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Executive Summary

EXCELENCIA SEVERO OCHOA

CRG Centre for Genomic Regulation

Institució CERCA Centres de Recerca de Catalunya

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Foreword

Luis Serrano
DIRECTOR

2020 has been an unprecedented year worldwide, dramatically shaping and changing every aspect of our way of life. Science, as a fundamental component of our society, has also been affected. For many at the CRG, the COVID-19 pandemic has resulted in social isolation, particularly for young scientists working away from home. Researchers have also suffered from disruption caused by restrictions imposed to working conditions.

On one level, the time at home helped give pause to reflect that perhaps we were travelling too much, and that we could organize many meetings on-line in an efficient way. Our scientists found breathing space to think about their research, the goals they want achieve and the required experiments necessary to get there. Despite the circumstances, we kept our labs running where possible, ensuring the safety of our personnel while allowing them to carry out crucial experiments that put Barcelona on the map for cutting-edge biomedical science.

Most importantly, the crisis also shined a light on the ingenuity, adaptability and resilience of our members, as well as our duty to help society at its greatest time of need. At the request of the regional government, the CRG developed a mass PCR screening system for residential care homes and healthcare workers. The initiative, called Programa Orfeu, was developed from scratch thanks to the tireless efforts of more than one hundred volunteers from the CRG's administration, core facilities and research personnel. At its peak, the program carried out nearly 4,000 PCR tests per day, providing the Catalan healthcare system with vital testing capacity to protect people's lives.

Setting up Programa Orfeu has been the first of three major achievements in 2020. The second has been keeping the CRG open and running in some of the most uncertain and unpredictable times in recent memory. The third is that despite these troubling times, we launched one new start-up based on knowledge generated by CRG scientists. All this was only possible due to the unrelenting dedication of our staff, determined to showcase the CRG's positive social impact. I would particularly like to extend my warmest thanks to Juan Valcárcel for his invaluable dedication to both Programa Orfeu and to the CRG more widely during his term as Associate Director, which ended in 2020.

I welcome you to dive into the following pages, where I am immensely proud of our scientific achievements, new discoveries, technological approaches, spin-offs, institutional projects, collaborations and public engagement activities.

A look back at the year

2020 was a challenging and historic year for the whole world, as well as for the Centre for Genomic Regulation, due to the Covid-19 global pandemic. At the same time, it was a year that highlighted the important value of research for society. When the pandemic was at its peak, the Government of Catalonia asked the CRG to coordinate a task force, which included the Institute for Research in Biomedicine (IRB Barcelona) and the Institute for Bioengineering of Catalonia (IBEC), to repurpose our labs and set up a mass testing service to stop the spread of the new coronavirus outbreak. Thanks to the expertise and dedication of our volunteers, we developed brand new protocols and pipelines at breakneck speed to. We modified existing instruments, as well as buying and borrowing new ones, to meet the standards necessary. This led to the successful validation of tens of thousands of PCR tests, crucial to combatting the pandemic in hospitals and nursing homes across Catalonia.

All throughout the year, we joined efforts and worked to design the new CRG strategic plan 2021-2024. Our vision for the next few years is that the CRG contributes to the current paradigm shift affecting biomedical research, where it is being transformed from a descriptive discipline into one that is quantitative, predictive and actionable. While continuing to nurture a stimulating environment and developing cutting-edge technologies to conduct innovative fundamental research, we will use new quantitative and computational approaches to address challenging questions in biology and medicine, keeping the CRG as an international reference in genomics and its applications to biomedicine and biotechnology.

Science & Technology

CRG research has resulted in important discoveries and technological advances. Notable examples from 2020 include a novel technology for genome-scale genetic screens in single cells (Velten); a new method to detect diverse RNA molecules, such as viral RNAs, in samples with minimal biological material (Novoa); advances in predicting tissue-specific mutation probabilities in human cancers (Weghorn); the continuous development of the NextFlow pipeline language (Notredame); the identification of the major cell types in the human body, and of the impact of sex on human tissue transcriptomes (Guigó); the identification of a new gene in pancreatic cancer (Ferrer); and genome-wide analyses of protein turnover and metabolic pathway activity in a minimal bacterium (Serrano). In cell biology, CRG researchers found out how the nucleus senses and measures physical and morphological changes in cell shape and re-establishes homeostasis (Ruprecht).

Due to the pandemic, the CRG spearheaded and participated in different initiatives to contribute to the global research on SARS-CoV-2, promoting openness and access to its results in this field. The H2020-funded infrastructure project EASI-Genomics (Gut) opened a specific call to support genomics projects on COVID-19, and one of the supported studies highlighted the causes of severe COVID-19 disease in young patients. Other highlights include the deployment of a parallelization software (Tartaglia) to examine the interactions between stretches of RNA in SARS-CoV-2 to understand the structure of the viral genome and its interactions with the molecular components of the cells in infected individuals; the study on the susceptibility of infection to SARS-CoV-2 for individuals with Down Syndrome (Dierssen); the contribution to many diagnostic and seroprevalence studies by producing several SARS-CoV-2 viral proteins and the ACE-2 human protein, one of the main entry human receptors for SARS-CoV-2 (Carolis); the launch of a database, which is a publicly-available, free-to-use resource for researchers to study how different variations of the SARS-CoV-2 virus grow, mutate and make proteins (Novoa); the development of a computer programme, MasterOfPores, to standardise the analysis of publicly available SARS-CoV-2 nanopore sequencing data (Novoa & Ponomarenko); the insights into why the SARS-CoV-2 virus only infects certain species (Serrano); and granting free access for researchers and non-profit organisations of a previously developed tool, FoldX, to test how ACE2 interacts with proteins on surface of the new coronavirus (Serrano).

The CRG continues to co-host the European Genome-Phenome Archive (EGA) together with the European Bioinformatics Institute (EMBL-EBI), thanks to the valuable support of “la Caixa” Foundation. In 2020, the EGA

Team achieved great results in the improvement of the Beacon Discovery platform for human genomic data and the development of Viral Beacon for the discovery of SARS-CoV-2 genomic variants.

The CRG also led and participated in several European and international projects. Particularly, in the framework of H2020, several ERC grants were awarded to CRG PIs: two ERC Synergy grants (Malhotra & Surrey), one ERC Advanced Grant (Lehner) and one ERC Consolidator Grant (Irimia). The '1+ Million Genomes' Initiative (Serrano, EGA and CNAG-CRG), aiming to have 1 million sequenced genomes accessible within the EU by 2022, obtained further funding through the Health Societal Challenges, which also funded the initiative to integrate AI in new personalised medicine platforms or models in oncology (EGA). We also received funding to kick-start PROTrEIN (Sabidó), a new European Innovative Training Network coordinated by the CRG, whose mission is to train a new generation of computational proteomics researchers.

From a knowledge transfer perspective, in spite of the global crisis, the CRG managed to raise 2M€ from venture capital funds to incorporate Pulmobiotics, the first CRG spin-off company focused on therapeutic products. **Pulmobiotics** is based on more than 10 years' research of the *Mycoplasma* bacteria at Dr. Luis Serrano's lab. This shows how curiosity-driven science can generate new products to fight infectious diseases in the lung and boost vaccine development. New projects to develop drugs against cancer (Novoa) were also funded by pharmaceutical companies. The validation of a diagnosis technology for neurological disorders was also funded by the 'Impulse Validate' program of the 'la Caixa' Foundation (Lao).

Strategic priorities

By the end of 2020, the CRG passed the baton of the SOMMa leadership to the Spanish National Cancer Research Center (CNIO), and its director, María Blasco, who will be the Chair of the alliance for the next period. SOMMa, together with ASEICA and ASEBIO, launched a joint statement, signed by nearly fifty research and innovation organisations in Spain, to call for changes to national science policy. The campaign was highly successful, resulting in an official government response.

As part of the EU-LIFE alliance, we continued to consolidate our position as an influential voice in the European research and innovation ecosystem. In 2020, the alliance published a position paper describing their long-term vision for European science, which generated considerable interest. Being part of EU-LIFE, the CRG also participated in the campaign to support a proper budget for research in the multi-annual financial framework Horizon Europe.

As a part of our commitment towards open science, CRG open access publications in 2020 surpassed 82%. 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. Within the ORION project, in 2020 the CRG successfully developed the public dialogue co-creation experiment, which due to the pandemic was held in a virtual environment with very positive results and interesting inputs coming from citizens and our stakeholders. Some of their feedback was included in our new strategic plan. Our new citizen science project, Genigma, a phone game co-created

with citizens to assemble genomes in 3D in a crowdsourced manner, continued to advance, with many activities, playtests and co-creation events. The game will help researchers uncovering genomic alterations in cancer cell lines. The Gender Balance Committee launched a new Equality, Diversity and Inclusion plan 2020-2023, developed a new protocol against any form of harassment and developed guidelines for using gender-neutral language. Thanks to our collective efforts to push for gender equality over the past years, in 2020, 46.2% of junior group leaders at the CRG are women.

Talent

Last year we welcomed two junior group leaders; Renée Beekman ('la Caixa' fellow), from the Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), in Barcelona, Spain; and Lars Velten, from the European Molecular Biology Laboratory (EMBL), in Heidelberg, Germany. Our best farewell wishes go to junior group leaders Guillaume Filion, who left after almost nine years at the CRG to take a faculty position at the University of Toronto, in Canada; and Gian Gaetano Tartaglia, who left for a full professor position at University La Sapienza and a PI position at Istituto Italiano di Tecnologia (IIT), in Italy. We also said goodbye to Timo Zimmermann, Head of the Advanced Light Microscopy Unit since 2007, who left to become Team Leader of Advanced Microscopy Technology Development and Service Provision within the new EMBL Imaging Centre in Heidelberg, Germany.

The whole CRG community worked under exceptional circumstances due to the Covid-19 crisis, particularly during the lockdown. The CRG developed a Covid-19 contingency plan to allow essential work to continue, and provide a safe work environment to its members. We strived to provide specific resources to our community and implement specific measures, such as teleworking regulations, work-life balance guidelines, tips to support our community wellbeing and mental health, and new communication channels and support groups. We would like to extend our warm thanks to all CRG community members for the continued support and resilience during the last year and for observing the safety measures. This has undoubtedly contributed to the very limited incidence of Covid-19 at the CRG and to ensure that our institute is a safe work place.

Scientific Highlights

01

Getting a street view of cells

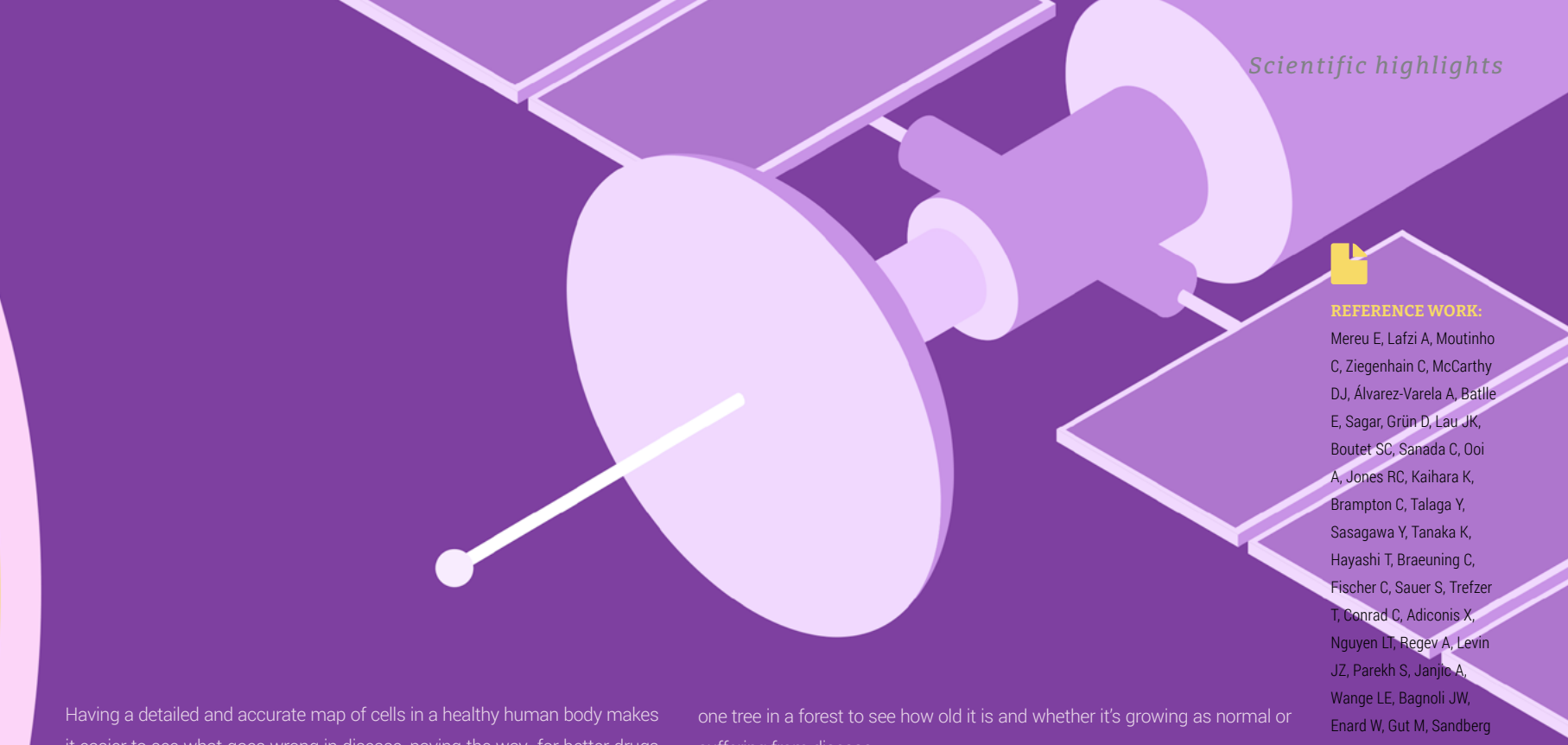
Mapping the cellular makeup of the human body

In the same way that we can use satellite imaging, online maps and Google street view to create detailed pictures of our cities and towns, the Human Cell Atlas aims to map the trillions of cell types that make up the human body.

There are many emerging techniques for single cell RNA sequencing which can classify different cell types according to the genes that are active within them. But which methods give us the most accurate picture of the cellular world?

To find out, a team led by Dr Holger Heyn of the Centre for Genomic Regulation analysed approximately 3,000 cells of various types. These included blood cells, immune cells, and cells from the kidney and digestive tract from humans, mice and dogs. Of the 13 techniques that they compared, one in particular - Quartz-seq2 - stood out in its performance.

The Human Cell Atlas requires a high level of precision, as even cells in the same organ can have vastly different functions. For example, it was previously accepted that our livers had a small handful of different types of cell. Thanks to new techniques like Quartz-seq2, the Human Cell Atlas project has discovered many previously unknown subtypes. The ability to tell these similar cells apart is like using satellite images to zoom into a street, not only to compare the front doors of two homes, but to compare their structure.



Having a detailed and accurate map of cells in a healthy human body makes it easier to see what goes wrong in disease, paving the way for better drugs and new therapies.

"Our goal now is to move this into a clinical context, where we can compare a cell from a patient with the healthy reference," says Holger.

The team hopes that these benchmarked techniques can be developed to determine not just the cell's type but how active it is and whether it is still replicating. This would be analogous to using Google street view to look at one tree in a forest to see how old it is and whether it's growing as normal or suffering from disease.

"In the tumor microenvironment, immune cells can become 'exhausted,'" explains Holger. But this process may be reversible if we can target those cells accurately. "The plan is to identify those cells and reactivate them again to defeat the cancer."

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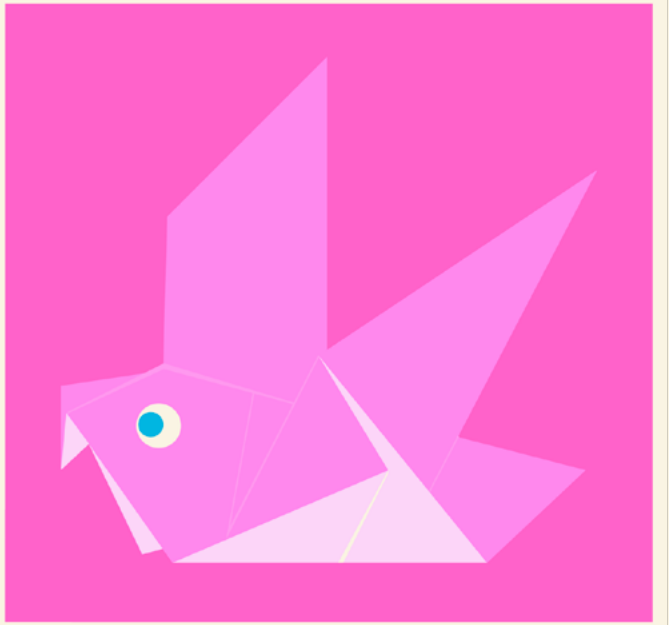
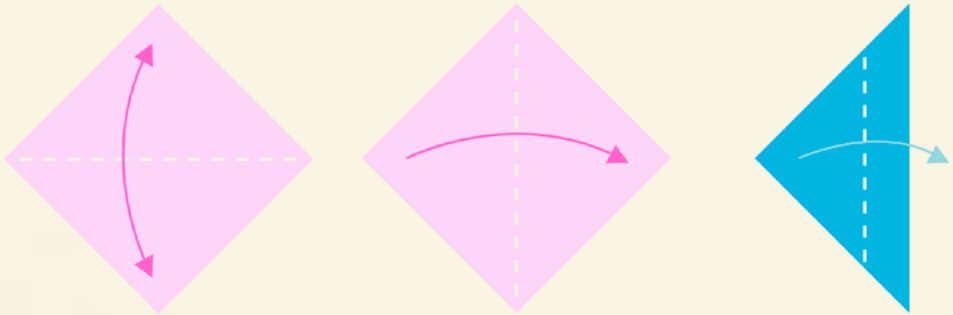




02

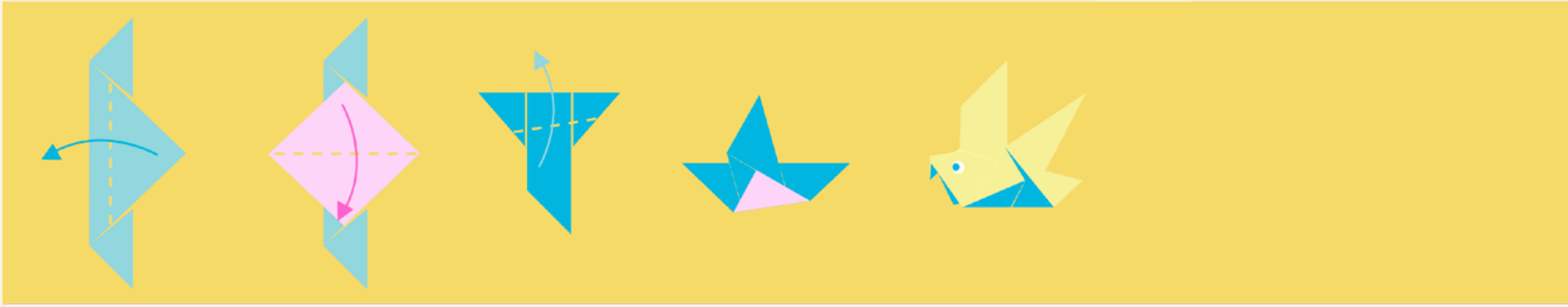
Knowing Where to Fold

Learning More About Genomic Origami

Every cell in your body contains two metres of DNA that have to be unravelled and read when genes are activated, folded into a space just a few thousandths of a millimetre thick. But this folding isn't just a matter of fitting into a smaller space. Just as a piece of paper can become a swan, flower or frog depending on its folds, the folding of DNA leads to different results. When the genome's three-dimensional shape changes, different genes can be read, telling the cell what to do next.

One particular protein, CTCF, has long been thought to be an essential pin holding the genome in place. But new research suggests that it's possible for genomes to change their folded shape even without CTCF.

Ordinarily, CTCF proteins bind to each other and to DNA, forming 'loops' within the genome. This type of connection creates small-scale structures called topologically associating domains or TADs. If a TAD changes, the genes that are switched on in the cell also change.



To investigate the connection between CTCF, TADs and three-dimensional structure, Dr Thomas Graf and his team at the Centre for Genomic Regulation in Barcelona developed an experiment where one type of human immune cell is triggered to become another type through a single cell division. The team used a genetic engineering technique called CRISPR to reduce the levels of CTCF in the precursor cells, which prevented the formation of the vast majority of TADs in the cell.

"Full knockout of CTCF is impossible because it is essential for the cell cycle," explains Dr Grégoire Stik, a senior postdoc in Thomas's team. If a reduction in CTCF affects gene expression then there should be a disturbance in the cells' transformation from one type to the other. Instead the cells managed the metamorphosis with very little disruption.

This surprised the team, says Thomas. "We had assumed that TADs are important for many basic functions of the cell, but what we found is that cells can do without TADs and still make these incredible changes in gene expression."

"Cell transformation still happens without CTCF," adds Grégoire. "There must be other players that are still able to fold the genome."

However, the investigators found that CTCF is required in a different context, namely the cells' rapid response to bacteria, showing that specific TADs are important for fine-tuning the expression of inflammatory response genes.

With this research, we're a step closer to knowing how genome folding controls the fates of our cells.

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03

A Face in the Crowd

Spotting Sequences in Samples

Who's out there in the crowd? Computer algorithms can learn to pick out identifying facial features from the noisy signals generated by tens, hundreds, or even thousands of people as they pass through a camera's field of view.

Dr Eva Novoa from the Centre for Genomic Regulation and her team have now applied similar techniques to recognise specific sequences within large RNA molecules - a type of genetic code found within cells.

Rather than passing in front of a camera, strands of RNA are placed in a flow cell - a thin, etched plate about the size of a microscope slide. From here they pass through a nano-scale pore embedded in a membrane, which is connected to an electrical current. As each RNA moves through the pore it causes the current to change in a characteristic way, creating a unique digital signature for that specific RNA sequence.

The challenge of working with RNA is that the amount of material is limited, especially in patient-derived samples. While DNA in samples can be amplified, the amount of native RNA is limited to what's there already. This is a challenge that becomes particularly important when hunting for tiny RNA-based viruses like SARS-CoV-2, which causes Covid-19.

"The assay requires 500 nanograms of RNA material, so if you don't have 500 nanograms in your sample you can't sequence it," explains Eva.

But what if it was possible to spot individual sequences in a crowd of samples? Eva's innovation allows researchers to analyse RNA sequences from multiple samples in one single flow cell. Her approach uses a convolutional neural network - the type of machine learning most commonly used for facial recognition - to identify which RNA sequences are present in that crowd.

To do this, the RNA digital signatures are converted into two dimensional 'images', making it easier to spot individual sequences in samples that contain many strands of RNA. This technique can translate a sequence's electrical signature into an image in six one-thousandths of a second, allowing the neural network to identify RNA sequences with 99 percent accuracy and making new kinds of analysis possible.

"We are collaborating with other labs to analyse viral RNA modifications present in infected cells, as well as in samples from Covid-infected patients. The lab is expanding this method to recognise many more sequences to allow us to use it in patient derived samples," Eva says.

No matter how small the sample, viruses are running out of places to hide.

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04

Making Elbow Room

Cells Strike Out when they Feel the Pinch

It might not be a feeling you've experienced lately, but you can probably remember the discomfort of a crowded Metro carriage. We now know that individual cells can feel the pinch in much the same way.

Dr Verena Ruprecht, from the Centre for Genomic Regulation, studied cells as they feel the squeeze, shedding light on how tissues develop and how mobile cells navigate around the body.

"You can think of our equipment as like a sandwich toaster," explains Verena. "Using microfabrication we make pillars that define the distance between two plates. We put in cells, close the sandwich toaster and watch what happens."

The team discovered that cells experience a kind of proprioception that allows them to sense changes in their shape.

"We already knew that, like humans, cells have chemoreceptors that can detect chemicals around them: think of the smell of someone's armpit in a crowded carriage," Verena says. "But the feeling of being physically squashed and how a cell reacts to it; that's something where we've found a cellular strategy for the first time with this experiment."

As cells are squeezed, the nuclear membrane that surrounds and protects DNA also changes shape.

"Ordinarily the nuclear membrane is wrinkled," explains Verena. "But if you start to deform the cell the wrinkles smooth out."

Cell proprioception may go beyond a sense of being penned in. By forcing cells to swell, Verena's team also looked at what happens when cells stretch.

"We saw two types of signals at work. The smoothness of the nuclear membrane acts as a signal that the cell is changing shape, while the distance between the nuclear and outer cell membrane distinguishes whether the cell is being squashed or stretched," she says.

Verena's team observed that the 'crowding' signal triggers a cascade of activity in the cell, enabling it to change shape and wriggle away from the throng. In the original study, Verena and an international team of collaborators observed the migratory behaviour in zebrafish embryo cells. The same effect has since been observed driving the patrolling behaviour of immune cells, and it might also cause cancer cells to spread around the body.

"A cell that wants to colonise another part of your body has to move into different tissue," says Verena.

Diseased cells might want to strike out for space, whether we want them to or not. Armed with this new understanding of the signals that help cells to move, it may soon be possible to stop dangerous cell movements in their tracks.

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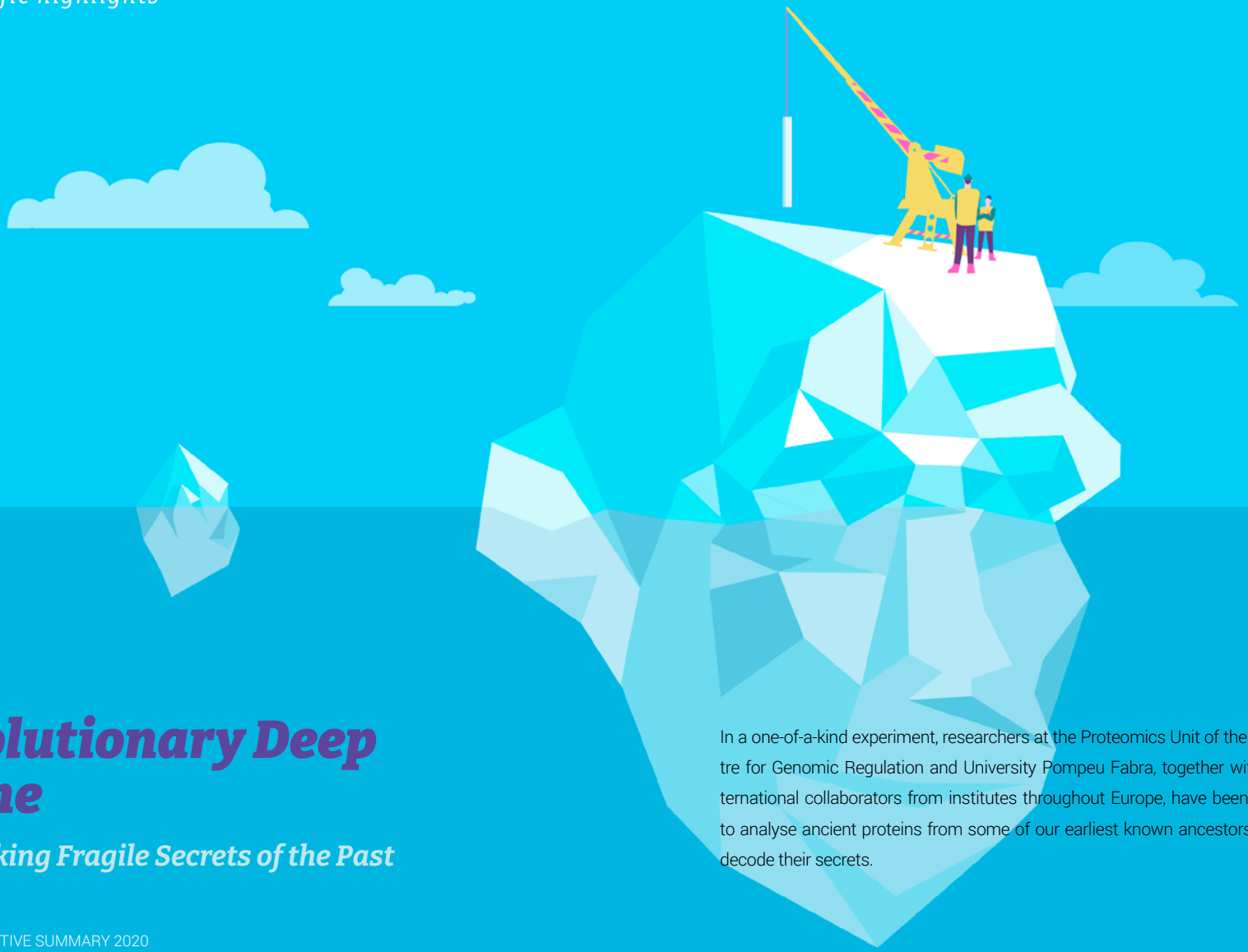

05

Evolutionary Deep Time

Unlocking Fragile Secrets of the Past

In a one-of-a-kind experiment, researchers at the Proteomics Unit of the Centre for Genomic Regulation and University Pompeu Fabra, together with international collaborators from institutes throughout Europe, have been able to analyse ancient proteins from some of our earliest known ancestors and decode their secrets.

In much the same way that scientists identify can analyse the molecules trapped in drilled fragile ice-cores to understand how our planet's environment has changed over aeons, Dr Eduard Sabidó and Dr Cristina Chiva, are looking far back into our evolutionary past by studying extremely ancient dental fossils that are around a million years old.

With such rare artefacts, it's not always possible to study them by sequencing DNA.

"Ancient DNA is only preserved in certain temperature and humidity conditions, but some protein molecules are much more robust," Eduard explains.

Rather than looking for DNA, the team instead used a technique called mass spectrometry to analyse proteins in teeth from two ancient hominids: a 1.7 million year old *Homo erectus* fossil, and a *Homo antecessor* fossil thought to be close to a million years old. They compared the forms of these proteins with those found in two more modern human teeth recovered from burial sites that were 200-300 years old.

This requires strong nerves and a steady hand.

"It's a lot of responsibility to analyse a million year old sample, One cannot just repeat the experiment. It's stressful but very exciting," says Dr Cristina Chiva.

The comparison of ancient and modern teeth helped to settle a long-running debate in evolutionary biology of exactly where these ancient species sit in the family tree of human ancestry.

"There was a lot of controversy over the place of *Homo antecessor* in the evolutionary tree" explains Cristina. Now using the molecular data generated in this study, *Homo antecessor* can be placed as a species closely related to, but not part of, the group composed of Late Pleistocene hominins. The study also opens up new frontiers in evolutionary research by using proteins rather than DNA to understand the relationships between ancient species.

The Proteomics Unit is now collaborating with the Institute of Evolutionary Biology (IBE UPF-CSIC) in Barcelona to look at the protein makeup of other archaic fossils.

"One of the most interesting aspects of this research is the ability to tackle unsolved evolutionary questions." Eduard says. "We want to see how far back we can go."

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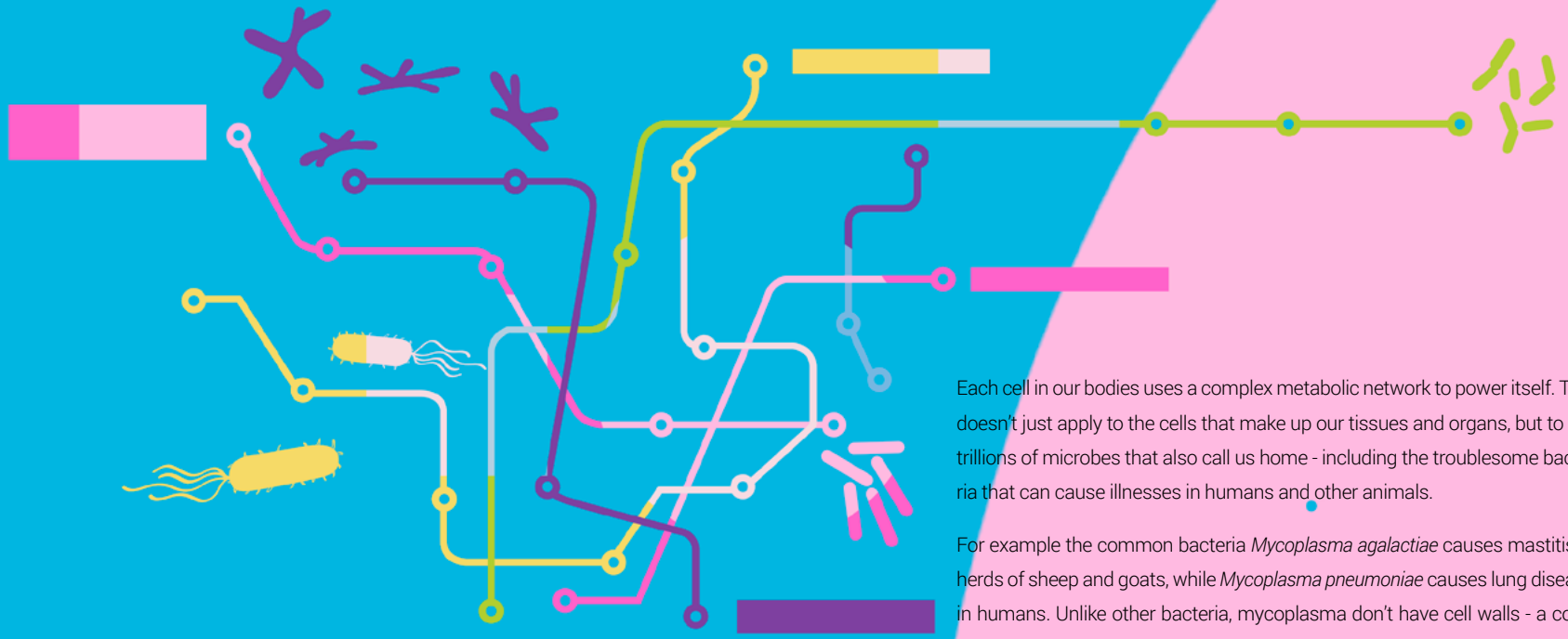

06

Navigating New Treatments with Metabolic Maps

Each cell in our bodies uses a complex metabolic network to power itself. This doesn't just apply to the cells that make up our tissues and organs, but to the trillions of microbes that also call us home - including the troublesome bacteria that can cause illnesses in humans and other animals.

For example the common bacteria *Mycoplasma agalactiae* causes mastitis in herds of sheep and goats, while *Mycoplasma pneumoniae* causes lung disease in humans. Unlike other bacteria, mycoplasma don't have cell walls - a common target for antimicrobial drugs - and can't be treated with most known antibiotics. But by understanding their metabolic networks, we could finally get a better understanding of how to tackle these evasive microbes by disrupting their power supply.

For some time the study of cell metabolism has been carried out using a technique called metabolic flux analysis.

"Imagine a network of Metro lines and stations," says Dr Luis Serrano, director of the Centre for Genomic Regulation. "Metabolic flux analysis is like labelling

everyone who arrives at a certain station with a particular colour, then seeing where they go."

Here in Barcelona, that would mean giving everyone who boards at Hospital de Bellvitge a red sticker, everyone who boards at Paral.lel a purple sticker, everyone who boards at Zona Universitària a green one and so on, and then counting how many people with each coloured sticker leave the Metro at the other stations in the network.

But while metabolic flux analysis tells you where the travellers are going, it can't reveal how fast they're travelling or by what route.

"The Metro map shows you all the possible ways of going from one place to another, but on some lines there will be one train every six hours and on another there is a train every five minutes," Luis explains.

To measure the rate of flow the team altered the metabolic network of the candidate bacteria and observed which pathways suffered the most disruption. They did this in two ways: firstly by changing what the bacterial colonies were fed, which allowed faster flows between some points but left others unaltered. Looking at how well the bacteria grew let the team infer which routes were most critical in these species' metabolic maps.

Then they inserted two extra genes into *M. agalactiae.* These genes encode proteins that are used to metabolise glucose in other cell types, analogous to adding a new interchange in the Metro network. With this new 'station', the bacteria showed even greater levels of growth in the presence of glucose.

Dr Ariadna Montero-Blay, first author on the study, says, "In *M. agalactiae* we used this technique to identify an essential protein that is necessary for the cell to grow. Using a toxic analogue of that protein stopped the bacterial growth, showing that we can control bacteria by manipulating their metabolism."

As well as pointing towards novel antibiotic drugs, the same technique could be used to engineer beneficial variants of these microbes. For example, the team hopes to develop a metabolically modified harmless version of *M. pneumoniae* as a potential treatment for human lung diseases.

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07

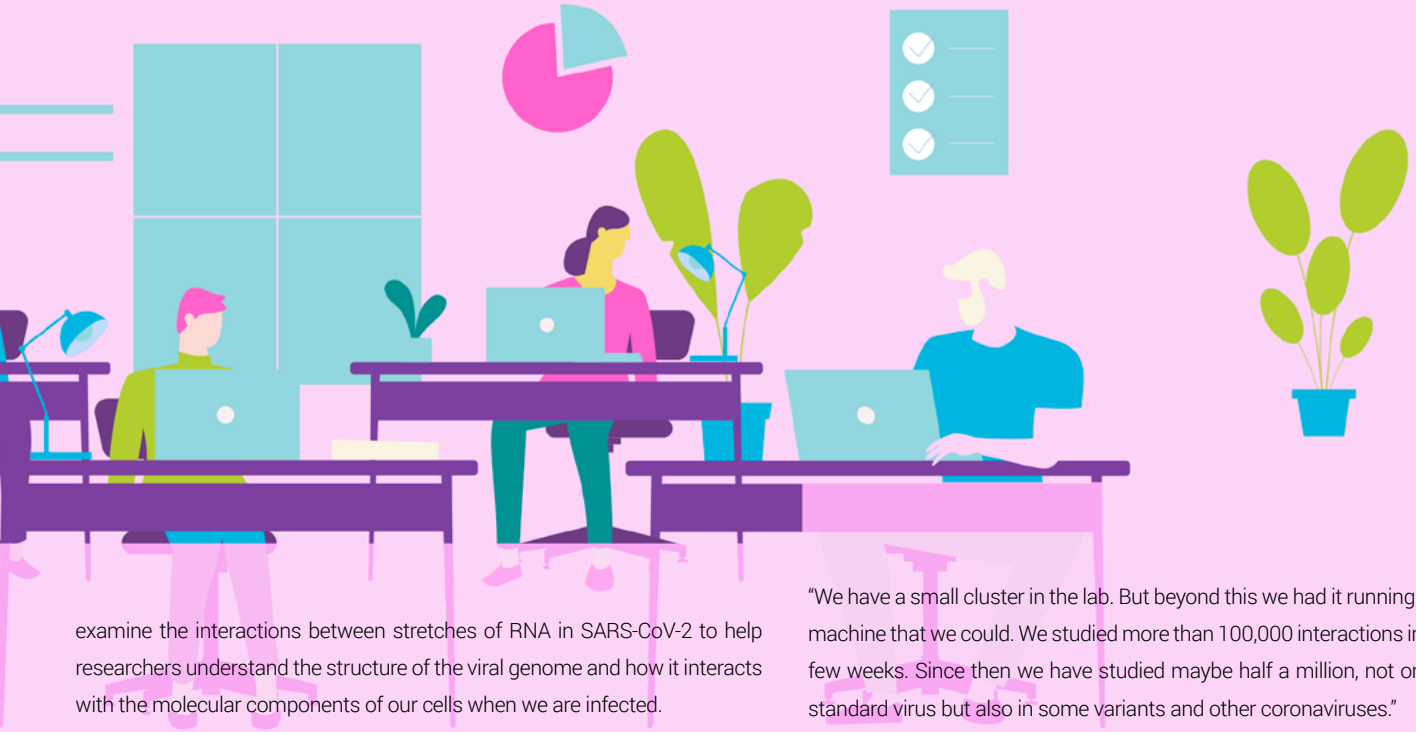
The Power of Parallel

How a Strategy of Divide and Conquer Unlocked the Secrets of SARS-CoV-2

What do you do when a brand new pandemic hits and you need to understand the virus that's causing it as quickly as possible? What was a fairly abstract question eighteen months ago came into sharp focus at the beginning of 2020 with the global outbreak of Covid-19.

While many of us were still getting to grips with Zoom, Dr Gian Gaetano Tartaglia turned his attention to another form of technology altogether in order to understand the structure of the RNA genetic code inside coronaviruses like SARS-CoV-2, which causes Covid-19.

He and his group at the Centre for Genomic Regulation had previously created software that could speed up the work of RNA sequence analysis sharing it across many computers all working on a small part of the problem at the same time. The new technique, known as parallelization, was deployed to



examine the interactions between stretches of RNA in SARS-CoV-2 to help researchers understand the structure of the viral genome and how it interacts with the molecular components of our cells when we are infected.

Overnight this relatively new technique went from being a time-saving convenience to a life-saving necessity, shaving months off the initial investigation into the new virus.

"We developed this parallelization method some time ago to study other things," says Gian. "Normally the analysis of a novel virus would have taken six to nine months, but we were able to analyse the sequence in around 50 days.".

Achieving this feat meant using every available machine that they could beg or borrow.

"We have a small cluster in the lab. But beyond this we had it running on every machine that we could. We studied more than 100,000 interactions in the first few weeks. Since then we have studied maybe half a million, not only in the standard virus but also in some variants and other coronaviruses."

Understanding the variability in virus variants is shedding light on how the virus might be evolving and the development of vaccines against new strains.

"We've discovered that the spike-coding region is highly conserved, meaning that it's almost exactly the same in every version of the virus" Gian says.

"It's likely that if there are mutations in this region that they probably make the virus ineffective. If you know that the virus is constrained in this way, then it becomes possible to study the spectrum of possible changes that could theoretically occur there, which will help with the search for future vaccines."

REFERENCE WORK:

Vandelli A, Monti M, Milanetti E, Armaos A, Rupert J, Zacco E, Bechara E, Delli Ponti R, **Tartaglia GG**. *"Structural analysis of SARS-CoV-2 genome and predictions of the human interactome."* Nucleic Acids Res. 2020 Nov 18;48(20):11270-11283. doi: 10.1093/nar/gkaa864.

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 & GENOMICS PROGRAMME

Coordinator: **Roderic Guigó**

The programme has welcomed a new member, Lars Velten, who joined us from the EMBL in Heidelberg in early 2020. The programme's highlights for the year include the development of a novel technology for genome-scale genetic screens in single cells, advances in predicting tissue-specific mutation probabilities in human cancers to enable the characterisation of mutational processes and the inference of cancer driver mechanisms, the identification of the major cell types in the human body based on the analysis of transcriptomic data, the study of the impact of sex on human tissue transcriptomes, the continued development of the NextFlow pipeline language, the elucidation of the role of HNF1A in pancreatic cancer and the structural analysis of the SARS-CoV-2 genome.

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

The programme has continued to deploy and support the European Genome-phenome Archive (EGA) in collaboration with the European Bioinformatics Institute (EMBL-EBI). The CRG EGA team has achieved excellent results in the improvement of the Beacon Discovery platform and in the foundation of the Federated EGA Network, scheduled for 2021.

CELL & DEVELOPMENTAL BIOLOGY PROGRAMME

Coordinator: **Vivek Malhotra**

The mission of the scientists in the Cell and Developmental Biology programme is to employ quantitative approaches to unravel the mechanisms through which a cell is compartmentalised, grows and divides and how it is engineered and assembled into a tissue. The department is staffed by Vivek Malhotra (protein secretion mechanisms), Isabelle Vernos (microtubule and spindle dynamics), Sebastian Maurer (cytoplasmic RNA localisation), Verena Ruprecht (cell and tissue dynamics), Elvan Boke (oocyte biology and cellular dormancy) and Thomas Surrey (intracellular self-organisation). Numerous outstanding papers were published by departmental members, although there is one that merits a special mention. This paper by the Ruprecht laboratory, Venturini et al. Science (2020), describes how the nucleus senses and measures physical and morphological changes in cell shape and re-establishes homeostasis by controlling actomyosin contractility and migration plasticity.

In 2020, Vivek Malhotra spearheaded a programme called CATCAT for Cell and Tissue research in CATalonia. Thirty-five (35) laboratories from different institutes in Barcelona are involved in this programme, whose objective is to hold joint meetings, seminars, exchange technology, personnel and ultimately share students and postdocs to promote research into cell and tissue engineering in Barcelona.

The department enjoys international recognition and is well funded by external grants. Elvan Böke is an ERC Starting Grant awardee, and new ERC Synergy Grants were awarded to Thomas Surrey and Vivek Malhotra, respectively. Ruprecht was elected an EMBO YIP and Vivek Malhotra received the Alexander von Humboldt research award.

GENE REGULATION, STEM CELLS & CANCER PROGRAMME

Coordinator: **Juan Valcárcel**

In 2020, we welcomed Renée Beekman as a new Junior Group Leader. Renee is an MD PhD who has produced ground-breaking postdoctoral work in epigenetic regulation in leukaemias and lymphomas with Elias Campo and Iñaki Martín-Subero at IDIBAPS (Barcelona). Her group is now studying how the three-dimensional organisation of the genome impacts oncogenic transformation in these malignancies. In 2020, we also bid farewell to Guillaume Filion and his group, after almost nine years at the CRG, who used high-throughput DNA integration to explore chromatin dynamics, for example to study HIV latency reversal. Guillaume has taken up a Faculty position at the University of Toronto. An external evaluation panel reviewed the Programme's science in October and rated its research as excellent, singling out many impactful publications, the high level of cooperation between groups and its positive culture. The evaluation resulted in the appointment of Luciano Di Croce and Fátima Gebauer as joint Programme Coordinators. Finally, during the COVID-19 crisis, many members of our Programme teamed up with volunteers from other Programmes and Administrations to work in the Orfeu project, which produced tens of thousands of validated PCR tests that helped to fight the epidemics in Hospitals and nursing homes all over Catalonia.

SYSTEMS BIOLOGY PROGRAMME

Coordinator: **Ben Lehner**

How do we advance biology to the point where we can quantitatively understand the behaviour of molecules, cells and tissues, accurately predict their responses, and successfully build new systems with desired properties? Despite a good conceptual understanding, we are still very bad at predicting the quantitative behaviour of biological systems or designing them *de novo*. This is true at the levels of cells, tissues and organs, but it is also true for individual proteins and RNAs. In the Systems Biology programme we want to change this and to help transform molecular biology into a quantitative, predictive and engineering science. The programme covers a wide range of systems and scales: from microbes and non-model animals to human genetics, neuroscience and aging. Underlying this diversity, however, is a common approach of data-driven modelling that combines quantitative data collection with mechanistic, machine learning or statistical models.

Some highlights of 2020 include insights into when it is not possible to predict the combined effects of multiple mutations and development of software for analysing deep mutational scanning data (Lehner lab), insights into the evolution of genomic regulatory blocks (Irimia lab) and animal defense strategies (Stroustrup lab), genome-wide analyses of protein turnover and metabolic pathway activity in a minimal

bacteria (Serrano lab), and insights into why the SARS-CoV-2 virus causing the current COVID-19 pandemic only infects certain species (Serrano lab) and the impact of the pandemic on individuals with Down Syndrome (Dierssen lab).

During 2020 the Lehner and Irimia labs were awarded ERC Advanced and Consolidator Grants, respectively and Mara Dierssen received prizes recognising her work on Down syndrome from the International Foundation for Women Entrepreneurs, the Autonomous University of Barcelona and the Entrepreneurs Association of Cantabria.

CORE FACILITIES

Head: **Mònica Morales**

The core facilities programme currently comprises seven Core Facility Units. In the course of 2020, the core facilities were deeply involved in projects related to COVID-19. In March, in response to the request from the Government of Catalonia to set up the ORFEU programme for the detection of SARS-CoV-2 by PCR, we established a project involving the Genomics, Protein Expression and Bioinformatics units in conjunction with the CNAG-CRG Bioinformatics team and more than 20 CRG volunteers to deploy a protocol to perform more than 3,000 diagnostic PCRs per day. The programme, directed by Luis Serrano, Juan Valcárcel and Mònica Morales, was successfully implemented in one month and we were sending diagnostic results of an average of 1,500 PCR reactions a day to the Catalan Health system. The programme was established at a time when hospitals lacked the capacity to perform massive testing and lasted 3 months.

The Protein Expression unit also contributed to many diagnostic and seroprevalence studies by producing several Sars-CoV-2 viral proteins and the ACE-2 human protein, one of the main entry human receptors for Sars-CoV-2. The unit produced proteins for researchers at Hospital Clínic, IDIBAPS, ISGlobal, IMIM, the Spanish Astrobiology Center in Madrid and the Ingenasa company.

In June, we resumed our normal activity, which had been left on hold for 3 months. Despite this setback, thanks to the steadfast commitment of all our core facility staff, we managed to complete more than 90% of our services compared to 2019.

At programme level, we have implemented several new features in Agendo, the request management software for Core Facilities, and we have defined a sizeable number of protocols and workflows to homogenize and integrate the Programme's different units even further.

CNAG-CRG

Director: **Ivo Gut**

At the beginning of the year, we were honoured with a visit by the Spanish Minister of Science and Innovation, Pedro Duque, and the Secretary General for Research, Rafael Rodrigo. In April, we were party to setting up, designing and operating the ORFEU SarsCov2 PCR-testing platform.

Clinical Genomics: Thanks to our EASI-Genomics Infrastructure project, we completed a study into the cause of severe Covid-19 disease in young patients in a very short time. This study found that interferon and the proteins of its signalling pathway are predictive markers of severity in these individuals. We also helped to develop expression signals that permit the stratification of glioblastoma patients.

Cancer Genomics: 2020 heralded the culmination of the International Cancer Genome Consortium's PanCancer Study, which produced 23 simultaneous publications. We made significant contributions to several of these articles and to several follow-on publications. This PanCancer study gathered nearly 3,000 cancer whole genomes covering 38 types of cancer that were processed homogeneously and analysed together. This yielded an unprecedented degree of resolution of the cancer genome and provided insights into myriad aspects of tumour biology.

Single-Cell Genomics: The number of single-cell studies at the CNAG-CRG has taken off. We published a landmark study on the benchmarking of different single-analysis methods which was quickly adopted by the scientific community as a reference in the field. It was developed within our activity in the Human Cell Atlas.

With regard to technology, we have added simultaneous single-cell, transcriptomic, epigenetic and protein analysis. Methods for single-cell analysis *in situ* have also been implemented.

Ancient DNA: By studying the genomes of Palaeolithic humanoids, we were able to determine genes and gene variants that were crucial to the development of our species and are now associated with behavioural disorders such as Attention Deficit Hyperactivity Disorder (ADHD).

Biodiversity is a long-time favourite at the CNAG-CRG and we have developed key expertise in de novo genome assembly and annotation. This year, we added several high-quality de novo assembled and annotated genomes to our ever-expanding list. We completed the mussel, *Paramuricea Clavata* coral and mayfly genomes. The insights we have gleaned are multi-faceted and help to explain the evolution of wings and their relationship with the development of gills, the effects of climate change on endangered species and how to deal with highly polymorphic genomes.

3D Genomics and the Genome in Action: Great progress was made this year in the analysis of the genome as it is packed in the nucleus. We used high-resolution imaging to ascertain which parts of chromosomes interact with each other to perform a function. This tells us how the genome is behaving in different cells at different times and the dynamics of transitions of states. We determined the difference in the behaviour of the nucleus of a healthy cell and the corresponding diseased cell, which is particularly relevant to cancer, which is a disease of the genome.

Personalised Medicine: We have been developing tools that facilitate the identification of gene variants and mutations that are responsible for disease for many years now. This year, we were awarded funding to support the implementation of genomic analysis in Spain through the IMPACT Project by the Instituto de Salud Carlos III. This project affords us the opportunity to branch out in our clinical sequencing expertise, genomic analysis tools and accreditation framework to cover the whole of Spain.

EUROPEAN GENOME-PHENOME ARCHIVE (EGA)

Team Leader: **Arcadi Navarro**

The European Genome-phenome Archive (EGA) is a repository for permanent archiving and sharing of personally identifiable genetic and phenotypic human data resulting from biomedical studies. Jointly managed by the European Bioinformatics Institute (EMBL-EBI, Cambridge, UK) and the Centre for Genomic Regulation in Barcelona, the EGA provides an invaluable service to the biomedical research community in Catalonia, Europe and the rest of the world. The EGA Team at the CRG is involved in several partnerships and consortia in which it contributes to ambitious international projects in a wide range of fields. In addition, the team works strategically in collaboration with the Barcelona Supercomputing Center (BSC-CNS). In the course of 2020, three new collaborative projects were awarded to the team, complementing the twelve ongoing ones. Four new team members were recruited to the multidisciplinary team, which now numbers seventeen17. Together they have achieved great results in the improvement of the Beacon Discovery platform for human genomic data and the development of Viral Beacon for the discovery of SARS-CoV-2 genomic variants. The EGA-CRG Team is also co-leading the foundation of the Federated EGA Network planned for 2021.

New hirings

Two outstanding early-career scientists set up their new research groups at the CRG in 2020.

RENÉE BEEKMAN

After taking her PhD in Medicine at Erasmus University in Rotterdam, the Netherlands, in 2013 Renée joined the Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), in Barcelona, Spain, where she stayed until 2019, first as a Rubicon Postdoctoral Fellow and then as a Marie Curie Postdoctoral Fellow, and finally as a 'la Caixa' Junior Leader Fellow. In January 2020, she joined the CRG's Gene Regulation, Stem Cells and Cancer Programme as a junior group leader and 'la Caixa' Junior Leader Fellow. She is also affiliated to the Centro Nacional de Análisis Genómico (CNAG-CRG) and the department of Oncology and Haematology at IDIBAPS, both of them in Barcelona.

Renée is an MD PhD who has produced ground-breaking postdoctoral work in epigenetic regulation in leukaemia and lymphomas with Elias Campo and Iñaki Martín-Subero at IDIBAPS. Her group seeks to shed light

upon how malignant cells arise in healthy individuals by creating a better understanding of early epigenetic events that contribute to tumorigenesis.

All tumours originate from a normal cell which, at a given moment, acquires tumour-initiating genetic events, such as translocations and somatic mutations affecting key proto-oncogenes or tumour suppressor genes. These genetic hits turn normal cells into pre-malignant cells, but do not lead to immediate tumour formation. This requires secondary genetic events, as well as epigenetic hits, also known as epimutations. Her objective is to create a better understanding of how epimutations arise and how they contribute to tumorigenesis. She will do this in the context of non-Hodgkin lymphomas, such as mantle cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma and Burkitt lymphoma.

She is also interested in the heterogeneity of oncogenic events in healthy individuals and in pre-malignant cells *in vitro* and *in vivo* using cutting-edge single-cell technologies. A further objective of hers is to define cell-intrinsic mechanisms, such as enhancer activation and 3D chromatin interactions, that influence the heterogeneity observed. Overall, she seeks to create new insights into the source of epimutations with the ultimate goal of achieving a better understanding of the complex process of tumour formation.

LARS VELTEN

Lars obtained his PhD in Genomics at the European Molecular Biology Laboratory in Heidelberg, Germany, where he stayed for an additional three-year period as a research staff scientist. In January 2020, he joined the CRG's Bioinformatics and Genomics Programme as a junior group leader.

A better understanding of stem cell biology is key to both regenerative medicine and oncology. While adult stem cells fuel healthy tissue regeneration by indefinite self-renewal and multilineage differentiation, the accumulation of mutations specifically in stem cells is often required for cancer formation. Tissue regeneration and oncogenesis are therefore two sides of the same coin.

Lar's lab uses single-cell genomics, high-throughput genetic screens and artificial intelligence to study the regulation of differentiation programmes in haematopoietic and leukemic stem cells. In the past, they created single-cell atlases of healthy and leukemic bone marrow, developed new tools for high-throughput genetic screens in single cells and worked on new approaches to lineage tracing in human stem cell systems. His lab's long-term goal is to transform stem cell research into a data science discipline and thereby enable a quantitative, predictive understanding of stem cell biology.

The lab is pursuing two main lines of research. Working in the healthy haematopoietic system, they use high-throughput genetic screens to unravel the logic of gene regulatory elements. In acute myeloid leukaemia, they attempt to identify cancer stem cell-specific drug targets by combining single-cell transcriptomics and lineage tracing. They are passionate about integrating experimental and computational approaches into their work.

Awards

José Luis Gómez Skarmeta Award to the Scientific Excellence in Developmental Biology 2020

Manuel Irimia

King Jaume I Awards 2020

Miguel Beato

Alexander von Humboldt - J.C. Mutis Research Award

Vivek Malhotra

University-Society Award, Social Council of the Autonomous University of Barcelona

Mara Diersen

FIDEM Award: Professional Career

Mara Diersen

Special Mention: Professional Career, XX Businesswoman Award, Businesswomen Association of Cantabria

Mara Diersen

ERC grantees at CRG

STARTING GRANTS

Manuel Irimia

Nicholas Stroustrup

Elvan Böke

Sara Sdelci

Arnau Sebé-Pedrós

ADVANCED GRANTS


Jorge Ferrer


Juan Valcárcel


Luis Serrano


Ben Lehner (*)

CONSOLIDATOR GRANTS


Ben Lehner


Manuel Irimia (*)

PROOF OF CONCEPT GRANTS


Miguel Beato


Luis Serrano

SYNERGY GRANTS


Miguel Beato


Ivo Gut


Thomas Graf


Holger Heyn


Guillaume Filion


Vivek Malhotra (*)


Marc A. Marti-Renom


Thomas Surrey (*)

(*) Awarded in 2020, grant starting in 2021

Facts & figures (*)

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

Publications

303
Total Publications

82.2%
Open Access Publications

78.1%
1st Quartile Publications

9.9
Average Impact Factor

Funding (M€)

TOTAL BUDGET
(Operations and investments)

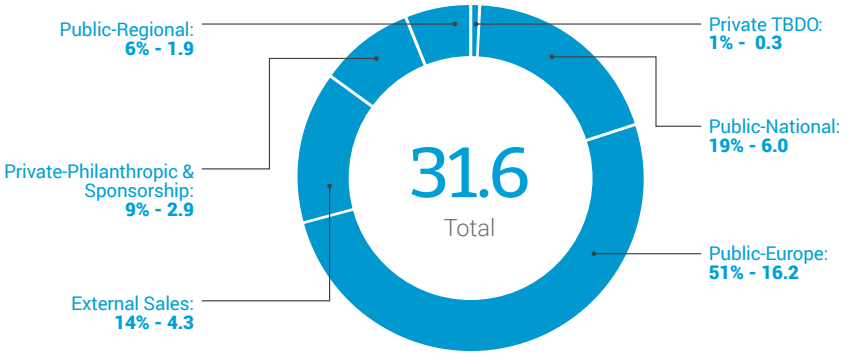
43.3
Total

35.2
CRG

8.1
CNAG-CRG

ATTRACTED FUNDS

The graph includes competitive funds obtained during 2020 and pending for final notice of award or grant agreement as of 31/12/2020.



Projects

151 Total Ongoing Research Projects and Networks

14 are Ongoing ERC Projects

8 are Ongoing EU Coordinated Projects

31 are Other Ongoing H2020 Research Projects and Networks

16 are International Ongoing Research Projects (non-EC)

27 Total Ongoing Postdoctoral Fellowships

8 Total Ongoing EU Coordinated Projects

MYCOSYNVAC

cell viewer

DivIDE

ORION open science

CHROMDESIGN

EASI Genomics

PROTrEIN

International Nucleome Consortium (INC)

Staff

479.01*
Total

* FTE, full-time equivalent

410
CRG

86
CNAG-CRG

41
Nationalities represented

57%
Group Leaders+Heads of Unit

64%
Postdoctoral Researchers

60%
PhD Students

60%
Total Research Staff

RESEARCH STAFF

295.85*
Total

284
CRG

22
CNAG-CRG

* FTE, full-time equivalent

SCIENTIFIC SERVICES

98.94 *
Total

42
CRG

60
CNAG-CRG

* FTE, full-time equivalent

ADMINISTRATION & SCIENTIFIC SUPPORT

71.62*
Total

69
CRG

4
CNAG-CRG

* FTE, full-time equivalent

RESEARCH GROUPS *

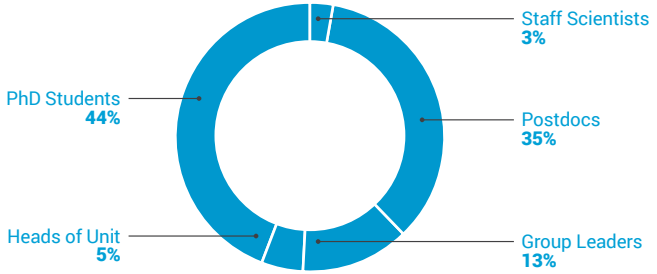
31
Total

28
CRG

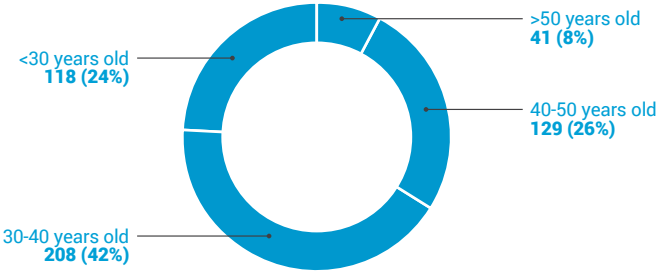
3
CNAG-CRG

* by 31st Dec 2020

RESEARCH CATEGORIES



AGE



Gender

% FEMALE BY PROFESSIONAL CATEGORIES

FEMALE INVITED SPEAKERS

43%

(2019 39%)

APPLICANTS TO OUR SELECTION PROCESSES

WOMEN	MEN
1,720	2,136
45%	55%

SELECTED / HIRED CANDIDATES

WOMEN	MEN
53	37
59%	41%

Events

2
International Events

79
High-profile Seminars

Advanced training

THESES

20

PhD Theses defended

COURSES @CRG

2

International courses

63

Participants

SCIENTIFIC & TECHNOLOGY COURSES

22

Internal courses

585

Participants

TRANSFERABLE SKILLS & CAREER DEVELOPMENT TRAININGS

9

Internal courses

180

Participants

Technology & business development

13

Ongoing Valorisation Projects

17

Active Patent Families

17

Invention Disclosures

8

Services, Scientific Collaborations and Licenses Agreements

19

Other Agreements

Communications, public engagement & science education

Media Relations

960	286	25	611	26	12
Media Appearances	Written Media	Radio	Online Media	TV	Blogs

Social Media (by 31st Dec 2020)

TWITTER FOLLOWERS

16,356
@CRGenomica

3,154
@cnag_eu

FACEBOOK

4,143
Likes

4,480
Followers

LINKEDIN FOLLOWERS

15,675
CRG

3,431
CNAG-CRG

YOUTUBE

222,322
Channel views

1,487
Subscribers

Public Engagement and Science Education

79

Activities Organised

(17 different categories of activities)

26,162

Audience Reached

2,137

Schools and Students

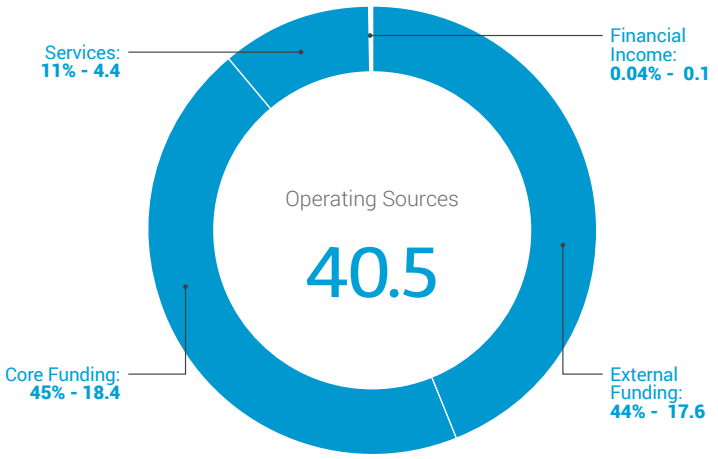
24,025

General Public

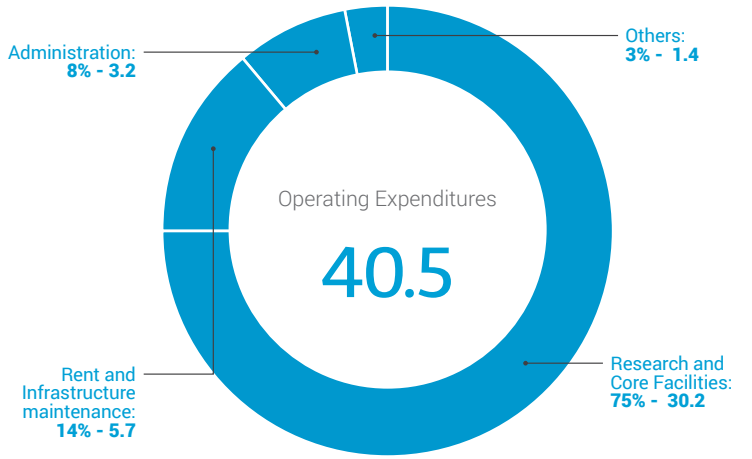
Financial Report

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 Union

erc 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

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***

Private Funders

"LA CAIXA" FOUNDATION

The "la Caixa" 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 8 INPhiNIT PhD grants and 3 major grants from the Health Research Call (F. Gebauer, M.P. Cosma and L. Serrano). In 2020, we were awarded 1 INPhiNIT PhD grant (P. Cosma's lab), 1 Caixa Impulse grant (O. Lao) and two major grants from the Health Research Call (L. Di Croce, together with M.A. Marti-Renom, and M. Irimia).

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 second chair holder for a 3-year term.

FUNDACIÓN RAMÓN ARECES

The Ramón Areces Foundation provided four-year funding to 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 science career. Key activities include scientific summer stays at the CRG within the Joves i Ciència programme, at which students participate 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 Jerome 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-Jerome Lejeune Award in 2010. They also supported 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) and a new project by Mara Dierssen, entitled 'EpiGenetic Change Generator in Down Syndrome (2017-2019)'. In 2020, they awarded

two new grants: one to Susana de la Luna for her project 'Organization of the DYRK1A interactome through docking domains: searching for novel targeting approaches'; and one to Laura Batlle, for her project 'Molecular analysis of the non-cell autonomous effects in Down syndrome cortex using mouse ESC-derived brain organoids', which will run until 2022.

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. This fellowship ended in 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 for which as yet there is no cure. We intend to test cell fusion-mediated reprogramming as therapy in rd10 mice, an RP mouse model, with the ultimate goal of regenerating photoreceptors and achieving functional rescue of vision. 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.

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.

CHAN ZUCKERBERG INITIATIVE (SILICON VALLEY COMMUNITY FOUNDATION)

The Chan Zuckerberg Initiative (CZI), an advised fund of the Silicon Valley Community Foundation, awarded two grants to Roderic Guigó and Holger Heyn 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 Guigó is entitled 'Deciphering intra- and inter-individual variation at single cell resolution'; and the project awarded to Heyn is entitled 'Developing tools and standards for integration of multi-dimensional HCA data' and will run until June 2022.

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 ended in 2020. In 2019, the junior group leader Manuel Irimia was awarded a grant under the EFSD/Lilly European Diabetes Research Programme for his project 'The functional impact of a novel program of microexons in beta cell function and diabetes', which will run until the end of 2021.

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' (2019-2021). The objective of the project is to develop a new genomic methodology to overcome the current technical limitations that hamper 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).

EUROPEAN HEMATOLOGY ASSOCIATION (EHA)

In the 2019 EHA Research Grants call, the project 'Occurrence Of Sporadic Oncogene Activation In Normal B Cells And Its Implications For Lymphomagenesis' by junior researcher Renée Beekman was awarded an Advanced Research Grant. The project started in January 2020 and will end in December 2021.

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