Through EU-LIFE, we continue to consolidate our position as a reliable, respected and influential voice in European research and innovation. Highlights for 2019 include the policy workshop "Towards recognition of the role of small and medium sized research infrastructures (SMRI) in Europe" held in Brussels and the five nominations secured of EU-LIFE individual members for each of the following high-level policy committees: EIC Pilot Advisory Board, ERC Scientific Council, Cancer Mission Board and Missions' Assemblies.

As a part of our commitment towards open science, our Open Access publications in 2019 reached 80%. The H2020 ORION Open Science project continues to promote institutional changes in research funding and performing organisations, to make them more receptive to societal needs and to embrace the principles of open science. At the CRG we are leading the way through a public dialogue co-creation experiment, as well as a new citizen science project. This project, called GENIGMA, will be a videogame co-created with citizens to assemble genomes in 3D in a crowdsourced manner, helping researchers uncover genomic alterations in cancer cell lines. The Gender Balance Committee continued to work on the legacy of LIBRA, an EU project led by the CRG, and have started working on a new Equality, Diversity and Inclusion plan for 2020-2023. As a result of this task, four out the last eight group leaders who have been recruited at the CRG in the last couple of years are women.

SCIENCE

The CRG's overarching research discipline has been integrative biology, for which many of our researchers have combined different approaches from physics to bioinformatics to systems biology, amongst others. See the *Scientific Highlights* and *Research and Scientific Services* sections ahead. The CRG leads and participates in several European and international projects, such as the '1 Million Genomes' Initiative, aiming to have 1 million sequenced genomes accessible within the EU by 2022, linking access to existing and future genomic databases across the continent and providing a sufficient scale for new clinically impactful associations in research. Our single-cell analysis projects have grown dramatically, for which we have received grants from the European Commission and the Chan Zuckerberg Initiative, to standardise single-cell analysis techniques and create a single-cell atlas of the pancreas (Heyn). The ERC Synergy grant BCLL@las (Gut & Heyn) is being used to analyse B-cell lineage and chronic lymphocytic leukaemia at single-cell resolution.

The funding levels secured in 2019 were consistent with the outcome of the previous year. Highlights include awards by Worldwide Cancer Research (Valcárcel), the Jérôme Lejeune Foundation (De la Luna), the European Foundation for the Study of Diabetes (Irimia/Ferrer), "la Caixa" Foundation (Serrano), and the Fundació La Marató de TV3 (Heyn, Gut, De la Luna). Additionally, new projects received financial support specifically to close the gap between the most innovative biomedical research and their translation toward the market, with a view to eventually delivering finding novel treatments for lung cancer (Hernández) and ventilator-associated pneumonia (Lluch). Under the Horizon 2020 framework programme, three junior group leaders were awarded a distinguished ERC Starting Grant (Sebé-Pedrós, Sdelci, Stroustrup).

PEOPLE

Last year we welcomed two junior group leaders; Sara Sdelci, from the Research Center of the Austrian Academy of Sciences (CeMM) in Vienna,

and Arnau Sebé-Pedrós, from the Weizmann Institute of Science in Israel, as well as senior group leader Thomas Surrey from the Francis Crick Institute in London. Our best farewell wishes go to junior group leaders Toni Gabaldón, who left for a joint position at the Institute for Research in Biomedicine (IRB Barcelona) and the Barcelona Supercomputing Center (BSC-CNS), and Jérôme Solon, who joined the Biofisika Institute as an Ikerbasque Professor in Bilbao.

Our first artist-in-residence, the designer Carolin Vogler, joined the CRG in 2019. Through her project **'Inside-Out: Knitted DNA'**, Vogler created chromatin and genome-inspired knitted fashion pieces that translated complex scientific topics into common and nice objects.

In November, the CRG's Administration team was evaluated for the second time ever by an international external expert panel as a tool for continuous improvement. The panel congratulated the personnel for their performance and for the significant progress achieved since the first evaluation, formulating several recommendations for further improvement. This ground-breaking initiative, which is a highly uncommon process in Spain, serves as a model for other national institutes.

TECHNOLOGY

The CRG continues to co-host the European Genome-Phenome Archive (EGA) together with the European Bioinformatics Institute (EMBL-EBI), thanks to the strong commitment of "la Caixa" Foundation, which was renewed in 2019. The EGA database is currently considered one of the main foundations that enables cutting-edge genomics research worldwide.

The RD-Connect Genome Phenome Analysis Platform (GPAP), developed thanks to EU funding, is being used as the system of choice for data for the Solve-RD and European Joint Project on Rare Diseases EU-funded projects. In 2019, this database surpassed 10,000 patient entries. As an IRDiRC-recommended resource, it plays an important role into the research and diagnosis of rare diseases.

In 2019, we have started devising the new strategic plan for the CRG. While continuing with our integrative biology goal, as well as fostering gender equality and inclusiveness, in this plan we would also like to address the sustainability goals of the United Nations. Taking advantage of our world-class expertise in genomics, we will emphasise analysing genome diversity and the relationship between environment and human health.

SCIENTIFIC HIGHLIGHTS

SCIENTIFIC HIGHLIGHTS

01

CONTROLLING THE INFLAMMATION FACTORY

Helping the fight against unintended immune responses and excessive inflammation

Our cells are busy little factories, producing proteins on demand to keep our bodies healthy and working properly. One of these proteins, IL-1β, is essential for fighting off bacterial infections.

Immune cells sense that bad bacteria are around by detecting chemicals called lipopolysaccharides (LPS), which are found on the surface of the bugs. When that happens, the cells ramp up production of IL-1β which causes inflammation to fight off the infection.

But sometimes our molecular factories go overboard, producing far more of these inflammatory proteins than are necessary and running the risk of setting up long-term health problems. Although anti-inflammatory drugs can help, an alternative approach is to figure out either how to slow down the biological assembly line responsible for making IL-1β and slow down the rate at which these proteins leave the 'factory gate' and head out into the body.

To do this, Dr Vivek Malhotra and his colleagues at the Centre for Genomic Regulation in Barcelona have been studying mice that have been genetically engineered to remove a key gene long suspected to control protein dispatch. This gene, GRASP55, is thought to be essential in transporting IL-1β from inside the cell to its surface (a process known as secretion). And, as might be expected, removing it causes a dramatic effect.

"We gave unaltered mice cells the danger signal, LPS, and 20 minutes later we see IL-1β coming out at the surface of the cell," Malhotra says. "But where GRASP55 is not present, the IL-1β protein isn't secreted."

It's not that the cell can't make the protein - the production line is working just fine. Instead, the lack of GRASP55 leads to a shutdown of the dispatch department.

According to Malhotra, GRASP55 has to work together with two other proteins - IRE1 and PERK - in order to transfer IL-1β to the surface of the cell so it can be secreted.

PERK plays an important role in the final stages of IL-1β production, making sure that any unnecessary bits are trimmed away and the protein is properly finished. And if IRE1 isn't working properly then IL-1β builds up inside the cell, like boxes piling up in a factory warehouse with no way of shipping them out.

"Between them, PERK, IRE1 and GRASP55 ensure that IL-1β is well formed, and can be transported where it is needed to fight infection," Malhotra explains.

This knowledge can also help in the fight against unintended immune responses and excessive inflammation through the development of more effective anti-inflammatory drugs.

"Billions of dollars have been invested in recent years developing drugs designed to control the levels of IL-1β in the body, but nothing has materialised," says Malhotra.

"Our hope is that by better understanding how the stages of IL-1β production and secretion work together, we can suggest new approaches for developing anti-inflammatory treatments."

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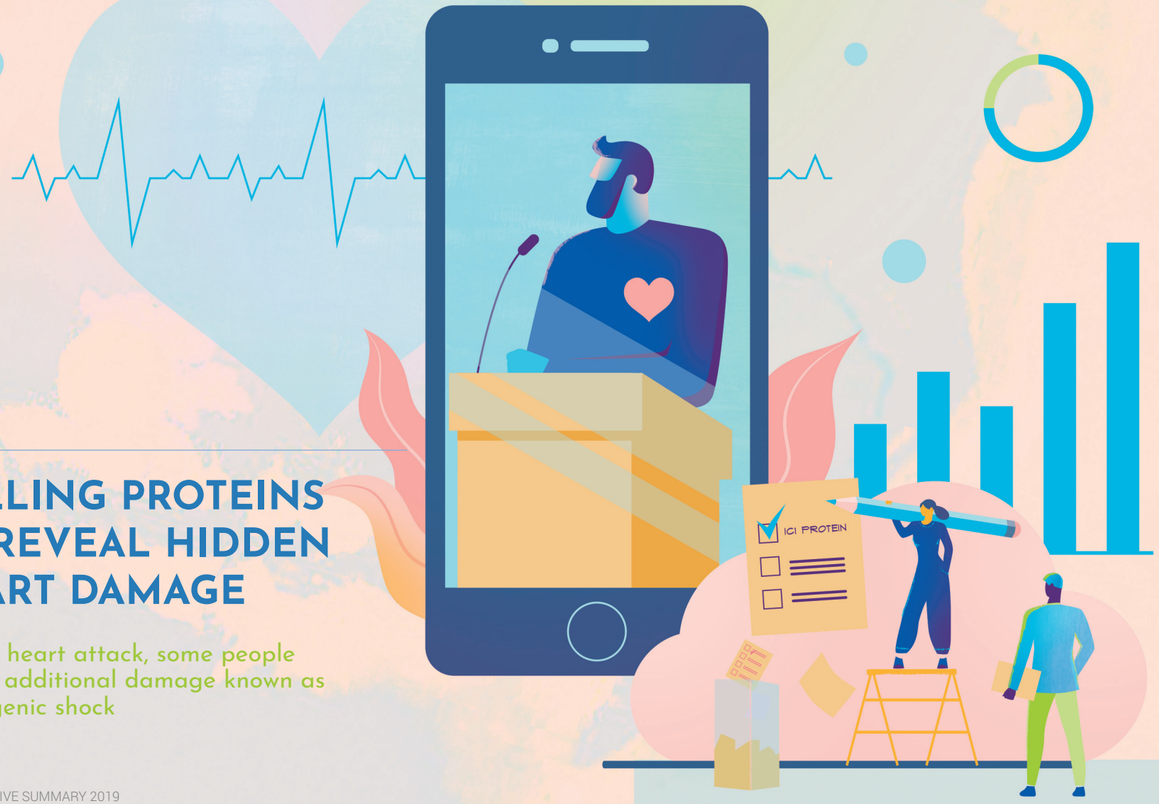

02

POLLING PROTEINS TO REVEAL HIDDEN HEART DAMAGE

After a heart attack, some people sustain additional damage known as cardiogenic shock

Opinion polls are a useful tool for providing political pundits with an idea of the candidates that are most likely to fare well in an election and who's likely to flop. Individual electoral votes are private, but asking a sample of people how they think they will vote is a common way of predicting the final outcome.

That's not the only way that sampling can help to predict unknown outcomes and reveal hidden information. By measuring the levels of certain proteins in a small sample of blood from a patient, researchers can make a prediction about likely outcomes in the aftermath of injury or disease. In turn, this information can be used to make sure that the patient is properly monitored and gets the most appropriate treatment.

For example, after a heart attack, some people sustain additional damage known as cardiogenic shock. This can lead to widespread inflammation and multi-organ failure if left untreated, and may be fatal. However, the evolution of a cardiogenic shock is difficult in the early stages, before the more serious symptoms become obvious.

In order to identify which patients are likely to experience potentially fatal cardiogenic shock, Dr Eduard Sabidó, Dr Eva Borràs and their collaborators from Institut Germans Trias i Pujol (IGTP) have been studying blood samples from 155 people with cardiogenic shock.

To start with, they measured the levels of more than 2,000 proteins in the patient samples, eventually narrowing this down to a panel of just 51 candidates for detailed testing. The results showed that the levels of four of these proteins were significantly different between patients who survived 90 days after their heart attack and those who did not.

Borràs thinks that these proteins could form the basis of a test to predict which patients with cardiogenic shock are most risk of dying in the short term, so that doctors can target more intensive treatment to those who would benefit the most.

"Knowing the risk of short-term mortality is crucial to decide the right treatment for each patient," she says. "The better we know what's going on inside the patient, the more accurately the doctors can adapt their current surgical procedures to maximize quality of life."

The four proteins also suggest what might be happening within the bodies of patients who have suffered from cardiogenic shock.

Those patients who were least likely to survive had raised levels of three proteins that are involved in kidney and liver failure. They also had reduced amounts of a protein called IC1 - an anti-inflammatory protein that helps to protect against damage once normal blood flow is restored after a heart attack.

According to Sabidó, this knowledge could be used to create a new analytical test in the coming years.

"We're working with Professor Bayés from the Hospital Germans Trias i Pujol to carry out a pilot of the test," he explains. "This will result in a prototype that we will also develop in the hospital, which should be informative enough to classify patients and ensure they get the best treatment according to their risk."

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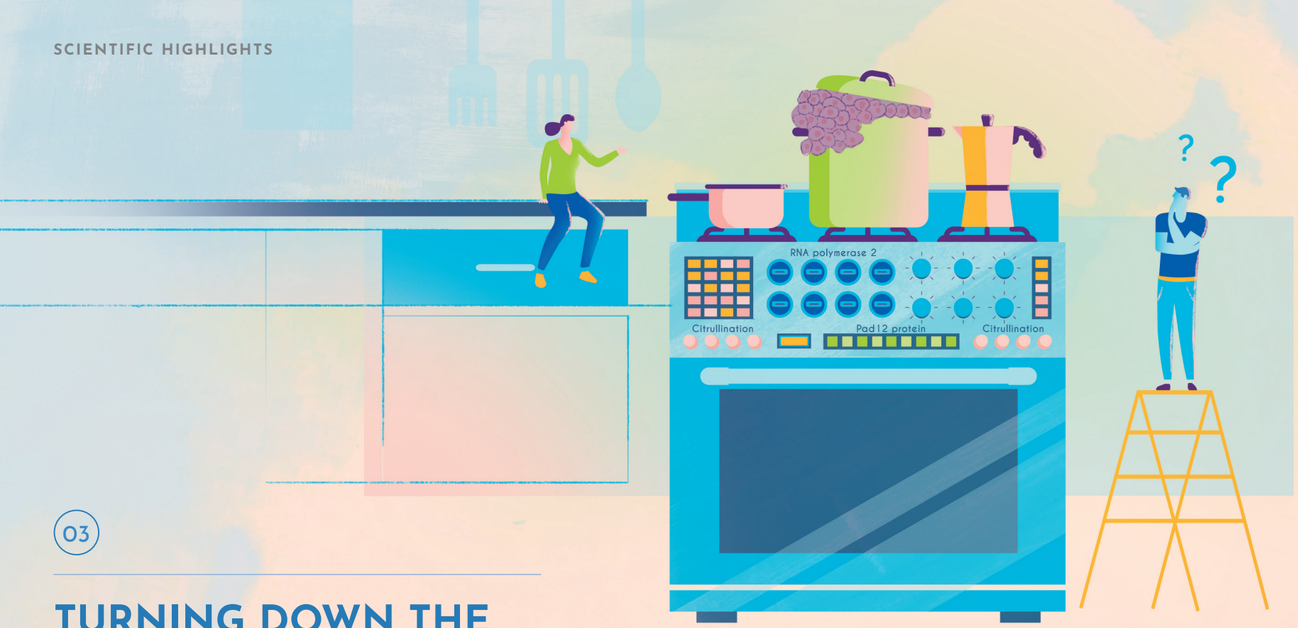

03

TURNING DOWN THE HEAT ON CANCER

How to target the runaway growth of tumours without damaging healthy cells

We've all had too many pots on the stove at once. The sauce may be simmering away nicely, but the pasta is boiling over. The solution is easy: just turn down the heat under the problem pan and leave the rest alone.

In biology, things are a bit more difficult. Cancers, like overboiling pots, are overactive to the point of danger. But unlike a kitchen stove, we don't have easy access to their controls.

Many cancer treatments rely on targeting processes that are overactive in cancer cells and drive them to grow out of control. But the same processes are often important in normal cells too. Simply switching everything off can cause serious side effects by suppressing these processes in healthy tissue.

Thanks to new work by Dr Priyanka Sharma and Dr Miguel Beato at the Centre for Genomic Regulation in Barcelona, together with a team of international collaborators, we now have a better understanding of how to specifically target the runaway growth of tumours without risking damage to healthy cells.

The genes that tell a cell to proliferate are usually very tightly controlled, making sure that new cells are made only when and where they're needed. The rest of the time, the gene-reading machinery (known as RNA polymerase 2) is held in a paused state - a bit like keeping a pan gently simmering on a low heat - ready to be released at a steady, controlled speed.

Sharma and Beato have discovered that a protein called PADI2 in cancer cells flips a chemical switch on RNA polymerase 2 through a process called citrullination. This leads to overactivation of the genes involved in proliferation, cranking up the 'heat' and making the cells multiply out of control like an overboiling pot.

"We initially found citrullination at work in breast cancer, but it is also prevalent in ovarian, lung and stomach tumours," says Sharma.

But although it's possible to turn down citrullination as a potential way of treating cancer, this needs to be done carefully. While one of the effects of the citrullination process is to boost the proliferation of cancer cells, it also has several known beneficial effects in the body - for example, in protecting against bowel cancer - and probably many more as-yet-unknown ones.

"We've identified a very specific target in one of the proteins involved in the citrullination, which seems to control the 'booster' that drives gene activity," says Sharma. "Understanding exactly how PADI2 and RNA polymerase work together to switch on genes in tumours could help us to develop drugs that specifically damp down the rapid proliferation of cancer cells while leaving healthy cells alone, leading to much more precise therapies with fewer side effects."

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04

NAME THAT TUNE: SPOTTING MODIFICATIONS IN RNA

EpiNano is a machine learning algorithm to spot RNA modifications

Imagine DNA as a vast orchestral score containing all the genetic instructions that are needed to create the music of life.

The original score is precious and easily damaged, so in order for a cell to 'play' a single gene, the 'notes' are copied out into RNA - a more disposable molecule that can be easily altered if the cell needs to improvise and adapt the tune.

RNA is written with just four chemical 'notes', or bases: A (adenine), C (cytosine), G (guanine) and U (uracil). The order of these bases makes up the basic genetic 'tune', but each one can be subtly modified, like making a musical note sharp or flat, which changes the way it is played.

Dr Eva Maria Novoa of the Centre for Genomic Regulation (CRG) is focusing on one particular RNA modification known as m6A, created when a chemical tag called a methyl group is stuck onto adenine (A). Though it's a small change, it's an essential part of life's symphony.

"You might as well ask what m6A doesn't do!" Novoa laughs, explaining how it seems to be involved in everything from telling cells what jobs to do to controlling our body clocks.

"The modification from A to m6A seems to be important when it comes to regulating processes from the level of the individual cell to the whole organism."

Although the switch between A and m6A is clearly pivotal to the normal functions of cells, we currently lack accurate methods to detect and measure it reliably at the level of individual RNA molecules.

Novoa and her team have devised a new tool, a sort of Shazam for RNA, that can identify modified bases in RNA extracted from living cells.

Similar to spotting a song from its soundwaves, their approach involves pulling RNA through a tiny hole in an electrically charged membrane, using the fluctuations in the electrical current to generate a distinctive pattern.

The key features of these patterns are then fed into a computer programme (algorithm) which compares them with the signal from an identical but unmodified section of RNA to see which 'notes' have been altered.

"We realised that when there was a modification in the RNA, the interpretation algorithm gave us an error message because it couldn't match up the two sequences," Novoa says.

Realising that these 'errors' were actually an important signal, Novoa and her team devised a machine learning algorithm called EpiNano. This algorithm was initially trained on synthetic RNA sequences -with and without m6A modifications- that had been designed and created in the lab. The team then tested it on RNA extracted from living yeast cells.

EpiNano not only spotted many known m6A modifications in the yeast RNA, but also identified several previously unknown ones.

Novoa and her team are now comparing EpiNano's results against other RNA sequencing methods - and also using the same approach to map other RNA modifications with currently unknown biological functions - to get a more complete picture of how these modifications change life's tune.

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05

THE MUTATION DETECTIVES: FINDING THE FAULTY GENES THAT DRIVE CANCER

How to find the true culprit behind each patient's cancer, and choose the best ways to outwit it

Being a cancer detective just got a lot easier. Just as the famous sleuth Sherlock Holmes could deduce a suspect's likely occupation as a dock worker based on the pattern of calluses on their palms, oncologists can now deduce the source of genetic changes driving cancer growth, thanks to new results from Dr Ivo Gut and his colleagues at the Centro Nacional de Análisis Genómico, part of the Centre for Genomic Regulation.

Sherlock Holmes may have painstakingly classified 140 different types of cigar ash in his quest to fight crime, but Gut and his team have catalogued 45 million genetic alterations (mutations) of which 1.2 million are shared between at least two patients in 37 different types of tumour.

This 'criminal database' for cancer can provide important clues about the cause of an individual patient's disease and the best possible treatment.

"Ultraviolet light causes a specific class of mutations found in skin melanomas, while other types of cancers have their own distinctive set of mutations," Gut explains, pointing out that oesophageal (gullet) tumours have genetic changes that might be linked to stomach acid reflux - a major suspect in causing the disease.

"Even cancers in different parts of the body may seem distinct, but breast and ovarian cancers share the same kinds of mutations across patients indicating some common causes," he adds.

However - as in most detective novels - clinicians still need to be on the lookout for red herrings. Around 10 percent of cancers are only diagnosed from secondary tumours that have spread through the body, while the initial primary tumour remains hidden.

"Sometimes clinicians just walk past the primary. Sometimes the primary isn't even there anymore," says Gut. Knowing that the true culprit - the Moriarty behind the scenes - is located elsewhere can help to ensure that these patients get a more accurate diagnosis and the most appropriate treatment for their disease.

Armed with this knowledge, clinicians can find the true culprit behind each patient's cancer, and even choose the best ways to outwit them. For example, some may respond better to immunotherapy rather than chemotherapy, depending on the underlying genetic alterations that are driving tumour growth. And finding the real villain means tackling the disease at its primary source, even if it is a master of disguise.

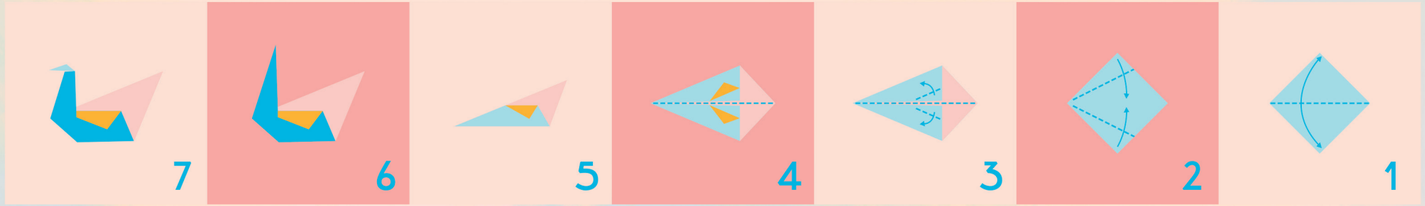
"If you have a classification system based on the cancer's genetic makeup then we can tell that it originally came out of the liver or somewhere like that," Gut explains. "Then you can think about whether you screen that organ, or whether you need to treat that primary cancer as well."

Armed with this new information, today's cancer doctors have a better chance of bringing a happy ending to each patient's story than ever before.

REFERENCE WORK:

Miranda D. Stobbe,Gian A. Thun,Andrea Diéguez-Docampo,Meritxell Oliva,Justin P. Whalley,Emanuele Raineri,Ivo G. Gut. *"Recurrent somatic mutations reveal new insights into consequences of mutagenic processes in cancer."* Plos Computational Biology, November 25, 2019, https://doi.org/10.1371/journal.pcbi.1007496

SCIENTIFIC HIGHLIGHTS



06

LEARNING LIFE'S ORIGAMI

If a protein isn't folded correctly, it can seriously damage your health

In origami, the Japanese art of paper folding, intricate three-dimensional shapes like cranes or frogs are created by precisely creasing and folding a two-dimensional sheet of paper according to a set of instructions.

Similarly, DNA encodes instructions that lead to the construction of three-dimensional proteins from long chains of building blocks (known as amino acids) in a kind of biological origami.

These protein chains fold up into different structures depending on the underlying sequence of amino acids and the chemical interactions between them, creating a huge diversity of proteins of all kinds of shapes and sizes.

But unlike paper origami, the resulting structures aren't simply aesthetically appealing. A protein's shape determines its function - whether that's fighting an infection, carrying a message, breaking down nutrients, or building bodily structures.

If a protein isn't folded correctly it can't do its job properly: a misplaced crease in an origami crane might be frustrating, but a wonky fold in a protein can seriously damage your health.

The traditional process of figuring out the three-dimensional structures of proteins is expensive and time consuming and difficult in many cases. As a result there are still thousands of protein families whose structures remain unknown. This includes many 'disordered' proteins, which don't conform to a single defined structure. To address this, Dr Jörn Schmiedel and Dr Ben Lehner of the Centre for Genomic Regulation in Barcelona have developed an approach for working out a protein's structure by analysing the results of systematic tiny changes (mutations) in the underlying amino acid sequence.

Their approach - known as deep mutational scanning (DMS) - involves swapping out every amino acid, either singly or in pairs, for each of the other 19 possibilities, then and seeing how this alters how well the protein functions.

One example is a so-called salt bridge, which happens when a negatively and a positively charged amino acid are close together in the three-dimensional structure. The opposite charges attract, bonding the two amino acids together and helping the protein to fold up correctly.

If the charge of just one of these amino acids is flipped, then there will be two positive or two negative charges. Instead of attracting each other and pulling parts of the protein together, the amino acids push each other away - like trying to force two positive poles of a magnet together. This can have a significant effect on the protein's shape and function.

"Instead of forming a salt bridge, the two amino acids repulse each other, disrupting the structure and make the protein less good at its job," says Schmiedel. "However, if you mutate both amino acids to reverse the charges, the bond and the correct structure can be restored."

By creating many patterns of compensating changes and comparing their effects on the resulting proteins, the technique reveals which parts are close together in three-dimensional space. For the very first time, this new technique allows the researchers to decipher the structures of proteins as they are carrying out their regular tasks inside living cells - something that isn't possible using previous methods. By comprehensively analysing the effects of thousands of mutational combinations on protein folding, Schmiedel and Lehner are starting to understand the rules of this complex biological origami.

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Nature Genetics, 51:1177–1186 (2019).

07

TIME TO ALIGN

The most detailed 'family tree' of life on Earth to date

Many of us are fascinated by our ancestry. There are whole websites dedicated to helping people peer deep into the past, searching for intriguing ancestors or rogue relations that share our roots. Finding common characteristics - and key differences - helps us to understand our own identity and how we got here. But instead of focusing on one family, biologists are attempting to do something similar with the relationships between humans and all other living things on earth.

Thanks to advances in DNA sequencing, we have more information about the genes of these far-flung relations than ever before. Researchers rely on computer programmes (algorithms) to line up and compare multiple genes or proteins (the biological molecules encoded by genes).

Stacking up sequences from many different species and looking for regions that are identical or similar reveals the evolutionary relationships between species. For example, our more recent relatives, such as chimps or other mammals, share more similarities with our own species, while we have less in common with more distant relations like bacteria, fungi and plants.

Current algorithms rely on matching the longest sequences of similar genes or proteins first, then pairing up progressively smaller fragments. But although this approach works well on datasets with up to 200,000 different sequences, it simply can't cope with the explosive growth of data that is now pouring out of sequencing machines all over the world.

Dr Cedric Notredame and his team from the Centre for Genomic Regulation in Barcelona have devised a new approach to address this challenge. Rather than matching the longest, most similar DNA first, they begin by aligning the least related sequences first. The new technique allows Notredame and his team to line up 1.5 million or more different sequences across many species with greater speed, accuracy, and efficiency than has ever been achieved on this scale.

"On a regular computer, like the kind of PC used for video gaming, it would take about five hours for our algorithm to process a million individual datasets in our fastest mode, and about 20 hours using a slower, more accurate mode," says Notredame. In contrast, none of the standard methods that the team tested were able to match so many DNA sequences at once.

The new technique has allowed the team to draw up the most detailed 'family tree' of life on Earth to date, revealing new details about the complex evolutionary journeys that different species took from the first cell to the present day. Tracing the tree of life back to its roots is fascinating in and of itself, but the additional benefits of being able to compare sequences at this unprecedented scale are immense.

Notredame hopes that his new algorithm will open up new research avenues by illuminating previously unknown similarities and differences between species.

One application is in conservation, shedding light on what might have happened to long-lost species whose traces remain only within the genomes of the modern-day descendants. "Knowing which genes have been preserved or lost through time, especially in previous mass extinctions, may point towards preservation actions that can be taken at a global level," he says.

There are also important uses in medicine. For example, identifying genes or proteins that are preserved across all living species could be useful for predicting whether a drug designed to target a protein in bacteria or parasites is also likely to hit it in humans and cause side effects.

The technique could also be used to compare sequences from different strains of viruses. One example could be the hundreds of coronaviruses in existence, of which the current COVID-19 virus is just one. This information might help researchers to predict which viruses are likely to jump between animals and humans, potentially sparking another pandemic in the future.

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Nat Biotechnol 37, 1466–1470 (2019). https://doi.org/10.1038/s41587-019-0333-6

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

Coordinator: **Roderic Guigó**

The programme's scientific highlights in 2019 included the development of Nextflow to enable scalable and reproducible scientific workflows using software containers. Nextflow has become one of the most popular domain-specific languages and is used all over the world; the development of methods which for the first time ever make it possible to build very large alignments of over one million sequences; the creation of a genomic 3D map to investigate the genetic mechanisms associated with the development of type-2 diabetes; the analysis of data suggesting that the phase separation drives X-chromosome inactivation; and the discovery of autoregulatory splicing events coupled with nonsense-mediated mRNA decay.

Our programme is also leading the efforts to sequence all the eukaryotic species living in the Catalan Countries, as part of the Earth Biogenome Project (https://www.scb.cat/biogenoma/en/home/). 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, FAANG 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 and also one of the European Open Science Cloud (EOSC) Science Pilot demonstrators.

CELL AND DEVELOPMENTAL BIOLOGY

Coordinator: **Vivek Malhotra**

The mission of the scientists in the Cell and Developmental Biology programme is to unravel the mechanisms of cell compartmentation and division and tissue organisation. The department is staffed by Vivek Malhotra (mechanisms of protein secretion), Isabelle Vernos (microtubule and spindle dynamics), Sebastian Maurer (cytoplasmic RNA localization), Verena Ruprecht (cell and tissue dynamics), Elvan Boke (oocyte biology and cellular dormancy) and Thomas Surrey (intracellular self-organisation). Our former colleague Jerome Solon has been appointed Ikerbasque professor at the Instituto Biofisika in Bilbao since 2019. Thomas Surrey, senior group leader from the Francis Crick Institute in London, is a leading figure in the mechanism of microtubule and spindle dynamics and joined our department in November 2019. Numerous outstanding papers were published by members of our department, although one in particular merits special note. This paper from the Malhotra laboratory, Chiritoiu *et al. Dev Cell* (2019), describes how interleukin 1ß, a key component of the inflammatory response, is secreted without entering the conventional secretory pathway. The unfolded protein response of the endoplasmic reticulum plays a key role in the production, maturation and secretion of interleukin 1ß, and these findings could help in controlling inflammation. Vivek Malhotra received one of the 2019 SGRF Excellence in Science Awards from the SciGenom Research Foundation in India. Elvan Boke is funded by a European Research Council (ERC) Starting Grant.

GENE REGULATION, STEM CELLS AND CANCER

Coordinator: **Juan Valcárcel**

In 2019, we welcomed Sara Sdelci who, after her pioneering postdoctoral work with Stefan Kubicek at the Research Center for Molecular Medicine in Vienna, set up her group at the CRG to study the interface between cancer metabolism and the epigenetic modifications of chromatin, a highly promising area both for the fundamental understanding of cancer cells and for identifying novel therapeutic avenues in oncology.

Work in the programme made important strides in 2019 in two main lines: the molecular mechanisms of gene control and the epigenetic regulation of cellular pluripotency. The progress made in gene regulation included new analytical methods for the detection of 6 methyl modification in adenosine residues of RNA, which are important in the emerging field of epitranscriptomics; the identification of arginine citrullination as a modification of RNA polymerase II, important for transcription elongation; discovering the role of clustered transcriptional enhancers as HIV-1 integration sites; new insights into the DYRK1A kinase function in neurogenesis, pancreatic cancer and DNA Damage Response; and a general scaling law that explains the effects of mutations on alternative splicing (in collaboration with the Systems Biology Programme).

Advances in stem cell biology included identifying a role for the regulator of DNA methylation PRDM14 in the epigenetic reprogramming of migrating primordial germ cells; establishing the function of the Wnt/beta catenin signalling pathway in the maintenance of the epigenetic status and homeostasis of stem cells; discovering a role for the metabolic enzyme AHCY in stem cell proliferation using novel chromatin capture approaches; and identifying the elusive origins of cellular heterogeneity that constitute a barrier to efficient cell reprogramming.

SYSTEMS BIOLOGY

Coordinator: **Ben Lehner**

Despite a wealth of data, structures and mechanistic understanding, we are unfortunately still embarrassingly bad at predicting the behaviour of biological systems. In the Systems Biology Programme we want to change this and to be able to quantitatively predict how biological systems respond to perturbations. The programme covers a wide range of questions: from genetics and gene regulatory networks to systems neuroscience and aging. Underlying this diversity, however, is a common goal to combine systematic and quantitative data collection with computational models to arrive at a deeper understanding of complex biological processes and how they respond to changes in the environment and upon mutation.

Some highlights of 2019 include the development of a new method that uses deep mutagenesis to determine the 3D structures of proteins (Lehner lab), the elucidation of the evolutionary origins of an entire regulatory programme active in our brains – microexons (Irimia lab), and the determination of the 'complete' gene regulatory network of an organism (Serrano lab).

This year two groups – Nick Stroustrup and Arnau Sebé-Pedrós – received ERC starting grants, bringing the total number of groups in the programme funded by ERC grants to 5 out of 6 (!). In addition, Mara Dierssen and Luis Serrano were awarded substantial grants from the USA National Institutes of Health and the la Caixa foundation, respectively. All of this helps to further our goal of making the programme the leading centre in Europe for quantitative biology.

CORE FACILITIES

Director: **Mònica Morales**

The Core Facilities programme currently comprises seven Core Facility Units and the Histology Service, which was incorporated into the Tissue Engineering unit in 2019. In the course of 2019, in response to our users' needs, we developed and implemented the following applications:

- PiggyBac transposon directly in embryos
- Customised targeted re-sequencing method reducing costs to 25% of initial cost

- Generation and production of in-house Tn5 transposase for use in low-input RNA library prep and for genomic DNA libraries
- Hepatic organoids from mouse adult stem cells
- Cardiomyocyte differentiation from human ES cells and calcium sparks assay

In April 2019, we launched Agendo, a new request management software. After several phases of customization, Agendo has now become our communication channel with users and delivers an integrated solution for tracking requests, samples and projects across facilities.

We also launched several working groups across facilities to promote further interaction within the programme and to attain a higher level of integration. These working groups address important questions such as quality control, data management, establishing guidelines for service versus collaborations or promoting the visibility of Core Facilities inside and outside CRG.

CNAG-CRG

Director: **Ivo Gut**

In 2019, we celebrated our tenth anniversary of operations. The year brought a major degree of evolution and numerous success stories:

1. The RD-Connect Genome Phenome Analysis Platform (GPAP) that was developed with EU funding is being used as the system of choice for data for the Solve-RD and European Joint Project on Rare Diseases EU-funded projects. In 2019, we surpassed the figure of 10,000 patient entries. As an IRDiRC-recommended resource, it plays an important role in research into and the diagnosis of rare diseases. It has been extended to integrated cancer data and data from personalised medicine projects.

2. Single-cell analysis has grown dramatically, and we can now process dozens of studies for internal and external collaborators. We have received some substantial grants for single-cell analysis from the European Commission and the Chan Zuckerberg Initiative to work on the standardisation of single-cell analysis techniques and to create a single-cell atlas of the pancreas. The ERC Synergy grant BCLL@las commenced in 2019, which we are using to analyse B-cell lineage and chronic lymphocytic leukaemia at single-cell resolution.

3. The production phase of B-Cast of sequencing 300 target genes in 10,000 breast cancer patients was completed. Technically and organisationally, this was a huge challenge that will undoubtedly produce one of the most valuable datasets in breast cancer and will further our understanding of this very common and dangerous disease.

4. We ran a beautiful *de novo* assembly and annotation project of 500 Carbapenem-resistant bacterial strains. Through a combination of Illumina and Nanopore sequencing, we managed to capture the entire bacterial genomes, including plasmids that avoid an Illumina-only analysis, demonstrating how our technologies can be applied to provide information hitherto unknown and which has an impact in clinical practice.

We embarked upon our EASI-Genomics EU-funded infrastructure project, issuing the first two trans-national access calls. Thirty-two (32) projects from the first call were selected and are currently being managed by the infrastructure.

The inclusion of a second Illumina NovaSeq6000 and an Oxford Nanopore GridIon has allowed us to increase our capacity for short- and long-read sequencing. We are now also certified for Oxford Nanopore sequencing as a service and are moving toward clinical accreditation. Our joint activity has continued to bring us closer to the clinical practice in support of personalized medicine.

EUROPEAN GENOME-PHENOME ARCHIVE (EGA)

Team Leader: **Arcadi Navarro**

The European Genome-phenome Archive (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. Data are collected at the EGA from individuals whose consent agreements authorise data release only for specific research use or to bona fide researchers.

The EGA is managed collaboratively by the European Bioinformatics Institute (EBI), in Hixton, Cambridge, UK, and by the Centre for Genomic Regulation (CRG), in the Barcelona Biomedical Research Park (PRBB). It emerged from a worldwide need to combine two fundamental human rights; the right to share genomic data to help to improve knowledge and health and the right to privacy. The EGA database now has the highest number of studies in the world; it currently contains data from more than 1 million people and more than 2,000 studies from all over the world.

In short, the EGA may be said to be "(...) a custodian, a distributor but, above all, a promoter and accelerator of research worldwide" *Arcadi Navarro.*

NEW HIRINGS

One renowned senior scientist and two outstanding early-career scientists, set up their new research groups at the CRG in 2019.

THOMAS SURREY

Thomas obtained his PhD in Biochemistry at the University of Tübingen in Germany. After a three-year period as postdoctoral fellow at Princeton University, USA, he moved to EMBL Heidelberg, in Germany, first as postdoctoral fellow/staff scientist, and subsequently as team/group leader. In 2011, he moved to London and took up a position as a senior group leader at the London Research Institute, Cancer Research UK. After a six-year spell there, he took up a senior group leader position at the newly-created The Francis Crick Institute, also in London, UK. In October 2019, Thomas joined the CRG's Cell and Developmental Biology Programme as ICREA Research Professor and senior group leader.

The Surrey lab studies how cells' internal structure self-organises, and seeks to understand how the different parts of the cytoskeleton, the cell's internal scaffold, work together to form distinct architectures and how they change as the cell divides or differentiates. The ultimate goal is to ascertain how complex biological structures can be created from simple, smaller parts. In many experiments, the researchers construct a mini version of the cytoskeleton from a limited set of purified components. Using fluorescence microscopy, quantitative analysis and modelling, they can elucidate how the components of the mini-cytoskeleton come together and organise themselves into different structures. They want to understand how self-organising scaffolds change in response to changing conditions inside the cell. These changing conditions may be caused by normal cell cycle activity changes, by signals stimulating differentiation or by disease-inducing factors.

By combining engineering, chemistry and biology approaches, they set out to discover the design principles underlying intracellular order and mechanics, revealing new information about the fundamental physical properties of living cells.

SARA SDELCI

Sara is an Italian scientist who took her PhD at the Institute for Research in Biomedicine (IRB Barcelona), Spain, before taking up a six-year tenure at the Research Center for Molecular Medicine of the Austrian Academy of Sciences (CeMM), Austria, first as JDRF postdoctoral fellow and then as senior postdoctoral researcher. In January 2019, she joined the CRG's Gene Regulation, Stem Cells and Cancer Programme as junior group leader.

The pivotal role of metabolic rewiring during cancer progression is undeniable, although its direct impact on chromatin remodelling, epigenetics and gene transcription has been poorly investigated. Cancer metabolism and epigenetic regulation are known to influence each other 1) by increasing or reducing the metabolites needed for the epigenetic modifications of DNA and histones and 2) by favouring or repressing the expression of specific metabolic enzymes. Nevertheless, as yet, very few examples of a functional interaction between metabolic enzymes and chromatin have been uncovered. Recently, the evidence that the accumulation of metabolites in subcellular compartments can orchestrate specific cellular processes is replacing the old belief that metabolites simply diffuse in the cell to be used if necessary.

In line with this hypothesis, Sara's lab investigates whether the enzymes involved in cancer metabolism directly influence chromatin remodelling, epigenetic regulation and gene transcription by localizing in the chromatin environment and influencing the in loco concentration of metabolites. To address this question, the team applies a functional chromatin reporter strategy they developed, integrating it with cutting-edge techniques and genome-centric approaches. They will thus identify novel targetable vulnerabilities of cancer cells and uncover the basic principles of the interplay between the epigenetic landscape and cancer metabolism.

ARNAU SEBÉ-PEDRÓS

After taking his PhD in Genetics at the University of Barcelona (UB), Spain, Arnau took up a three-year position as research associate at the Institute for Evolutionary Biology (CSIC-UPF), also in Spain. He then went on to take up a four-year position at the Weizmann Institute of Science (WIS), in Israel, as EMBO/WIS Postdoctoral Fellow. In January 2019, Arnau joined the CRG's Systems Biology Programme as junior group leader.

One fundamental question in biology is how the diverse cell types observed in a multicellular organism are encoded by a single genome sequence and which genome regulatory mechanisms orchestrate the deployment and maintenance of cell type-specific transcriptional programs. However, the diversity and evolutionary dynamics of cell type programmes remains almost unexplored beyond selected tissues in a few species. Similarly, little is known about the emergence of complex genome regulatory mechanisms that support cell type-specific programs and cellular memory, for example genome spatial compartmentalisation and repressive chromatin modifications.

In recent years, the development of advanced functional genomics technologies has revolutionised the study of cell type and genome regulation, even at single-cell resolution. This opens up the path to the comparative analysis of genome regulation in species that represent diverse levels of biological complexity: ranging from unicellular temporal differentiation and simple multicellular behaviours (e.g. in some protistan eukaryotes), through loosely integrated and limitedly diversified ensembles of cell types (e.g. in early-branching animals) to organisms with elaborate tissue and bodyplan organisation (e.g. in bilaterian animals).

Arnau's lab combines high-throughput epigenomics and single-cell genomics technologies with advanced computational methods in order to dissect cell-type programmes and genome regulatory architectures in phylogenetically diverse systems. The comparative analysis of these data allows us (i) to trace the evolution of cell types and genome regulatory mechanisms; (ii) to identify shared principles in genome function; and (iii) to reconstruct regulatory innovations linked to major transitions such as the origin of eukaryotic cells or the emergence of multicellular organisms.

AWARDS

EJE&CON Award to Genderless Talent (Institutions category)
CRG

2019 SGRF Excellence in Science Award, SciGenom Research Foundation (India)
Vivek Malhotra

Silver Medal, Cantabria's Medical Society
Mara Diersen

Leadership Award for Women Revolution
Mara Diersen

ERC GRANTEES AT CRG 2019

STARTING GRANTS

Manuel Irimia

Arnau Sebé-Pedrós

Elvan Boke

Nicholas Stroustrup

Gian G. Tartaglia

Sara Sdelci

CONSOLIDATOR GRANTS


Ben Lehner

ADVANCED GRANTS


Jorge Ferrer


Juan Valcárcel


Luis Serrano

SYNERGY GRANTS


Miguel Beato


Marc A. Marti-Renom


Thomas Graf


Ivo Gut


Guillaume Filion


Holger Heyn

PROOF OF CONCEPT GRANTS


Juan Valcárcel


Luis Serrano


Miguel Beato

FACTS AND FIGURES (*)

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

PUBLICATIONS

286
Total Publications

79.6%
Open Access Publications

82.5%
1st Quartile Publications

8.8
Average Impact Factor

FUNDING (M€)

ANNUAL OPERATING BUDGET

40.7
Total

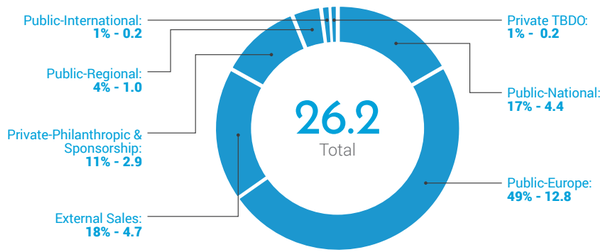
32.5
CRG

8.2
CNAG-CRG

EXTERNAL FUNDING

External Funding awarded in 2019

Note: The above graph includes competitive funds obtained during 2019 and pending for final notice of award or grant agreement as of 31/12/2019.



PROJECTS

134
Total Ongoing Research Projects and Networks

15 are Ongoing ERC Projects

11 are Ongoing EU Coordinated Projects

27 are Other Ongoing H2020 Research Projects and Networks

13 are International Ongoing Research Projects (non-EC)

26
Total Ongoing Postdoctoral Fellowships

11
Total Ongoing EU Coordinated Projects

MYCOSYNVAC

LIBRA

miniCELL

Opathy

DivIDE

cell viewer

ORION open science

CHROMDESIGN

EASI Genomics

Hermes Super Resolution Microscopy System

International Nucleome Consortium (INC)

STAFF

490.4* Total

* FTE, full-time equivalent

422 CRG

86 CNAG-CRG

41 Nationalities represented

58% Group Leaders + Heads of Unit

62% Postdoctoral Researchers

58% PhD Students

59% Total Research Staff

RESEARCH STAFF

310.7* Total

298 CRG

23 CNAG-CRG

* FTE, full-time equivalent

SCIENTIFIC SERVICES

96* Total

40 CRG

59 CNAG-CRG

* FTE, full-time equivalent

ADMINISTRATION & SCIENTIFIC SUPPORT**

71.2* Total

69 CRG

4 CNAG-CRG

* FTE, full-time equivalent

** Additionally 13.5 positions externally funded

RESEARCH GROUPS*

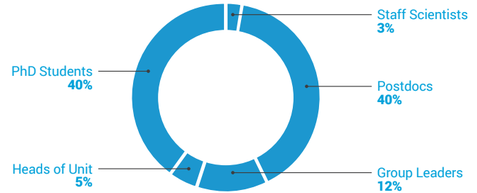
31 Total

28 CRG

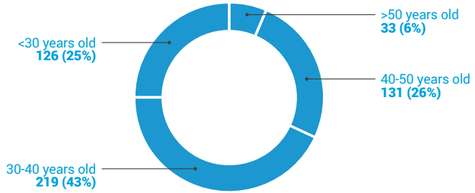
3 CNAG-CRG

* by 31st Dec 2019

RESEARCH CATEGORIES



AGE



GENDER

% FEMALE BY PROFESSIONAL CATEGORIES

% FEMALE INVITED SPEAKERS

39%

(2018 32%)

APPLICANTS TO OUR SELECTION PROCESSES

WOMEN	MEN
1,205	930
56%	44%

SELECTED / HIRED CANDIDATES

WOMEN	MEN
41	39
51%	49%

EVENTS

9
International Events

126
High-profile Seminars

ADVANCED TRAINING

THESES

21
PhD Theses defended

COURSES @CRG

4	130
International courses	Participants

SCIENTIFIC & TECHNOLOGY COURSES

27	342
Internal courses	Participants

TRANSFERABLE SKILLS & CAREER DEVELOPMENT TRAININGS

9	60
Internal courses	Participants

TECHNOLOGY & BUSINESS DEVELOPMENT

10
Valorisation Projects

9
Active Patent Families

20
Invention Disclosures

29
Agreements signed with companies

COMMUNICATIONS, PUBLIC ENGAGEMENT & SCIENCE EDUCATION

Media Relations

1,746	174	16	1,339	4	213
Media Appearances	Written Media	Radio	Online Media	TV	Blogs

Social Media (by 31st Dec 2019)

TWITTER FOLLOWERS

13,634
@CRGenomica

2,647
@cnag_eu

FACEBOOK

3,958
Likes

4,013
Followers

LINKEDIN FOLLOWERS

11,900
CRG

1,993
CNAG-CRG

YOUTUBE

185,878
Channel views

1,024
Subscribers

Public Engagement and Science Education

212
Activities Organised
(40 different categories of activities)

17,701
Audience Reached

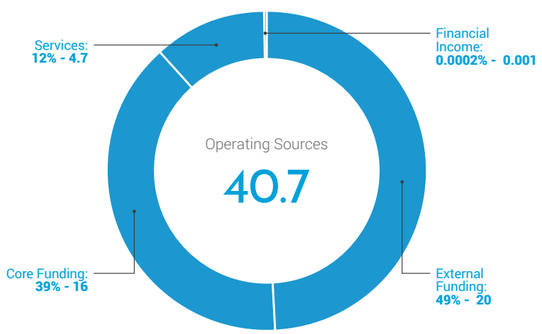
10,475
Schools and Students

7,226
General Public

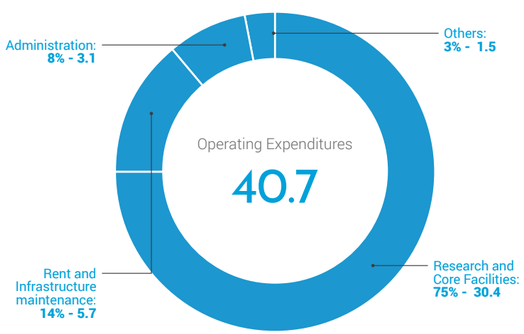
FINANCIAL REPORT

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

Generalitat de Catalunya

Gobierno de España · Ministerio de Ciencia e Innovación

upf. Universitat Pompeu Fabra Barcelona

"la Caixa" Foundation

PUBLIC FUNDERS

European Research Council

Gobierno de España · Ministerio de Ciencia e Innovación

Gobierno de España · Ministerio de Educación y Formación Profesional

Generalitat de Catalunya Departament d'Empresa i Coneixement

Generalitat de Catalunya Departament de Salut

European Union · European Regional Development Fund

European Union · European Social Fund

EMBO excellence in life sciences

AGAUR Agència de Gestió d'Ajuts Universitaris i de Recerca

FECYT

Barcelona Cultura · Ajuntament de Barcelona

NIH National Institutes of Health

ICREA

HFSP

wellcome

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

PRIVATE FUNDERS

"LA CAIXA" FOUNDATION

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). Ongoing projects from different competitive calls include one 'Caixa Impulse' award, 4 INPhiNIT PhD grants and 2 major grants from the First Health Research Call (F. Gebauer and M.P. Cosma). In 2019, we were awarded 4 INPhiNIT PhD grants and a major grant from the Health Research Call (L. Serrano). Serrano's project will produce a bacterial lung chassis for treating human lung infectious diseases.

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 chairholder 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 second chairholder for a 3-year term.

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 candidates, selected in a competitive call, were Xavi Hernández (Luis Serrano's lab) and María de las Mercedes Barrero (Bernhard Payer's lab), who will do their PhDs between September 2018 and 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 the CRG within the Joves i Ciència programme, at which students take part in sessions and events focused on scientific topics with the aim of ultimately 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 this 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), one project from the 2015 edition on 'Diabetes and Obesity' (Jorge Ferrer), two projects from the 2016 edition on 'Strokes and traumatic spinal cord and brain injury' (Marc Marti-Renom and Mara Dierssen), and three projects from the 2018 edition on 'Cancer' (Ivo Gut, Holger Heyn and Susana de la Luna).

FONDATION JERÔME LEJEUNE

The relationship between the CRG and the Jerôme Lejeune Foundation began many years ago. They provided support to several of Mara Dierssen's research initiatives related 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-Jerôme 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 'Epi-Genetic 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, due to 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 cell lung cancer, to understand their resistance to therapy. The fellowship will run until September 2020. In 2019, Gregoire Stik (in Thomas Graf's lab) was awarded a postdoctoral fellowship for his project about the changes in the genomic architecture of B-cell acute lymphoblastic leukaemia, which will run until 2021.

THE VELUX FOUNDATIONS

The Velux Foundations funded the research project titled 'Regenerating Photoreceptors in Retinitis Pigmentosa', by our own PI Pia Cosma, from 2015 to 2019. Retinitis pigmentosa (RP) is a severe disease that affects 1 in every 3,500 individuals, who undergo a progressive loss of vision and for which as yet there is no cure. The intention is 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. To continue with this research, in 2019, this organisation awarded her a new project entitled 'Cell fusion-mediated therapy to regenerate human retinae', which will run until 2022.

BARCELONA INSTITUTE OF SCIENCE AND TECHNOLOGY (BIST)

The BIST is contributing to several ongoing initiatives at the CRG. Firstly, it is co-funding 2 FI PhD Fellowships from AGAUR in the labs of our PIs Pia Cosma and Roderic Guigó for four years. Moreover, Jofre Font (Miguel Beato lab) received the Ignite Call award for his project 'Role of phase separation in gene regulation and chromatin architecture'.

CLÍNICA EUGIN

In March 2018, CRG and Eugin signed a 4-year collaboration agreement on molecular research applied to assisted reproduction. The project entails the creation of four working groups whose research will focus on gaining insights into the aging of ovules, their sensitivity to the passage of time and on studying whether changes in vaginal microbiota have an impact on assisted reproduction. The CRG groups involved are those of Isabelle Vernos, Toni Gabaldón, Bernhard Payer and Elvan Böke. This agreement consolidated an existing relationship between both organisations, through Isabelle Vernos' group, with whom Eugin worked for four years to promote interdisciplinary research targeting patients and society.

NOVO NORDISK FOUNDATION CENTER FOR BASIC METABOLIC RESEARCH

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

CHAN ZUCKERBERG INITIATIVE (SILICON VALLEY COMMUNITY FOUNDATION)

The Chan Zuckerberg Initiative (CZI), an advised fund of the Silicon Valley Community Foundation, awarded a grant to Holger Heyn, from CNAG-CRG, and a further 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 health and disease studies. The project awarded to Heyn is entitled "Benchmarking single-cell RNA sequencing methods" and ran from April 2018 until March 2019.

WORLDWIDE CANCER RESEARCH

In 2019, Juan Valcárcel was awarded a grant from the UK-based Research Charity Worldwide Cancer Research. The grant will support different aspects of the development of novel reagents known as splicing-modifying antisense oligonucleotides (AONs) that can revert the splicing alterations observed in tumours. The grant will make it possible to carry out work geared towards validating and optimising these reagents for therapeutic use in different lung cancer types. Given the high incidence, poor prognosis and lack of efficient therapies for lung cancer, this grant may contribute to a deeper understanding of these regulatory mechanisms and to translate fundamental knowledge into applications of potential medical value (2019-2021).

EUROPEAN FOUNDATION FOR THE STUDY OF DIABETES (EFSD)

In 2019, Irene Miguel-Escalada, from Jorge Ferrer's lab, was awarded the EASD Rising Star Symposium & EFSD Research Fellowship, supported by Novo Nordisk. The research project associated with this postdoctoral fellowship is entitled "Molecular dissection of a new genome regulatory programme that underlies beta cell formation" and will run until 2020.

FUNDACIÓN BBVA

In the 2019 call by the BBVA Foundation Leonardo Grants for Researchers and Cultural Creators, our junior group leader Arnau Sebé-Pedrós was awarded a grant for his research project entitled 'A new method for the transcriptomic analysis of cellular ontogeny in individual embryos'. The objective of the project is to develop a new genomic methodology to overcome the current technical limitations that hinder the analysis of gene expression in individual embryos with cellular resolution, as it is currently impossible to study such small specimens.

KING BADOUIN FOUNDATION

Through an agreement with the King Badouin Foundation, J.W. Mouton, from Luis Serrano's lab, was awarded a grant to study microbiome dysbiosis, inflammation and macular degeneration (Nov 2019 to Oct 2021).

SPONSORS

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EXCELENCIA SEVERO OCHOA

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