Annual Report

2021

EXCELENCIA SEVERO OCHOA

CRG Centre for Genomic Regulation

Institució CERCA Centres de Recerca de Catalunya

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Foreword

Luis Serrano
DIRECTOR

We look back on a 2021 that was significantly better than the unprecedented year that came before it, though one that still challenged us in many different ways. The coronavirus pandemic offered some respite, but restrictions for travelling and holding in-person meetings held us back from a true return to normality. Despite this, our people showed incredible team spirit and came back to the labs with an unwavering dedication to safety measures. Breaking isolation and re-establishing human contact among our people fostered a sense of cohesion that is unique to the CRG's culture.

On the other hand, one of the consequences caused by the pandemic is that a lot of people have reflected about their professional lives and decided to make changes in their careers. This worldwide trend has not left the CRG unscathed. Several key people in the administration and research support team have decided to move to other exciting career opportunities. One of the main losses was Bruna Vives, our Administrative Director, who decided to step down and take some time to plan for a new step ahead in her professional career. CRG founder and former Director, Miguel Beato, has also retired and become the first Emeritus Group Leader of the institute. Miguel is an excellent scientist who has been key for the creation of the CRG and for its international visibility. I would like to extend my most heartfelt thanks to Miguel for his invaluable dedication to the institute over the last 20 years.

Once again, 2021 has been an excellent year for the advancement of science and attraction of funds. The CRG has some of the world's leading experts, many of which have been awarded several internationally-renowned and competitive grants from the European Research Council and the recently created European Innovation Council, one of which has been to support the creation of a new company. The CRG has also been awarded the Severo Ochoa Centre of Excellence grant for a record third time, a fabulous achievement that recognises the CRG as a bulwark of cutting-edge research. None of this would have been possible without the work of the great scientists and support staff we have at the institute.

Finally, 2021 also saw us setting up a new scientific advisory board that will visit the CRG every year and serve exclusively as an advisory body, rather than an evaluation body.

Overall, throughout these unprecedented times, the essence of the CRG has remained steadfast. We expand the frontiers of knowledge for the benefit of people, society and the environment. We also generate new companies and are a motor of growth that provides to the economic wellbeing of citizens. I hope that, reading through the following pages you will be able to appreciate the achievements and merits of our wonderful institute, which I am immensely proud of.

A look back at the year

We look back on a 2021 that challenged us in a different way than 2020. The pandemic, through the different variants and subsequent waves, conditioned life at the CRG and worldwide. Restrictions and safety measures were constantly changing, requiring us to adapt to the incessant whims and evolution of the indicators, affecting daily activity.

But there was also hope and progress. It was the year of mass vaccination campaigns, which allowed us to start seeing the light at the end of the tunnel. People were able to return to the lab and carry on with their professional lives. On the other hand, most non-experimental and administration staff continued working from home. This situation started changing during the second half of the year, with the CRG adopting a hybrid onsite-remote system. This is a new model that seems to be here to stay. It has proved to be very efficient, allowing best of both worlds; much-needed face-to-face relationships with colleagues and good work-life balance.

We kicked-off our brand new Strategic Plan 2021-2024, focused on quantitative biology, where biomedical research is being transformed from a descriptive discipline into one that is quantitative, predictable and actionable. Thanks to the third Severo Ochoa Centre of Excellence grant awarded to the CRG in July, we will be able to optimally deploy the necessary resources to address challenging questions in biology and medicine, helping keep the institute as an international reference in genomics and its applications to biomedicine and biotechnology. This is a fabulous achievement and recognition for the CRG and attests for the great scientists and support staff we have at the institute.

SCIENCE & TECHNOLOGY

The CRG has produced excellent results and our research studies published in top-tier journals. Prominent examples include the delineation of a comprehensive single-cell map of the human bone marrow (Velten); the findings that reveal that newly formed embryos clear dying cells to maximise their chances of survival, seen as the earliest display of an innate immune response found in vertebrate animals to date (Ruprecht); the development of a single cell tumour immune atlas that can be used for precision oncology (Heyn); the creation of the first 'living medicine' to treat antibiotic-resistant bacteria growing on the surfaces of medical implants (Serrano); new findings about how the process of DNA being copied into RNA indirectly shapes the architecture of the genome (Cosma); the development of a new method to measure the abundance of RNA modifications in much finer detail than previously possible (Novoa); and the development of the first atlas of all of the different types of cells in *Stylophora pistillata*, a reef-building stony coral, that will aid conservation efforts to protect coral reef ecosystems (Sebé-Pedrós).

2021 was also a great year for attracting competitive funds. Thomas Surrey and Vivek Malhotra were awarded ERC Synergy grants, to unlock secrets of cell division and to test 'liquid crystal' hypothesis, respectively. Junior group leaders Renee Beekman and Eva Novoa, obtained ERC Starting grants to understand how chromosome translocations

impact lymphomagenesis, and to develop methods to detect RNA modifications and determine their relevance in transgenerational inheritance, respectively. Luis Serrano was awarded the third ERC Advanced grant in a row to engineer a lung bacterium to treat lung diseases such as pulmonary fibrosis. Leveraging the transfer of basic knowledge to innovation, Juan Valcárcel obtained the European Innovation Council (EIC) grant 'TAONAs-LUAD' to develop a company based on RNA therapeutics, and Pia Cosma obtained the EIC grant 'EcaBox' to build a box where a human eye could be maintained for an extended time period. Marc A. Marti-Renom, received a US National Human Genome Research Institute (NHGRI) grant to set up a 3D-Genome Imaging Center in collaboration with Harvard Medical School, Brown University and Baylor College of Medicine.

The EGA-CRG Team have been co-leading the foundation of the Federated EGA Network, which was essentially finalised in 2021. Together the team achieved great results in the finalisation of the Beacon Discovery specification for human genomic data, now under review at the Global Alliance in Health and Genomics, and the improvement of Viral Beacon for the discovery of SARSCoV-2 genomic variants. As part of the ERGA (European Reference Genome Atlas) CNAG-CRG was included in Biodiversity Genomics Europe, a large-scale European project on biodiversity, as one of the five centres taking care of the sequencing, assembly and annotation. This year also saw the launch of IMPaCT, a new infrastructure for precision medicine associated to science and technology in Spain and funded by the Instituto de Salud Carlos III (Ferrer, Gut).

In terms of innovation and entrepreneurship, in July, the CRG received the 2020 National Innovation Award for the Creation of a Science-Based Company, a new category within the National research Awards of Catalonia The Government of Catalonia and the Catalan Foundation for Research and Innovation (FCRI) recognised the CRG for creating Pulmobiotics S.L., a preclinical company that uses synthetic biology to develop new treatments and vaccines for various types of lung diseases. The CRG also signed an agreement with Chemotargets to accelerate the development of new targeted therapies that responds to unmet clinical needs in different fields including cancer. CRG and PerkinElmer's SIRION Biotech entered in to an agreement to develop new generation adeno-associated virus (AAV) vectors for type 1 and type 2 diabetes gene therapy. Finally, two researchers at the CRG (Montero) and CNAG-CRG (Matalonga), and one CRG alumni (Lluch), were selected to take part in the Academy for Women Entrepreneurs, a US State Department training programme organised by Foment del Treball, the Government of Aragon and the US Consulate in Barcelona.

STRATEGIC PRIORITIES

As a part of our commitment towards open science, CRG open access publications in 2021 surpassed 85%. The H2020 ORION Open Science project came to an end in September. The project promoted institutional changes in research funding and performing organisations to make them more receptive to societal needs and to embrace the principles of open science. A two-day conference celebrated the end of the project, wrapping up all of the activities, insights and opinions from a fruitful 4.5-year period. The conference provided an excellent opportunity to review ORION's achievements and share key lessons and experiences to help others to put open science into practice too.

Within the ORION project, we publicly presented and disseminated the results of the public dialogue held back in 2020, which aimed to understand the public's priorities for continuing to carry out fundamental research while simultaneously pursuing applications in genomics and molecular biology for human health, and the ethics of funding of these. Our new citizen science project, also developed in the framework of ORION, Genigma, is a smartphone game co-created with citizens to assemble genomes in 3D in a crowdsourced manner. Genigma has resulted in many activities, playtests and co-creation events. The game will help researchers uncovering genomic alterations in cancer cell lines.

Also within the framework of open science and citizen science, the European project, TIME4CS started in January. The CRG is one of the partners and the aim of the project is supporting sustainable institutional changes to promote citizen science in science and technology. During the year, a roadmap and a series of grounding actions have been designed, so the CRG can achieve the objectives of the project, which will run until the end of 2023.

The Gender Balance Committee continued to develop the actions of our new Equality, Diversity and Inclusion plan 2020-2023, which in 2021 included an awareness campaign very welcomed by the CRG community, to disseminate the protocol against any form of harassment,developed the year before. Also, we launched a second awareness campaign to disseminate the new guidelines for gender-inclusive language. Thanks to our collective efforts to push for gender equality over the past years, in 2021, 53% of junior group leaders at the CRG are women.

As part of the EU-LIFE alliance, we continued to stimulate excellent research through the development of policies to strengthen research & innovation in Europe, with a focus on the new European Research Area. In 2021, the alliance published several reports, hands-on guides, articles and policy briefs on a variety of topics such as research data management, support to postdoctoral careers, management models for research infrastructures (core facilities) and citizen science. Together with other members of EU-LIFE, the CRG is leading EMERALD (H2020 Marie Sklodowska-Curie grant), the first European-wide PhD programme for medical doctors. Through our partnership with EU-LIFE, CRG's members of staff had the chance to engage in capacity building workshops on topics ranging from developing novel narratives of fundamental research, tech transfer pitching and ERC Masterclasses to trainings on the role of active by-standers and institutional anti-bullying and harassment policies.

TALENT

2021 has seen many changes at the staff level, with new scientists arriving and some other key people leaving the CRG. We welcomed a new junior PI, Amelie Baud ('la Caixa' Junior Leader Fellow), from the European Bioinformatics Institute (EMBL-EBI), in Cambridge, UK, who joined the Systems Biology Programme; and the new Head of the Advanced Microscopy Unit, Nadia Halidi, from the University of Oxford, also in the UK, who joined the Core Technologies Programme.

The Head of International and Scientific Affairs, Michela Bertero, moved to IDIBAPS as Strategy Director; Imma Falero, in charge of the Academic Office, became the Coordinator of the Graduates Office at VHIO; and the Administrative Director of the institute, Bruna Vives, decided to step down and take some time to plan for a new step ahead in her professional career. In 2021, we have also seen the retirement of the CRG founder and former Director, Miguel Beato, who became the first Emeritus Group Leader of the institute. Junior Principal Investigator Sebastian Maurer left the institute for a new position as the Head of Applications at Eppendorf SE in Germany.

While this is a significant loss for the CRG, it shows the value of the institute as a place to give people the opportunity to develop their career and then move to other places at positions of relevance. It also shows the attractiveness of the CRG, as we were able to replace these key people by top new personnel in a very short period of time.

We recruited Joan Vives, who will join the CRG as Administrative Director in early 2022; Joaquim Calbó and Natalia Dave were promoted as Head and Deputy Head of International and Scientific Affairs, respectively; and Damjana Kastelic was also promoted as Head of Training and Academic Office.

The whole CRG community continued to work under special circumstances during 2021 due to the pandemic. However, and thanks to the measures and resources established in 2020, everything ran smoothly and we could get back to some kind of normality during the second half of the year. Our warmest thanks goes to all the CRG community for their continued support and excellent work during this exceptional period.

01

What does a blood cell wear to work?

Studying the unique 'uniform' worn by different types of blood cells helps researchers understand how they work.

Knowing how blood cells are produced, and what happens when this process goes wrong, is important for studying, diagnosing and treating blood disorders and cancers such as leukaemia and lymphoma. But with over 40 different stages and types of blood cell in the human body, each with a very specific job, figuring out exactly which cell is misbehaving is a tricky task.

One big problem is that the most common technique that researchers use to study blood cells, known as flow cytometry, isn't able to distinguish all these different types of cells due to a lack of distinctive markers.

Just as we wear different styles of clothes or uniforms as we grow up and move into various jobs - from a baby onesie to jeans, a business suit or a firefighters' protective gear - blood cells also 'wear' a unique combination of molecular surface markers that can precisely identify their stage of maturity and their particular role in the body.

"The limitation with flow cytometry now is that it only measures a handful of markers," explains Dr Lars Velten, group Leader in the Bioinformatics and Genomics program at the Centre for Genomic Regulation. "But because different blood cell types can carry some of the same markers, it makes it almost impossible to separate them all out."

For example, imagine a businesswoman and a firefighter, who both wear dark blue trousers at work. At first glance, this similarity might suggest they do the same job. It's only by taking a closer look at what else they're wearing - such as their jackets - that the difference in their function becomes obvious.

Lars, his collaborator Dr Simon Haas and their teams carried out an in-depth analysis of more than 100,000 individual cells, precisely mapping what each cell type 'wears' as it matures and specialises into a particular job in the body.

"We now have a much clearer picture of how this repertoire of surface markers changes as blood cells form and specialise, providing a more granular set of characteristics to look for," he says. These new marker profiles form a highly precise 'identity guide' for analysing blood samples.

"Our findings can be immediately applied in research and clinics using the usual, cheap flow cytometry technology but the results will be faster and more accurate than ever," Lars explains.

"Soon I expect to see flow cytometry combined with AI to automatically home in on which exact cell type is driving a blood disorder, at what stage of development it went wrong and how best to treat it."

REFERENCE WORK

Triana, S., Vonficht, D., Jopp-Saile, L. et al. "*Single-cell proteo-genomic reference maps of the hematopoietic system enable the purification and massive profiling of precisely defined cell states.*" Nat Immunol 22: 1577–1589 (2021). doi: 10.1038/s41590-021-01059-0

Nature's cleaners keep embryos tidy

02

Embryonic epithelial cells step into the role of 'cleaners', taking away dead and dying cells to ensure that development goes smoothly.

Growing a new life, from a single cell to many millions, is a messy business. Cells are dividing fast with lots of opportunities for things to go wrong, and any damaged or faulty cells need to be cleared away so they don't interfere with the normal processes of development. But, until now, how this happened was a complete mystery.

"We can't study these processes in human embryos, so we use zebrafish as a stand-in," explains Dr Verena Ruprecht, group Leader in the Cell and Developmental Biology program at the Centre for Genomic Regulation. "They're easy to grow in the lab and we can watch them under the microscope as development unfolds."

While studying what happens to cell debris in early zebrafish embryos, Verena and her colleague Dr Esteban Hoijman made an unexpected discovery: dead cells were moving around. Looking closer, they discovered that epithelial cells, which make up the outer layer of the embryo, were responsible for this motion.

Fascinatingly, they saw that these epithelial 'cleaners' were working in two different ways. Either they engulfed nearby dead or dying cells, like picking up litter and putting it in a trash bag, or extended a kind of cellular 'broom' to sweep dead cells away for another cleaner cell to collect - a behaviour that has never been seen before in either embryonic or adult tissues.

"This makes sense as it allows the cells to work efficiently together to clean up," explains Verena. "Epithelial cells are stuck together to give structure to the outer layer of the embryo and can't move around in the same way that immune

cells would do in adult tissue, so they have to work together to push debris to a place where another cell can engulf it."

Cellular 'cleaners' are an important part of the immune system in adult tissues, but this is the first time that such a response has been seen in early embryos. And there's a lot more that Verena and her team still need to find out about how they work to ensure that embryos develop properly.

"The question of how embryos can develop despite cellular errors led us to an exciting discovery about the immune response in the earliest stages of life, and now we have dozens more questions to investigate," says Verena. "For example, how do epithelial cells choose whether to pick up or to sweep away a dead cell? And how do they know when their internal 'trash bag' is full?"

"Being able to see this happening in living embryos gives us a window into this incredibly dynamic process, and will help us to understand what happens when development goes wrong and pregnancies fail."

REFERENCE WORK

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To save a species, start with a single cell

03

Analysing individual coral cells will help to protect reefs against the impact of climate change in the future.

Vibrant coral reefs house the highest diversity of any ecosystem on the planet. But reefs around the world are in peril due to the effects of climate change and ocean acidification.

Every reef is made up of millions of interconnected individual coral cells, so in order to save these fragile ecosystems, we need to understand how they develop and grow. And because corals consist of many different cell types and developmental stages, this isn't a simple task.

Dr Arnau Sebé-Pedrós, group leader in the Systems Biology program at the Centre for Genomic Regulation (CRG), recently applied cutting-edge techniques to study the genes at work in stony coral – a reef-building coral found in oceans around the world.

Working with collaborators at the University of Haifa and the Weizmann Institute of Science in Israel, the research team collected living corals from the Gulf of Eilat on the northern edge of the Red Sea. They were then transported back to the CRG for analysis.

Just as each candy in a box of chocolates has its own distinctive taste, each cell type within a coral has its own unique pattern of gene activity. Simply looking at all the genes that are active in a large lump of coral won't tell you anything about the characteristics of individual cells, the same way that melting, mixing and tasting a whole box of chocolates misses all the unique flavours.

Single-cell transcriptomics – a technology that measures gene activity within individual cells - overcomes this problem.

"With single cell-transcriptomics, we can see how different groups of genes work together in specific contexts in time and space, in different coral cell types, tissues, and during development," Arnau explains.

Using this approach, the team identified the gene activity patterns underlying 40 unique cell types in stony coral, including specialised immune cells and crucial skeleton-building cells.

They also discovered the genes that are involved in the coral's symbiotic relationship with algae that live inside their cells and provide vital nutrients, as well as giving corals their characteristic colours. This has important implications for understanding coral bleaching, which happens when corals get too warm and expel the algae.

This detailed coral cell genetic atlas created by Arnau and his team will shed light on how such complex organisms have evolved over time, as well as helping to protect them into the future. And the implications of this research extend far beyond corals themselves.

"Corals are the equivalent of the trees in a rainforest. If the corals die, the whole ecosystem collapses – the whole reef," Arnau warns. "Understanding how corals respond to stress will be crucial in developing interventions to increase their resilience against environmental threats."

REFERENCE WORK

Levy, S., Elek, A., Grau-Bové, X. et al. *"A stony coral cell atlas illuminates the molecular and cellular basis of coral symbiosis, calcification, and immunity."* Cell 184: 2973-2987 (2021). doi: 10.1016/j.cell.2021.04.005

Doing the twist sends DNA loopy

The act of reading genes helps to keep DNA organised inside cells.

Every human cell contains more than two metres of long, string-like strands of DNA - the genetic instructions for life - tightly packed inside a structure called the nucleus. All this DNA has to be carefully organised in order for the right genes to be read at the right time, keeping cells healthy and functioning properly.

This organisational task falls to a molecule called cohesin. It acts like an elastic band, gathering the DNA 'string' into open loops that enable genes to be accessed and read. Researchers have known for a while that cohesin molecules move around on DNA, pushing out loops as they go. But they also suspected that the gene-reading DNA machinery, RNA polymerase, may be playing a role in creating loops too.

To find out what's going on, Dr Maria Pia Cosma and her colleagues in the lab, part of the Gene Regulation, Stem Cells and Cancer Programme at the Centre for Genomic Regulation, have been using incredibly high-powered microscopes to spy on DNA, cohesin and RNA polymerase inside human cells.

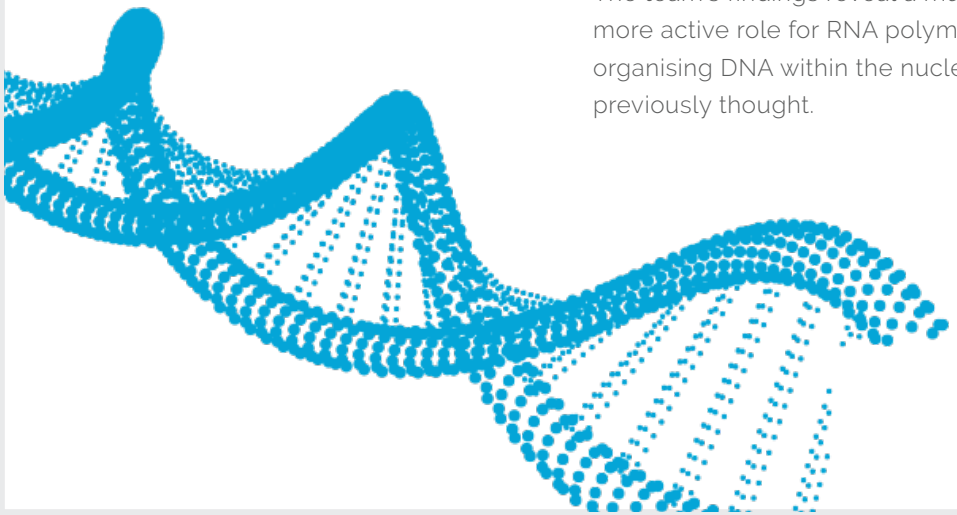
"We're using a technique called super-resolution microscopy that allows us to see things that are just 20 nanometres apart, so we can directly visualise DNA and the molecules that interact with it," Pia says. "Then by using a combination of genetic mutations and drugs that alter their function, we can start to tease apart their roles in organising the genome."

The team found that when there is a lot of cohesin around, DNA is arranged into many long, open loops. But when they blocked RNA polymerase from working, all the loops collapsed and compacted down. This proves that cohesin by itself isn't enough to maintain these structures, and that the act of gene reading by RNA polymerase (known as transcription) is playing a vital role in opening up DNA loops.

"DNA is a twisted double helix structure that has to be unwound as RNA polymerase moves along it," she explains. "This creates overtwisting or supercoiling further along the DNA strand, generating the rapid wave of force needed to push cohesin around and form loops."

The team's findings reveal a much more active role for RNA polymerase in organising DNA within the nucleus than previously thought.

"We've shown that the act of transcription itself is an important regulator of DNA organisation and helps to maintain patterns of gene activity in different cell types," Pia says. "We've known about DNA and genes for more than 50 years, but there's still so much more we need to learn about how the three-dimensional organisation within the nucleus affects gene activity, and how failures to keep genes organised properly can lead to disease."



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Neguembor, M.V., Martin, L., Castells-García, Á., et al. "*Transcription-mediated supercoiling regulates genome folding and loop formation.*" Molecular Cell, 81: 3065-3081 (2021). doi: 10.1016/j.molcel.2021.06.009

Counting all the 'colours' of the genetic code

A new method reveals the complexity of the molecular messages within cells.

Most people have heard of DNA - the twisted genetic code found inside every cell, which contains all the instructions for life. RNA, a related molecule that is produced whenever a gene is activated, may be less famous but it is no less important.

For a long time, researchers believed that RNA was made up of four chemical building blocks or bases, known as adenine, cytosine, uracil, and guanine. These are strung together in endlessly varied combinations, like many different patterned necklaces made from four colours of beads, conveying the information that cells need to build proteins and do other jobs.

We now know that the bases in RNA can be chemically modified, which affects how they function. Instead of four plain colours, the beads in these molecular necklaces come in many different shades and shapes.

To find out more about RNA modifications, Dr Eva Novoa and her team, part of in the Gene Regulation, Stem Cells and Cancer Programme at the Centre for Genomic Regulation, are using a technology called nanopore sequencing, which reads the order of bases in RNA strands by pulling them one at a time through a tiny hole. Each base causes a distinctive 'blip' as it passes through, enabling Eva and her team to reconstruct the sequence. But then they noticed something strange.

"We were seeing all these different kinds of errors in our data, and realised that each of them corresponded to a base that had been modified in some way," Eva explains. "We were able to develop a method that could accurately interpret and predict their presence based on these characteristic errors, and used it to discover entirely new types of modified RNA bases in yeast cells."

However, it's not enough to know that a particular type of RNA modification is present in a cell - we need more detail about exactly when and where these modifications happen in order to understand what they're doing. Going further, Eva and her colleagues developed their analysis to be able to show exactly which bases in any RNA strand were modified, and calculate how the proportion of modified RNAs changes when cells are grown in different conditions.

"Although we don't yet know how all these modifications affect the function of RNA, we can now say exactly how many and which specific ones change, to get an idea of what's actually going on functionally as cells respond to changes around them," she says. "For so long we just haven't been able to see all these modifications because we lacked the tools, but it's like we have put on the right glasses and we can suddenly see all the amazing colours and complexity."

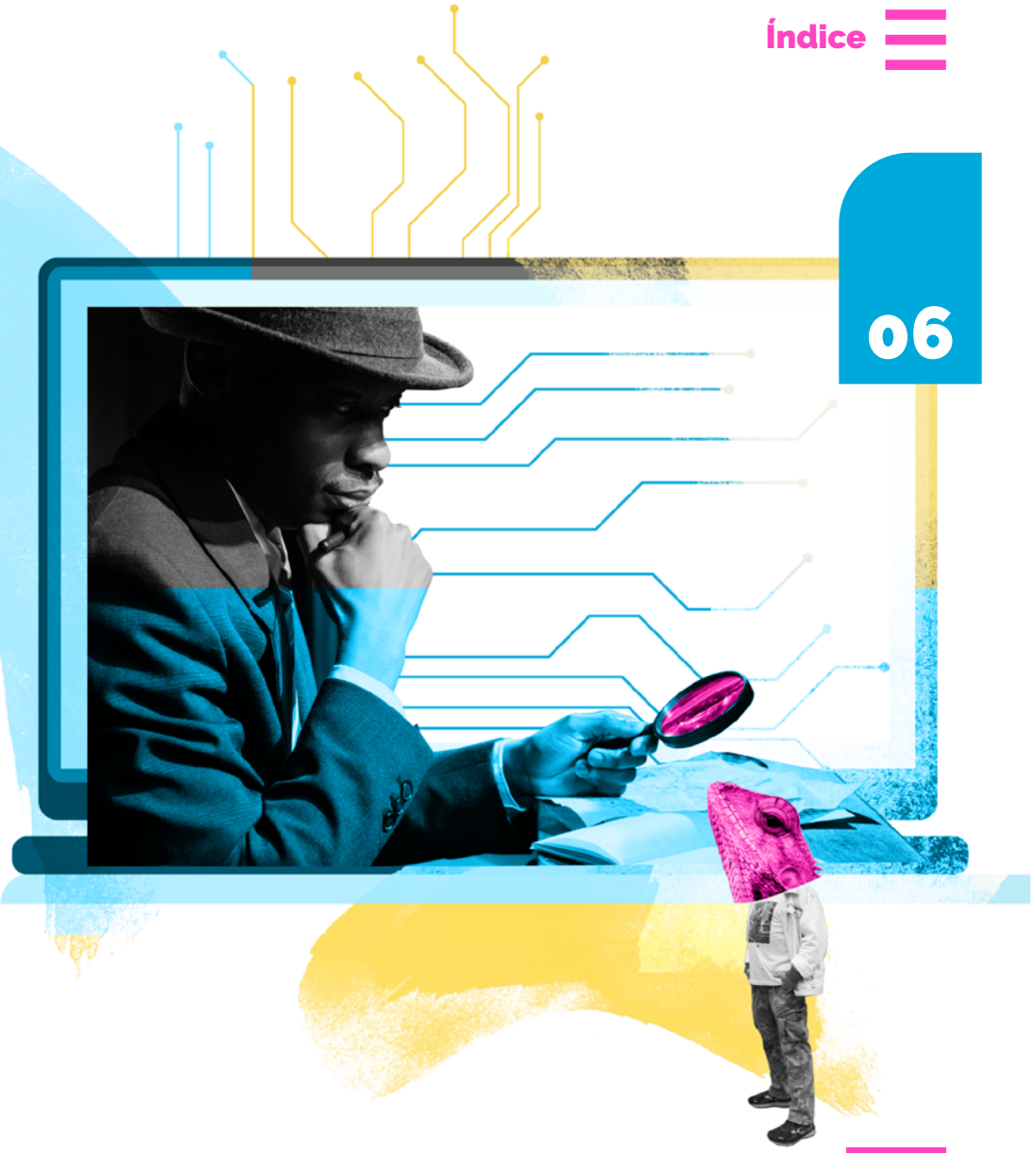
REFERENCE WORK

Begik, O., Lucas, M.C., Pryszcz, L.P. et al. "*Quantitative profiling of pseudouridylation dynamics in native RNAs with nanopore sequencing.*" Nat Biotechnol 39: 1278–1291 (2021). doi: 10.1038/s41587-021-00915-6

The rare disease detective

06

A clever computer platform pieces together clues to help doctors diagnose rare diseases.



As the name suggests, rare diseases don't happen very often. This results in a lack of information and research about the genetic alterations that are responsible for rare diseases, and it can take many years before a patient gets a diagnosis for their condition.

"Although the official definition of a rare disease is something affecting one in 2,000 people, many are much rarer than that - maybe one person in a whole country," says Dr Sergi Beltran, co-leader of Solve-RD data analysis and Head of the Bioinformatics Unit at Centro Nacional de Análisis Genómico (CNAG-CRG), part of the Centre for Genomic Regulation.

"We wanted to find a way to securely share data and expertise between the doctors treating these patients and researchers working on these conditions, pooling together clues and ideas to help them get a diagnosis."

The solution was to build the RD-Connect Genome-Phenome Analysis Platform (GPAP) - a sophisticated computer system that gathers together and integrates different kinds of information from individuals with a rare disease, including genetic data and clinical information, in search of a diagnosis.

It's like the supercomputer version of Sherlock Holmes, spotting clues and connections that were previously missed and delivering a list of the most likely suspects. Not only does this help to provide much-needed answers for patients and their families, it can also point towards potential treatments and clinical trials.

"Building the platform wasn't easy, as we had to make sure that all the personal patient information was kept secure and private," Sergi explains. "It also had to be capable of handling and analysing millions of data points at once, and coping with different kinds of data formats and languages."

RD-Connect GPAP is a core part of the larger European RD-Solve project dedicated to understanding rare diseases. Hundreds of patients have already been diagnosed, and the platform's capabilities have been described in a collection of six scientific papers published in the European Journal of Human Genetics. New data generated by Solve-RD is being continually added to the platform, making it smarter all the time.

"The platform works by bringing many sources of data together from many countries, just like the project itself," Sergi says. "Solve-RD is a very large, pan-European collaboration bringing together doctors, researchers, bioinformaticians and software engineers, all working together and sharing our knowledge, expertise and skills to make it happen."

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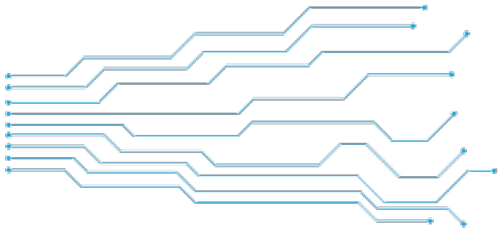
Matalonga, L., Hernández-Ferrer, C., Piscia, D. et al. *"Solving patients with rare diseases through programmatic reanalysis of genome-phenome data."* Eur J Hum Genet 29: 1337-1347 (2021). doi: 10.1038/s41431-021-00852-7



Research and Scientific Services

07

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 PROGRAMME

Coordinator: **Roderic Guigó**

In the course of this year, the programme highlights include, firstly, the delineation of a comprehensive single-cell map of the human bone marrow. This reference map particularly permits the automatic analysis of single-cell RNA-seq data and the design of cost-effective high-throughput cytometry schemes. Secondly, the development of methods for high-efficient splicing QTL mapping. Thirdly, the continued development of the NextFlow pipeline language and the emphasis on reproducible research, the finding that exons and introns exhibit similar mutation rates. 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 made an important contribution to the Federated EGA model, the world's first Genomic Data Federation.

The programme has been very active in initiating collaborative translational genomics projects, including the collaboration with the BarcelonaBeta Brain Research Center on the genomics of Alzheimer's disease.

CELL AND DEVELOPMENTAL BIOLOGY PROGRAMME

Coordinator: **Vivek Malhorta**

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). Departmental members published numerous outstanding papers, although one of them merits special mention. The paper by the Ruprecht laboratory, *Hoijman et al. Nature* (2021), reveals that newly-formed embryos clear dying cells to maximise their chances of survival. It is the earliest display of an innate immune response found in vertebrate animals to date.

In 2021, the drug discovery biotech firm Chemotargets and the CRG signed an agreement to accelerate the development of new targeted therapies that respond to unmet clinical needs in different fields. The first project under the agreement involves a new target identified by Isabelle Vernos' group.

In 2021, the CATCAT (Cell and Tissue Research in Catalonia) initiative spearheaded by Vivek Malhotra continued its activities, holding several meet-ups aimed at exchanging technologies, personnel and ultimately sharing students and postdoctoral researchers to promote research into cell and tissue engineering in Barcelona.

The department enjoys international recognition and is well-funded by external grants. In 2021, ERC Synergy Grants were awarded to Thomas Surrey and Vivek Malhotra, respectively. Plan Nacional Programme grants were awarded to Böke and Malhotra. Böke was elected an EMBO YIP and Thomas Surrey was made a fellow of the American Society for Cell Biology.

Finally, in 2021, the department said goodbye to Maurer's group. Sebastian Maurer moved to the private sector as Head of Applications at Eppendorf SE.

GENE REGULATION, STEM CELLS AND CANCER PROGRAMME

Co-coordinators: **Fátima Gebauer and Luciano Di Croce**

The Gene Regulation, Stem Cells and Cancer Programme addresses the molecular mechanisms of gene expression, from chromatin organisation and regulation to splicing, translation and RNA modification. We study these processes in the context of cell differentiation, reprogramming and cancer. In 2021, two of our Junior Group Leaders, Renee Beekman and Eva Novoa, obtained ERC Starting grants to understand how chromosome translocations impact lymphomagenesis and to develop methods to detect RNA modifications and determine their relevance in transgenerational inheritance, respectively. Leveraging the transfer of basic knowledge to innovation, Juan Valcárcel obtained the European Innovation Council (EIC) grant 'TAONAs-LUAD' to develop a company based on RNA therapeutics, and Pia Cosma obtained the EIC grant 'EcaBox' to build a box in which a human eye could be maintained for a prolonged period of time. In addition, the PhD student Oguzhan Begik received the RNA Society Eclipse Award for Innovation in High Throughput Biology for his work on the development of novel methods based on Nanopore long-read sequencing. Marc Martí-Renom, jointly appointed by the CRG and CNAG, received a U.S. National Human Genome Research Institute (NHGRI) grant to set up a 3D-Genome Imaging Center in collaboration with Harvard Medical School, Brown University and Baylor College of Medicine. Moreover, former CRG Director and member of our Programme Miguel Beato closed his lab at the end of 2021 and became Emeritus Group Leader.

Finally, in January 2021, Juan Valcárcel left the coordination of our Programme in the hands of Fátima Gebauer and Luciano Di Croce. We are immensely grateful to Juan for his work over these past 8 years.

SYSTEMS BIOLOGY

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 the desired properties? Despite having a good conceptual understanding, we are still very bad at predicting the quantitative behaviour of biological systems or at designing them de novo. This is true at the levels of cells, tissues and organs, although it is also true for individual proteins and RNAs. The Systems Biology programme seeks to change this and to help transform molecular biology into a quantitative, predictive engineering science. The programme straddles a wide range of systems and scales: from microbes and non-model animals to human genetics, neuroscience and aging. However, underlying this diversity is a common approach of data-driven modelling that combines quantitative data collection with mechanistic, machine learning or statistical models.

In 2021, we welcomed a new junior group leader to the programme, Amelie Baud. Baud performed her postdoctoral research between the European Bioinformatics Institute and the University of California San Diego, and holds a PhD in Genomic Medicine and Statistics from the University of Oxford. Her lab will bolster CRG's research in statistical genetics and address how the gut microbiome and social partners influence health and disease. Welcome, Amelie!

CORE TECHNOLOGIES PROGRAMME

Head: **Mònica Morales**

The programme involves seven Core Technology Units: Genomics, Proteomics, Bioinformatics Protein Technologies, Advanced Light Microscopy, Flow Cytometry and Tissue Engineering. In the course of 2021, we implemented several new features in Agendo, the request management software for Core Technologies, and established common procedures across all units that comprise the homogenisation of workflows and the collection of metadata from experimental projects.

CRG core technologies are not only well established locally and nationally (the proteomics unit is a node in the ICTS Omicstech), they are also recognised **partners in European initiatives**. The Proteomics unit is a partner in the INFRAIA (H2020) consortium EPIC-XS. The Advanced Light Microscopy Unit is a partner in the ESFRI initiative EuroBioimaging (EuBI). All the units and the programme are members of the Core Facilities Excellence Alliance "**Core For Life**" (www.coreforlife.eu), which also includes EMBL (Heidelberg, Germany), VIB (Gent/Leuven, Belgium), MPI-CBG (Dresden, Germany), VBCF (Vienna, Austria), the FGCZ (Zurich, Switzerland), and the Institut Pasteur and Institut Curie (Paris, France). Core For Life aims at sharing and consolidating procedures, joining efforts in personnel training and technology validation and sharing access to technologies across institutes.

CNAG-CRG
Director: **Ivo Gut**

CNAG made great inroads in 2021. We produced more data and supported more research projects that rely on high-throughput sequencing and analysis than in any previous year. For many years, we have developed tools that facilitate the identification of gene variants and mutations that are responsible for disease. An informatic tool for this, our RD-Connect Genome Phenome Analysis platform, now has more than 20,000 annotated genomes and exomes and is used by more than 500 researchers to identify pathogenic variants in their patients. This year witnessed the launch of the IMPACT project to support the implementation of genomic analysis in healthcare in Spain funded by the Instituto de Salud Carlos III. This project gives us the opportunity to bring our expertise in genomic analyses in rare diseases and cancer into play to the benefit of the citizens. There has also been a strong push in our accreditation framework, where we are now coordinating interlaboratory comparisons and benchmarks at the National and European level through EASI-Genomics, B1MG and the 1+Million Genomes Initiative.

The Population Genomics group published on the population structure of an isolated region in the Pyrenees and collaborated in a large consortium to elucidate the origin of the first Bronze Age civilisations in Europe. The group moved to the Institut de Biologia Evolutiva of the UPF and the CSIC at the end of the year.

Single-cell analysis has been further consolidated with the inclusion of spatial transcriptomics supported by in-house-developed software tools that allow the deconvolution and attribution of cell types in tissue sections. A single-cell tumour immune atlas has been developed that can be used for precision oncology. We are adding high-resolution imaging technology for the investigation of the nucleus funded through grants from the NIH and 'la Caixa'. Using this technology, we charted the first three-dimensional genomic map of healthy and cancerous lymphocytes in collaboration with researchers at the IDIBAPS.

Biodiversity has been a long-standing topic at the CNAG and we have developed key expertise in de novo genome assembly and annotation, particularly through our expertise in long-read sequencing. The number of de novo assemblies is increasing steadily and will receive a major boost through the funding secured this year. As part of the ERGA (European Reference Genome Atlas), we were included in Biodiversity Genomics Europe, a large-scale European project on biodiversity, and we will be one of the five centres tasked with sequencing, assembly and annotation.

This year, we continued to attract funding for exciting new projects for training networks (PROTrEIN), 3D omic landscapes (3D Omics), single-cell analysis (OncoCell), personalised medicine and artificial intelligence (Genomed4All) and rare diseases (Screen4Care and iGenCo). These projects have led the centre to grow, through almost 20 new recruits and will help to consolidate our mission even further.

EUROPEAN GENOME-PHENOME ARCHIVE (EGA)

Team Leader: **Arcadi Navarro**

07

The European Genome-phenome Archive (EGA) is a repository for the 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, and in collaboration with the Barcelona Supercomputing Center (BSC-CNS), the EGA provides an invaluable service to biomedical research worldwide. The EGA-CRG Team has been co-leading the foundation of the Federated EGA Network that was essentially finalised in 2021. Furthermore, the team participates in several national and international funded projects in a wide range of fields. In 2021, three new collaborative projects were awarded to the team, complementing the twelve ongoing ones. Two new members were recruited to the multidisciplinary team, which now numbers eighteen and will continue to grow. Together, the team has achieved great results in the finalisation of the Beacon Discovery specification for human genomic data, now under review at the Global Alliance in Health and Genomics, and the improvement of Viral Beacon for the discovery of SARSCoV-2 genomic variants. Importantly, our services are always updated to provide the fastest and secure solution for EGA users: the latest updates were published this year.[1]

[1] Freeberg MA, Fromont LA, D'Altri T, Romero AF, Ciges JI, Jene A, Kerry G, Moldes M, Ariosa R, Bahena S, Barrowdale D, Barbero MC, Fernandez-Orth D, Garcia-Linares C, Garcia-Rios E, Haziza F, Juhasz B, Llobet OM, Milla G, Mohan A, Rueda M, Sankar A, Shaju D, Shimpi A, Singh B, Thomas C, de la Torre S, Uyan U, Vasallo C, Flicek P, Guigo R, Navarro A, Parkinson H, Keane T, Rambla J. *The European Genome-phenome Archive in 2021*. Nucleic Acids Res. 7th January 2022; 50(D1):D980-D987. doi: 10.1093/nar/gkab1059. PMID: 34791407; PMCID: PMC8728218.

New Hirings

In 2021, one outstanding early-career scientist and one recognised unit leader joined the CRG.

08

Amelie Baud

After taking her PhD in Genomic Medicine and Statistics within the Wellcome Trust doctoral training programme at the University of Oxford, UK, in 2013 she joined the European Bioinformatics Institute in Cambridge, UK, and the EMBL Rome, in Italy, as an Interdisciplinary Postdoctoral Fellow. In 2015, she undertook a second postdoctoral research period between the European Bioinformatics Institute in Cambridge, UK and the University of California San Diego, US, as a Sir Henry Wellcome Postdoctoral Fellow. In 2021, she joined the CRG's Systems Biology Programme as a 'la Caixa' Junior Leader Fellow and in October she became Junior Group Leader.

How do social partners and the gut microbiome influence health and disease? To address this question, her laboratory leverages the fact that many characteristics of social partners and the gut microbiome can be predicted from the genes of social partners and the genes of the gut microbiome, respectively. Thus, instead of trying to measure all the traits of social partners and/or the microbiome that might influence a phenotype of interest, they simply sequence the genes of social partners and/or the genes of the microbiome and model those genes' effect on the phenotype of interest, measured in focal individuals.

Her laboratory primarily uses laboratory rodents as models, although in the future she will also investigate indirect genetic effects in humans (e.g. indirect genetic effects from roommates and spouses). The projects in her lab can be purely computational or be a combination of experimental and computational work. She has many ongoing collaborations with researchers in Europe and the UK, as well as in the US.

Nadia Halidi

Nadia obtained her PhD in Biophysics at the École Polytechnique Fédérale de Lausanne (EPFL), Switzerland, in 2011, and then moved as a postdoctoral fellow to the Department of Cell Biology, at Harvard Medical School in Boston, US. In 2017, she took up a postdoctoral researcher and imaging facility manager position at the Botnar Research Centre of the University of Oxford, and one year later she joined the Micron Oxford Advanced Bioimaging Unit, also at the University of Oxford in UK, first as an assistant manager and subsequently as a manager, where she stayed until 2021. In February 2021, she joined the CRG's Core Technologies Programme as Head of the Advanced Light Microscopy Unit.

The objective of the unit that she runs is to provide instruments covering the whole application spectrum of advanced light microscopy and to make them available to researchers from the CRG, as well as to visitors from other research institutions. As a Core Facility for light microscopy, the unit provides a number of advanced light microscopy systems, equipment for sample preparation and maintenance prior to imaging and resources for the subsequent processing of the image data. The staff assist researchers in the experimental planning of light microscopy experiments and provides in-depth training for the operation of the microscopes and for specific imaging techniques. Additionally, support is provided in the processing, rendering and analysis of the acquired datasets. If needed, custom analysis routines could be also designed.

Honours & Awards

09

Catalan National Award to the Creation of a Company with Scientific Base (for Pulmobiotics SL)
Severo Ochoa Centre of Excellence
HR Excellence in Research Award (renewal)
Centre for Genomic Regulation

EMBO Young Investigator (YIP)
Elvan Böke

Fellow of the American Society of Cell Biology
Thomas Surrey

Bioinformatics Resource Innovation Award 2021, Swiss Institute of Bioinformatics
Cedric Notredame

‘Scientific Article’ Catalan Society of Biology Award 2021

Verena Ruprecht
(award collected by Valeria Venturini in the picture)

‘Start-up’ Catalan Society of Biology Award 2021

Pulmobiotics SL

RNA Society Eclipse Award for Innovation in High Throughput Biology

Oguzhan Begik, PhD Student

‘Pioner’ Award to her Thesis, CERCA

Ariadna Montero Blay, PhD Student

ERC GRANTEES AT THE CRG

10

STARTING GRANTS

Elvan Böke

Arnau Sebé-Pedrós

Nicholas Stroustrup

Sara Sdelci

Renée Beekman

Lars Velten

Eva Novoa

10

ADVANCED GRANTS

Jorge Ferrer

Luis Serrano (2)

Juan Valcárcel

Ben Lehner

CONSOLIDATOR GRANTS

Manuel Irimia

SYNERGY GRANTS

Ivo Gut

Holger Heyn

Vivek Malhotra

Thomas Surrey

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

Índice

Facts & Figures

Publications

313
Total Publications

85.3%
Open Access Publications

72.8%
1st Quartile Publications

10.2
Average Impact Factor

Funding (M€)

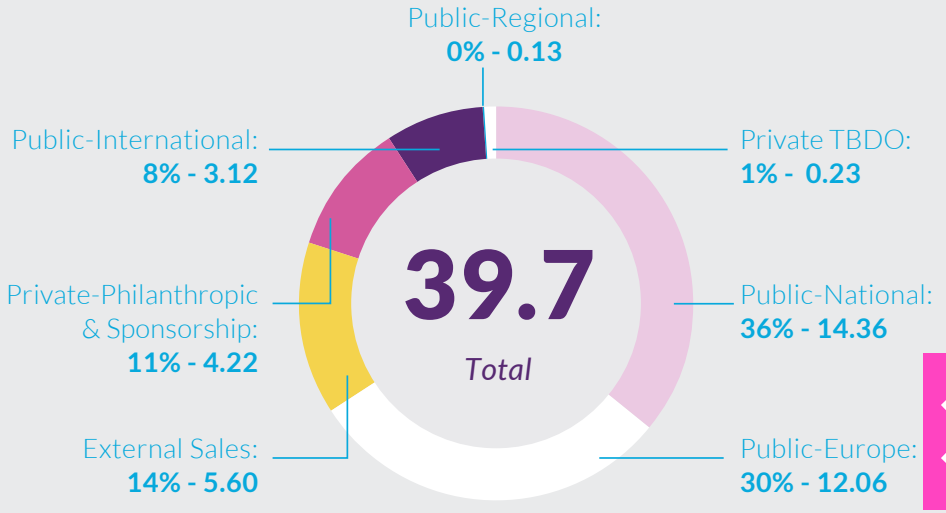
35.4
CRG

12
CNAG-CRG

47.4
Total Funding

EXTERNAL FUNDING AWARDED IN 2021

Note: The graph includes competitive funds obtained during 2021 and pending for final notice of award or grant agreement as of 31/12/2021.



Projects

169
Total Ongoing Research Projects and Networks

11 *Ongoing ERC Projects*

7 *Ongoing EU Coordinated Projects*

34 *Other Ongoing H2020 Research Projects and Networks*

23 *International Ongoing Research Projects (non-EC)*

29
Total Ongoing Postdoctoral Fellowships

7
Total Ongoing EU Coordinated Projects

ORION open science

CHROMDESIGN

EASI Genomics

PROTrEIN
Training of computational proteomics researchers

ECaBox
EYES IN A CARE BOX

International nucleome consortium

CorEuStem

Staff

493.35*
Total Staff
**FTE, full-time equivalent*

416 CRG
94 CNAG-CRG

317.86*
Research Staff
**FTE, full-time equivalent*

301 CRG
27 CNAG-CRG

98.57*
Scientific Services
**FTE, full-time equivalent*

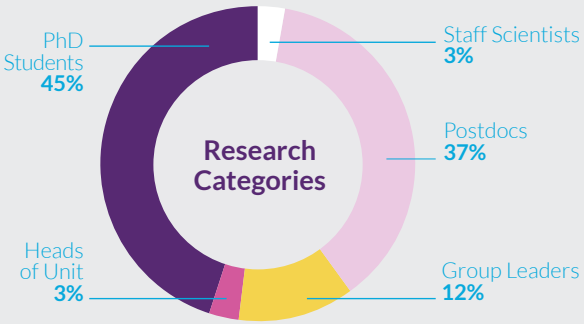
40 CRG
62 CNAG-CRG

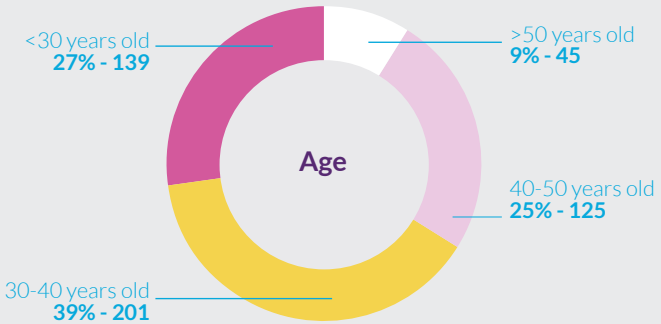
71.62*
Administration & Scientific Support
**FTE, full-time equivalent*

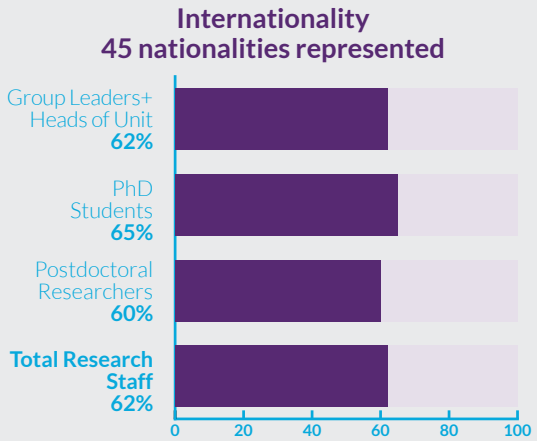
75 CRG
5 CNAG-CRG

30
Research Groups
by 31st Dec 2021

28 CRG
2 CNAG-CRG

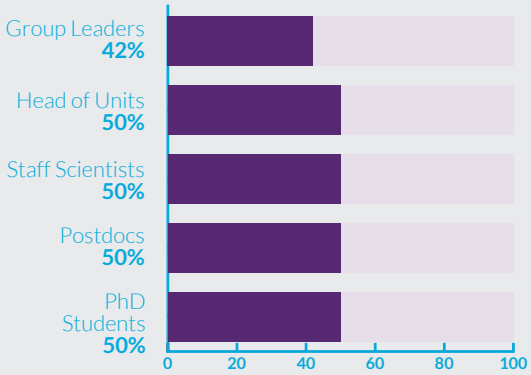




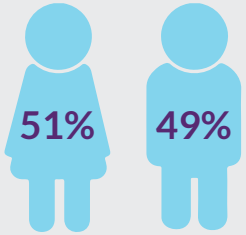


Gender

% Female by Professional Categories

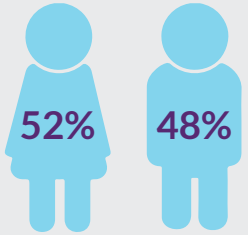


Applicants to our Selection Processes



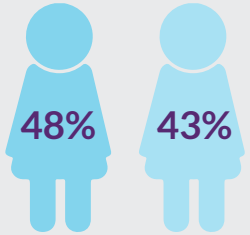
1,303 1,232

Selected / Hired Candidates



66 62

% Female invited speakers



2021 2020

Advanced Training

PhD Theses defended

18

Courses@CRG

6 *international courses*

170 *participants*

Scientific & Technology and RR Courses

22 *internal courses*

536 *participants*

Transferable & Innovation Skills Courses

16 *internal courses*

219 *participants*

Career-related Events & Training

11 *internal courses*

428 *participants*

Events

44

High-profile Seminars

Technology & Business Development

12

Ongoing Valorisation Projects

19

Active Patent Families

19

Invention Disclosures

18

Services, Scientific Collaborations & Licenses Agreements

132

Other Agreements

Communication, Public Engagement & Science Education

MEDIA RELATIONS

695
Media Appearances

125
Written Media

525
Online Media

22
Blogs

14
Radio

9
TV

SOCIAL MEDIA (by 31st Dec 2021)

Twitter followers

18,327
@CRGenomica

3,672
@cnag_eu

Facebook

4,290
Likes

4,401
Followers

LinkedIn followers

18,116
CRG

4,097
CNAG-CRG

YouTube

273,607
Channel views

1,896
Subscribers

PUBLIC ENGAGEMENT & SCIENCE EDUCATION

21
Categories of Activities Organised

7,502
Audience Reached

3,815
Students

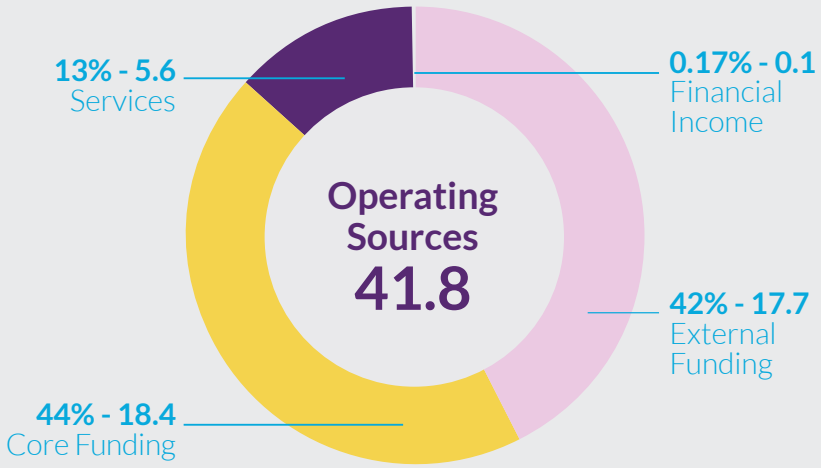
3,687
General Public

Índice

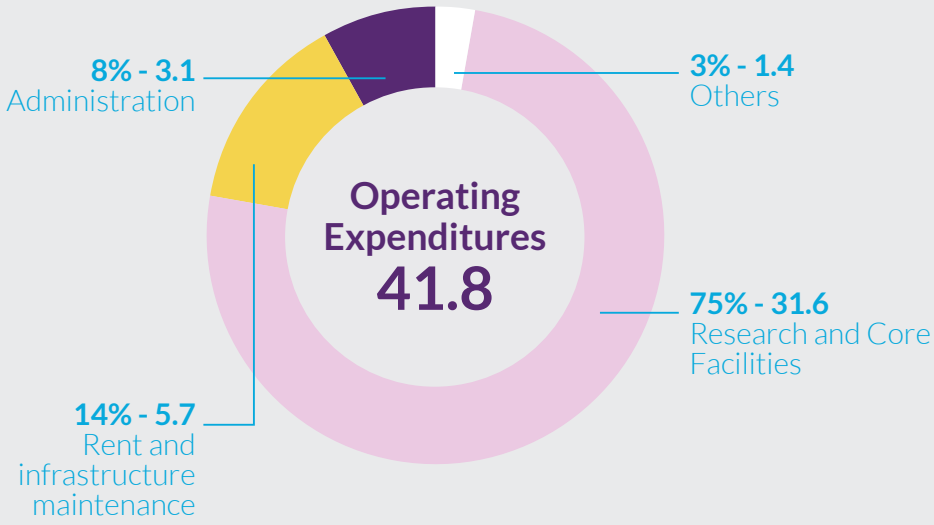
Financial Report

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

Fundació "la Caixa"

PUBLIC FUNDERS

European Union

erc European Research Council

Gobierno de España · Ministerio de Ciencia e Innovación

Generalitat de Catalunya Departament de Recerca i Universitats

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

Note: ERDF and ESF funds have been instrumental over the years through different funding schemes and in a variety of activities in supporting our research and keeping our infrastructures state-of-the-art. Further details on the projects co-financed by these funds can be found in the ERDF AND ESF FUNDS AT THE CRG

"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 13 INPhiNIT or other 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 CaixaImpulse grant (O. Lao), 1 'la Caixa' Retaining grant (R. Beekman) and two major grants from the Health Research Call (L. Di Croce, together with M.A. Marti-Renom, and M. Irimia). In 2021, we were awarded 2 Junior Leader Fellowships (A. Baud, P. Rodriguez), 2 grants from the Health Research Call (B. Lehner, J. Valcárcel), 1 CaixaImpulse grant (J. Valcárcel/J. Hernández) and two INPhiNIT PhD Grants (L. Bianchi in V. Ruprecht's lab, and G. Zolotarov in A. Sebé-Pedrós' lab).

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. In 2021, Dr Ben Lehner was re-appointed chair holder for a 2-year period.

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 MARATÓ 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), three projects from the 2018 edition on 'Cancer' (Ivo Gut, Holger Heyn and Susana de la Luna) and four projects from the 2019 edition on 'Rare Diseases' (Pia Cosma with an individual grant, Jordi Rambla and Holger Heyn as partners in two different coordinated projects, and Sergi Beltrán as coordinator of one project).

FONDATION JEROME LEJEUNE

The relationship between the CRG and the Jerome Lejeune Foundation began many years ago. They provided support to several of Mara Dierssen's research initiatives 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 and 2023, respectively. In 2021, Mara Dierssen was awarded a new grant for her project 'Memory engram pathology and underlying cellular and molecular alterations in Down syndrome', which will run until 2023.

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, which ended in 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 2023. In 2021, Eva Novoa was awarded a grant under the 'Proyectos de la AECC' call, for her project 'Native RNA nanopore sequencing as a novel technology for rapid cancer screening and monitoring', ending in 2024; and Pau Pascual (in Luciano Di Croce's lab) obtained a postdoctoral fellowship for his project 'Functional characterisation of diffuse intrinsic pontine glioma', which will run until 2023.

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 the ones led by 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 multidimensional 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 with potential medical value (2019-2022).

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 ran 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 ended in December 2021.

FEDERATION OF EUROPEAN BIOCHEMICAL SOCIETIES (FEBS)

In 2021, Maximilian Stammnitz (B. Lehner's lab) was awarded a FEBS Long-Term Fellowship for his project 'DrugDeep: Massively parallel drug target and resistance mutation mapping by deep mutational scanning', which will run until 2022.

MELANOMA RESEARCH ALLIANCE

Fátima Gebauer received a MRA Established Investigator Grant Award in 2021 for her project 'CSDE1 proteoforms as novel targets for melanoma treatment and prognosis', which will run until 2024.

MERCK HEALTHCARE

Eva Novoa was awarded a Merck Research Grant in 2021 to research a drug discovery programme targeting cancer-specific RNA modifying enzymes, which will run until 2024.

RESEARCH FOUNDATION FLANDERS (FWO)

In 2021, the research project 'Rational design of biologics for therapeutic development' was awarded a grant from FWO. Luis Serrano is one of the partners of this project, which will run until 2025.

SIRION BIOTECH (A PERKINELMER INC. BUSINESS)

SIRION Biotech, a world leader in viral vector-based gene delivery technologies for gene and cell therapy and vaccine development, a business of PerkinElmer, Inc., and the CRG entered into an agreement to jointly develop new generation adeno-associated virus (AAV) vectors for type 1 and type 2 diabetes gene therapy in the pancreas. The collaboration combines SIRION's AAV technology platform and expertise in viral vector development and production with Jorge Ferrer CRG's deep knowledge of genetic regulatory mechanisms. The ultimate goal is to develop AAV vectors that target specific pancreatic cell types and contain payloads that express therapeutic genes under control of cell-specific regulatory elements. This new approach aims to increase the precision, safety and efficacy of future AAV-based gene therapies for diabetes (2021-2023).

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