Annual Report

2022

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CRG Centre for Genomic Regulation

CERCA Centres de Recerca de Catalunya

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Foreword

Luis Serrano
DIRECTOR

The year 2022 was an excellent one for the CRG. After the unprecedented years of the coronavirus pandemic, most things went back to normal, although the first months were still a bit challenging, with cases increasing and restrictions measures still in place. However, from the 20th of April the use of the mask was no longer mandatory in indoor spaces and this, somehow symbolically, marked the end of the pandemic.

The new year came with a new Administrative Director, Joan Vives, an experienced professional with a successful and outstanding background in the research management environment, in organisations such as the ISGlobal, the MRC Unit the Gambia and IRB Lleida. Other key people that left the CRG during the year were rapidly replaced by talented and motivated people, which will continue to help the CRG maintain its place at the forefront of science.

In 2022, we continued with the CRG's amazing track record in obtaining prestigious competing funds like three ERC Starting Grants, one ERC Proof of Concept Grant, and two ERC Synergy Grants, plus several large EU collaborative projects coordinated by CRG groups or with CRG as a partner. We also obtained the maximum qualification in the evaluation that CERCA carries out for Catalonia's research institutes.

We continued producing excellent science as attested by the number and quality of our research publications and at the same time we ensure that our scientific advances result in the creation of quality jobs and economic return to society by creating new companies. We also saw a record in economic return to CRG due to licenses, selling of shares and competitive projects related to translational research.

A big change has been reorganising the research programs, each of which have had their names changed to be aligned with the scientific strategic plan. We have now appointed two coordinators per programme, allowing closer parity in gender at senior positions and ensures that we will have rotation at these very important positions. Sadly, 2022 has seen the split of the CNAG from CRG to become an independent institute. As a result, CRG has decided to potentiate its Genomics core facility to provide customized services to the scientific community, hiring a new head and providing service in single-cell genomics and spatial transcriptomics.

We have overcome some really challenging times in the last few years, but over the last year CRG has been at the forefront of the worldwide scientific community that is focused on enhancing our knowledge and using that for the benefit of humanity. Our drive and passion for that continues.

A look back at the year

We look back on a 2022 that fortunately entailed the last breath of the coronavirus pandemic and a return to normality. All in all, we can say that it was a very good year for the CRG.

The most exciting development of the year was the inauguration of the Barcelona Collaboratorium for Modelling and Predictive Biology. This major new initiative is a joint project between the CRG and the European Molecular Biology Laboratory (EMBL), with the goal to strengthen Barcelona as a centre of reference for computational and quantitative biology. The Collaboratorium is designed to be truly interdisciplinary, with research covering all fields of modelling in biology and biological problems at all scales – from molecules to cells and organs through to organisms and ecosystems. Research areas will include Artificial Intelligence, Dynamical Systems, Statistics and Theoretical Biology. The Collaboratorium kicked off in October 2022 with an inaugural symposium entitled "Programmable Life" which featured diverse speakers from Europe and beyond.

Another significant achievement for the institute was getting the maximum qualification in an evaluation carried out by CERCA, the collective organisation for all research centres of excellence in Catalonia. CERCA ensures these centres develop successfully by promoting synergies and strategic cooperation improving their visibility and the impact of their research and promoting the dialogue amongst both public and private stakeholders.

Another big change moving forward is that the Centro Nacional de Análisis Genómico (CNAG) will officially split off from the CRG to become an independent institute. This separation process started with the creation of the CNAG Consortium as a new legal entity, a process which will reach completion by June 2023. Our best wishes and good luck go to CNAG for the new endeavour ahead.

SCIENCE & TECHNOLOGY

Our scientists continued to produce ground-breaking research that was published in top-tier journals. These include findings that explain how human egg cells remain dormant in ovaries for up to 50 years without losing their reproductive capacity (Böke); a new technique that revealed the existence of multitude of therapeutic targets that control protein function which could be targeted to dramatically change the course of diseases such as dementia, cancer and infectious diseases (Lehner); a study that found a switch that regulates the activity of a gene that causes diabetes, highlighting potential new vulnerabilities in the disease and could led to the development of new therapeutic strategies (Ferrer); the discovery that a gene which normally suppresses the formation of tumours is reprogrammed at the onset of acute promyelocytic leukaemia, a finding that could pave the way for the development of new drugs to prevent it (Di Croce); the development of a new method to study DNA methylation at single-cell level, and unveiling the contribution of chromosomal translocation in leukaemia progression (Beekman); transcriptome innovation in primates revealed by single-molecule long-read sequencing (authors include Fornas and Sabidó); and the development of a new method to sequence the human mitochondrial genome (Gut).

In 2022, the CRG continued its extraordinary track record in terms of attraction of competitive funds. Eva Novoa, Renee Beekman and Lars Velten were awarded ERC Starting Grants to study the role of sperm RNA in passing paternal hereditary information,

for example through diet; to study the impact of translocations, a phenomenon where a chromosome breaks and a portion of it reattaches to a different chromosome, on the formation of tumours; and to combine deep learning and single-cell screening techniques to create new models of gene regulation in the human blood-forming system, respectively. Luis Serrano obtained a new ERC Proof of Concept Grant to explore new methods that improve the therapeutic effectiveness of cytokines. Verena Ruprecht and Juan Valcárcel were awarded ERC Synergy Grants to understand control mechanisms and robustness of symmetry breaking in multicellular systems; and to address the gaps in basic knowledge of regulated splicing and its modulation with small molecules, which will enable future novel therapeutics to be developed, respectively. In 2022, the national initiative 'Complementary Plan for Biotechnology Applied to Health' is coordinated by the Institute for Bioengineering of Catalonia (IBEC), with the CRG as one of the partners. The research programme is funded by the Spanish Government and the Government of Catalonia through the Next Generation EU funds. Within the framework of this initiative, Luciano Di Croce and Isabelle Vernos were awarded two research projects to identify and validate therapeutic targets for diffuse midline glioma; and to validate the potential of a new therapeutic target (enzyme involved in modifying microtubules) by using single-cell technologies to analyse samples from breast cancer patients, respectively. This 'Complementary Plan' also provided the Core Technologies programme with resources to set up a transversal single cell and spatial transcriptomics platform, which will perform single cell and CRISPR screening assays to provide access to technologies that will advance precision medicine projects for clinical research.

The EGA-CRG Team have been co-leading the foundation of the Federated EGA Network, a network of European national repositories. FEGA was launched in September 2022 with five inaugural nodes and is growing under the drive of the EBI and CRG teams, with more than 10 nodes across the world showing interest in joining. Software engineers at the CRG have developed the toolkit of applications that enable FEGA national nodes at the technical level.

In terms of innovation and entrepreneurship, we ensure that our scientific advances result in the creation of high-quality jobs and economic return to society by creating new companies. This year, we have seen a record in economic return to CRG due to licenses, selling of shares, and competitive projects related to translational research, as detailed above. A new spin-off, Orikine, was created, whose platform delivers optimised best-in-class cytokines to maximise clinical benefits. Initial focus is on anti-inflammatory and regenerative auto-inflammatory and auto-immune diseases with potential to extend to other cytokines and diseases such as cancer and allergy. CRG spin-off Seqera Labs, the leading provider of data organisation and workflow software in the life sciences raised 22 million euros in Series A funding – one of the top investment rounds in the country at this stage – in addition to the 4.4 million euros of seed capital raised one year before. Pulmobiotics, start-up founded in 2020 at the CRG, received a grant from the European Innovation Council (EIC) to work on a 'living medicine' to improve efficacy of lung cancer treatment. The EIC Transition scheme will support the company to mature and validate their breakthrough technology and to build a business case for future commercialisation. Finally, the project "Towards a new treatment for metastatic breast cancer", led by Roni Wright, CRG alumni, now at the International University of Catalonia, was selected in the 2022 CaixaResearch Validate call, launched by 'la Caixa' Foundation. The grant offers economic support of up to 100 thousand euros and specialised training in key areas such as technology transfer and marketing. By the end of the year, the Milner Therapeutics Institute lead a pharma partner visit to IRB Barcelona and CRG. The objective was to foster collaboration between pharma companies and research centres and accelerate the impact of scientific research for patients.

STRATEGIC PRIORITIES

As a part of our commitment towards open science, CRG open access publications in 2022 reached nearly 90%.

As part of the H2020 ORION Open Science project, which ended in September 2021, the CRG launched the #GenigmaChallenge, a videogame designed to detect alterations in genomic sequences and ultimately advance breast cancer research. The game was the result of a two-and-a-half-year long citizen science project, which was created to boost worldwide research efforts that depend on cancer cells lines, a critical resource used by scientists to study cancer and test new drugs to test the disease. The project ended on the 16th of June, with more than 39,000 players from 154 countries. More than 600,000 solutions were gathered in a matter of 20 weeks and 181 areas of interest of the genome in breast cancer research were identified. The scientific team behind this project is, since then, working on the analysis of the data provided by the Genigma players, and the results will be published in the near future.

Also within the framework of open science and citizen science, the CRG continued to work on the EU project TIME4CS. 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, the CRG has been working on the actions previously defined, such as a series of trainings on citizen science, citizen science guidelines, citizen science policy, etc.

The Gender Balance Committee continued to develop the actions of the CRG Equality, Diversity and Inclusion plan 2020-2023, which in 2022 included several training sessions on inclusion, the improvement of some internal policies, activities to raise awareness on gender balance issues, such as the participation in the initiative #100tífiques, which gathered more than 400 women scientists in Catalonia that gave inspirational talks to schools, the organisation of the Ada Lovelace workshop (a bioinformatics workshop) at the PRBB Open Day aimed at engaging girls into bioinformatics, social media campaigns on the International Day of Women and Girls in Science and on the International Women's Day, etc. Thanks to our collective efforts to push for gender equality over the past years, in 2022, 57% of junior group leaders and 43% of research programme coordinators 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 (ERA). In 2022, EU-LIFE engaged in several actions and publications having to do with the reform of research assessment, advocating for IP issues within the EC, identifying common challenges in research infrastructures, a booklet to ensure the success of future applicants of MSCA Postdoctoral Fellowship program, and trainings on the role of active by-standers and institutional anti-bullying and harassment policies. Together with other members of EU-LIFE, the CRG continued to led EMERALD (H2020 Marie Sklodowska-Curie grant), the first European-wide PhD programme for medical doctors. Finally, the EU-LIFE team started the preparation of the celebrations of the alliance's 10th Anniversary, which will be in June 2023, in Portugal.

TALENT

In 2022, we welcomed two junior PIs, Mafalda Dias and Jonathan Frazer, both from Harvard Medical School, in the US, who joined the Computational Biology and Health Genomics Programme and lead a lab together; and a new Head of the Genomics Unit, Berta Fusté, from the Centro Nacional de Análisis Genómico, in Barcelona, who joined the Core Technologies Programme.

During the year, we finished the reorganisation of the research programmes, which changed their names to be aligned with the CRG Strategic Plan. Jorge Ferrer replaced Roderic Guigó as coordinator of the Computational Biology and Heath Genomics Programme (former Bioinformatics and Genomics Programme). We would like to extend our most sincere thanks to Roderic for his invaluable dedication to the program over the last few years. Luciano Di Croce and Fátima Gebauer were appointed co-coordinators of the Genome Biology Programme (former Gene Regulation, Stem Cells and Cancer Programme). Isabelle Vernos was appointed co-coordinator, and together with Vivek Malhotra, will run the Quantitative Cell Biology Programme (former Cell and Developmental Biology Programme). Finally, Pia Cosma was also appointed co-coordinator, and together with Ben Lehner, will run the Systems and Synthetic Biology Programme (former Systems Biology Programme). The appointment of three women co-coordinators brings the CRG closer to parity in gender at direction positions and ensures that there will be a rotation at these relevant positions in the future.

At Administration and Research Support, there were also many changes, the most significant being the arrival of Joan Vives, the new Administrative Director, who moved to the CRG from the Institute of Biomedical Research in Lleida. With more than 16 years of experience leading biomedical research institutes in Europe and Africa, Joan brings a unique set of skills and commitment to continue to lead CRG into the future, building on the already extraordinary former accomplishments and achievements of the institute.

The former International and Scientific Affairs (ISA) office has transformed into a new department known as Strategy and Funding, led by Joaquim Calbó, with Natàlia Dave as the Deputy Head. The Grants Office was abolished, with members and functions of pre-award tasks transferred to the new SaF department. The remaining members, in charge of grants management tasks, moved to the new Controlling and Grants Management area, led by Mariana Morlans, within the Finance Department. Other changes include a transformation of the programme secretaries, who are now part of the Operations Support Department, led by Reyes Perza. Finally, Yann Dublanche became the new Deputy Head of IT.

During the year, we also said goodbye to the heads of two key Administration departments: Jaume Bacardit, Head of Finance, who undertook a new position as Managing Director at the Research Institute of the Hospital de la Santa Creu i Sant Pau, in Barcelona; and Olalla Bagüés, Head of Human Resources, who moved to the Vall d'Hebron Research Institute (VHIR), as Director of the Human Resources Area, also in Barcelona.

Thanks to the attractiveness of the CRG, we were able to replace these key people quite quickly. Alicia Llamas joined the CRG as new Head of Finance in November, coming from the Fundació Privada Hospital de la Santa Creu i Sant Pau, in Barcelona; and a new Head of Human Resources was identified by the end of the year, who will start in her new position at the beginning of 2023.

Our sincere congratulations go to the whole CRG community for their continued efforts and support, and their amazing work, aimed at accomplishing the institute's objectives and strategic priorities in 2022.

01

Making sense of the tags of cellular history

Tags in our genome provide a narrative of the lifelong history of a cell. A new method detects these tags with high confidence, revealing new differentiation states.

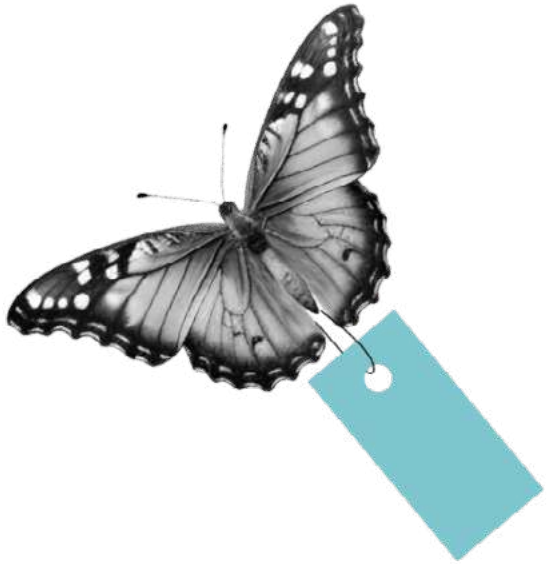
DNA methylation is a key mechanism of epigenetic regulation, a process that involves modifications to the DNA molecule that can alter gene expression without changing the underlying DNA sequence. Like adding a tag to an item of clothing, DNA methylation involves a methyl group to a nucleotide, the building blocks of DNA.

One of the primary targets for methylation in mammalian genomes are CpG sites, around 27 million regions of human DNA where a cytosine nucleotide is followed by a guanine nucleotide in the linear sequence. Methylation of CpG sites is crucial for

human health and disease because they can repress gene transcription, meaning cells tag these sites to control which genes are turned “on” or “off”, influencing protein production and cell function.

Extensive sequencing, far too prohibitive with current techniques, are required to research CpG methylation. This makes the study of rare cell types, cellular heterogeneity, and differentiation processes challenging.

A research team led by Dr. Renée Beekman and Lars Velten at the CRG set out to address this by creating a new tool dubbed single-cell Targeted Analysis of the Methylome, or scTAM-seq for short. The method, described in October in the journal *Genome Biology*, was used to reveal DNA methylation dynamics across B-cell differentiation in blood and bone marrow, unmasking previously hidden intermediate differentiation states. The researchers believe the tool shows promise for detailed epigenetic studies and potential clinical applications due to its low false positive and false negative rates.



“The newly developed single-cell DNA methylation method scTAM-seq paves the way to unravel so far unresolved details in a large variety of biological systems, from early development and stem cell biology to differentiation and cancer,” says Dr. Renee Beekman.

REFERENCE WORK

Bianchi, A., Scherer, M., Zaurin, R. *et al*. scTAM-seq enables targeted high-confidence analysis of DNA methylation in single cells. *Genome Biol* **23**, 229 (2022). https://doi.org/10.1186/s13059-022-02796-7

02

How ‘standby mode’ keeps oocytes healthy for decades

Skipping a fundamental metabolic reaction is key for avoiding dangerous byproducts and keeping oocytes in pristine condition

Human eggs are first formed in the ovaries during foetal development, undergoing different stages of maturation. During the early stages of this process, immature egg cells known as oocytes are put into cellular arrest, remaining dormant for up to 50 years in the ovaries. These cells have an extraordinary task: they must remain pristine - avoiding any damage or degradation - for up to five decades in order to carry out their function and give rise to the next generation.

How they do this has remained an open question, and understanding the underlying biology could help shed light on why one in four cases of female infertility are unexplained – a fact that highlights a huge gap of knowledge in our understanding of female reproduction. In part, this is because much of the underlying biology of human oocytes remains unknown, knowledge that is of fundamental importance in addressing demographic challenges in the 21st century.

Researchers led by Dr. Elvan Böke at the CRG have made important contributions to solving this mystery. Publishing their findings in July in the journal Nature, the team showed that oocytes skip a fundamental metabolic reaction thought to be essential for generating energy. By altering their metabolic activity, the cells avoid creating reactive oxygen species, harmful molecules that can accumulate, damage DNA and cause cell death.

A complex protein and enzyme known as complex I is the usual 'gatekeeper' that initiates the reactions required to generate energy in mitochondria. This protein is fundamental, working in the cells that constitute living organisms ranging from yeast to blue whales. However, the researchers found that complex I is virtually absent in oocytes. The only other type of cell known to survive with depleted complex I levels are all the cells that make up the parasitic plant mistletoe. Avoiding using complex I is a long-term maintenance strategy akin to putting batteries on standby mode, representing a brand-new paradigm never before seen in animal cells.

The findings could also lead to new strategies that help preserve the ovarian reserves of patients undergoing cancer treatment. "Complex I inhibitors have previously been proposed as a cancer treatment. If these inhibitors show promise in future studies, they could potentially target cancerous cells while sparing oocytes," said Dr. Elvan Böke.

REFERENCE WORK

Rodríguez-Nuevo, A., Torres-Sanchez, A., Duran, J.M. *et al.* Oocytes maintain ROS-free mitochondrial metabolism by suppressing complex I. *Nature* **607**, 756–761 (2022). https://doi.org/10.1038/s41586-022-04979-5

03

The shapeshifting genomic architecture of aggressive blood cancers

In acute promyelocytic leukaemia, chromosomes break and reattach to other chromosomes. Scientists are turning to mouse models that mimic the disease to reveal how changes in genomic architecture cause the disease and discover new clues for treating it.

Genome organization plays a crucial role in transcription. However, how transcription factors rewire the structure of the genome to maintain the programs that lead to oncogenic transformation remains poorly understood.

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For example, acute promyelocytic leukaemia (APL) is an aggressive type of blood cancer that is responsible for 5-15% of all types of leukaemia. APL occurs because of chromosomal translocations, in which a chromosome breaks and a portion of it reattaches to a different chromosome. This results in a gene fusion event between the promyelocytic leukaemia (PML) and retinoic acid receptor alpha (RARα) genes.

Previously healthy stem cells begin to express a new protein – PML/RARα – which blocks their differentiation. Eventually, the bone marrow fills up with abnormal white blood cells known as promyelocytes that lead to a shortage of other types of blood cells and prevent normal blood production.

Despite the importance of chromosomal translocations in initiating the disease, little is known about how PML-RARα changes the genomic architecture of cells. ICREA Research Professor Luciano Di Croce overcame this challenge by using mouse models that closely mimic the progression of APL in humans to study changes in cells during the onset and progression of the disease.

Dr. Di Croce demonstrated that PML-RARα initiates a series of alterations that result in changes to the structural support of chromosomes and the repression of transcription, as well as changes in chromosomal compartments that 'open' or 'close' access to particular regions of the genome.

One of the genes most affected by these changes at an early stage was KLF4, which codes for a protein that binds to DNA to control the rate of transcription of genetic information, also known as a transcription factor. Klf4 activity was inactivated during the progression of APL. The researchers found that, when cells were manipulated to overexpress Klf4, it suppressed the self-renewal traits of cancerous cells and reversed the effects caused by the actions of PML-RARα.

The findings, published in April in the journal *Genes & Development*, can lead to the development of new treatments for this type of aggressive blood cancer. "The steps that initiate cancer are the most interesting because they are the equivalent of the snowball that turns into an avalanche. This approach could be used to understand the very first effects of other oncogenic proteins that act as transcriptional repressor, leading to the development of new therapies that target a mechanism before it spirals out of control," said Dr. Di Croce.

REFERENCE WORK

Mas, G., Santoro, F., Blanco, E. *et al.* In vivo temporal resolution of acute promyelocytic leukemia progression reveals a role of *Klf4* in suppressing early leukemic transformation. *Genes & Dev* 36, 451-467 (2022). https://doi.org/10.1101/gad.349115.121

04

Deciphering the code of our cellular ‘battery packs’

All life generates energy by using mitochondria. However, reconstructing mitochondrial DNA to study human health and disease has been an imperfect process. A new tool is set to change that and greatly boost mitochondrial research.

Imagine you’re trying to assemble a jigsaw puzzle where the picture isn’t clear. That’s the situation scientists regularly face when studying a special type of DNA found inside our cells known as mitochondrial DNA (mtDNA). Mitochondria are like our cells’ power plants, and understanding their DNA can tell us a lot about how our cells work.

Researchers led by Ivo Gut at the Centro Nacional de Análisis Genómico came up with a new way of solving mitochondrial DNA sequences using the DNA-cutting tool Cas9. Their new method helps mark the start and end points of the puzzle, making it easier for scientists to read the full length of mtDNA accurately, even when it's a tough puzzle with missing pieces.

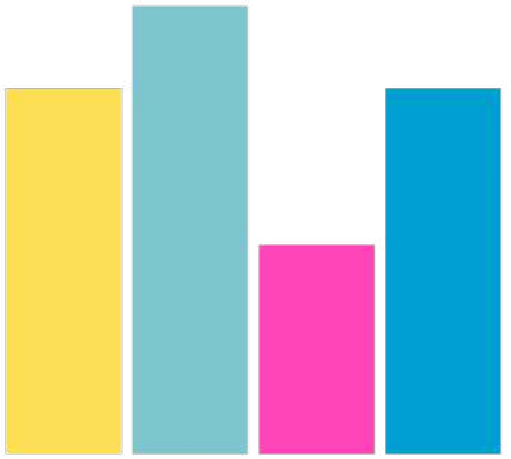
Thanks to a specially-designed software called baldur, the tool doesn't just read the DNA, it can also spot when and where changes to the DNA have occurred, including even the tiniest differences. The findings were published in October 2022 in the journal *Nature Communications*.

Why does this matter? Well, changes or modifications to mtDNA can sometimes lead to disease. So, this tool could potentially help us better understand, detect, and maybe even treat certain health conditions. "At the moment, our method can be applied in the context of research. However, in the future it could be introduced as a general test for clinical diagnostics of patients suffering from mitochondrial diseases," said Dr. Ivo Gut.

The tool will also have implications for studying biodiversity and evolution. In mitochondria, there's no mixture of paternal and maternal DNA like in the cell nucleus, which simplifies the tracking of lineages. Because each cell contains many mitochondria and each mitochondrion has multiple copies of the mtDNA, it's also easier to extract and study mtDNA compared to nuclear DNA, especially from ancient or degraded samples. The new method can help detect these mtDNA changes over time and help us understand human evolution and how species are related – ultimately contributing to the construction of a massive family tree for all life on Earth.

REFERENCE WORK

Keraite, I., Becker, P., Canevazzi, D. *et al.* A method for multiplexed full-length single-molecule sequencing of the human mitochondrial genome. *Nat Commun* **13**, 5902 (2022). https://doi.org/10.1038/s41467-022-33530-3



05

The molecular smart sensor keeping diabetes at bay

Researchers have discovered a DNA regulatory element which dials down a diabetes gene if it transcribes too much or boosts its activity if slacking. The findings shed light on how non-coding genomic regions regulate genes.

HNF1A is a gene that provides instructions for making a protein called hepatocyte nuclear factor-1 alpha. The protein is expressed in many tissues but is particularly important for the pancreas, where it plays a role in developing beta cells. Beta cells produce the hormone insulin, which regulate blood sugar levels.

Mutations in HNF1A cause cells to create a protein that doesn't work normally, which in turn affects the function of beta cells. This results in individuals developing a disease known as maturity-onset diabetes of the young, where symptoms such as high blood sugar can appear before individuals reach the age of 30.

Though this disease accounts for just 1% of all types of diabetes, it is high in terms of absolute numbers due to the high prevalence of diabetes amongst the worldwide population (5-10%). HNF1A is also known to play a key role in the susceptibility for the more common form of the disease, type 2 diabetes, in concert with other genetic and non-genetic factors.

Understanding how the HNF1A gene is switched on or off in beta cells could have important implications for understanding why defects in this gene lead to diabetes, or how it could be harnessed to correct the underlying problem.

Using a combination of mouse and human models, Dr. Jorge Ferrer studied an enigmatic part of the genome near HNF1A that has a unique function that has not been described before. Sharing their findings in October 2022 in the journal *Nature Cell Biology*, the research team found that this DNA regulatory element works like as rheostat; if the HNF1A gene transcribes too much it dials it down, if the gene is slacking it dials it back up.

"We coined this a stabilizer, in contrast to other DNA regulatory elements such as enhancers, promoters and silencers, and call this particular element HASTER, for HNF1A stabilizer," said Dr. Ferrer.

The researchers found that HASTER controls the production of RNA molecules which do not code for proteins. Mutations in HASTER caused diabetes in mice comparable to deleting HNF1A itself.

By showing that changes to the function of gene regulatory elements such as HASTER can drastically change cell function akin to disrupting the gene itself, the researchers pave the way for future studies that explore the role of non-protein coding sequences in promoting disease.

"A lot more space in the human genome is devoted to regulating genes than to the genes themselves. In this study we have experimentally validated just one region to ascertain its function. It's likely this is just the tip of the iceberg," said Dr. Ferrer.

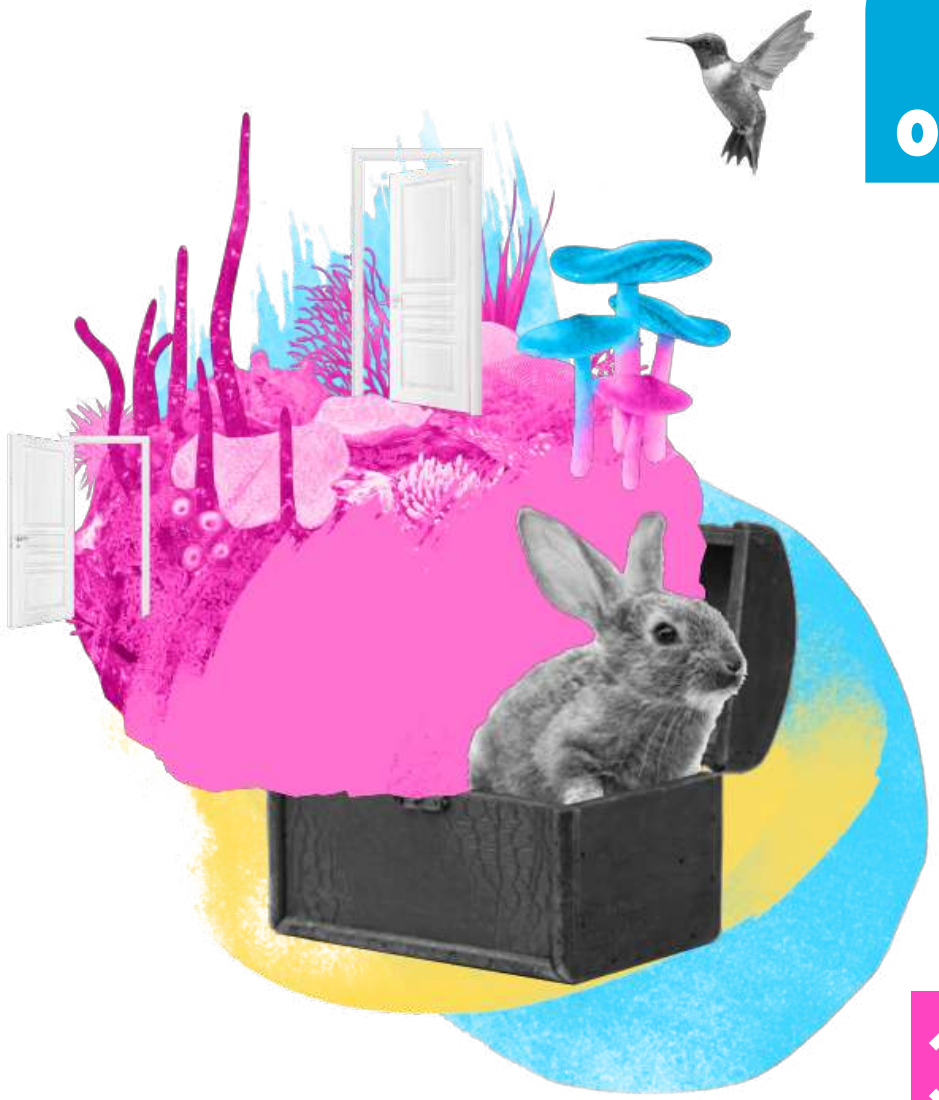
REFERENCE WORK

Beucher, A., Miguel-Escalada, I., Balboa, D. *et al.* The *HASTER* lncRNA promoter is a *cis*-acting transcriptional stabilizer of *HNF1A*. *Nat Cell Biol* **24**, 1528–1540 (2022). https://doi.org/10.1038/s41556-022-00996-8

Charting the ‘second secret of life’

06

A new method charts allosteric sites which control protein function and could, in theory, be targeted to dramatically change the course of diseases as varied as dementia, cancer and infectious diseases



The number of potential therapeutic targets on the surfaces of human proteins is much greater than previously thought, according to the findings of a study in the journal *Nature* published in April 2022.

A ground-breaking new technique developed by a research team led by ICREA Research Professor Ben Lehner has revealed the existence of a multitude of previously 'secret doors' that control protein function which could, in theory, be targeted to dramatically change the course of diseases as varied as dementia, cancer and infectious diseases.

The method, in which tens of thousands of experiments are performed at the same time, has been used to chart the first ever map of these elusive targets, also known as allosteric sites, in two of the most common human proteins, revealing they are abundant and identifiable.

The approach could be a game changer for drug discovery, leading to safer, smarter and more effective medicines. It enables research labs around the world to find and exploit vulnerabilities in any protein – including those previously thought 'undruggable'.

Allostery is one of the great unsolved mysteries of protein function. Allosteric effects occur when a molecule binds to the surface of a protein, which in turn causes changes at a distant site in the same protein, regulating its function by remote control. Many disease-causing mutations, including numerous cancer drivers, are pathological because of their allosteric effects.

Despite their fundamental importance, allosteric sites are incredibly difficult to find. This is because the rules governing how proteins work at the atomic level are hidden out of sight. For example, a protein might shapeshift in the presence of an incoming molecule, revealing hidden pockets deep within its surface that are potentially allosteric but not identifiable using conventional structure determination alone.

The researchers addressed this challenge by developing a completely new method called double deep PCA, which they describe as a 'brute force experiment'. "We purposefully break things in thousands of different ways to build a complete picture of how something works", said Dr. Lehner. "It's like suspecting a faulty spark plug, but instead of only checking that, the mechanic dismantles the entire car and checks it piece by piece. By testing ten thousand things in one go we identify all the pieces that really matter."

One of the great advantages of the method is that it is an affordable technique accessible to any research lab around the world. The researchers are already on working on using the technique to rapidly and comprehensively map the allosteric sites of human proteins one by one.

REFERENCE WORK

Faure, A.J., Domingo, J., Schmiedel, J.M. *et al*. Mapping the energetic and allosteric landscapes of protein binding domains. *Nature* **604**, 175–183 (2022). https://doi.org/10.1038/s41586-022-04586-4

Research & Scientific Services

07

COMPUTATIONAL BIOLOGY AND HEALTH GENOMICS PROGRAMME

Coordinator: **Jorge Ferrer**

The scientists in this programme are interested in understanding the genome function in human populations and across species, addressing this with advanced genome technologies and computational models. The Computational Biology and Health Genomics programme evolved from the Bioinformatics and Genomics programme in 2022.

Throughout the past year, the programme members published several noteworthy studies, including a method that enables the simultaneous analysis of DNA methylation and other molecular markers in thousands of single cells. Another two studies uncovered mechanisms through which the disruption of non-coding portions of the genome causes diabetes. Finally, another paper revealed genetic variants that influence disease susceptibility by modifying RNA splicing patterns.

The programme members participate in different Human Cell Atlas initiatives, and are also involved in major large-scale genome projects including ENCODE, GTEx and PanCancer. In 2022, the programme kicked off a project named IMPaCT-T2D, geared towards deploying whole genome sequences for precision medicine in type 2 diabetes. It hosted an international symposium on this topic and co-organized a Wilhelm and Else Heraeus Foundation Meeting on Cancer Evolution. The programme has started a new transversal Medical Genomics data club series that brings together scientists from several CRG programmes, the Universitat Pompeu Fabra and the Hospital del Mar.

The programme has continued to implement 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.

Finally, the programme is delighted to welcome a new team that joined in the autumn of 2022, led by Mafalda Dias and Jonathan Frazer. Jon and Mafalda joined us from Harvard Medical School and use probabilistic machine-learning approaches to predict the impact of genome variation in human disease and throughout its evolution.

QUANTITATIVE CELL BIOLOGY PROGRAMME

Co-coordinators: **Vivek Malhotra and Isabelle Vernos**

07

The mission of the scientists in the Quantitative Cell 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), Verena Ruprecht (cell and tissue dynamics), Elvan Böke (oocyte biology and cellular dormancy) and Thomas Surrey (intracellular self-organisation). Numerous outstanding papers have been published by departmental members, although one that merits special mention is a paper from the Böke Laboratory, Rodriguez et al. Nature (2022). This paper shows that human oocytes suppress the levels of mitochondrial complex 1 to reduce the levels of protein and lipid-damaging reactive oxygen species. The department also runs the CATCAT (Cell and Tissue Research in Catalonia) initiative to promote scientific interaction and research into cell and tissue engineering in Barcelona.

The department enjoys international recognition and is well funded by external grants. In addition to Thomas Surrey and Vivek Malhotra, who are funded by the ERC Synergy Grants, respectively, Elvan Böke was awarded an ERC Consolidator Grant and Verena Ruprecht an ERC Synergy Grant in 2022. Elvan was awarded the Premi de Ciutat de Barcelona (Barcelona City Award) in the Life Sciences Category in 2022. Malhotra, Surrey and Vernos are ICREA Research Professors, and Ruprecht was elected ICREA Research Professor in 2022.

GENOME BIOLOGY PROGRAMME

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

07

The former *"Gene Regulation, Stem Cells and Cancer"* Programme has been reorganised and renamed the *"Genome Biology"* Programme. The change of name is not just aesthetic, as it strongly reflects our goal of integrating quantitative biology and state-of-the art technologies to investigate, in a multi-disciplinary manner, aspects involved in genome organisation and regulation, including molecular mechanisms of gene expression, chromatin organisation, splicing and RNA translation and modification. As a result of this reorganisation, Miguel Beato was appointed *"emeritus investigator"*, providing mentoring and support to other CRG groups. Moreover, Pia Cosma has joined the *"Systems and Synthetic Biology"* Programme as co-coordinator, while continuing to maintain a dual affiliation with our Programme.

We study Genome Biology in the context of cell differentiation, reprogramming and cancer. In 2022, **Juan Valcárcel**, in a joint effort with the groups of Manuel Irimia and Jorge Ferrer, uncovered a program of microexons included in pancreatic beta cells which play important roles in the control of insulin secretion and are linked to diabetes. **Pia Cosma**, the recipient of the "EIC Woman Leadership Programme", developed a strategy to reveal how genes fold in 3D with unprecedented details to generate 3D models of genes with nanometric resolution. **Sara Sdelci's** lab was honoured with the "BIST Ignite" and "Leonardo-BBVA" awards for their work on the role of nuclear metabolism in the regulation of transcription. This topic has been also the research focus of **Miguel Beato**, who focused on the role of energy metabolism in gene expression and DNA repair, as well as on the role of progesterone receptor condensates in living cells. **Fátima Gebauer** has been appointed Vice-Chair of the European Network on Translation and Cancer, *"TRANSLACORE"*. Her lab has uncovered unconventional RNA-binding proteins in cancer which are emerging as promising therapeutic targets and suggest roles of RNA in unsuspected cellular compartments. **Renee Beekman**, with the support of an ERC Starting grant, developed, in collaboration with the Velten Lab, a new method to study DNA methylation at single-cell level and unveiled the contribution of chromosomal translocation in leukaemia progression. In addition, the PhD student Leone Abbiati received an *"EMERALD PhD4 MD"* fellowship to study early lymphoma formation. **Eva Novoa**, with the support of the MSCA-DN LongTREC, has developed several methods to quantify RNA abundance, as well as to quantify the poly(A) tail lengths and tail composition of individual RNA molecules. A study by the **Bernhard Payer** Lab discovered that turning the X chromosome "off and on again" is a critical event predicting whether mouse germ cells can develop into oocytes. Finally, **Luciano Di Croce** accepted the role of co-coordinator of the "Epigene3sis" network, which connects many of the European labs working on epigenetics mechanisms in development and disease. His lab recently dissected epigenomic and topological reprogramming during leukemogenesis and used p-topological information to identify new drivers of malignant transformation.

SYSTEMS AND SYNTHETIC BIOLOGY PROGRAMME

Co-coordinators: **Pia Cosma and 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 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 cell, tissue and organ level, but it also applies to individual proteins and RNAs. The Systems and Synthetic Biology Programme sets out to change this and to help transform molecular biology into a quantitative and predictive engineering science. The Programme covers 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 data-driven modelling approach that combines quantitative data collection with mechanistic, machine-learning or statistical models.

The most exciting development in 2022 was the inauguration of the Barcelona Collaboratorium for Modelling and Predictive Biology (https://barcelonacollaboratorium.com/). This major new initiative is a joint project between the CRG and the European Molecular Biology Laboratory (EMBL), its goal being to consolidate and expand Barcelona as a centre for computational and quantitative biology.

The Collaboratorium occupies an entire purpose-built floor of the Pasqual Maragall Foundation building close to the PRBB, with room for more than 40 new researchers funded by the Government of Catalonia, the Spanish Ministry of Science and Innovation, the CRG and EMBL. This purpose-built open-plan space will host CRG- and EMBL-affiliated Research Fellows, as well as an approximately equal number of visitors and Sabbatical Fellows hailing from all over the world. The Collaboratorium will also provide space for Independent Research Fellows – new CRG faculty members afforded the opportunity to pursue independent research at an early stage in their career, with room for a small team.

The Collaboratorium is designed to be truly interdisciplinary, with research covering all fields of modelling in biology and biological problems on all scales – from molecules to cells and organs through to organisms and ecosystems. The fields of research will include Artificial Intelligence, Dynamical Systems, Statistics and Theoretical Biology.

The Collaboratorium kicked off in October 2022 with an inaugural symposium entitled "Programmable Life", which featured diverse speakers from Europe and further afield. The centre will also host a series of weekly seminars every Thursday morning, starting in 2023.

We are truly excited to welcome all the new "Collaboratorians" and to help transform Barcelona into a quantitative and predictive biology hub!

CORE TECHNOLOGIES PROGRAMME

Head: **Mònica Morales**

The Core Technologies Programme is comprised of seven Technology Units: Genomics, Proteomics, Bioinformatics, Protein Technologies, Advanced Light Microscopy, Flow Cytometry and Tissue Engineering, which provide researchers with state-of-the-art services and expertise to advance research and to support the CRG in being a world-leading centre in biomedical science.

In 2022, the Core Technologies Programme expanded its user base and supported more clinical research projects than in any previous year, with a special focus on proteomics and genomics applications.

The Complementary Plans Programme, launched by the Ministry of Science and Innovation, awarded the 'Biotecnología aplicada para la Salud' [Applied Biotechnology for Health] project to the CRG and five other Catalan Institutions. This project, coordinated by IBEC, has provided CRG Core Technologies with resources to set up a transversal single-cell and spatial transcriptomics platform that will place the CRG at the forefront of technologies in several life sciences disciplines. We will also perform single-cell and CRISPR screening assays to provide access to technologies that will advance precision medicine projects for clinical research.

CRG Core Technologies are partners in many 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 for Life" (www.coreforlife.eu) Core Facilities Excellence Alliance, 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's objective is to share and consolidate procedures, to team up in personnel training and technology validation and to share access to technologies across the Institutes.

CNAG-CRG

Director: **Ivo Gut**

In 2022, the CNAG-CRG worked intensively towards fulfilling its commitment to implement projects in genome analysis that contribute to meaningful improvements in people health and quality of life. Once again, we surpassed ourselves in all our areas of focus. 2022 was a year in which we made further headway towards achieving several of our goals: we generated more data and supported and analysed more research projects that rely on high-throughput sequencing than any previous year. For many years now, we have been developing tools that facilitate the identification of gene variants and mutations responsible for disease. We have furthered our work on the RD-Connect Genome-Phenome Analysis platform to manage cancer data through funding from Instand-NGS4P. The IMPACT Project, whose objective is to support the implementation of genomic analysis in healthcare in Spain, and is funded by the Instituto de Salud Carlos III, is now into its production phase, and tools developed by the CNAG-CRG are now being deployed at the two other IMPACT sequencing centres in Navarre and Galicia, and patients are already benefiting from the initial results. We have created significant visibility for Spain in Europe through the 1+Million Genomes Initiative, where the RD-Connect-Genome Phenome Analysis Platform was used for the proof of concept of a European-wide federated system for rare disease diagnostics. The CNAG-CRG is convinced that the way forward in sequence analysis is helping our partners and the scientific community to achieve their own missions.

Single-cell analysis has been further consolidated with the inclusion of spatial transcriptomics supported by in-house-developed software tools for the deconvolution and attribution of cell types in tissue sections. The main driving force here was provided by a move to higher resolution thanks to the inclusion of two new imaging systems with which subcellular features and present transcripts can be visualised. A landmark review on spatial genome technologies was written and published by CNAG-CRG researchers this year.

This year also witnessed the beginning of the European-funded Biodiversity Genomics Europe project which supports the ERGA (European Reference Genome Atlas), in which we support sequencing, assembly and annotation species of interest. The Iniciativa Catalana per a l'Earth BioGenome Project (CBP) contributed to generating the genomes of several endogenous species.

We also launched a citizen science project through the GENIGMA initiative. A videogame that recruited more than 39,000 citizens to solve puzzles was used to generate real-world scientific data. Alterations in genomic sequences are detected and ultimately help to advance breast cancer research. The players managed to resolve the genome structure of several commonly-used breast cancer cell lines.

In 2022, we continued to attract funding for challenging new projects: Instand-NGS4P, the Genomic Data Infrastructure (GDI), Biodiversity Genomics Europe, CGI-Clinics, TAGWAS and several personal grants to CNAG members.

The CNAG-CRG workforce has grown and now employs more than 100 professionals of more than 30 nationalities. This is an important asset and resource with a view to driving innovation. Finally, right at the year end, we attained another important milestone, namely to establish our independence as the CNAG through the creation of our own legal entity and identity. Next year, we will implement the administrative infrastructure for the CNAG to support its operation. This is a significant step in the CNAG's 14-year history and will further consolidate the CNAG as a world reference centre for genomics analysis with some of the most cutting-edge technology. In summary, a new period that will thrust us into a promising future packed with challenges, effort and commitment to our science, innovation and society.

EUROPEAN GENOME-PHENOME ARCHIVE (EGA)

Director: **Arcadi Navarro**
Team Leader: **Jordi Rambla**

07

The European Genome-phenome Archive (EGA) is a global network for the permanent archiving and sharing of personally identifiable genetic, phenotypic and clinical data. Our goal is to advance biomedical research and promote personalised medicine the world over by enabling the discovery of and access to human genomic and health research data. With our expertise in data management and our technical infrastructure, we promote FAIR data reuse and enable researchers to share their data securely. By leveraging public funding and our strategic partnerships, the EGA provides a free service for permanent data storage, data discovery and secure data access[1].

The EGA teams at the CRG and at the European Bioinformatics Institute (EMBL-EBI, Cambridge, UK) jointly manage the central EGA and the Federated EGA (FEGA), a network of European national repositories. The FEGA was launched in September 2022 with five inaugural nodes and is now growing under the drive of the EBI and CRG teams, with more than 10 interested nodes already. The CRG's software engineers have developed a toolkit of applications to permit the technical operation of the FEGA national nodes.

The CRG's EGA team numbered 20 members in 2022, including four scientific project managers, six bioinformaticians and four software engineers. All of them are involved in 24 competitive projects, 6 of them awarded in the course of 2022, addressing topics ranging from mental health to cancer and data access. One particularly noteworthy achievement is the team's leadership in the development of the Beacon Discovery specification (version 2) for human genomic data, now an approved standard at the Global Alliance in Health and Genomics[2].

[1] Freeberg, MA, Fromont LA, et al. (2022) The European Genome-phenome Archive in 2021, *Nucleic Acids Research*, 50, D1, D980–D987, https://doi.org/10.1093/nar/gkab1059

[2] Rambla, J, Baudis, M, et al (2022). Beacon v2 and Beacon networks: A "lingua franca" for federated data discovery in biomedical genomics, and beyond. *Human Mutation*, 43, 791– 799. https://doi.org/10.1002/humu.24369

New Hirings

Two outstanding early-career scientists and a recognised unit leader joined the CRG in 2022.

08

MAFALDA DIAS

After taking her PhD in Theoretical Physics at the University of Sussex, UK, in 2013, she stayed on as a Postdoctoral Researcher. In 2015, she took up a Fellow position at The Deutsches Elektronen-Synchrotron (DESY) in Germany. From there, she moved to Harvard Medical School in 2018 as a Senior Postdoctoral Fellow. In 2022, she joined the CRG's Computational Biology and Health Genomics Programme, as Junior Group Leader, heading a lab jointly with Jonathan Frazer (see below).

JONATHAN FRAZER

Jonathan obtained his PhD in Theoretical Physics at the University of Sussex, UK, in 2013, and then moved to the University College London, also in the UK, as Postdoctoral Researcher. In 2015, he took up a Fellow position at The Deutsches Elektronen-Synchrotron (DESY), in Germany, until 2018. He subsequently moved to Harvard Medical School as Senior Postdoctoral Fellow. In 2022, he joined the CRG's Computational Biology and Health Genomics Programme, as Junior Group Leader, heading a lab jointly with Mafalda Dias (see above).

According to Mafalda and Jonathan, we are entering an era of population-scale sequencing of humans, global efforts to obtain reference genomes for all life on Earth, and experiments that can test the effects of millions of genetic variants. These datasets contain the information to transform our use of genomic data in diagnosis and preventive care, in protein and drug design, and a great deal more, although we need new computational strategies to extract this information.

The Dias & Frazer Lab develops machine-learning methods (often generative, often Bayesian) to predict the effect of genetic variation on phenotype, with the emphasis on research that will directly impact the diagnostic yield of patient sequencing. From a machine-learning perspective, they are interested in how recent developments in deep learning may be adapted for modelling genetic sequence data, which poses modelling challenges different to other data typically seen in machine learning. From an evolutionary biology perspective,

they are interested in the relationship between fitness and phylogeny and how the genetic variation seen on different evolutionary timescales from within populations and across the entire tree of life can be used to learn about disease and molecular function.

BERTA FUSTÉ

After taking her PhD in Biology at the University of Barcelona, Spain, in 2005, she moved to the Pompeu Fabra University as a Postdoctoral Fellow. That same year, she took up the position of DNA Next-Gen Sequencing Manager at the Genomic Unit of the Scientific and Technological Centres of the University of Barcelona, where she stayed until 2013. In January 2014, she accepted a position as Senior Project Manager at the Centro Nacional de Análisis Genómico, which has been part of the Centre for Genomic Regulation since 2015. In September 2022, she joined the CRG as Head of the Genomics Unit.

Honours & Awards

09

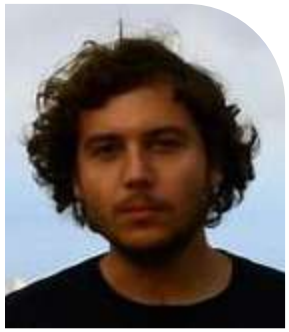
Premi Ciutat de Barcelona (Barcelona City Awards), Life Sciences category
Elvan Böke

EMBO Young Investigator
Arnau Sebé-Pedrós

EMBO Young Investigator
Lars Velten

Elected Numerary Academic of the Royal Academy of Medicine of Catalonia
Mara Dierssen

Winner, 'Tresis Amgen Transferciència' Contest, by Amgen and Catalan Foundation for Science and Technology
Xavier Hernández



First prize, Rin4' Contest, Universitat Pompeu Fabra / Awardee, 1st CRG Call on 'Mentoring for Innovators' (MenTT4Inn), Proof of Concept Innovation Projects
Ivan Milenkovic

09

Special prize, Rin4' Contest, Universitat Pompeu Fabra
Júlia Urgel

Awardee, 1st CRG Call on 'Mentoring for Innovators' (MenTT4Inn), Proof of Concept Innovation Projects
Albert Escobedo

ERC Grantees at 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

Ben Lehner

CONSOLIDATOR GRANTS

Manuel Irimia

SYNERGY GRANTS

Ivo Gut

Holger Heyn

Vivek Malhotra

Thomas Surrey

SYNERGY GRANTS

Verena Ruprecht

Juan Valcárcel

PROOF OF CONCEPT GRANTS

Luis Serrano

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

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Facts & Figures

Publications

228
Total Publications

89.5%
Open Access Publications

74.6%
1st Quartile Publications

11.9
Average Impact Factor

Funding (M€)

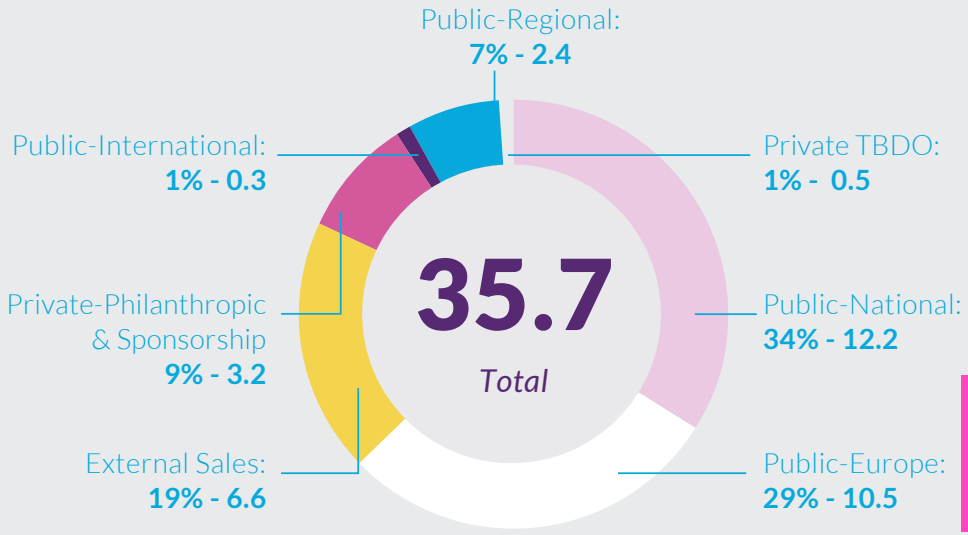
35.8
CRG

15.1
CNAG-CRG

50.9
Total Funding

EXTERNAL FUNDING AWARDED IN 2022

Note: The above graph includes competitive funds obtained during 2022 and pending for final notice of award or grant agreement as of 31/12/2022.



Projects

158
Total Ongoing Research Projects and Networks

15 *are Ongoing ERC Projects*

9 *are Ongoing Coordinated Projects*

39 *are Ongoing H2020 Research Projects and Networks*

21 *are International Ongoing Research Projects (non-EC)*

35
Total Ongoing Postdoctoral Fellowships

9
Total Ongoing Coordinated Projects (finished or ongoing during 2022)

iMPaCT T2D

CHROMDESIGN

EASI Genomics

PROTrEIN
Training of computational proteomics researchers

ECaBox
EYES IN A CARE BOX

Emerald
International PhD Programme for Medical Doctors

TAONas-LUAD

PLAST_CELL

CorEuStem

Staff

512.93*

Total Staff
*FTE, full-time equivalent

422 CRG

99 CNAG-CRG

305.41* *Research Staff* (*FTE, full-time equivalent)

275 CRG

33 CNAG-CRG

120.18* *Scientific Services* (*FTE, full-time equivalent)

63 CRG

60 CNAG-CRG

87.32* *Administration & Scientific Support* (*FTE, full-time equivalent)

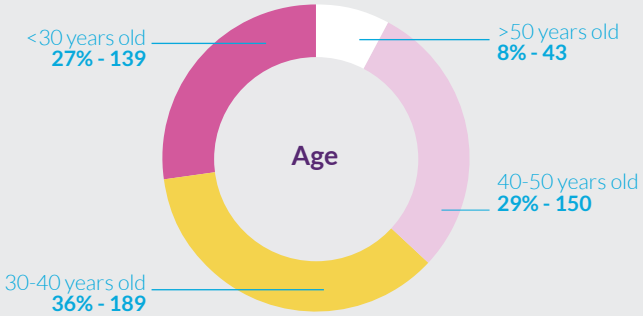
84 CRG

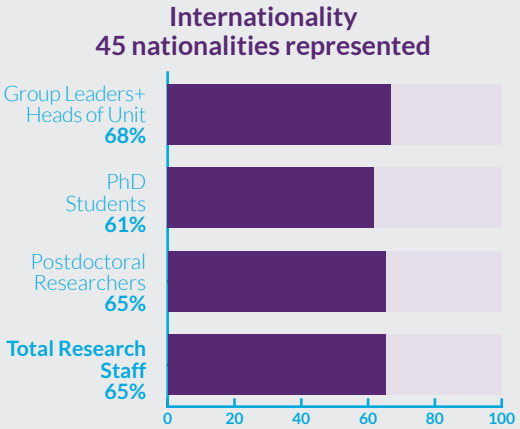
6 CNAG-CRG

32 *Research Groups* (*by 31st Dec 2022*)

30 CRG

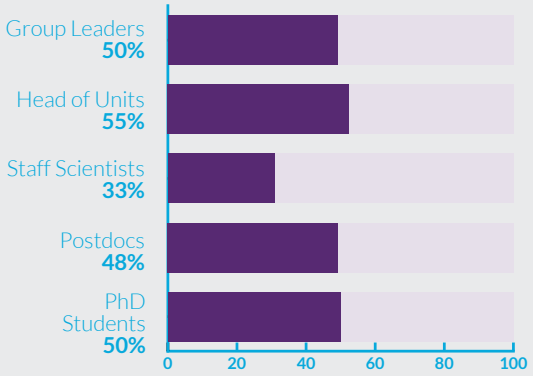
2 CNAG-CRG



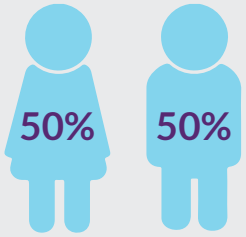


Gender

% Female by Professional Categories

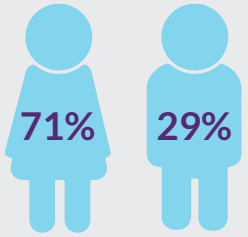


Applicants to our Selection Processes



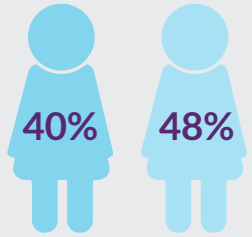
1,121 1,102

Selected / Hired Candidates



87 36

% Female invited speakers



2022 2021

Advanced Training

PhD Theses defended

19

Courses@CRG

5 *international courses*

284 *participants*

Scientific & Technology and RR Courses

27 *internal courses*

535 *participants*

Transferable & Innovation Skills Courses

13 *internal courses*

259 *participants*

Career-related Events & Training

4 *internal courses*

72 *participants*

Events

60

High-profile Seminars

Technology & Business Development

15

Ongoing Valorisation Projects

22

Active Patent Families

21

Invention Disclosures

259

Other Agreements

6

Spin-offs

26

Services, Scientific Collaborations & Licenses Agreements

Communications, Public Engagement & Science Education

MEDIA RELATIONS

1,535
Media Appearences

218
Print Media

1,278
Online Media

28
Radio

11
TV

SOCIAL MEDIA (by 31st Dec 2022)

Twitter Followers

20,592
@CRGenomica

4,015
@cnag_eu

Facebook

4,455
Likes

4,843
Followers

LinkedIn Followers

21,915
CRG

5,208
CNAG-CRG

YouTube

284,730
Channel Views

2,000
Subscribers

PUBLIC ENGAGEMENT AND SCIENCE EDUCATION

38
Categories of Activities Organised

115,069
Audience Reached

21,247
Students

93,822
General Public

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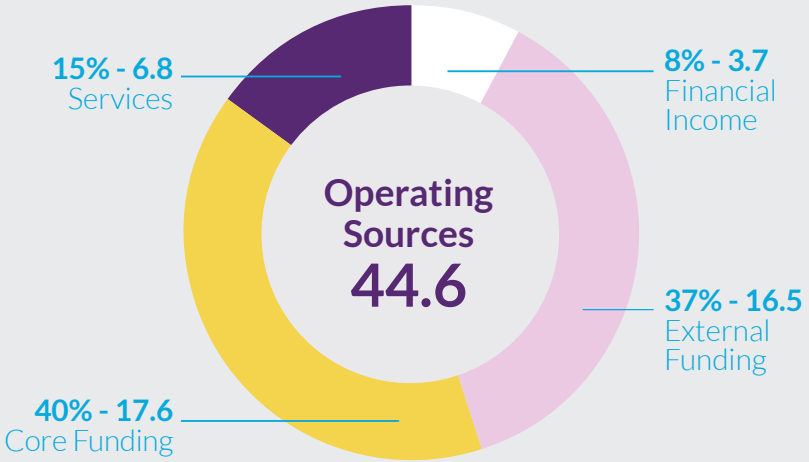
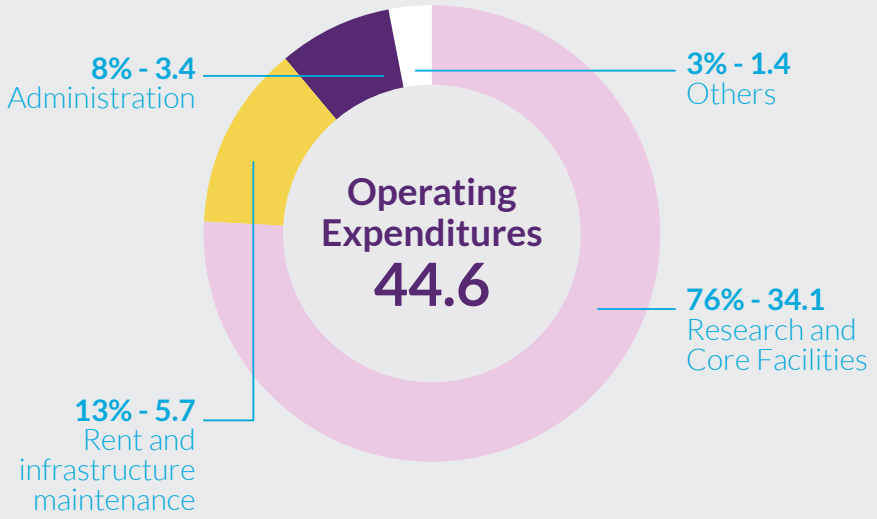
Financial Report

SOURCES & USES MANAGED

Operating Sources in M€



Operating Expenditures in M€



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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

PRIVATE FUNDERS

FUNDACIÓN "LA CAIXA"

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).

Alongside all the previous awarded grants and ongoing INPhiNIT PhD grants, CaixaImpulse grants, 'la Caixa' Retaining grants, grants from the Health Research Call, and Junior Leader Fellowships, in 2022 the CRG was awarded 2 new INPhiNIT PhD Grants (Sdelci's lab and Sebé-Pedrós' lab), and 2 new grants from the CaixaResearch Health 2022 call (Heyn's 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 did their PhDs between September 2018 and September 2022.

FUNDACIÓ MARA TÓ 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.

Since 2015, the Foundation has funded several projects across CRG research groups. Current grantees include Susana de la Luna, with her project 'Organization of the DYRK1A interactome through docking domains: searching for novel targeting approaches' (which ended in 2022); and Laura Batlle, with her project 'Molecular analysis of the non-cell autonomous effects in Down syndrome cortex using mouse ESC-derived brain organoids', which will run until 2023; and Mara Dierssen, with her project 'Memory engram pathology and underlying cellular and molecular alterations in Down syndrome', which will run until 2023. In 2022, René Crans (M. Dierssen's lab) was awarded a postdoctoral fellowship for two years (2022-2024).

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 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. In 2022, Juan Valcárcel was awarded a grant under the 'Proyectos de la AECC' call, for his project 'Generation of optimised anti-tumour drugs targeting the spliceosome', and Lars Velten was awarded another grant under the 'Lab AECC 2022' call, for his project 'Single cell multi-omics for the identification of preventative and diagnostic strategies for clonal hematopoiesis'. Both projects will run until November 2025.

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 ended in 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 was entitled 'Deciphering intra- and inter-individual variation at single cell resolution'; and the project awarded to Heyn was entitled 'Developing tools and standards for integration of multidimensional HCA data', and both ended in 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 run until the end of 2021. In 2022, Diego Balboa, from Jorge Ferrer's lab, was awarded the EASD Rising Star Symposium & EFSD Research Fellowship, which will end in 2023.

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). In 2022, Sara Sdelci was awarded a new BBVA Foundation Leonardo Grant for Researchers and Cultural Creators, in the Biology and Biomedicine Category, which will run until October 2023. The grant will help determine whether the location of the IMPDH2 enzyme in chromatin (the natural form of DNA inside the cell nucleus) has a metabolic vulnerability in triple negative breast cancer. This is the most aggressive type of breast cancer and has a prevalence of between 10 and 15% of all breast tumours. Also in 2022, Arnau Sebé-Pedrós received a Grant to Scientific Research Projects for his project on how to increase the resilience of corals facing climate change, which will run until June 2024. The objective is studying the response to the environmental stress of three different coral species with different resistance levels to bleaching.

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 (2020-2021). In 2022, Lars Velten was awarded an EHA Advanced Research Grant for his project 'The role of the DNA methylation landscape in regulating HSC fate biases, fate restriction, and lineage differentiation', which will run until 2024.

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 ended in 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).

INSTITUCIÓ CERCA

This organisation developed an agreed funding programme with the CERCA centres, to support their knowledge transfer projects, particularly in terms of protecting intellectual and industrial property rights, known as the GINJOL Patents Fund. Under this funding scheme, in 2022, CERCA awarded two grants to the projects 'Epigenome profiling at single cell resolution' (R. Guigó) and 'Targeting tumours through a novel mechanism of genome instability' (I. Vernos) (Jan 2022-May 2023).

ANDORRA RECERCA I INNOVACIÓ (FUNDACIÓ PRIVADA)

In 2022 the CRG entered into an agreement with the government of Andorra, through the private foundation Andorra Recerca i Innovació, to jointly develop the Metaland project ("Metabarcoding of Andorra's lakes"), aimed at obtaining a first glimpse of the microbial biodiversity of the six main lakes of Andorra (2022-2024).

NEUROENDOCRINE TUMOR RESEARCH FOUNDATION (NETRF)

In 2022, the NETRF awarded Juan Valcárcel with a research grant for his project 'Alternative Splicing in PNET: an unexplored source of therapeutic targets'.

SPONSORS

CENTRE FOR GENOMIC REGULATION

Dr. Aiguader, 88
Edifici PRBB
08003 Barcelona

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

communications@crg.eu
https://www.crg.eu

MEMBERS OF THE BOARD OF TRUSTEES:

MEMBER OF:

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

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

GRAPHIC DESIGN:
Ondeuev Comunicació S.L.

PHOTOGRAPHY:
Ivan Martí

ILLUSTRATIONS:
Rocío Quirós

Scientific Highlights