ANNUAL REPORT 19

Josep Carreras
LEUKAEMIA
Research Institute

ANNUAL REPORT / 2019

President of the Board of Trustees

"After three decades of work, we are facing a new challenge. We have to improve patients' quality of life but, above all, we must find a definitive cure for leukaemia. In 2010, therefore, the Josep Carreras Foundation, together with the Catalan government (*Generalitat de Catalunya*), launched a historic and unprecedented project: the first European research centre devoted exclusively to leukaemia and other malignant blood diseases, and one of the few in the world. As of 2019, we had three campuses and a building devoted to this goal."

Josep Carreras
President of the Board of Trustees
Josep Carreras Leukaemia Research Institute

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FOREWORD

2019. What a wonderful year that was!

Dr. Manel Esteller
Director
Josep Carreras Leukaemia Research Institute

A year in which the Josep Carreras Leukaemia Research Institute (IJC) rose to prominence as a world-leading scientific centre for the study of leukaemia, lymphoma and other malignant disorders of the blood and lymph nodes. This was made possible by the efforts of many. First of all, our scientists, technicians, managers and all of our hard-working and committed personnel. Second, the many national and international funding agencies and benefactors whose support represented a decisive factor in our success.

What a privilege has been to serve as director of the Institute at a time when we have grown so much in terms of quantity, but best of all, in terms of the quality of the discoveries that will eventually help end the suffering associated with such terrible diseases. I am very grateful to former director Dr. Evarist Feliu, who exemplifies my belief that "If I have seen further, it is by standing on the shoulders of giants". We are lucky to be able to count on him as a mentor in our activities.

The disruptive change brought about by the research carried out at the Institute started with the incorporation, in the middle of the year, of the groups belonging to the Cancer Epigenetics and Biology Programme, which has provided excellence since its creation in 2008 under my direction and with the support of the Catalan government (*Generalitat de Catalunya*). Thus, our wonderful new building and our headquarters in Badalona are now home to the groups of Dr. Ballestar, Dr. Vaquero, Dr. Parra, Dr. Sanchez-Cespedes and Dr. Guil, as well as my own, thereby contributing to the centre's success. I am very thankful for the warm reception of all groups, and extremely happy to see that fruitful collaborations have already been established between all them, once more demonstrating that we are one big family with a common goal. We play a decisive role in finding a cure for cancer, particularly leukaemia. Most importantly, in the autumn of 2019, the Institute also recruited three young groups, led by Dr. Cuartero, Dr. Sardina and Dr. Roue, whose expertise in chromatin, stem cells and

Dr. Manel Esteller
Director

the molecular biology of lymphoma brought the fresh young blood that is so necessary for a vibrant centre.

This top-notch research could not have been developed without the effort of the management staff and the core facilities. Grateful for the enormous task performed by Ms Ana Garrido to organize the everyday administrative complexity of an Institute that has accomplished so much in so little time. I would also like to highlight the opening of new technical services that represents another important piece of our success story of 2019, from the Genomics Unit that allows the fast study of the genetic an epigenetic material, to the Proteomics Unit that has generated so much interest in the community and the Bioinformatics Unit, the seed of a future growth in the area of Big Data in haematology.

Most importantly, we made this colossal jump in the excellence of our discoveries by reinforcing the research activity of many other groups in Badalona, Hospital Clinic and Hospital de Sant Pau, by sharing resources, visibility and teamwork, and by pooling the skills, experience and knowledge in the basic, translational and clinical areas of all three campus of the Josep Carreras Leukaemia Research Institute. This multidisciplinary approach makes us unstoppable.

The soul of our institute is Mr. Josep Carreras. Every time we meet our common goal becomes clear. Closer than ever to more cures for all haematological malignancies. Moving forward to beat leukaemia. It is my pleasure to invite you to read more about our activities to achieve this aim in the following pages.

Sincerely,

ABOUT US / **WHO WE ARE**

The Josep Carreras Leukaemia Research Institute is a non-profit research institute based in Badalona (Barcelona) dedicated to biomedical research and personalized medicine in leukaemia and other malignant blood diseases. It conducts excellent research into the basic, epidemiological, preventive, clinical and translational aspects of leukaemia and other haematological malignancies.

The Josep Carreras Leukaemia Research Institute, directed by Dr. Manel Esteller, was launched in 2010 by the Josep Carreras Foundation, together with the Catalan government, and is the first European research centre devoted exclusively to leukaemia and other malignant blood diseases.

Research efforts are imperative to provide patients with high-quality healthcare, and our specialists combine their extensive knowledge to focus on patients' needs. Our aim is to understand the origins and development of leukaemia and other malignant haematological pathologies with a view to their prevention, and our efforts are directed towards identifying new therapeutic targets and developing effective treatments with fewer side effects through cutting-edge research.

The ultimate goal of our interdisciplinary team is to ensure that leukaemia is a curable disease in all cases, and we won't stop until we have achieved this.

The Josep Carreras Institute is a collaborative hub for basic and translational researchers who work together on the fundamental biological and clinical aspects of leukaemia at our state-of-the-art facilities, which provide an excellent work environment and serve as a magnet for outstanding researchers from all over the world.

It is home to 26 research groups and an increasing number of associated clinicians from three independent, coordinated scientific campuses: Hospital Clínic-UB Campus, Sant Pau Campus and Can Ruti Campus. Our laboratories on three clinical campuses allow us to collaborate closely with clinicians from the three associated hospitals: Hospital Clínic, Hospital de Sant Pau and Hospital Germans Trias i Pujol.

Sant Pau Campus and its research foundation are located within the healthcare facilities of the Hospital de la Santa Creu i Sant Pau and the Autonomous University of Barcelona (UAB) and are coordinated by Dr. Jordi Sierra.

Hospital Clínic-UB Campus, located at the research facilities of Barcelona's Hospital Clínic, and those of the Faculty of Medicine at the University of Barcelona (UB), is coordinated by Dr. Álvaro Urbano Ispizua, under Research Director Dr. Pablo Menéndez.

Can Ruti Campus, located near Hospital Germans Trias i Pujol, its research foundation and the Autonomous University of Barcelona (UAB), serves as Josep Carreras Institute's main research base and forms part of the Can Ruti Biomedical Campus, which hosts 135 principal investigators and research clinicians. Our researchers take part in a range of scientific activities on the campus and have access to state-of-the-art facilities and technology.

ABOUT US / **MISSION, VISION AND VALUES**

MISSION

The Josep Carreras Leukaemia Research Institute's mission is to carry out research into the epidemiological, preventive, clinical, translational and basic aspects of leukaemia and other malignant blood diseases through innovation, with the ultimate aim of finding a cure.

VISION

The Josep Carreras Leukaemia Research Institute's vision is to be a world-renowned, multi-campus research centre of excellence that contributes towards improved outcomes and a cure for patients suffering from leukaemia and other malignant blood diseases through innovation, sustainability, social responsibility, talent and professional expertise.

VALUES

Altruism, in accordance with the Josep Carreras Foundation's principles

A close, patient-centred approach

Staff commitment

Corporate alignment of the three campuses and the Foundation

Participative scientific leadership

Continuing cooperation and the forging of alliances with stakeholders

Integration of research and healthcare

Continuous improvement and perseverance as a way of working

Conceptual, methodological and technological innovation

Management dynamics that respect the environment

Continuous evaluation and accountability

Efficacy and efficiency in the optimization of resources

Transparency and integration with the fabric of society

ABOUT US / **GOVERNING BODIES**

The highest governing body is the Board of Trustees, which is represented by the Josep Carreras Foundation, the Catalan government's Ministry of Business and Knowledge, the Catalan government's Ministry of Health, the Autonomous University of Barcelona (UAB), the University of Barcelona (UB), Badalona Town Council, the Directorate General for Health Research and Planning, the Catalan Institute of Oncology, the Northern Metropolitan Territorial Area Administration, the Catalan Foundation for Research and Innovation, Hospital Clínic / the August Pi i Sunyer Biomedical Research Institute (IDIBAPS), the UB Hospital Coordination Committee and the Research Centres of Catalonia Institution Foundation (iCERCA).

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ABOUT US / **DIRECTOR**

Dr. Manel Esteller

Dr. Manel Esteller is Chairman of Genetics at the University of Barcelona's Faculty of Medicine and an ICREA Research Professor. Since May 2019, Dr. Esteller has been the Director of the Josep Carreras Leukaemia Research Institute.

Dr. Esteller is considered to be among the top 0.01% of world scientists based on impact by Stanford University (METRICS).

He is also a member of numerous international scientific societies and his work has been recognized by numerous awards, including the World Health Summit Award (2010), the Rey Jaime I Research Award (2013), the National Award in Oncology (2014), the Dr. Josep Trueta Medal from the Catalan government (2015), the National Research Award from the Catalan government (2015), the Gold Medal from the Parliament of Catalonia (2016), the International Award of Catalonia (2016), the Innovation in Healthcare Oncology Award (2018), the Lansdowne Lecture Award, University of Victoria, British Columbia, Canada (2019) and the Narcís Monturiol Medal from the Catalan government (2020).


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CONTRA LA LEUCÈMIA
Josep Carreras

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Dr. Josep Maria Ribera
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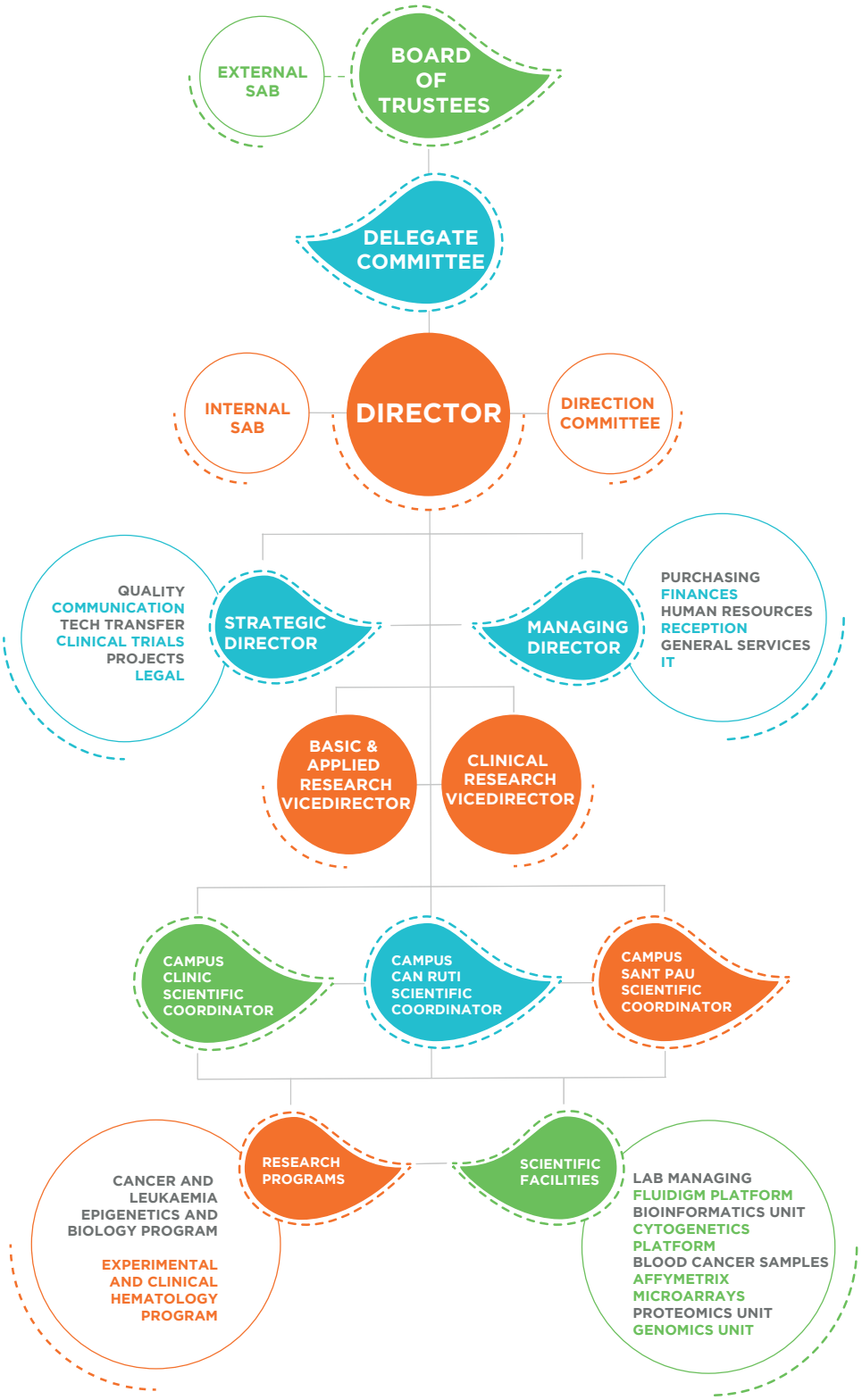
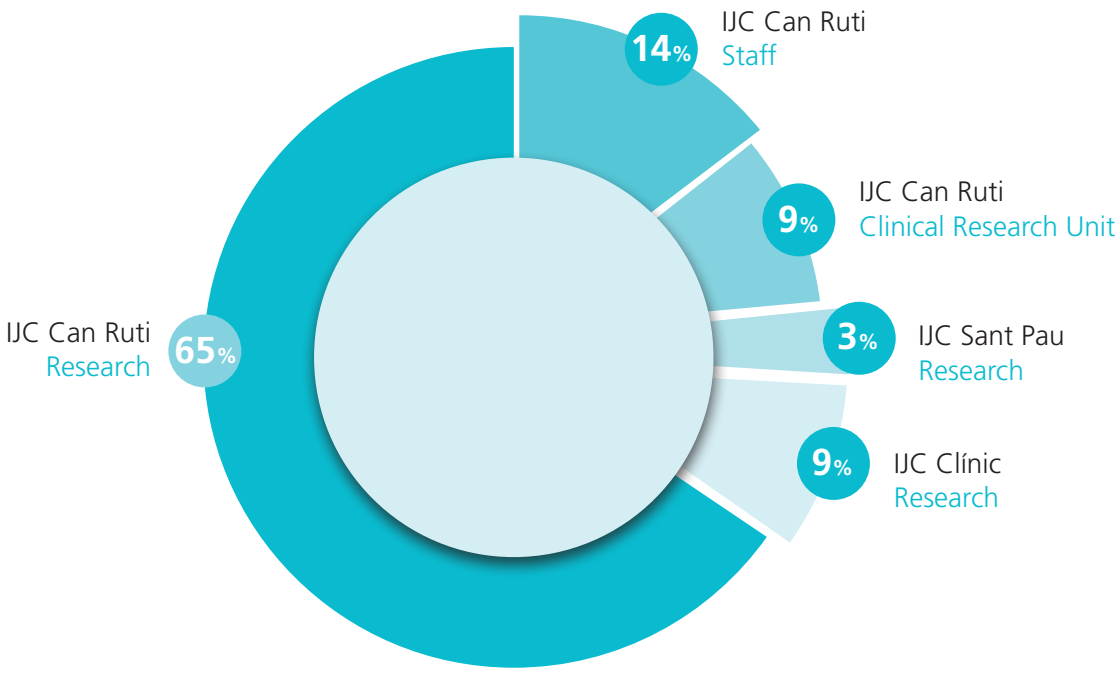
ABOUT US / **ORGANIZATIONAL CHART**



ABOUT US / **OUR STAFF**



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Josep Carreras Institute

Ascribed
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Collaborators

*Data updated in December 2022 due to improvements in institutional databases.

RESEARCH PROGRAMS

Our **26 research groups** study from fundamental science to the development of new treatments and diagnostics and are divided into two programs: the ***Cancer and Leukemia Epigenetics and Biology Program*** and the ***Experimental and Clinical Hematology Program.***

Cancer and Leukemia Epigenetics and Biology Program (PEBCL)

11 groups

1. Cancer epigenetics
2. Cancer genetics
3. Chromatin biology
4. Chromatin, metabolism and cell fate
5. 3D chromatin organization
6. Epigenetics and immune disease
7. Lymphocyte development and disease
8. Regulatory genomics
9. Regulatory RNA and chromatin
10. Epigenetic control of haematopoiesis
11. Transcriptional dynamics in leukemia

Experimental and Clinical Hematology Program (PHEC)

15 groups

12. Acute lymphoblastic leukemia
13. Barcelona Endothelium Team
14. Functional cytomics
15. Myeloid neoplasms
16. Immunohematology and glycobiology
17. Leukemia stem cell
18. Lymphoid neoplasms
19. Multiple myeloma
20. Myelodysplastic syndromes
21. Stem cell biology, developmental leukemia and immunotherapy
22. Stem cell transplantation and cellular immunotherapy
23. Epigenetic therapies
24. Lymphoma translational
25. Oncogenesis and antitumor drugs
26. Cellular immunotherapy and gene therapy

RESEARCH GROUPS

Cancer and Leukemia Epigenetics and Biology Program (PEBCL)

1

CANCER EPIGENETICS

Led by

Manel Esteller

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Technician

Malignant cells behave differently to the rest of the tissue; they present capacities reserved for stem cells, such as proliferation. Since all cells in an organism share the same genetic information, the difference between any cell type, including malignant cells, lies in the subset of information to which they have access. The term epigenetics refers to the many control layers that limit a cell's access to only those parts of the genome relevant to its organic function.

Our research

To shed light on this emerging field, the Cancer Epigenetics group focuses on the establishment of epigenome and epitranscriptome maps for normal and transformed cells, the study of the interactions between epigenetic modifications and noncoding RNAs and the development of new epigenetic drugs for cancer therapy.

Our group's main lines of research are:

1. Defining the epigenome of cancer cells. Basic knowledge of the DNA methylation profile and histone modifications in tumour suppressor genes is of paramount importance to identify what drives cancer formation from an epigenetic perspective. The ability to identify the epigenetic differences between a healthy cell and a transformed cell represents the starting point for our research.

2. Study of the epigenetic machinery and mechanisms. In addition to knowledge of the epigenome, we are interested in understanding the role and function of DNA methyltransferases, the large group of proteins directly responsible for interacting with DNA and shaping the open or closed transcriptional state.

3. Use of epigenetic markers to predict response to antitumour therapies. Our group has a long-standing interest in translating the use of epigenetic knowledge gained from research into biomarkers to predict clinical outcomes. For example, we have demonstrated the relationship between MGMT methylation and the response to alkylating agents in glioma and lymphoma; between BRCA1 and the response to PARP inhibitors in breast and ovarian cancer; and between the protein degradation mediators DERL3 and SVIP and the response to glycolysis inhibitors. Methylation of SRBC and SLFN11 have also been identified as resistance markers for platinum derivatives in human tumours, the regulator of EGFR TBC1D16 has been identified as a sensitizer for therapies with BRAF and MEK inhibitors and the epigenetic loss of the rRNA modifier NSUN5 has been shown to provide sensitivity to cellular stress-targeted compounds.

4. Preclinical testing of epigenetic compounds. We are interested in the development and study of new epigenetic drugs that target DNA methylation and histone modification writers, readers and erasers, and that could exert an anti-cancer effect. We assess its *in vivo* antitumour biological effects in cell lines and mouse models, and study its synergy with immunotherapy agents. Examples characterized in the lab include bromodomain inhibitors and a new inhibitor of histone deacetylase.

We also have a long-standing interest in research into monogenic disorders affecting epigenetic genes, particularly in Rett syndrome. The disease is associated with a germline mutation in MECP2, a protein that is attracted to methylated DNA. Over the years, we have identified the gene targets for MECP2, studied the genomics of Rett syndrome in detail and developed pre-clinical drug studies. In a similar context, we are also curious about the epigenomic profiles of common diseases such as cardiovascular alterations and Alzheimer's and other neurodegenerative diseases.

Finally, we have a keen interest in the establishment of new epigenomic platforms to create comprehensive DNA methylome maps. Our lab is a pioneer in the validation of commonly used DNA methylation microarrays such as 450K and EPIC/850K. The use of these approaches has led to a number of breakthroughs, including the establishment of DNA methylation signatures that are predictive of early dissemination in lung cancer; diagnosis of tumour type in cancer of unknown primary (CUP); and a better understanding of the response to anti-PD1 immunotherapy.

Keywords

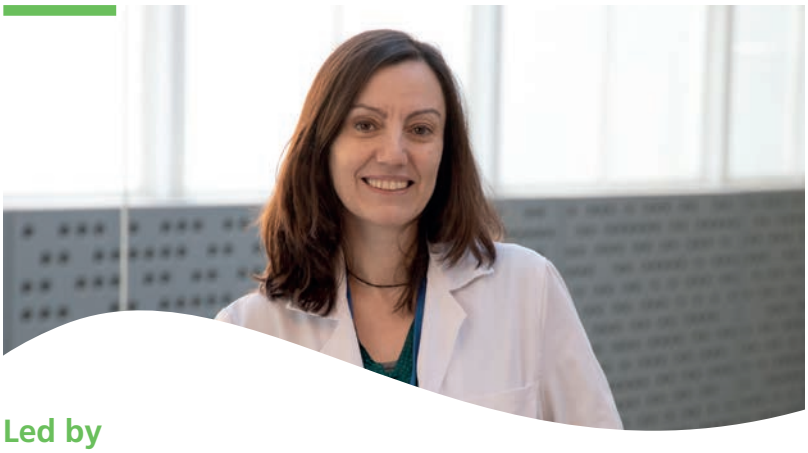
Cancer epigenetics; DNA methylation; RNA epitranscriptomics; histone modification; epigenetic gene silencing.

RESEARCH GROUPS

Cancer and Leukemia Epigenetics and Biology Program (PEBCL)

2

CANCER GENETICS



Led by

Montse Sanchez-Cespedes

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Lung cancer (LC) causes over 1.3 million deaths annually and remains the deadliest type of cancer worldwide. Although efforts in recent years to fully characterize human cancer on a genetic and molecular level have provided important insights to increase our understanding of the gene alteration profile underlying the development of LC, the impact of this knowledge in the survival of patients remains modest. Our group is devoted to the genetic, epigenetic and molecular study of the mechanisms that drive LC development. Ultimately, our purpose is to implement the clinical management of cancer patients and to design novel therapeutic strategies.

Our research

Our laboratory is currently engaged in a number of important projects:

Screening for factors that determine tumour immunoescape and the response to immunotherapy. In the past, we have become increasingly interested in the study of those biological factors, which allow tumours to escape control of the immune system and also determine the response to immunotherapy, especially ICIs. In this regard, we pioneered the discovery of genetic alterations at factors that are involved in antigen presentation (e.g. B2M, HLA-I and TAP1-2) or in the response to gamma interferon (e.g. JAK2) in a subset of LCs and that are associated with a negative immune-related profile and a poor response to ICIs. Currently, we are collaborating with clinicians and pathologists in our associated hospital to pursue the identification and characterization of novel genetic and molecular mechanisms to predict immunoescape and response to ICIs

Genomic and genetic profiling of lung tumours to identify novel targets for therapeutics and determinants for the primary and acquired response to tyrosine kinase inhibitors (TKIs). Over the past few years, we have used high-throughput genomic sequencing technologies, such as whole exome and RNA-sequencing, to gather information about the genetic background and gene expression profiles of lung tumours from both smokers and non-smokers.

Genetic alterations at epigenetic factors: biological understanding and opportunity for novel therapeutics. Over the past 15 years, our group has provided key information to understanding cancer biology. We have pioneered the identification of genetic inactivation at SMARCA4 (the ATPase of the SWI/SNF complex), now recognized as an important tumour suppressor gene, and reported that this protein orchestrates the response to retinoid acid, glucocorticoids and histone deacetylase inhibitors. Furthermore, we have unveiled inactivating mutations at MAX, a key controller of gene expression, in small-cell lung cancer, a very aggressive form of LC. Currently, we are using high-throughput technologies, including chromatin immunoprecipitation sequencing and immunoprecipitation-mass spectrometry, to understand the functional connection between these pathways and the way in which their abnormal function contributes to tumour development and to identify molecular vulnerabilities that can be used therapeutically.

Keywords
Targeted therapeutics; immunotherapy; epigenetic regulation; SWI/SNF-complex; MYC/MAX-pathway.

3 CHROMATIN BIOLOGY

Led by
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PhD Student

The response to genotoxic or metabolic stress conditions has a major impact on the maintenance of genome integrity and is intimately linked to the development of many human pathologies. The onset and development of haematological diseases like leukaemia are strongly influenced by this response, which represents a promising therapeutic approach. Our main goal is to define the epigenetic mechanisms governing this response and its functional implications in genome stability and cancer through a multidisciplinary approach.

Our research

Although the majority of sirtuins are NAD+-dependent deacetylases, some family members also harbour a second enzymatic activity, an ADP-ribosyltransferase (ADPRT) activity. This functional duality is intriguing and represents one of the group's central lines of research. Sirtuins play an important role in the haematopoietic system; as they have been shown to be involved in the maintenance of haematopoietic stem cells, cell differentiation and the immune response, they are also associated with the development of some types of leukaemia.

In this regard, the group's main objectives are:

- **First, to understand the enzymatic duality of sirtuins and their specific contribution to sirtuin function.** In particular, we focus our efforts on the poorly understood topic of ADPRT activity.

- **Second, to characterize sirtuin-dependent mechanisms of genomic stability**, including constitutive heterochromatin integrity, DNA damage signalling and repair, and cell cycle checkpoint control.

- Third, to define **the role of sirtuins in B-cell differentiation.**

- Fourth, to **characterize the functional implication of sirtuins in cancer**, in particular in the context of haematopoietic pathologies such as leukaemia and lymphoma. Our main efforts are currently focused on two types of leukaemia, paediatric B-ALL and AML.

- Fifth, to understand the **involvement of sirtuin function in the beneficial effects of nutrient restriction on ageing development.**

- Finally, we are also developing **a new methodology to measure the activity of sirtuins *in vivo*.**

The development of our lines of work should provide key evidence to shed light on the molecular basis of the pathologies of B-ALL and AML forms of leukaemia and of the ageing process. Moreover, the identification of the proteins involved in these processes and the development of a new methodology should also provide a new approach to the prognosis and treatment of these pathologies.

Keywords
Stress response; sirtuins; epigenetics; leukaemia; ageing.

4

CHROMATIN, METABOLISM AND CELL FATE

Led by
Marcus Buschbeck

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Epigenetic information is written in chromatin. But how exactly do epigenetic mechanisms operate on the molecular level? How do chromatin and, in particular, histone variants contribute to cell fate transitions? How does the environment influence these processes? And how does the metabolic state of a cell impact on its chromatin structure and epigenetic memory? These are the questions we address in the lab.

Our research

Our research focuses on two main lines. Firstly, we mine the chromatin regulatory space to identify novel drug targets that can either help improve current treatments or intercept disease at an early asymptomatic stage. In this regard, we coordinate two research networks: the national RESPONSE network (PIE16/00011), which addresses the problem of intrinsic and acquired drug resistance. By bringing together clinical and experimental groups, we aim to identify urgently needed response-predicting biomarkers and new combinatorial drug targets to increase the rate and durability of response. With the European Innovative Training Network INTERCEPT-MDS, we seek to develop strategies that will allow us to identify and intercept disease cells before the asymptomatic phase.

Secondly, histones form the protein core of the nucleosome, which is the modular building block of chromatin structure. The histone variants macroH2A are unique in their tripartite structure consisting of an N-terminal histone-fold, an intrinsically unstructured linker domain and a C-terminal macrodomain. In relation to these histone variants, we have recently made two major discoveries: the first was that macroH2A proteins play a major role in nuclear organization (Douet et al., 2017, JCS; Kozlowski, Corujo et al., 2018, EMBO Rep). This has the potential to explain how these proteins can act as tumour suppressors, promoters of differentiation and barriers to somatic cell reprogramming (discussed in Buschbeck and Hake, 2017, Nature Reviews). Our second discovery relates to the fact that macroH2As can bind metabolites through their macrodomain and, thus, provide a direct interface between chromatin and metabolism (Posavec Marjanovic, Hurtado-Bagès et al., 2017, NSMB; Hurtado-Bagès et al., 2020, Mol Metabolism).

Keywords

Myelodysplastic syndrome; acute myeloid leukaemia; chromatin; nuclear organization; histone variants.

5
3D CHROMATIN ORGANIZATION

Led by
Biola M. Javierre

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PhD Student

Laureano Tomás Daza
PhD Student

We are a group of passionate scientists with an insatiable thirst for learning about the spatiotemporal architecture of the genome. Our group combines cutting-edge experimental and bioinformatics approaches to understand the specific 3D chromatin organization of normal and malignant haematopoiesis and its interaction with non-coding determinants and trans-regulatory elements. Our long-term goal is to keep making progress in the fight against cancer. We will not stop until a cure is found.

Our research

Our lab's main research goals, which are motivated by this gap in the knowledge, are as follows:

1. To define the cell type-specific 3D chromatin organization in human haematopoietic cells. Human haematopoietic differentiation dogma is currently a subject of debate. All blood cells originate from haematopoietic stem cells (HSCs), which represent the apex of a differentiation cascade of progenitor cell types that gives rise to billions of new differentiated cells every day. HSC differentiation, which progresses through stepwise hierarchical restriction of lineage potential, has been extensively characterized at epigenetic, transcriptional and functional levels.

However, the contribution of genome architecture in regulating haematopoiesis remains unexplored. Previously, we analysed 17 primary differentiated human blood cell types. We showed that promoter interactions are highly cell-type specific. In fact, the promoter interactome, the term used to define the set of interactions in which promoters are involved, segregates according to the relationships of the haematopoietic tree, consistent with the dynamic remodelling of the nuclear architecture during differentiation.

For this reason, we aim to investigate whether the dynamic changes in chromatin interactions between gene promoters and regulatory elements can shape transcription decisions controlling haematopoiesis. These insights could lead to improvements in regenerative medicine strategies, especially bone marrow transplants, which represent one of the most promising approaches to treating many diseases, including blood cancer.

2. To identify the altered DNA topology in blood cancer. The genome architecture plays a key role in genome expression regulation. Chromatin interactions are therefore crucial for cellular health, and errors in these interactions can give rise to the development of a broad range of diseases, including blood cancer. Research into these altered 3D structures can help improve knowledge of the tumour process, thereby providing new opportunities for the development of novel treatment approaches and diagnostic strategies.

3. To prioritize new candidate genes and pathways related to blood cancer. Omics studies have identified thousands of cis and trans determinants associated with blood cancer, but most of them lie in or target non-coding regions, which makes them difficult to interpret. Interestingly, these non-coding regions could exert a regulatory activity, thus suggesting a potential role for these in the deregulation of target genes.

Previously we demonstrated that spatial genome conformation can help connect non-coding single nucleotide polymorphisms (SNPs) with autoimmunity to target genes. Now we want to go one step further by addressing blood cancer.

By studying the physical interactions between gene promoters and regulatory elements, we will be able to connect blood cancer cis and trans determinants to putative target genes, thereby prioritizing new candidate genes and pathways and offering an insight into the genomic regulatory mechanisms underlying cancer.

In addition, the interpretation of the non-coding regions altered in disease will also help us improve patient outcome prediction and allow us to design better, more personalized treatments.

Keywords

Genome architecture, spatial-temporal chromatin organization, haematopoiesis, blood cancer, cis non-coding determinants, enhancer-promoter interactions.

6
EPIGENETICS AND IMMUNE DISEASE

Led by
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We aim to understand the mechanisms that underlie the deposition and removal of epigenetic modifications in immune cells, the influence of genetic and environmental determinants and the acquisition of epigenetic alterations in immune-mediated disease, including primary immunodeficiencies and autoimmune and autoinflammatory diseases. We also investigate the impact of the epigenetic regulation of immune cells in the microtumour environment.

Our research

We began our lines of research more than 10 years ago when we started studying the occurrence of DNA methylation alterations in the context of systemic lupus erythematosus (SLE), an archetypical systemic autoimmune disease. Our study that compared the DNA methylomes of monozygotic (MZ) twins discordant for SLE (Javierre et al., 2010, Genome Res) represented the first high-throughput methylation analysis in autoimmune disease and has served as a reference in the growing field of epigenetics in immune-mediated diseases.

Later, we performed new studies with MZ twins discordant for common variable immunodeficiency (CVID), the most prevalent symptomatic primary immunodeficiency. After obtaining the DNA methylome of different B cell subsets, we found that memory B cells, and not naïve B cells, display DNA methylation alterations (Rodríguez-Cortez et al., 2015 Nat Commun). Interestingly, memory B cells are generally present in lower numbers in CVID patients.

More recently, our team also demonstrated the occurrence of DNA methylation alterations in monocytes in representative autoinflammatory syndromes (Vento-Tormo et al., 2016, J Allergy Clin Immunol). We showed that alterations in the DNA methylome of peripheral blood monocytes reflect the disease activity in rheumatoid arthritis mediated by the elevated levels of inflammatory cytokines present in such a state (Rodríguez-Ubreva et al., 2019, Annals Rheum Dis). These results are related to other studies in our lab, where we showed the direct influence of cytokines and other factors that influence changes in the DNA methylome in a very specific manner in relation to the acquisition of a given phenotype or in pathological contexts such as sepsis (Lorente-Sorolla et al., 2019, Genome Med).

Our main lines of research and specific goals are:

- **To understand the role of epigenetic control and its upstream determinants in relation to immune function.** We aim to understand how immune cell-cell crosstalk, cytokines and other factors, cell signalling pathways and transcription factors determine epigenetic control and impact immune cell function.

- **To identify epigenetic alterations in immune-mediated diseases and investigate their clinical relevance.** Our studies focus on different diseases, including primary immunodeficiencies, such as common variable immunodeficiency (CVID) and hyper IgM type 2 syndrome, and autoimmune diseases, such as rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus.

- **To investigate the effects of immunomodulators and epigenetic compounds in shaping the epigenome and responses of immune cells.** We dissect the molecular consequences of different immunomodulators as well as inhibitors of epigenetic enzymes in immune cells.

Keywords
Epigenetics; DNA methylation; immune-mediated disease; autoimmune disease; primary immunodeficiency.

7

LYMPHOCYTE DEVELOPMENT AND DISEASE

Led by
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Differentiation of haematopoietic stem cells into the distinct blood cell types is a complex process that requires tight regulation through a wide network of transcriptional regulators that define the final identity of each cell lineage. Our research focuses on elucidating the transcriptional and epigenetic mechanisms that determine the identity of B lymphocytes and their deregulation in haematological malignancies such as leukaemia and lymphoma.

Keywords
B lymphocyte development; Epigenetics and transcriptional regulation; HDAC7; B cell acute lymphoblastic leukaemia (B-ALL); Diffuse large B-cell lymphoma (DLBCL).

Our research

Our current research focuses on four main lines:

1. Understanding the entire role of HDAC7 in early and terminal B-cell development *(basic and candidate approach)*

HDAC7 is an epigenetic modulator that represses functional or lineage-inappropriate gene expression in B lymphocytes (J Exp Med, 2016; PLoS Genetics, 2013). We found that HDAC7 is essential for early B-cell development by testing deletion in B-cell progenitors (pro-B cells) in a mouse model, and reported that HDAC7 impairs the expression of inappropriate myeloid and T-cell genes in pro-B cells (J Exp Med, 2016). Furthermore, more recently we defined the function of HDAC7 in the formation of the germinal centre (GC) at secondary lymphoid organs such as the spleen. For this purpose, we have incorporated a mouse model into our research that allows for the deletion of HDAC7 at GC B cells.

2. Establishing HDAC7 as a novel biomarker and potential therapeutic target in pro-B acute lymphoblastic leukaemia (pro-B-ALL) and diffuse large B-cell lymphoma (DLBCL) *(pre-clinical and translational approaches)*

We found that the deregulation of HDAC7 may be involved in the pathogenesis of acute lymphoblastic leukaemia (Cell Death and Disease, 2015). More recently, we established a research line on the role of HDAC7 in acute lymphoblastic leukaemia (ALL) originating at pro-B stage. B-ALL is the most common haematological malignancy among infants under a year old. A specific subgroup of these patients presents an aberrant chromosomal translocation of embryonic origin that involves the MLL and AF4 genes (which generates the MLL-AF4 fusion protein). This subgroup presents an extremely adverse outcome, with a survival rate of below 35%. We have observed that HDAC7 is underexpressed in these infants (Leukemia, 2020), which has led us to conduct in-depth research into the mechanisms underlying this aberrant regulation and explore potential new therapeutic strategies that can restore HDAC7 expression.

Alongside our data on leukaemia patients, the group's previous data demonstrated that HDAC7 is also underexpressed in cell lines from DLBCL, a specific type of adverse prognosis lymphoma. We aim to identify the mechanisms responsible for the loss of HDAC7 expression. Our main goal is to uncover novel small molecules for combinatorial and precision therapy.

3. Working towards precision medicine against DLBCL heterogeneity using organoid culture systems *(proof of concept for drug screenings, unbiased approach)*

We are investigating additional epigenetic regulators in normal and aberrant B-cell generation and implementing 3D organoid cultures from DLBCL sample patients. DLBCLs have enormous heterogeneity and tend to rapidly develop resistance to chemotherapeutic drugs. The implementation of 3D organoid models for testing DLBCL patient responses will represent a game changer in the field; proof of concept and an innovative tool to perform compound library screenings to unveil new drugs for use in combinatorial therapy with current treatments in a personalized manner.

4. Improving immunotherapy combinatorial therapy in DLBCL *(pre-clinical and translational unbiased approaches)*

R-CHOP is the gold standard treatment for DLBCL patients. R-CHOP therapy combines anti-CD20 antibody (immunotherapy) with cyclophosphamide, doxorubicin, vincristine and chemotherapy. The inclusion of rituximab has led to a significant improvement in patient outcomes. However, 30-50% of patients are still not cured under this therapeutic regimen. A significant subset of patients who relapsed after R-CHOP treatment (around 40%) presented a drastic reduction in CD20 expression, which is associated with decreased survival. We apply compound library screenings to identify potential new drugs that could be used in combination with R-CHOP to overcome the high incidence of relapse and resistance in DLBCL patients. Through this unbiased approach, we also aim to unveil potential new markers and candidates for the design and development of novel immunotherapies.

8
REGULATORY GENOMICS

Led by
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We are a group of computational biologists seeking to understand how gene expression is affected by mutations, drug treatments and environmental exposure. Our research approach involves analysing high-throughput gene expression and related data with a view to testing or proposing hypotheses about molecular mechanisms and shedding light on the interaction between environment, genotype and phenotype. We work with genomic data from public databases, as well as data generated in collaboration with labs with complementary expertise.

Our research

Our research focuses on three main areas. Firstly, we study the effect of the environment on gene expression changes that are transmitted from parents to their offspring. We want to understand how information about our exposure to different environments may be encoded in molecules - other than DNA - inside germ cells that are transmitted between generations. Transmission of non-genetic information can influence an individual's phenotype, or disease risk. We would like to find out which molecules in the germline carry such information.

Secondly, we work on non-coding RNAs and other non-coding elements that influence gene expression. We are interested in which non-coding elements affect gene expression and how. These include distal enhancers, small non-coding RNAs and transposable elements. Most genetic variations between individuals occur within the non-coding parts of our genomes. We want to understand which of these variations influence gene expression and potentially phenotype/disease risk.

Finally, we want to understand how epigenetic drugs affect gene expression and chromatin in different genomic contexts. Epigenetic drugs currently used in the clinic include those for the treatment of patients with acute myeloid leukaemia and myelodysplastic syndrome. Our work involves analysing data from experiments on human cell lines. A more in-depth understanding of the effects of these drugs and how they work may lead to improved or more personalized medicine in the future.

Our aim is to contribute to a better understanding of gene regulation and the consequences of drug treatments and inter-individual genetic variation in gene expression. Although most of our research is based on data from animal model organisms or cell lines, we hope that, in the long term, the knowledge acquired will increase our understanding about humans. Extensive aberrant gene expression and genome deregulation are extremely common in cancer, especially haematological forms, and treatments targeting gene regulation pathways are being used for haematological malignancies. Last, but not least, we hope that the data we generate and the analysis methods we develop serve as useful tools for the wider research community.

Keywords
Bioinformatics; gene regulation; epigenetic inheritance; germline; genomics.

9
REGULATORY RNA AND CHROMATIN

Led by
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We study the emerging roles of noncoding RNAs as key regulators of gene expression in physiological cellular programmes and at the onset or during progression of human diseases, with a major focus on tumorigenesis and neurodevelopmental diseases. The research carried out by our group combines biochemical, cellular and global genomic approaches to dissect mechanisms of gene expression regulation with the participation of ncRNAs, with the ultimate aim of revealing molecules of therapeutic/biomarker interest for clinical translation.

Our research

The current lines of research conducted by the group address the following specific topics:

1. New regulatory roles for long noncoding RNAs (lncRNAs): specifically, we study antisense transcripts and their mechanism of action as gene expression modulators, especially as epigenetic regulators. In many instances, these lncRNAs function by interacting and guiding chromatin remodelling complexes (including both DNA and histone modifiers) towards their target sites in the genome to exert gene activating or repressing roles. Their dysregulation forms the basis for a variety of pathologies, including cancer.

2. Oncofoetal lncRNAs: we investigate the function of certain lncRNAs in maintaining undifferentiated, highly proliferative states during normal embryonic development and tissue differentiation and how their expression is reactivated in cancer to sustain cancer cell stemness.

3. RNA-RNA interactions and their impact on fundamental cellular processes: we are especially interested in miRNA biogenesis; a variety of proteins can fine-tune the processing and maturation of specific miRNA sequences in both the cell nucleus and the cytoplasm. We investigate how certain lncRNAs can also influence miRNA production through direct RNA-RNA interaction by enhancing or interfering with the microprocessor machinery.

4. Molecular basis of Rett syndrome: we aim to profile the alterations in the noncoding transcriptome that contribute to this severe neurodevelopmental disease. The brain is the tissue in which RNA-dependent regulatory mechanisms present their highest level of complexity. We use both murine and new human models of the syndrome to investigate how changes in specific ncRNA species help define its physiopathology. With the use of stem cell technology and genome editing, we are currently focusing our efforts on understanding the role of circular RNAs and transcribed ultraconserved regions, two of the most poorly characterized RNA species.

Keywords
Noncoding RNAs; cancer epigenetics; gene expression regulation; stem cells; Rett syndrome.

10

EPIGENETIC CONTROL OF HAEMATOPOIESIS

Led by
Jose L. Sardina

DNA methylation-related genes (including DNMT3A and TET2) are among the most frequently mutated in blood malignancies. Traditionally, studies aimed at understanding the effect of aberrant DNA methylation in cancer patients have focused on gene promoters. However, it has recently been reported that DNMT3A and TET2 preferentially bind to distal gene regulatory regions (enhancers), thereby highlighting enhancers as the most important regions in dynamic DNA methylation studies. Therefore, we are studying how aberrant DNA methylation dynamics impact on the chromatin structure at enhancers during blood cancer onset and progression.

Our research

Since October 2019, we have studied how aberrant DNA methylation at distal gene regulatory regions poisons the chromatin to trigger corrupted gene expression signatures in the cells, thus eventually leading to the onset and progression of haematological neoplasms. This line of research has evident implications for a broad spectrum of patients suffering from blood diseases (CML, AML, CMML, MDS, MPN, MDS/MPN, etc.), all of which share an abnormal genome-wide DNA methylation landscape.

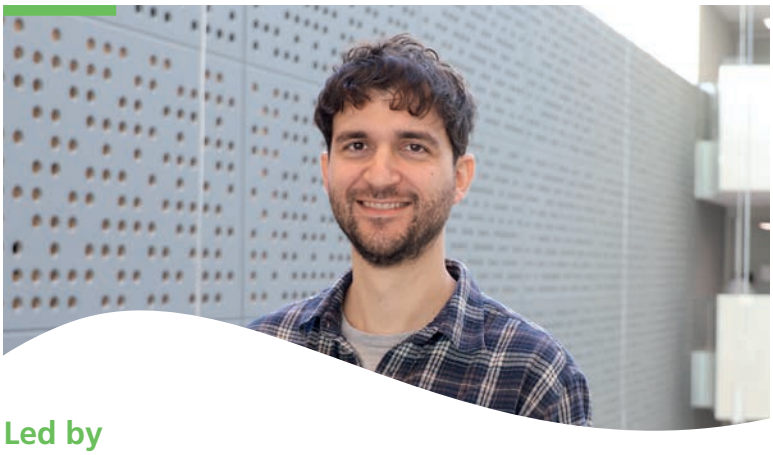
We aim to unravel the different layers of intricated epigenetic information that specify which subsets of genes are expressed in every one of the cells of the haematopoietic system, thereby defining their cellular identity. We hope to apply this knowledge to better understand how and when deleterious transcriptional programmes leading to cellular transformation are activated, thus leading to the discovery of new treatments that will potentially end up in improving the quality of life of patients suffering from a wide range of blood diseases.

Keywords

DNA methylation; TET enzymes; Chromatin; Haematological malignancies; Stem cells.

11

TRANSCRIPTIONAL DYNAMICS IN LEUKAEMIA



Led by
Sergi Cuartero

Normal development of blood cells requires the precise regulation of thousands of genes. As a consequence of malignant mutations in transcriptional regulators, this control can be lost, thus leading to blood diseases such as leukaemia. The main interest of our lab lies in understanding the mechanisms that control transcription in normal and malignant blood cell development. We employ a combination of genome-wide approaches, advanced microscopy imaging and single-cell technologies to address questions regarding the integration of haematopoietic differentiation signals with gene regulatory mechanisms. By answering these questions, we aim to uncover vulnerabilities in haematologic malignancies and open up new therapeutic opportunities.

Our research

To understand how this occurs, we study the mechanisms that regulate transcription during haematopoietic differentiation and investigate the leukaemogenic potential of mutations in transcriptional regulators and epigenetic modifiers. We have previously investigated the role of mutations in proteins that drive the three-dimensional organization of the genome. We demonstrated that these mutations impair the transcriptional response to inflammatory signals. Specifically, we showed that mutations in the cohesin complex, which are frequently found in AML, promote increased resistance to the differentiation-inducing effects of inflammation and alter the normal progress of haematopoietic development.

Now we would like to expand on these findings to explore how extracellular signalling pathways become uncoupled from transcriptional activity through cohesin mutations and other frequently mutated transcriptional regulators.

Our main goals are:

- **To understand the role of mutations in haematopoietic transcription factors and chromatin regulators in acute myeloid leukaemia (AML).** More than 70% of all AML patients carry mutations in proteins that are responsible for the proper regulation of genes. Most of these proteins control thousands of genes, and the precise reason why their mutations promote leukaemia are not fully understood. Using genetic models to mimick these mutations, we aim to dissect their impact on gene expression and thus understand how they promote a selective advantage.

- **To characterize the impact of inflammatory signalling on normal haematopoietic differentiation and during leukaemic progression.** Inflammatory signals have a strong influence on blood development, and chronic inflammation has been associated with myeloid diseases such as myelodysplastic syndromes (MDS). We want to understand the impact of inflammation on the progression of myeloid malignancies and how are they linked to the most common mutations.

Keywords
Haematopoiesis; chromatin; AML; MDS; cohesin; inflammation.

12

ACUTE LYMPHOBLASTIC LEUKAEMIA GROUP (ALL GROUP)

Led by
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Our research focuses on analysing the genomic and epigenomic landscape of patients with adult ALL (acute lymphoblastic leukaemia) to find out genetic alterations that predict patients' response to treatment and to identify new alternative (targeted) therapies to apply to those patients. In this way, we aim to design more personalized treatments to increase the probability of survival of ALL patients.

Our research

The group's current research is divided into two main areas, according to the two main subtypes distinguished in ALL:

1. Precursor B-cell acute lymphoblastic leukaemia (BCP-ALL):

BCP-ALL is the most prevalent ALL subtype and accounts for 75% of ALL cases. Although it is a highly heterogeneous disease at genetic level, different cytogenetic subtypes have been identified and, more importantly, their prognosis has been clearly established in many clinical trials. This has allowed clinicians to stratify patients according to their genetic profile to schedule intensive or less intensive treatments. However, not all patients within the same cytogenetic subtype show the same degree of response when receiving the same treatment, which would suggest that additional genetic alterations may modulate the intrinsic prognosis of each cytogenetic subtype. In this regard, we are interested in the in-depth characterization of as many patient samples as possible to identify these genetic alterations that lead to treatment resistance and disease recurrence. To achieve this objective, we work at both clinical and translational level.

2. T-cell acute lymphoblastic leukaemia (T-ALL):

T-ALL is the least common ALL subtype (25% of adult ALL cases), and the most complex and heterogeneous at genetic level, with a dismal prognosis. Traditionally, therapeutic protocols for ALL do not take account of the differences in the molecular background of the two main ALL subtypes, and few new alternative therapies are available only for refractory or resistant ALL, especially T-ALL. In light of this scenario, we believe that if we want to improve the survival rate of patients with T-ALL, we first need to obtain detailed and relevant molecular information to accurately define the risk and thus decide on the treatment. Secondly, we need specific therapeutic alternatives to apply to these new oncogenetic T-ALL subgroups.

We are convinced that new treatments for ALL patients can be obtained only through basic research. The valuable information on the genome and epigenome extracted from patient samples will make it possible to detect genetic lesions that involve critical pathways for the proliferation of ALL cells and could be targetable with new drugs. This research is changing the treatment paradigm of ALL and will contribute significantly to improve patient survival.

Our main goals are:

- To identify the genetic alterations leading to treatment resistance and disease recurrence in adult ALL.
- To accurately define the risk of ALL by genetic analysis at diagnosis and relapse in order to decide on the most appropriate treatment.

Keywords
Acute lymphoblastic leukaemia; adults; genomic analyses; minimal residual disease; treatment resistance.

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BARCELONA ENDOTHELIUM TEAM

Led by
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The Barcelona Endothelium Team (BET) is a research group focused on the study of the endothelium and the endothelial damage associated with various pathologies. One of our most productive lines is the characterization of endothelial damage in the context of both autologous and allogeneic haematopoietic cell transplantation (HCT). In this research area, we explore the mechanisms involved in endothelial dysfunction, the role of the endothelium in the development of some complications observed after HCT, and the search for pharmaceutical agents that could protect the endothelium and, consequently, prevent these complications.

Our research

Since 2009, we have been exploring the pathophysiology of endothelial complications associated with HCT.

Our group has extensive experience in the study of the endothelial dysfunction that develops in association with different vascular pathologies, such as the early complications associated with haematopoietic cell transplantation, obesity, chronic kidney disease, thrombotic microangiopathies and sepsis.

We also explore strategies for the protection of this endothelial dysfunction to improve patient health. In this regard, one of our main interests is to evaluate different compounds that potentially exhibit the capacity to protect the endothelium and to decipher their mechanisms of action.

A more in-depth understanding of the mechanisms that induce and modulate endothelial dysfunction may help prevent some HCT complications and thus improve our patients' quality of life and outcomes.

Our main lines of research are:

- To characterize the endothelial activation and dysfunction associated with cardiometabolic diseases through *in vitro* models.
- To elucidate the mechanisms that lead to endothelial dysfunction.
- To investigate agents with potential protective effects on the endothelium to prevent complications.
- To find soluble markers with prognostic and diagnostic value for vascular complications.
- To study complement pathways and complement deficiencies in thrombotic microangiopathies.
- To assess platelet physiology and alterations of haemostasis by using perfusion devices to explore adhesive and cohesive properties of platelets under flow conditions.

Keywords
Endothelium; Inflammation; Diagnostic and prognostic markers; Thrombotic microangiopathies (TMA), Drugs.

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FUNCTIONAL CYTOMICS

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The ability to bridge large-scale and single-cell approaches at a functional level is key to identifying biomarkers expressed in rare cells, and particularly in cancer stem cells (CSCs). Our interdisciplinary group investigates and develops key experimental approaches to understand the principles underlying the emergence and prevention of tumourigenesis and cancer therapy resistance, with the aim of translating biomedical science to integrated clinical practice and public health through certified transfer processes in cooperation with trusted allies and partners.

Our research

Our current research projects use innovative approaches to study the expression of primitive stem cell markers during the origin, progression and maintenance of cancer and the management of cancer; the quality and safety of haematopoietic blood progenitor and stem cell grafts; the role of myeloid-derived suppressor cells in immunotherapy and targeted therapy for clinical decision-making; new cytomic strategies for whole blood and marrow immunostaining; the use of natural compounds for cancer treatment; and the accurate detection and significance of minimal residual disease in acute leukaemia.

Our goal is to provide patients with a wide range of scientific support strategies, through precision, oversight and accuracy, to achieve:

- Clinical implementation of functional cytomic assays, and precision/personalized high-quality assays for individual patients by integrating functional cytomics to accelerate new experimental approaches for *ex vivo* and *in vivo* drug sensitivity.
- Translation of functional screening to novel clinical strategies. Measurement of the impact of exogenous interventions such as drug exposure on tumour cell phenotype. Functional screening delivers precise cytome information regarding the capacity of drugs to elicit the apoptotic responses/drug resistance of cancer cells without prior knowledge of the molecular mechanistic underlying such responses.
- An understanding of drug resistance and prediction of effective drug combinations. Examples include strategies to tackle resistance to tyrosine kinase inhibitors in a rare population of cancer stem cells known as the "side population" from patients with chronic myelogenous leukaemia, myelodysplastic syndromes, acute leukaemia and other malignant haematologic diseases that affect patients of all ages.
- A reduction in costs by obtaining specialized instrumentation and personnel for the execution of cytomic screening in partnership with stakeholders and biotechnological partners.
- Functional and immunophenotyping datasets aimed at understanding complex functional-to-phenotype correlations, thereby accelerating discovery of the biology of leukaemogenesis and the clinical implementation of novel therapies.

Keywords
Cytometry; cancer stem cells; cytome; human cytome project.

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MYELOID NEOPLASMS

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Genetic profiling for haematological malignancies involves chasing a moving target. Not so long ago, leukaemias were stratified based on karyotype abnormalities. In recent years, however, knowledge of molecular genetics in haematology has increased significantly, thus offering new clinical opportunities. It has now been shown that gene expression, mutations and other genetic and epigenetic abnormalities also have diagnostic, prognostic and therapeutic implications.

Our research

Our research focuses mainly on the following areas:

- **Chronic myelomonocytic leukaemia (CMML)** is a clonal haematopoietic malignancy characterized by features of both myelodysplastic syndromes and myeloproliferative neoplasms, an average overall survival of 20 months and 15-30% of progression to acute myeloid leukaemia (AML).
- **The classification and prognosis of the group of diseases termed myelodysplastic syndromes (MDS)** depend on the blast count, number of cytopenias and cytogenetic data. Chromosomal abnormalities can be detected in just 50% of patients. For this reason, the detection of an aberrant methylation pattern for MDS or a common mutation gene profile may be useful for the diagnosis of this haematologic malignancy. Additionally, the detection of a characteristic methylation pattern or mutations in genes involved in epigenetic regulation could be associated with response to hypomethylating agents, thereby making it possible to select a more personalized, dose-adjusted treatment adapted to the characteristics of each patient.
- **Chronic myeloid leukaemia (CML)** is a clonal haematopoietic malignancy characterized by the presence of the BCR-ABL1 fusion gene, which gives rise to a protein with high tyrosine kinase (TK) activity. The first-line treatments for CML are TKI (e.g. imatinib), which leads to a cytogenetic and molecular response in most patients in the chronic phase. However, some patients do not respond to this treatment or lose their initial response.
- ***BCR-ABL1* negative classic myeloproliferative neoplasms (MPNs)** include polycythaemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). These disorders may undergo phenotypic shifts and may specifically evolve into secondary myelofibrosis (MF) or acute myeloid leukaemia (AML). The discovery of the *JAK2V617F* and *CALR* mutations in the MPNs has stimulated great interest in the underlying molecular mechanisms and treatment of these diseases.

Keywords
Myeloproliferative neoplasms; chronic myeloid leukaemia; myelodysplastic syndromes; MPN/MDS; acute myeloid leukaemia.

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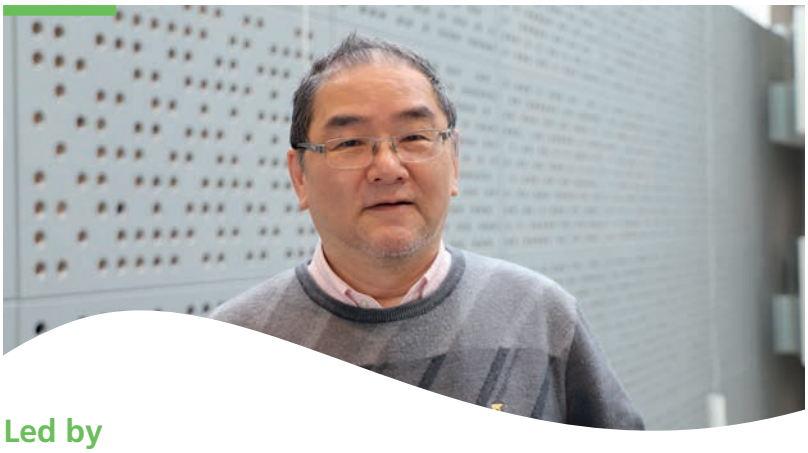
IMMUNOHEMATOLOGY AND GLYCOBIOLOGY



Led by
Fumiichiro Yamamoto

Group members

Miyako Yamamoto
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Emili Cid Roldós
Postdoctoral Investigator

Glycans on glycoproteins and glycolipids play an important role in various biological phenomena of cells, tissues and organs, at both physiological and pathological level. We have spent the last three decades studying the ABO blood group system, the ABO gene, the A and B glycosyltransferases (AT and BT) and the A and B glycan oligosaccharides through a range of scientific disciplines, including molecular genetics, enzymology, biochemistry, glycobiology, forensic science and even the study of evolution. Recently, we have shifted our research focus towards elucidating the molecular genetic basis of glycan alterations in cancer and developing a new cancer immunotherapy targeting cancer-specific glycans.

Our research

The ABO polymorphism confers differential susceptibility to cancer. For example, individuals in group A are 25% more likely to develop stomach or pancreatic cancer than those in group O. Furthermore, A and B antigens are often expressed aberrantly in cancer. Their expression may decrease or be lost due to the downregulation of the transcription of the A/B gene. On the other hand, the A(-like) and B antigens can be expressed in tumours, respectively, of individuals in group B and O and individuals of group A and O, and it is therefore assumed that these people do not express these glycans genetically.

In addition to A and B antigens, genetically incompatible glycan expression in cancer is also observed with other blood group systems. The heterophilic Forssman antigen (FORS1) can also appear in cancer, although humans are a Forssman-negative species and almost all humans possess anti-FORS1 antibodies.

Unlike the relatively low incidence of these genetically incompatible antigens, cryptic glycan antigens, such as Tn and TF(T), appear more frequently. These glycans are masked in normal tissues, but highly exposed in human solid tumours and haematological malignancies. All humans also have abundant anti-Tn and anti-TF(T) antibodies.

We have recently been studying the molecular genetic mechanisms for the expression of genetically incompatible glycan antigens and have thus far revealed several potential mechanisms, including the appearance of FORS1 induced by the deletion of exon 3 or 4 of the AT mRNA. Because altered splicing is a hallmark of cancer, this mechanism may be responsible, at least partially, for FORS1 expression in group A and AB individuals.

We are currently investigating the potential mechanism by which incompatible A antigens appear in group O individuals through complementation by recombination of DNA or trans-splicing of RNA and also expression of FORS1 due to changes in specificity resulting from incorrect intra-Golgi localization of modified glycosyltransferases.

Recently, we have begun to investigate the use of genetically incompatible and/or cryptic glycan antigens as molecular targets for medical intervention. Drawing on our expertise in immunohematology and glycobiology, we will develop a new immunotherapy that employs minitransfusion/injection of mismatched RBCs expressing cancer-specific genetically incompatible and/or cryptic glycans to enhance immunity against cancer cells expressing these glycans. In addition, we are also exploring the possibility of using the forced expression of genetically incompatible glycans to make cancer cells susceptible to natural immunity.

Keywords
Genetically incompatible glycan antigens; cryptic glycan antigens; cancer immunotherapy; disease susceptibility; ABO polymorphism.

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LEUKEMIA STEM CELL

Led by
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Leukaemic stem cells are the main cause of tumour initiation and maintenance, and eradicating them is essential to eliminate leukaemia. We search for new therapeutic targets that will enable us to gain a better understanding of the underlying biology of leukaemia, thereby uncovering their diagnostic and prognostic potential. In addition, we develop new, more effective and selective drugs.

Our research

Our research group also focuses on T-cell acute lymphoblastic leukaemia, a predominantly paediatric T lymphoid malignancy. Although the cure rate is high, relapse processes are difficult to manage clinically, so new treatments are needed to prevent such relapses, as well as the refractory response.

One thing that all these leukaemias have in common is that they originate in a population of leukaemic stem cells, which are also responsible for maintaining the disease. Therefore, eliminating these cells is crucial to eradicate leukaemia. In addition, this population displays greater resistance to chemotherapy and a longer half-life.

Due to the similarities between leukaemic stem cells and healthy haematopoietic stem cells, our research group is striving to develop differentiation therapies in combination; in other words, therapies that trigger the terminal differentiation of the population of leukaemic stem cells, which eliminates their capacity to initiate and maintain the disease and enhances its chemosensitivity.

Since 2011, our work has focused on searching for new therapeutic targets in these blood disorders to enable us to identify new biomarkers that can be used for prognostic and/or diagnostic purposes, thereby gaining greater insight into the biology behind these leukaemic processes and developing new drugs that specifically attack the population of leukaemic stem cells.

Using bioinformatic tools, we have described the different molecules involved in blocking differentiation, a characteristic feature of leukaemic stem cells. Moreover, we have studied the role of the different signalling pathways involved in the survival and differentiation capacity of leukaemic stem cells. In this respect, we have identified new chemical compounds with the power to modulate these signalling pathways that can be used as new drugs to treat these leukaemias. In addition, we evaluate the potential of these biomarkers for use during the diagnosis and/or prognostic stratification of patients.

Studying the molecular mechanisms responsible for leukaemic transformation mechanisms is essential for gaining a better understanding of leukaemic pathogenesis and guiding the rational development of individualized therapies for each patient.

Keywords

Leukaemia; leukaemic stem cell; drug development; haematopoiesis; differentiation therapies.

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LYMPHOID NEOPLASMS

Led by
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Our research is focused on the study of rare lymphomas, such as those that affect immunosuppressed patients, in terms of both clinical and genetic aspects. We have made important contributions to this field and our current objective is to reveal genetic and epigenetic characteristics of lymphoid neoplasms that occur mainly in immunosuppressed individuals. The purpose is to identify markers to improve the accuracy with which these patients are managed. Furthermore, we aim to implement liquid biopsy as a tool for diagnosis and follow-up of aggressive lymphomas.

Our research

Our group focuses mainly on the research of AIDS-related lymphomas (ARLs). The most frequent ARLs are diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL) and Hodgkin lymphoma (HL). Plasmablastic lymphoma (PBL) and primary effusion lymphoma (LEP) are less frequent, but typically present in immunosuppressed individuals. We also study other haematological disorders with an increased incidence in the HIV-positive population such as Castleman disease (CD).

In particular, we study the clinical aspects and biological mechanisms of lymphomas, especially those presenting in HIV-infected patients. In this sense, Tomás Navarro, the group's PI, has focused on the study of the clinical and biological aspects of these lymphomas throughout his entire career, and he and his research group at the Josep Carreras Institute (IJC) are currently carrying out an in-depth study of new markers and genetic aspects of these lymphoid neoplasms.

Our main areas of research are:

1. Genetic studies on HIV-related lymphomas: Diffuse large B-cell lymphoma is the most frequent type of lymphoma in the HIV-infected population. Although HIV-infected patients are treated with the same regimens as HIV-negative individuals and similar responses are obtained, their survival rate is lower due to the higher susceptibility to infections and secondary neoplasms. This is due mainly to the fact that the biological context of HIV-related lymphomas and the etiopathogenesis may be distinct from non-HIV lymphomas. Disclosure of the transcriptome of HIV-DLBCL and the altered signalling pathways could make it possible to define prognostic factors and to identify drugs that could revert abnormal cell functioning.

2. Liquid biopsy in aggressive lymphomas: A non-invasive method, such as a liquid biopsy, could represent an important advance in clinical practice for the diagnosis and follow-up of DLBCL. This technique could be useful to diagnose DLBCL earlier, and in a more comprehensive and accurate manner than with tissue biopsy alone. Moreover, liquid biopsy could be used to reveal treatment resistance and to monitor patients and detect lymphoma relapses earlier.

3. Genetic studies on plasmablastic lymphoma: Plasmablastic lymphoma (PBL) is a rare B-cell lymphoid neoplasm that especially affects immunocompromised individuals and has a poor prognosis. Unlike other lymphomas, the genetic and epigenetic alterations have been subject to few studies in patients with PBL.

We believe that genetic and epigenetic profiles will help clarify the mechanisms involved in lymphomagenesis and identify potential biomarkers, thus allowing cases to be classified more effectively. The possible diagnostic and/or prognostic impact of these markers could pave the way for the design of new targeted therapies, thus leading to new treatment approaches and improving the outcome of patients suffering from the lymphomas on which our research focuses, i.e. AIDS-related lymphomas, plasmablastic lymphoma and Castleman disease.

Our ultimate aim is to cure more patients with these rare diseases through strategies such as early detection, more accurate diagnosis, better follow-up and, finally, targets for new drugs.

Keywords

Non-Hodgkin's lymphoma; Hodgkin lymphoma; HIV; Epstein-Barr virus; diagnosis; prognosis; marker; treatment; targeted therapy; early detection.

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MULTIPLE MYELOMA

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Multiple myeloma is a cancer of plasma cells, a type of white blood cell that accumulates in the bone marrow and interferes with normal blood precursors and bone remodelling, thus causing anaemia, bone lesions, renal insufficiency and recurrent infections. Between four and five out of 100,000 people are diagnosed every year. Despite the fact that treatments and prognosis have greatly improved in recent years, multiple myeloma is not yet curable. It is a recurrent disease that can leave important sequelae after each relapse.

Our research

Since 2005, our clinical research team has participated in the main international collaborative phase I to phase III trials that have led to our current standards of care, with a particular focus on establishing the optimal combinations of agents with clinically relevant synergies, thereby providing the best disease-free intervals while minimizing the toxic cost of treatment. Still focusing mainly on clinical research, the IJC's association of clinical researchers and basic researchers has taken an integrative approach to provide translational insight with an impact on patients and society. Prior projects have focused on response kinetics to proteasome inhibitors and immunomodulating agents and the relationship between response kinetics and durability in terms of time to relapse and time to next treatment.

Active trials are already focusing on the efficacy of next-generation combinations, including antibody-drug conjugates, T-cell engagers and CAR-T cells. We are interested in the identification of subjects unlikely to respond to optimized first-line strategies and, therefore, of ideal candidates for such trials with novel immunotherapeutic approaches.

On the other hand, we aim to identify individuals who will present an optimal response to such combinations and who are candidates to discontinue treatment and avoid the toxicity associated with long-term treatment with minimal relapse risk. As part of a first-line clinical trial in newly diagnosed patients (ICOMM19), which was recently launched in hospitals associated with the Catalan Institute of Oncology, we will be able to study the baseline genetic characteristics of patients who will uniformly receive treatment with a combination of proteasome inhibitor and an immunomodulatory drug. We expect approximately 60% of those patients to present a prolonged response. There is significant interest in the characteristics of immunologic recovery in patients with multiple myeloma who achieve long-term remission. Such information is important to understand the interplay between immunosurveillance and residual or occult myeloma cells. However, it would also help define potential early therapeutic interventions in patients who are expected to relapse. Data on the immune status of this particular patient subgroup are scarce. Prolonged follow-up of patients enrolled in the ICOMM19 trial will allow us to study the presence and activity of several subgroups of lymphocytes involved in immune surveillance and define patient subgroups with different risks of progression.

Keywords:
Multiple myeloma; synergistic combinations; immuno-drug conjugates; T-cell engagers; CAR-T cells.

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MYELODYSPLASTIC SYNDROMES

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Our research focuses on unravelling the heterogeneity of myelodysplastic syndromes (MDS), mainly through the use of genomic techniques. Our projects aim to characterize the genetic alterations in MDS and integrate this data with clinical information to ascertain how they might impact patient healthcare. The integration of such information would help guide us in the diagnosis and prediction of clinical outcomes and the definition of biomarkers to better stratify the probability of response to specific treatments.

Our research

We study MDS patients who harbour a specific cytogenetic alteration: the deletion of the long arm of chromosome 5 (5q deletion). We have sought to improve the genetic characterization of these patients by studying the impact of adjunct cytogenetic abnormalities on their prognostic stratification; how cytogenetics and mutations can influence the response to lenalidomide treatment; the molecular landscape of MDS through next-generation sequencing techniques; and, finally, intratumoural heterogeneity before and after lenalidomide treatment using single-cell techniques.

In addition, we are interested in studying the whole spectrum of MDS and myeloid-related neoplasms.

Our research also addresses the following lines:

- Evaluating the feasibility of using peripheral blood samples to perform genetic analyses (SNP-A and NGS) in MDS.
- Monitoring mutational burden in low-risk MDS patients through the use of sequential peripheral blood samples to minimize invasive techniques on these patients.
- Genetic characterization of myelodysplastic syndromes / myeloproliferative neoplasms (MDS/MPN) to define the genetic changes that could contribute to the differential diagnosis and prognostic stratification of these patients.
- Genetic characterization of therapy-related myeloid neoplasms.
- Mechanisms of progression from clonal haematopoiesis to MDS.

We are also involved in national and international networking groups with a view to joining efforts to study bigger patient cohorts. Analysis of genetic alterations in large, well-characterized patient cohorts is essential to identify specific genotype-phenotype associations and establish the clinical impact of the alterations. One example of an study in which the MDS Group collaborated involved the definition of a prognostic scoring system specifically for MDS patients (Revised International Prognostic Scoring System, IPSS-R), and we are currently involved in the molecular scoring system IPSS-M.

Within these cooperative working groups, we also aim to establish a consensus regarding how to diagnose and treat MDS patients, how to deal with clonal haematopoiesis and how to apply NGS in the clinical management of MDS. These recommendations are translated into the creation of guidelines for the scientific and medical community.

Through our research, we intend to contribute to a better understanding of MDS from a genomic point of view. In addition, by integrating the results of our research into clinical information, we also expect to help refine the current criteria to diagnose MDS, predict patient outcomes and select the best treatment for each patient.

Keywords

Myelodysplastic syndromes; chronic myelomonocytic leukaemia; intratumoural heterogeneity; myelodysplasia; cytopenias; CHIP; TRMN.

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STEM CELL BIOLOGY, DEVELOPMENTAL LEUKAEMIA AND IMMUNOTHERAPY

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Our group is interested in understanding the cellular origin, aetiology and pathogenesis of childhood leukaemia. We aim to ascertain the cell in which mutations occur, i.e. the target cell. Moreover, we strive to discover which cells are responsible for triggering relapses, i.e. leukaemia stem cells. Lastly, we work to identify new therapeutic targets and develop more targeted, less toxic therapies. To achieve this, our laboratory uses various approaches, including genetic studies, epigenetic techniques and animal models, as well as adoptive cell immunotherapy tools.

Our research

Given that acute childhood leukaemia (including the B, T and myeloid variants), and childhood cancer in general, are relatively uncommon illnesses, with around 500 cases in Spain each year, it does not represent a priority target for the pharmaceutical industry. As a result, there is a serious lack of active programmes that aim to identify medicines to target childhood cancer. Since 2000, the researcher Pablo Menéndez, an international leader in this form of childhood leukaemia and the head of our research group, has been investigating the origin of this disease *in utero*, as well as its aetiological causes and physiopathological mechanisms. In 2016, we began researching non-toxic, targeted adoptive cellular immunotherapies for these children with the aim of preventing the long-term effects of current chemotherapy.

Our group is currently involved in various lines of research in pursuit of the following objectives:

1. To understand the aetiology and pathogenesis of leukaemia in breastfeeding infants. To do so, we use primary samples taken from patients and develop different animal and cellular models based on prenatal (embryonic, foetal) and postnatal (neonatal and adult) stem cells. Of all forms of childhood leukaemia, we are particularly interested in understanding the molecular and cellular origin of a specific subtype of ALL-B: ALL-B with translocation 4;11, which expresses the MLL-AF4 fusion oncogene. This leukaemia typically affects breastfeeding infants. It is extremely aggressive and responds very poorly to treatment. Currently there are no models that reproduce this pathology due to the fact that the molecular and cellular mechanisms underlying its aggressiveness and extremely short latency remain poorly understood.

2. To gain a better understanding of the role of bone marrow (BM) stroma in chemoresistance in acute myeloid leukaemia (AML) and identify new therapeutic targets for AML, which is the most common form of leukaemia in adults and whose prevalence increases with age. It is a haematological malignancy with an unfavourable prognosis and is associated with high rates of resistance to current treatments and frequent relapses. In the vast majority of patients, only allogeneic transplantation from haematopoietic progenitors has proven to be curative, although it is associated with not inconsiderable mortality rates and significant comorbidities, such as graft-versus-host disease.

3. To improve adoptive cellular immunotherapies against ALL-B, ALL-T and AML. To achieve this, we are searching for new therapeutic targets and developing new CARs (chimeric antigen receptors) for the different types of acute leukaemia. We aim to express the CARs in autologous or allogeneic effector T-lymphocytes generated without the need for genome editing to eliminate TCR, CD3 and other molecules that play a role in immunological synapse.

Keywords

Paediatric leukaemia; stem cells; immunotherapy; MLL rearrangements; PDX models.

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STEM CELL TRANSPLANTATION AND CELLULAR IMMUNOTHERAPY

Led by

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We conduct research into cell immunotherapy treatments for patients with advanced malignant blood disorders, who tend to have a very short life expectancy. To treat such patients, we develop CAR-T and CAR-NK therapies based on adding chimeric antigen receptors (CAR) to cells of the immune system, such as T-lymphocytes and NK cells, respectively. CARs help recognize and attack tumour cells exclusively, specifically and effectively, thereby preventing an autoimmune response and reducing secondary effects on healthy cells.

Our research

We are studying what happens at a molecular level between CART and CB-NK cells throughout the process of recognizing, making contact with and attacking tumour cells in order to identify which proteins and defence strategies are used by CART, CB-NK and other cells in the immune system. Moreover, we are examining what happens within the environment of the cells when they come into contact with tumour cells. This knowledge will help us develop better strategies to improve the efficacy of these therapies.

When there is cell-cell contact between CART and MM, they both release a secretome, or cocktail of molecules. The tumour secretome makes the CART cells go into senescence, which makes them lose their capacity to multiply, thereby reducing the efficacy of the treatment.

Identifying the proteins that compose the tumour secretome will enable us design inhibitors to prevent senescence and the loss of the CART cells' efficacy. Moreover, revealing the composition of the secretome of CART cells with anti-MM activity may have a very positive impact on several studies on T-cell immunology, as this will add new aspects to their functionality.

In short, through our research, we aim to achieve the best possible scenario: to cure patients and ensure that they do not relapse. To date, we have discovered that the combined use of CART and CB-NK cells is highly effectively against blood cancers such as MM. We are confident that, if we achieve greater efficacy of these treatments, our results will also have an impact on the treatment of haematological malignancies, as well as on solid tumours and other applications of immunotherapy.

Keywords

Multiple myeloma; B-cell malignancies; chimeric antigen receptors; T lymphocytes; NK cells; cord blood-derived NK cells; haematological malignancies; B-cell maturation antigen.

23 EPIGENETIC THERAPIES

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Epigenetic therapies aim to modify the epigenome, the set of molecular processes that regulate gene expression without altering the DNA sequence and can change the course of a disease and its phenotype. There are now examples of epigenetic drugs for treating haematological malignancies approved by the United States Food and Drug Administration (FDA). However, the volume of promising preclinical evidence far exceeds the number of epigenetic research projects that have resulted in clinical applications to patients. Therefore, more translational studies that may lead to the development of more specific epigenetic drugs and more robust biomarkers are required.

Our current research

Since 2011, we have focused on the concept of clinical epigenetics, or the clinical translation of epigenetic findings. Basically, we have been interested, firstly, on the definition of epigenetic-based biomarkers for clinical management; secondly, on therapeutic applications of drugs with epigenetic targets (in fact, this is the main focus of the recently formed EPITARGET group at IJC); thirdly, on rare diseases associated with epigenetic defects in the germline; and, finally, on the use of DNA methylation as a biomarker of safety and efficacy in regenerative medicine.

Our research in the Epigenetic Therapies group aims to ascertain the therapeutic benefit of targeting epigenetic alterations in cancer together with the epigenetic-based stratification of patients to predict therapy response. To achieve this, we develop research based on three specific aims:

1. Identification of the epigenetic alterations that act as drivers of tumour progression ("druggable epigenetic alterations"). We aim to explore the epigenetic network consisting of DNA methylation and discover potential epigenetic drivers that might play a causative role in haematological cancers. We apply the new possibilities offered by CRISPR-dCas9 directed genome targeting to set up epigenome editing systems that target DNA methylation and demethylation to differentially methylated regions identified in cancer cells. By combining these methods and in vitro proliferation assays, we identify those methylation changes that directly stimulate the growth of healthy cells or inhibit the growth of cancerous cells.

2. Validation of epidrugs that can efficiently revert aberrant epigenomes in cancer. We aim to determine whether cancer cells with genetic alterations that affect epigenetic genes are more susceptible to treatment with epigenetic drugs (e.g. AML carrying NUP98-fusions). To achieve this goal, we determine the therapeutic effect in vitro of drugs in cell lines with and without genetic defects. We use commercially available epidrugs when possible but, interestingly, we test novel small compounds designed as part of collaborations (e.g. members of the CM1406 COST action).

We perform basic functional assays to test their potential inhibitory effect on tumorigenesis (e.g. MTT, colony formation, wound healing, transwell migration assays, flow cytometry and apoptosis). Results derived from cell lines are validated in mouse models (in collaboration). In parallel, we study the genome-wide epigenetic pattern before and after treatment with epigenetic drugs to identify the main targeted pathways (e.g. CpG methylation arrays for DNMT inhibitors and ChIP-seq for histone modifier drugs).

3. Stratification of patients based on their epigenetic profile to predict response to immunotherapy. Epigenetics may have a mechanistic impact on antitumour immunity in human cancer patients via regulation of innate and adaptive immunity. We study the genome-wide CpG methylation profile of the immune blood cells to identify alterations that have a beneficial or detrimental effect on response to treatment. We focus on two immunotherapy strategies (anti-PD1/PD-L1 and BiTE) that are approved and included in clinical practice in the Spanish health system for the treatment of classical Hodgkin lymphoma (cHL) and B-cell acute lymphoblastic leukaemia (B-ALL). We aim to correlate the epigenetic signatures of responders and non-responders with clinical parameters to create a response prediction algorithm.

Keywords

Epigenetic drug; epigenetic editing; epidrug; haematological malignancies; targeted therapies.

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LYMPHOMA TRANSLATIONAL GROUP

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Our research is centred on the development of innovative preclinical models of B-cell lymphoma that can be used to unravel the complex role of tumour-lymphoma crosstalk during the development of the disease and the acquisition of refractoriness in current regimens. To that end, we intend to reproduce the original composition and architecture of tumours in the laboratory to carry out a complete transcriptomic and proteomic analysis and develop new pharmacological entities in collaboration with academic experts and clinical-level pharmaceutical companies, all with a view to fostering the bench-to-bedside transfer of new and tailored therapeutic strategies.

Our research

Most new therapies against aggressive B-cell lymphomas have not improved the general survival of patients, and there is currently no drug or drug combination that can cure the disease. Our group is designing drugs to attack this disease, which is highly variable, resistant and difficult to reproduce in preclinical models and the lab.

In fact, we develop *in vitro* and animal models with the intention of more accurately recreating the context of onset and progression of the lymphoma in each patient. In this regard, we take account of fundamental parameters that until now have been largely unexplored in preclinical research, such as the architecture of the original tumour, the components of the immune system that accompany it and the defects in the regulation of the proteins – not only of the genes – that characterize it.

Our main areas of research are:

1. Development of a patient-derived xenograft platform for the evaluation of new targeted therapies in aggressive B-cell lymphomas

The current therapeutic targets of particular interest in these entities include distinct signalling pathways that are activated constitutively by over-expression of MYC, BCL6 or CRBN, activation of phosphatidylinositol 3-kinase (PI3K) and B-cell receptor (BCR)-related kinases or deregulation of the apoptotic programme. Currently, there are several therapeutic agents directed specifically towards these signalling axes, although their efficacy, safety and mode of action are still to be determined in some B-cell lymphoma subtypes.

To confirm the efficacy, safety and transnationality of these studies, we propose that standard *in vitro* assays be associated with innovative *in vivo* models (PDX) to allow us, firstly, to work directly with primary tumour cells to validate the most effective therapies and the most relevant biological effects while taking into account the role of the tumour microenvironment; and, secondly, to guarantee that these therapies can be translated into clinical trials with molecular and genetic determination of the factors that condition the response to the best therapies tested in each patient.

2. Modulation of the lymphoid microenvironment by intrinsic protein homeostasis in aggressive B-cell lymphoma

The lack of efficacy of standard and experimental therapies in the clinic is likely due to the uncontrolled activity of some components of the tumour microenvironment (TME). Although major advances have been made over the last decade with respect to the role of accompanying immune effectors in the control of B-NHL tumour growth and resistance to standard and experimental therapies, the way in which MCL and DLBCL malignant B cells modulate their TME to better adapt to adverse conditions remains poorly understood.

The main objective of this project is the identification of new mechanisms related to intrinsic protein homeostasis that may regulate the complex interplay between MCL and DLBCL cells and their specific TME, through the use of *in vitro* (3D organoid) and *in vivo* (PDX) experimental models with the capacity to preserve the spatial architecture of the original tumours.

We will characterize the ubiquitome of malignant B cells through proteomic profiling and correlate these intracellular complexes with the immunological pattern of each tumour model in order to validate the impact of tumour protein homeostasis on the development of B-cell lymphoma and the intratumoural infiltration of immune cells.

Keywords

B-cell non-Hodgkin's lymphoma (NHL); tumour modelling; proteostasis; tumour microenvironment; immunotherapy.

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ONCOGENESIS AND ANTITUMOUR DRUGS

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Current treatments lack selectivity towards cancer cells, which induces insufficient anticancer activity and produces severe adverse effects that limit their dosage. We are developing self-assembling protein-based nanoparticles for the treatment of haematological and solid cancers that are highly selective in targeting receptors overexpressed in cancer stem cells. They display a wide therapeutic window by avoiding renal clearance while internalizing into and selectively eliminating cancer target cells and enhancing the uptake of the payload drug into cancer tissues, with negligible uptake or toxicity in normal tissues.

Our research

We are currently studying the differential features of our protein-based nanoparticles that proved to be more appropriate for therapy than other nanomedicines (non-targeted) or targeted drug-delivery approaches (e.g. antibody-drug conjugates), some of which are already being used in the clinic. Thus, unlike the majority of nanoparticles that have been developed, ours are fully degradable and therefore non-toxic. In addition, they have the capacity to self-assemble to reach a nanometric size (10-100 nm) by incorporating cationic peptides at their N- and C-terminus, which coordinate with divalent cations. After their intravenous administration, their nanosize allows for the increased recirculation in blood because of their capacity to prevent renal clearance. We are now studying the differences between the cations tested with respect to their capacity to ensure the stability in blood of the nanoparticles, depending on their coordination capacity.

We are also evaluating the mechanisms underlying the selective uptake capacity of the nanoparticles in tumour tissues, and specifically in cancer target cells. Thus, we have demonstrated that the absence of protein corona formation in blood (which non-protein-based nanoparticles undergo) allows them to maintain their capacity to target cancer cells in animal models and, therefore, their selectivity in drug delivery. In addition, they exploit the overexpression of the CXCR4 chemokine receptor (CXCR4+) found in cancer stem cells; for that reason, we have helped establish an association with disease dissemination, therapy resistance and poor prognosis, especially in AML and DLBCL. Targeting is achieved by incorporating into the nanoparticle the T22 ligand, which specifically interacts with the CXCR4 receptor expressed in the membrane of target cells, thus triggering its specific internalization in CXCR4+ cancer cells only. This is followed by the release of the payload drug in the target cell's cytosol, which triggers its selective elimination. We demonstrated that more than 80% of the injected nanoparticle dose is taken up by cancer tissues, in both DLBCL and CRC, and it is negligible in non-cancer organs. To further increase their therapeutic effect, we are currently exploring the incorporation of endosomal escape domains to prevent their lysosomal degradation.

Our aim is to develop nanomedicines that can effectively render cancers that have disseminated or relapsed sensitive to therapy by acquiring resistance to current therapy. In doing so, we expect to increase the cure and complete response rates, thereby leading to longer survival times. We hope this highly selective delivery of potent toxic drugs to CXCR4+ cancer cells will reverse therapy resistance and block metastatic dissemination at the clinically relevant sites. An additional goal is to ensure that the repeated administration of these novel nanomedicines induces potent anticancer activity, while maintaining low or absent toxicity in normal tissues, associated with a lack of, or tolerable, side effects.

Our highest priority is to offer hope to patients with relapsed or refractory DLBCL, AML and CRC who have developed disseminated disease, by engaging first in regulatory preclinical toxicology assays, and then in the clinical translation of these novel therapeutic products, with a high therapeutic window, to increase the chances of curing the patient while maintaining his or her well-being during treatment. We also expect to be able to compare their performance with current treatment protocols in clinical trials.

Finally, we also aim to develop a formulation of amyloid structured inclusion bodies whose capacity for the sustained release of therapeutic nanoparticles into the blood could be subcutaneously administered once a month. Their development will circumvent the need to administer the nanoparticles twice a week by intravenous injection, thus allowing patients to stay at home during treatment and avoid hospitalization.

Keywords

Biotechnology; nanomedicine; targeted drug delivery; oncotherapy; metastases.

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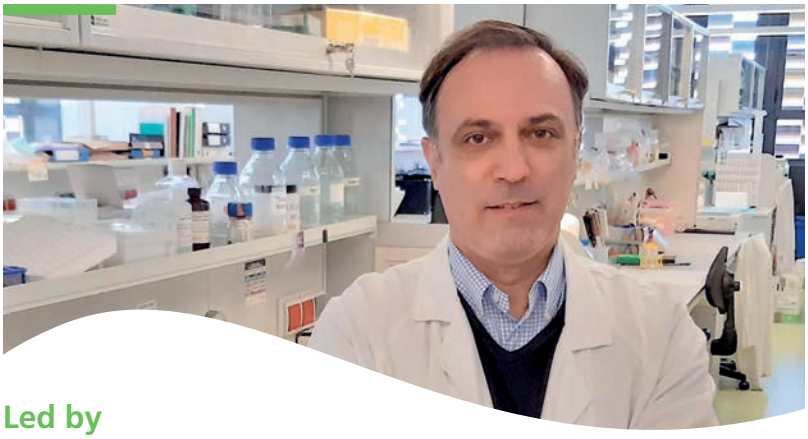
CELLULAR IMMUNOTHERAPY AND GENE THERAPY



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The Cellular Immunotherapy and Gene Therapy Group is focused on the study of genetically modified T-cells expressing chimeric antigen-specific receptors (CARs) and their clinical application in patients with blood cancer.

Our research

Blood malignancies, like leukemia and lymphoma, are challenging diseases affecting one or more blood cell lineages. Traditional treatments include chemotherapy to deplete altered cells as much as possible, followed by bone marrow transplantation from a compatible donor, when appropriate.

Recently, a new and powerful immune cell type has been discovered called memory stem T cells. These are scarce but very special and, despite being roughly a 1% of the cells in our blood, they have the ability to find, attack and destroy cancer cells very efficiently. We have developed mechanisms to expand memory stem T cells in the lab and grow them in greater numbers, to make their action more potent and long-lasting.

Also, the genetic modification of patient-derived memory stem T cells to make them express CAR receptors, the so-called CAR-T therapy, is proving an enhanced anti leukemic potential in the clinical trials.

The Cellular Immunotherapy and Gene Therapy Group is focusing on the advance of the CAR-T technology with the following lines of research:

- Functional antitumour research into subtypes of memory T-cells.
- Study of the antitumour efficacy of memory stem T-cells genetically modified with CARs.
- Development of new CARs targeted against haematological malignancies.
- Development of clinical immunotherapy trials with CAR T-cells on patients with lymphoid neoplasms.

Keywords:
CAR-T; T-Cells; Lymphoid Neoplasms.

PLATFORMS

Proteomics Unit

The Proteomics Unit of the Josep Carreras Leukaemia Research Institute offers mass spectrometry services to the academic and the private sector and is part of the institution's Scientific and Technical Services (SCT), whose main activity involves supporting academic research, although private for-profit organizations are becoming increasingly interested in accessing our services. The unit forms part of the Carlos III Health Institute (ISCIII) and the Proteomics Network ProteoRed.

One of the unit's main activities is to promote the incorporation of proteomics as a key tool for the development of clinical and basic projects at our institution.

One of the great challenges of biomedical research and precision medicine is the description of the mechanisms underlying pathological processes and the standardized definition, based on this, of measurable biomarkers and new therapeutic targets, generally protein in nature.

Our proteomics facility has a well-established background in proteomics and peptidomics by providing complementary content and insight for our strategic collaborators to develop more effective and more time- and cost-efficient healthcare solutions.

Our main work consists of offering innovative, high-quality proteomic and peptidomic services in the following disciplines: descriptive proteomics, quantitative proteomics/identification of biomarkers, protein characterization and identification of post-translational modifications, as well as the identification of biomolecular interactions. We aim to deliver innovative proteomic and peptidomic services that allow the best therapeutic and human health solutions to be selected.

The Bioinformatics Unit

The Bioinformatics Unit at IJC provides both internal and external researchers with high-quality computational analysis services to cover all aspects of research projects related to clinical and biological data.

In terms of human resources, the Bioinformatics Unit boasts highly skilled computational biologist professionals with almost two decades of experience at bioinformatics core facilities and private companies.

The Bioinformatics Unit offers a wide range of services, including experimental design for NGS or microarray experiments, statistical consulting, NGS and microarray data analysis and integration, scientific database management and software design and implementation. It also provides training on different bioinformatics topics and the use of HPC (high-performance computing) resources.

The main goal is to provide all clinical and biological researchers with access to the complexity of the latest advances in computational biology with a view to simplifying their research and speeding up the results and translation of their discoveries to the final patient.

PLATFORMS

Genomics Platform

The current ability to interrogate the entire human DNA (known as the genome) has opened the way for enormous possibilities in terms of the detailed analysis of patients' genetic information and the mechanisms of gene expression regulation, thereby fostering personalized healthcare.

The Genomics Unit at IJC aims to provide the IJC community and external researchers with scientific services. Several state-of-the-art technologies have been implemented in the unit to assess relevant genomic and epigenomic features and thus unravel basic molecular mechanisms of disease and contribute to the discovery of therapeutic targets and biomarkers.

The Genomics Unit is equipped with cutting-edge technology to offer solutions for both basic and translational epigenomic and genomic studies on many sample types (primary cells, cell lines, frozen and paraffin-embedded tissues, etc). We have long-standing experience in array-based genome-wide DNA methylation analysis, and also perform pyrosequencing for DNA analysis. We use next-generation sequencing (NGS) technology to investigate subsets of genes or specific genome regions with the MiSeqDx System from Illumina.

Applications

The applications provided by the Genomics Unit at IJC are:

1. **Infinium MethylationEPICTM BeadChip technology (Illumina):** Infinium MethylationEPIC BeadChip Kit, which allows over 850,000 methylation sites to be interrogated quantitatively across the genome at single-nucleotide resolution. It provides comprehensive genome-wide coverage, as interrogated sites include CpG sites outside of CpG islands, non-CpG methylated sites identified in human stem cells (CHH sites), differentially methylated sites identified in tumour versus normal, FANTOM5 enhancers, ENCODE open chromatin and enhancers, DNase hypersensitive sites and miRNA promoter regions. High throughput is supported by chip analysis performed using an Illumina HiScanTM SQ fluorescent scanner and the Freedom EVO® platform.
2. **MiSeqTMDx NGS sequencer (Illumina):** the MiSeqDx technology is used for targeted sequencing of DNA libraries from human genomic DNA extracted from peripheral whole blood or formalin-fixed, paraffin-embedded (FFPE) tissue. It can be used for basic research purposes or for in vitro diagnostic (IVD) assays. It reaches a throughput of 1–96 samples/run, depending on the assay, and gives a read length of up to 2 × 300 bp.
3. **PyroMarkTMQ48 (Qiagen):** pyrosequencing is a sequence-based platform that integrates detection and quantitative real-time data for the analysis of targeted short DNA sequences. It is used to characterize single nucleotide polymorphisms (SNPs), insertion-deletions (indels), unknown sequence variants and DNA methylation levels at both CpG and non-CpG (CpN) sites.

Our unit will continue in its goal of harnessing the power of genomic technology and science to improve health by contributing to the prediction and diagnosis of disease and the development of personalized treatments and interventions.

Sample Circuit-Biobank Platform

The Sample Circuit-Biobank platform of the IGTP-HUGTP (Germans Trias i Pujol Research Institute – Hospital Universitari Germans Trias i Pujol) was created in 2013 by the Josep Carreras Leukaemia Research Institute (IJC) ICO-GTP Campus with the aim of managing the voluntary donation of samples from patients with haematological malignancies, as well as the subsequent processing, storage and supervision of the samples.

The main applications of the Sample Circuit-Biobank platform are:

Storage of biological patient samples with a detailed medical history is a fundamental pillar of research. Thanks to the Biobank, our unit can offer the following services:

- Providing samples to researchers for basic and translational research.
- Providing biological samples to researchers at other centres, at both national and international level, to run cooperative projects with a high level of competitiveness.
- Enabling the study of genetic changes in tumour cells at diagnosis and over the course of the disease.
- Enabling the evaluation of treatment response.
- Enabling the prediction of the course of the disease and its potential progression.
- Conducting research into minimal residual disease.

PLATFORMS

Single Cell Unit

The Single Cell Unit is the scientific and technological support unit for high level research projects in the Single Cell Genomics field, assisting researchers from the experimental design to the data analysis.

The mission of the Single Cell Unit is to facilitate academic research by offering services based on cutting-edge single-cell and spatial genomics technologies. Single-cell genomics represent a powerful tool for the analysis of complex tissues and have significantly advanced our knowledge in basic and clinical sciences.

The Single Cell Unit is equipped with state-of-the-art instruments for single-cell isolation and provides support to the scientific community through the most advanced technology for single-cell analysis:

- Scientific and technological support for high level research projects in the Single Cell Sequencing field according to international standard procedures.
- Scientific advice to researchers, from the planning and optimization of new experiments to their execution and bioinformatic analysis.
- Contribution to the promotion of innovation in health technologies and the transfer of the knowledge generated to the NHS.

Microarrays Unit

The Microarrays Unit (MU) is a service oriented to research and genetic diagnosis, offering high-end equipment and technical assistance to the Institute's community and beyond. The Unit has processed more than four thousand samples since its foundation in 2012 and is part of GenQA, the European cytogenetics quality control service since 2013 for prenatal, postnatal and oncohematological modules. The Unit is also part of the Reproductive Health Reference Laboratory Program, a network of European reference centers by Thermo Fisher Scientific®.

The main services of the Unit are focused in the **analysis of genomic and expression microarrays** by using the GeneChip® technology from Thermo Fisher Scientific®, however we offer other services like the **construction of non-commercial DNA probes from BACs** for FISH, thanks to the library bought to the Children's Hospital Oakland Research Institute in 2012 and to the experience of Dr. Francesc Solé.

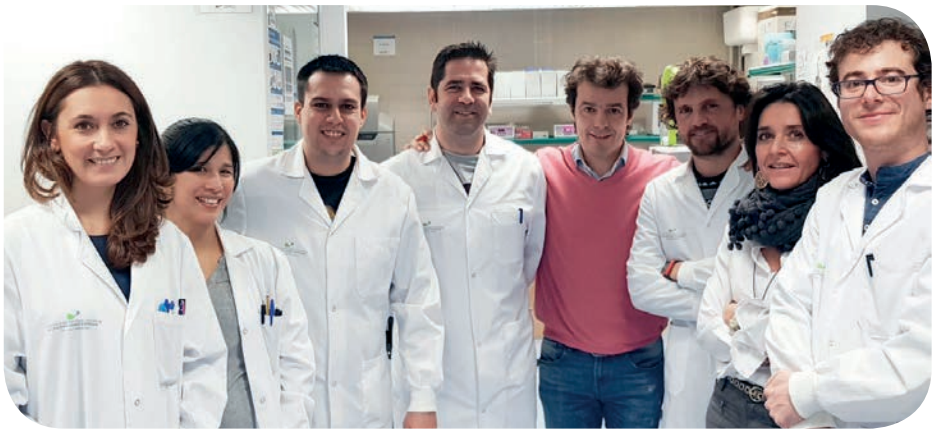
Also, the Unit is offering high **throughput Real Time PCR genotyping and gene expression analysis,** using Fluidigm's Biomark HD. This technology allows the processing of a large number of samples in a reduced time, using less resources than a conventional qPCR equipment, allowing high throughput analysis.

The objective of the Unit is to offer the best suited solution to the research community to speed up their research and shorten the path towards a future where leukemia is 100% curable.

COMMUNICATION

COMMUNICATION / **SELECTED PRESS RELEASES**

2019
January 16



A new therapeutic target for a rare infant leukemia with poor prognostic.

The group led by Pablo Menéndez publish research identifying a new therapeutic target for a rare infant leukemia with poor prognostic

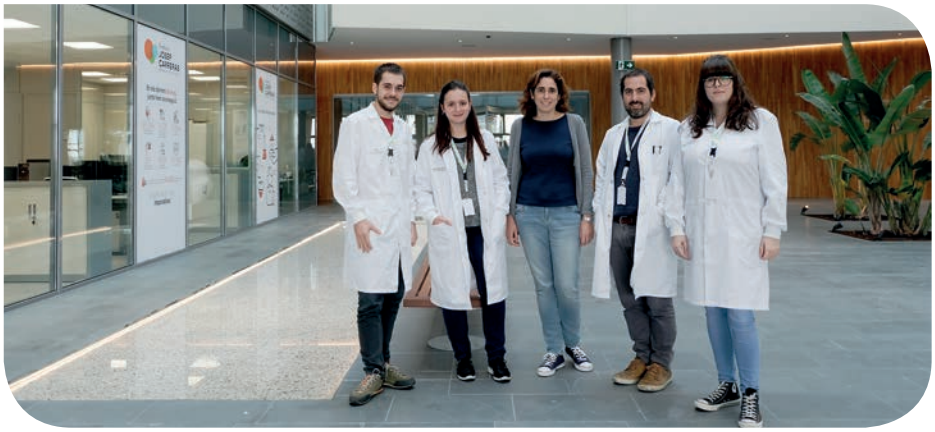
2019
March 18

The Acute Lymphoblastic Leukemia Research Group identifies microRNA signatures in cells that could give rise to leukemia with the idea to use it to target therapies

Eulàlia Genescà, Josep Maria Ribera and Javad Behravan from the Mashhad Universityhave published a paper in Molecular Biology Reports in which they describe work to further identify cells resistant to treatments in acute lymphoblastic leukemia in patients positive for Philadelphia chromosome.

COMMUNICATION /
SELECTED PRESS RELEASES

2019
September 6



Discovered the potential of a group of antihistamines that cause the death of leukaemic stem cells

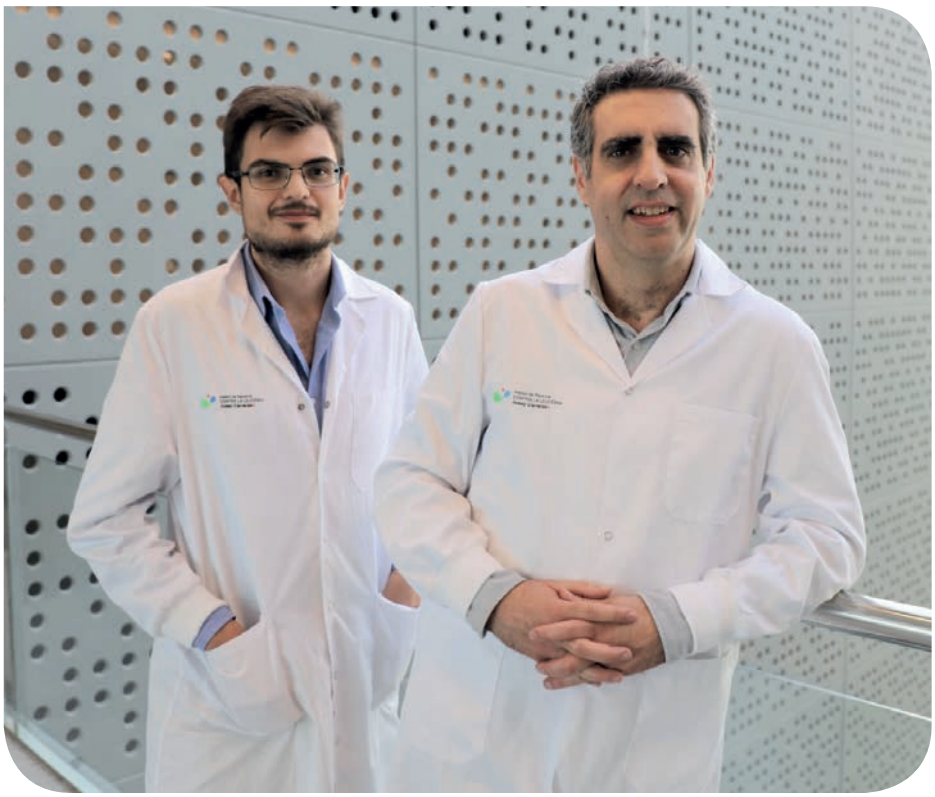
The Leukaemic Stem Cell research group, led by Ruth M. Risueño, has discovered in preclinical trials that a particular group of antihistamines can kill leukaemic stem cells.

2019
November 7

Discovered a new process of antitumoral response of NK cells in myeloma

The stem cell transplant and cell immunotherapy group of the Josep Carreras Leukemia Research Institute reveals how NK cells activate a set of actions that promote their antitumor capacity in the presence of myeloma cells.

2019
November 15



Leukaemia cells can transform into non-cancerous cells through epigenetic changes

Researchers of the Cancer Epigenetics Group, led by Dr. Manel Esteller, reveal that a leukaemic cell is capable of transforming into a non-cancerous cell through epigenetic changes.

COMMUNICATION / **SCIENTIFIC AWARDS**

2019
April 2

Biola Javierre

awarded a prestigious International Rising Talent prize by L'Oreal-UNESCO

Biola Javierre of the 3D Chromatin Organization Group at the Josep Carreras Leukaemia Research Institute is only the fifth Spanish woman to receive the award in the 21 years of its history. The 15 winners this year were chosen from 280 applications from all over the world; they all attended a presentation at the UNESCO headquarters in Paris.

2019
August 28

Jordi Petriz

elected Scientist Innovator
by Thermo Fisher Scientific

The biotechnology multinational, Thermo Fisher Scientific has chosen Dr. Jordi Petriz, head of the Josep Carreras Leukaemia Research Institute's functional cytometry group as scientific innovator for his research as a pioneer in the study of normal and cancerous stem cells, as well as in the field of resistance to chemotherapy.

2019
October 16

Manel Esteller
is recognized by Stanford University for its scientific impact worldwide

Manel Esteller, Director of the Josep Carreras Leukemia Research Institute (IJC), ICREA Researcher, and Professor of Genetics at the University of Barcelona, has been recognized by the prestigious Stanford University in the United States, among the 0.001% of researchers with the most significant impact worldwide in all areas of Science.

2019
November 6

Dr. Fumiichiro Yamamoto
receives the Karl Landsteiner Memorial Award and Lectureship

Dr. Fumiichiro Yamamoto has received the prestigious Karl Landsteiner Memorial Award and Lectureship from the American Association of Blood Banks (AABB), the last of the awards that recognize his work on blood groups.

2019
November 18

Manel Esteller
is referred as Highly Cited Researcher According to 2019 Web of Science Group List

Josep Carreras Leukaemia Research Institute director Manel Esteller has been named Highly Cited Researcher, according to the Highly Cited Researchers 2020 list from the Web of Science Group, released today.

COMMUNICATION / **INTERNATIONAL EVENTS**

Symposium on genetics and epigenetics in leukaemia and lymphoma: from knowledge to applications (19-20 sep 2019)

This conference brought together leading scientists and clinicians in the field of leukaemia and lymphoma. The goal of the meeting was to highlight the latest advances in our understanding of the molecular mechanisms driving blood cancers and to discuss how this knowledge can be translated into improved management of the disease, with a special focus on the role of genetic and epigenetic heterogeneity and the exploitation of epigenetic regulation for the development of biomarkers and novel treatment approaches.

This inaugural symposium was attended by more than 200 researchers, including the best scientists in the most advanced fields of haemato-oncology, such as stem cells, immunotherapy, personalized therapy, genetics and epigenetics.

COMMUNICATION / **SCIENTIFIC DISSEMINATION**

Health is a high-priority public issue, and the dissemination of basic health knowledge is essential to achieve optimal levels of development and human welfare across society as a whole. Knowledge transfer and dissemination of results from biomedical research are some of the key factors in tackling this challenge.

For this reason, it is vitally important to disseminate our work and strengthen our bonds with society and the public. We endeavour to integrate social corporate responsibility into our management model, a desire closely linked to the organizational values of the Josep Carreras Foundation.

In 2019, IJC actively participated in scientific dissemination, citizen participation and the engagement of high-school students to increase their understanding of what medical research involves. Examples include the Science Week at Badalona Town Council and Magic Badalona Running.

Science week at Badalona town council

Magic Badalona Running 2019

PUBLICATIONS / **INDICATORS**

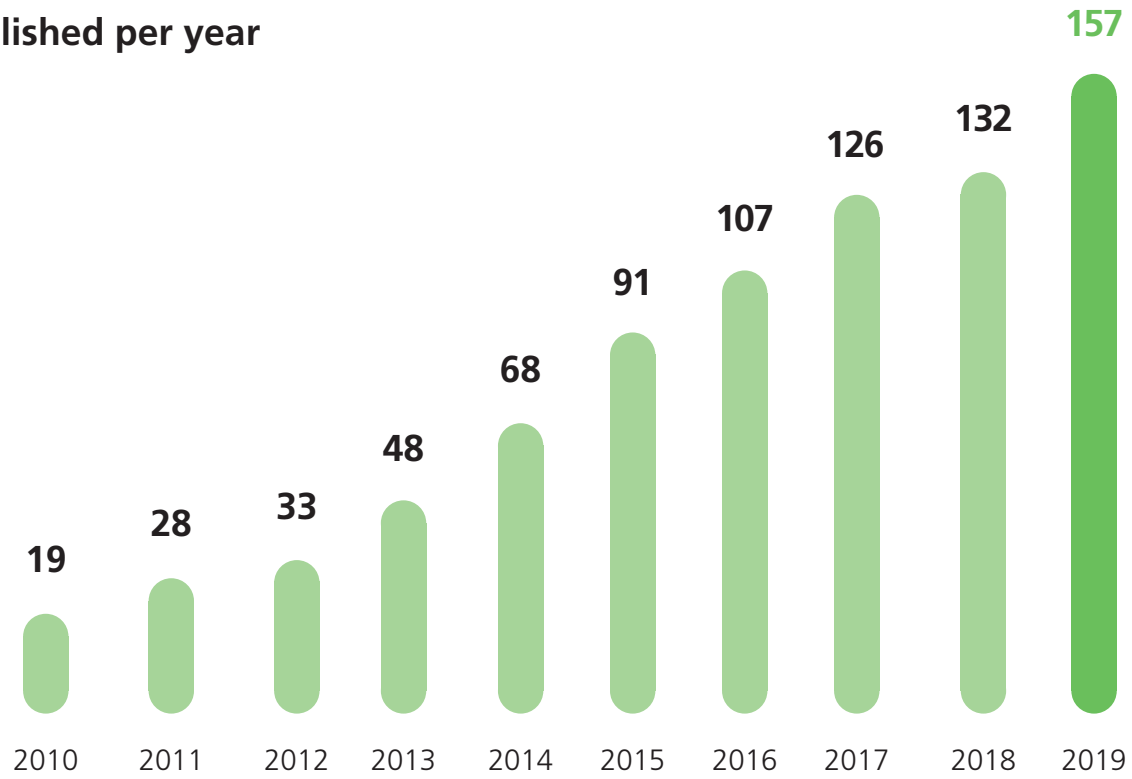
157
Papers

87 Q1
Papers Q1

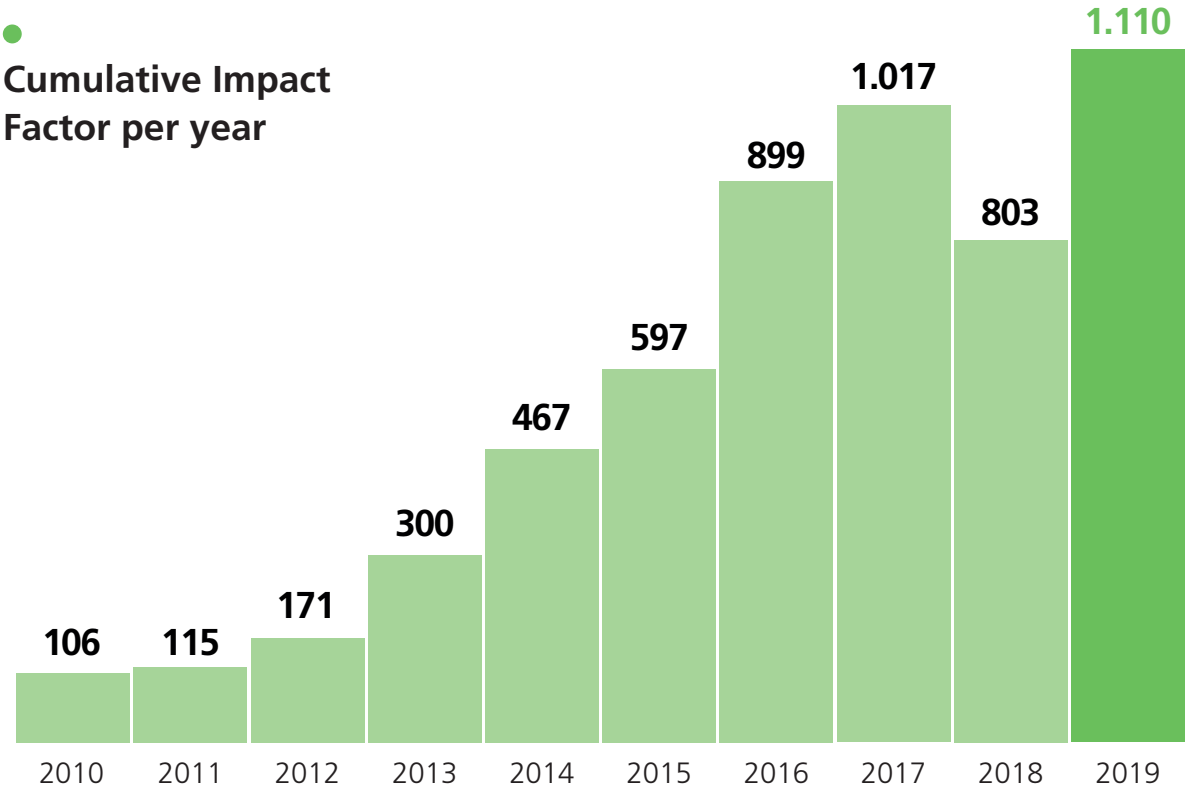
52 D1
Papers D1

33 IF
Papers with IF > 10

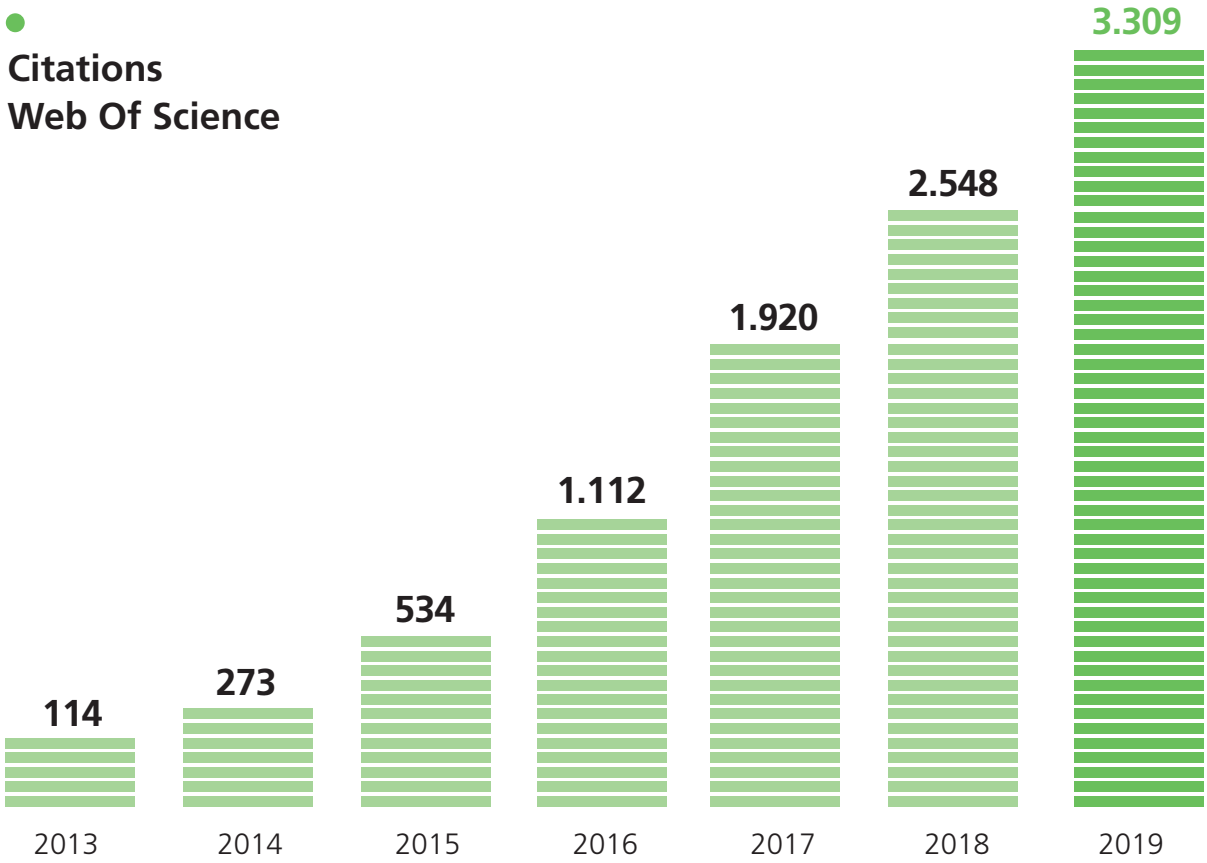
Number of indexed articles published per year



Cumulative Impact Factor per year



Citations Web Of Science



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Epigenetic therapies

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25.
Oncogenesis and antitumor drugs

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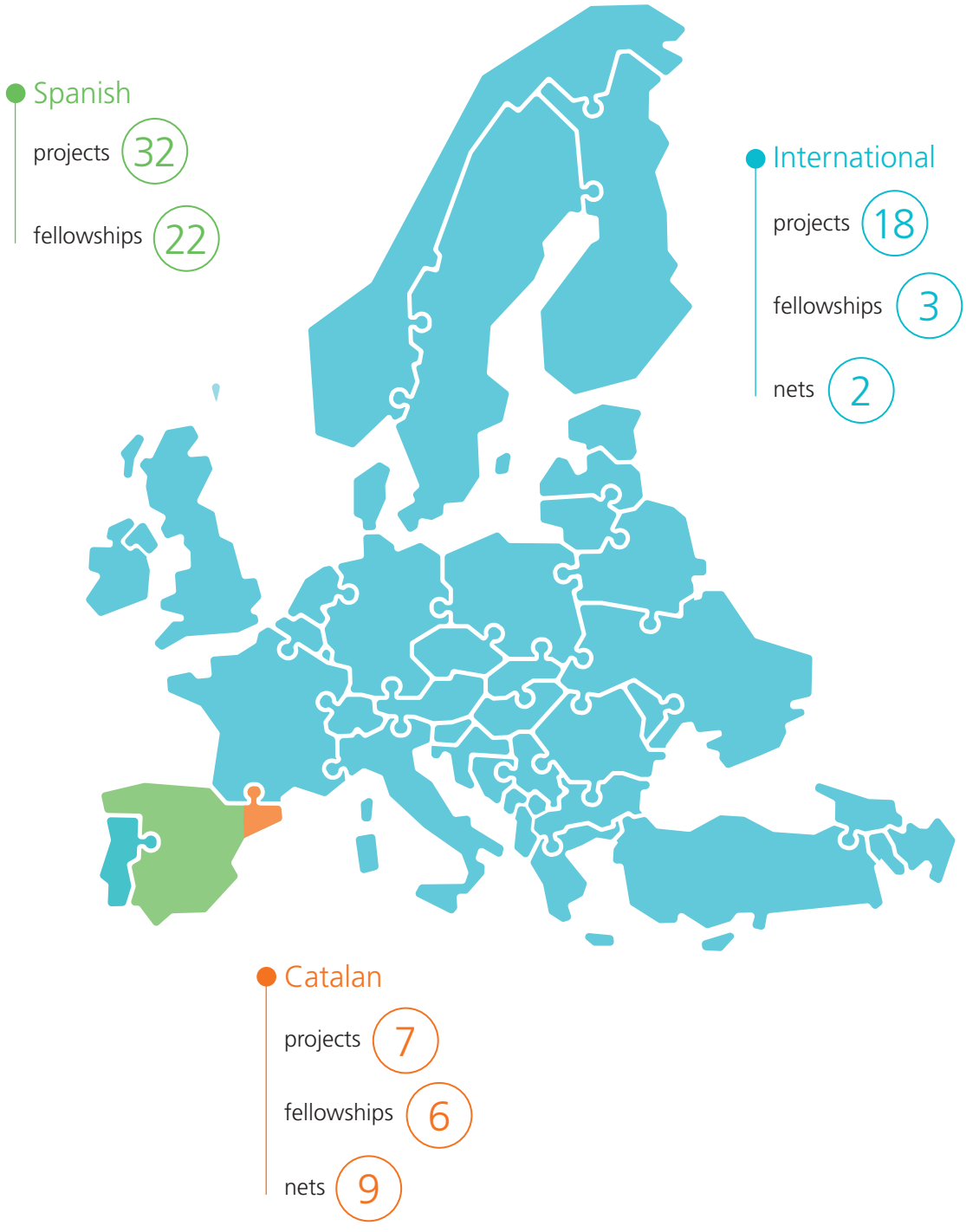
FACTS & FIGURES / **COMPETITIVE GRANTS AWARED AND ACTIVE PROJECTS**

Our researchers are highly competitive in a wide range of competitive grants launched at different levels (International, Spanish and Catalan):

Total Competitive Grants

Total	Projects	Fellowships	Nets
99	57	31	11



1.
Cancer epigenetics

2017 Fundación Científica de la Asociación Española Contra el Cáncer, Accelerator Award

Reference: A26825

Title: ACRCelerate: Colorectal Cancer Stratified Medicine Network

IP: ESTELLER BADOSA, MANEL

Period: 02/08/2019 - 31/10/2023

2016 Fundació La Marató de TV3: Ictus i lesions medul·lars i cerebrals traumàtiques

Reference: 201711.31

Title: Proyecto EPIGENESIS: Estudio epigenético y genético combinado con integrómica de datos y análisis funcional para encontrar genes asociados con el deterioro neurológico después de un ictus isquémico

IP: ESTELLER BADOSA, MANEL

Period: 01/06/2019 - 28/02/2021

2017 Fundación Científica de la Asociación Española Contra el Cáncer, Investigador AECC

Reference: INVES208DAVA

Title: EPINMUNE: Identificación de biomarcadores epigenéticos de predicción de respuesta a inmunoterapia

IP: DAVALOS VEGA, VERONICA

Period: 01/06/2019 - 30/11/2021

2017 Fundación Privada Olga Torres, becas postdoctorales, investigadores consolidados

Title: Bioinformatic prediction of chemosensitive profiles in colorectal cancer using Epigenomics

IP: ESTELLER BADOSA, MANEL

Period: 15/05/2019 - 31/12/2019

2018 Ministerio de Ciencia, Innovación y Universidades, Retos Investigación

Reference: RTI2018-094049-B-I00

Title: Disrupción epigenética y genética de las modificaciones del ARN en cáncer (EPIRNA)

IP: ESTELLER BADOSA, MANEL

Period: 01/01/2019 - 31/12/2021

2016 Departament de Salut, PERIS: Programes de recerca orientats - Estudis de cohorts

Reference: SLT/002/16/00201

Title: Caracterització dels determinants genètics dels fenotips de neuroimatge associats a la malaltia d'Alzheimer en participants de la cohort ALFA

IP: ESTELLER BADOSA, MANEL

Period: 01/01/2017 - 31/12/2019

2018 Agència de Gestió d'Ajuts Universitaris i de Recerca, Ajuts per a la incorporació de personal investigador postdoctoral al sistema català de ciència i tecnologia

Reference: 2018 BP 00250

Title: Senescence as a key factor in leukemogenesis and bone marrow homeostasis in aging

IP: FERRER AGUILAR, GERARDO

Period: 03/12/2019 - 02/12/2022

2015 Ministerio de Economia y Competitividad, Contratos Predoctorales para la formacion de doctores.

Reference: BES-2015-071452

IP: OBIOLS GUARDIA, AIDA

Period: 23/09/2019 - 24/11/2019

2018 Ministerio de Ciencia, Innovación y Universidades, Ayudas para la formación de profesorado universitario (FPU)

Reference: FPU2017-02423

IP: BUENO COSTA, ALBERTO

Period: 01/07/2019 - 30/09/2022

2015 Ministerio de Economia y Competitividad, Contratos Predoctorales para la formacion de doctores.

Reference: BES-2015-073053

Title: Desregulación epigenética extraordinaria en cáncer

IP: LLINAS ARIAS, PERE

Period: 12/06/2019 - 31/12/2019

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 1080

Title: Acreditación como "Grupo Consolidado Reconocido" al Grupo de Epigenética del Cáncer

IP: ESTELLER BADOSA, MANEL

Period: 01/01/2017 - 30/09/2021

2.
Cancer genetics

2019 Fundación Científica de la Asociación Española Contra el Cáncer, Investigador AECC

Reference: INVES19045ROME

Title: The CESAR Therapeutic Strategy (Cancer Epigenetic Short-circuit Adapted Response)

IP: ROMERO FERRARO, OCTAVIO

Period: 01/12/2019 - 30/11/2021

2015 Ministerio de Economia y Competitividad, Contratos Predoctorales para la formacion de doctores.

Reference: BES-2015-072204

IP: LLABATA BABIANO, PAULA

Period: 23/09/2019 - 31/12/2019

2014 Fundación Científica de la Asociación Española Contra el Cáncer, Grupos Coordinados Estables 2014

Reference: GCB14142170MONT

Title: Uso de estrategias moleculares de última generación para la identificación de nuevas dianas terapéuticas y marcadores pronósticos en tipos de carcinoma pulmonar pobremente caracterizados

IP: SANCHEZ CESPEDES, MONTSERRAT

Period: 01/08/2019 - 31/10/2020

2017 Ministerio de Ciencia, Innovación y Universidades, Programa Estatal de I+D+i Orientada a los Retos de la Sociedad

Reference: SAF2017-82186-R

Title: Disección funcional de las vías moleculares MYC/MAX y SWI/SNF para potenciar el desarrollo de nuevas terapia epigenéticas en cáncer (DEPICTER)

IP: SANCHEZ CESPEDES, MONTSERRAT

Period: 01/06/2019 - 31/12/2020

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 721

Title: Grup de Gens i Càncer, Grup de Recerca Consolidat

IP: SANCHEZ CESPEDES, MONTSERRAT

Period: 01/01/2017 - 30/09/2021

3.
Chromatin biology

2016 Agència de Gestió d'Ajuts Universitaris i de Recerca, ajuts per a la incorporació de personal investigador postdoctoral al sistema català de ciència i tecnologia dins del programa Beatriu de Pinós (BP 2016)

Reference: 2016 BP 00250

IP: VAZQUEZ PRAT, BERTA NIEVES

Period: 01/11/2019 - 31/08/2020

2015 Ministerio de Economia y Competitividad, Contratos Predoctorales para la formacion de doctores.

Reference: BES-2015-071251

IP: ESPINOSA ALCANTUD, MARIA DOLORES

Period: 23/09/2019 - 31/12/2019

2017 Worldwide Cancer Research, April 2017 grant round

Reference: 18-0404

Title: Dissecting the specific contribution of Sirtuin ADP-ribosyltransferase and deacetylase activities in tumorigenesis

IP: VAQUERO GARCIA, ALEJANDRO

Period: 01/08/2019 - 31/03/2021

2017 Ministerio de Ciencia, Innovación y Universidades, Programa Estatal de I+D+i Orientada a los Retos de la Sociedad

Reference: SAF2017-88975-R

Title: Protección de la estabilidad del genoma por sirtuinas en condiciones de estrés y sus implicaciones en cáncer y envejecimiento

IP: VAQUERO GARCIA, ALEJANDRO

Period: 01/06/2019 - 31/12/2020

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 148

Title: Grupo de Biología de la Cromatina, Grup de Recerca Consolidat

IP: VAQUERO GARCIA, ALEJANDRO

Period: 01/01/2017 - 30/09/2021

4.
Chromatin, metabolism and cell fate

2017 Ministerio de Economia y Competitividad, Ayudas para Personal Técnico de Apoyo 2017

Reference: PTA2017-13669-I

IP: CASQUERO GALINDO, RAQUEL

Period: 30/06/2019 - 30/06/2022

2018 European Cooperation in Science and Technology (COST), Cost Action proposals 2018

Reference: CA18127

Title: International Nucleome Consortium

IP: HURTADO BAGÈS, SARAH

Period: 13/05/2019 - 12/05/2023

2018 Josep Carreras Deutsche Leukämie Stiftung, Ayudas a proyectos de investigacion
Reference: DJCLS 14R/18

Title: Understanding and targeting epigenetic alterations in the hematopoietic stem cell niche for MDS therapy

IP: BUSCHBECK, MARCUS

Period: 01/05/2019 - 30/04/2022

2018 Ministerio de Ciencia, Innovación y Universidades, Retos Investigación

Reference: RTI2018-094005-B-I00

Title: Regulación de la arquitectura tridimensional de la cromatina por parte de las variantes de histona macroH2A y su capacidad de unir metabolitos.

IP: BUSCHBECK, MARCUS

Period: 01/01/2019 - 31/12/2021

2019 Comissió Europea, INFRAFRONTIER2020 Project - Trans-national Access call

Title: Induced secondary phenotyping screen under acute or more chronic inflammatory conditions - H2AFY encoding the histone variant macroH2A1.1

IP: BUSCHBECK, MARCUS

Period: 01/01/2019 - 31/12/2021

2017 Instituto de Salud Carlos III, Contratos Sara Borrell

Reference: CD17/00084

IP: DIESCH, JEANNINE

Period: 01/01/2018 - 31/12/2020

2016 Ministerio de Ciencia, Innovación y Universidades, Ayudas para contratos predoctorales para la formacion de doctores (FPI)

Reference: BES-2016-077251

IP: LE PANNERER, MARGUERITE MARIE

Period: 18/04/2017 - 17/04/2021

2016 Instituto de Salud Carlos III, Proyectos integrados de excelencia

Reference: PIE16/00011

Title: Biomarkers and combinatorial drug targets for a personalized therapy for three major cancers.

IP: BUSCHBECK, MARCUS

Period: 01/01/2017 - 30/06/2021

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 00305

Title: Modalitat GRPRE (Pre-Consolidats). Chromatin, Metabolism and Cell Fate.

IP: BUSCHBECK, MARCUS

Period: 01/01/2017 - 30/09/2021

2015 Comissio Europea, Chromatin-Metabolism Interactions for Healthy Living

Reference: H2020-MSCA-ITN-2015-675610

Title: Chromatin-metabolism interactions as targets for healthy living (ChroMe)

IP: BUSCHBECK, MARCUS

Period: 01/03/2016 - 29/02/2020

2014 Ministerio de Educación, Cultura y Deporte, Ayudas para la formación de doctores del programa nacional de formación de profesorado universitario (FPU)

Reference: FPU14/06542

IP: CORUJO, DAVID

Period: 01/10/2015 - 31/08/2019

5.
3D chromatin organization

2018 L´Oréal España, L'ORÉAL-UNESCO for Woman in Science International Rising Talents

Title: Deciphering Novel Molecular Targets for Therapies Aimed at Childhood Acute Lymphoblastic Leukaemia

IP: JAVIERRE MARTINEZ, BIOLA

Period: 14/03/2019 - 13/03/2020

2018 Ministerio de Ciencia, Innovación y Universidades, Retos Investigación

Reference: RTI2018-094788-A-I00

Title: Organización dinámica 3D de la cromatina en la hematopoyesis humana: descripción de nuevos genes asociados a enfermedades hematológicas.

IP: JAVIERRE MARTINEZ, BIOLA

Period: 01/01/2019 - 31/12/2021

2019 Fondation d'Entreprise l'Oreál, "For Women in Science" L'Oréal-UNESCO International Rising Talent

IP: JAVIERRE MARTINEZ, BIOLA

Period: 01/01/2019 - 31/12/2019

2018 Agència de Gestió d'Ajuts Universitaris i de Recerca, Ajuts per a la contractació de personal investigador novell per a l'any 2019. FI-DGR 2019

Reference: 2019 FI_B 00017

Title: Desxifrant noves dianes moleculars per a teràpies contra la leucèmia Limfoblàstica aguda infantil

IP: ROVIROSA MULET, LLORENÇ

Period: 01/04/2019 - 31/03/2021

6.
Epigenetics and immune disease

2016 Fundación Científica de la Asociación Española Contra el Cáncer, Ayudas para Investigadores en Oncología

Reference: AIO16163624GARC

Title: Regulación epigenética en la diferenciación a osteoblasto y osteoclasto en la lesión ósea asociada a mieloma múltiple

IP: BALLESTAR TARIN, ESTEBAN

Period: 01/11/2019 - 30/11/2019

2015 Ministerio de Ciencia, Innovación y Universidades, Ayudas para contratos predoctorales para la formacion de doctores (FPI)

Reference: BES-2015-074528

Title: Mecanismos de Regulación Epigenética en Procesos de Diferenciación Mieloide Relevantes a Enfermedad Autoinmune

IP: LORENTE-SOROLLA MARTINEZ-ACITORES, CLARA

Period: 07/10/2019 - 20/02/2020

2019 Jeffrey Modell Foundation, Translational Research Program, Cycle 5

Title: Assessing Epigenomic Geterogeneity and its Pathological Consequences in Common Variables Immunodeficiency

IP: BALLESTAR TARIN, ESTEBAN

Period: 01/08/2019 - 31/12/2019

2017 Ministerio de Ciencia, Innovación y Universidades, Programa Estatal de I+D+i Orientada a los Retos de la Sociedad

Reference: SAF2017-88086-R

Title: Células mieloides y plasticidad epigenética: mecanismos e implicaciones en procesos autoinmunes e inflamatorios

IP: BALLESTAR TARIN, ESTEBAN

Period: 01/06/2019 - 31/12/2020

2018 Instituto de Salud Carlos III, Acciones complementarias de programacion conjunta internacional

Reference: AC18/00057

Title: Integrative Multi-Omics Analysis of Primary Antibody Deficiency (PAD) Patients for Stratification According to Cellular Pathways

IP: BALLESTAR TARIN, ESTEBAN

Period: 01/01/2019 - 31/12/2021

2017 Instituto de Salud Carlos III, Contratos predoctorales de formación en investigación en salud. Modalidad Contratos i-PFIS: doctorados IIS-empresa en ciencias y tecnologías de la salud

Reference: IFI17/00034

IP: MORANTE PALACIOS, OCTAVIO

Period: 15/01/2018 - 14/01/2022

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 00720

Title: Grup de Cromatina i Malaltia Grup de Recerca Consolidat

IP: BALLESTAR TARIN, ESTEBAN

Period: 01/01/2017 - 30/09/2021

7.
Lymphocyte development and disease

2017 Ministerio de Ciencia, Innovación y Universidades, Juan de la Cierva-formación

Reference: FJCI-2017-32430

IP: DE BARRIOS BARRI, ORIOL

Period: 11/11/2019 - 31/12/2020

2019 Ministerio de Ciencia e Innovación, Acciones de dinamización «Europa Investigación»

Reference: EUR2019-103835

Title: B cell differentiation; unraveling gene silencing mechanisms

IP: PARRA BOLA, MARIA ISABEL

Period: 01/09/2019 - 31/12/2020

2017 Ministerio de Ciencia, Innovación y Universidades, Programa Estatal de I+D+i Orientada a los Retos de la Sociedad

Reference: SAF2017-87990-R

Title: Mecanismos de represión transcripcional en la diferenciación temprana y terminal de linfocitos B (HDAC7-BLYM)

IP: PARRA BOLA, MARIA ISABEL

Period: 01/06/2019 - 31/12/2020

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 00149

Title: Grup de Diferenciació Cel·lular, Grup de Recerca Pre-Consolidat

IP: PARRA BOLA, MARIA ISABEL

Period: 01/01/2017 - 30/09/2021

8.
Regulatory genomics

2016 Ministerio de Ciencia, Innovación y Universidades, Ayudas para incentivar la incorporación estable de doctores (IED)

Reference: IEDI-2016-00787

Title: Reconstrucción genómica y celular de la leucemia linfoblástica aguda del lactante con reordenamiento MLLAF4

IP: VAVOURI, TANIA

Period: 01/01/2017 - 31/12/2019

9.
Regulatory RNA and chromatin

2019 Fondo para la Investigación en Síndrome de Rett, 1ª Convocatoria de ayudas a la investigación en Síndrome de Rett de FINRETT

Title: Transcriptómica unicelular para el análisis de subtipos neuronales diferenciados en un modelo celular humano de síndrome de Rett

IP: GUIL DOMENECH, SONIA

Period: 01/11/2019 - 31/10/2020

2017 Instituto de Salud Carlos III, Contratos predoctorales de formación en investigación en salud. Modalidad Contratos i-PFIS: doctorados IIS-empresa en ciencias y tecnologías de la salud

Reference: IFI17/00006

IP: ROSSELLÓ TORTELLA, MARGALIDA

Period: 01/01/2018 - 31/12/2021

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 00722

Title: RNA regulador i cromatina, Grup de Recerca Consolidat

IP: GUIL DOMENECH, SONIA

Period: 01/01/2017 - 30/09/2021

12.
Acute lymphoblastic leukaemia (all group)

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Ajuts per a la contractació de personal investigador novell per a l'any 2018. FI-DGR 2018

Reference: 2018 FI_B 00970, 2019 FI_B100224

Title: Tutor: Eulalia Genescà

Estudio de la resistencia al tratamiento en la leucemia linfoblástica aguda de subtipo T (LAL-T) del adulto. Búsqueda de nuevas alternativas terapéuticas

IP: GONZALEZ GIL, CELIA

Period: 01/06/2018 - 30/05/2021

2016 Departament de Salut, PERIS: Programes de recerca orientats - Recerca clínica cooperativa independent

Reference: SLT002/16/00433

Title: Estudi observacional prospectiu de tractament adaptat al risc de la LMA i les SMD a Catalunya.

IP: RIBERA SANTASUSANA, JOSEP MARIA

Period: 27/03/2017 - 31/12/2019

2015 Comissió Europea, H2020 JTI-IMI2 2015-06

Reference: 116026

Title: Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in hematology

IP: RIBERA SANTASUSANA, JOSEP MARIA

Period: 01/01/2017 - 31/12/2021

2016 Fundación Científica de la Asociación Española Contra el Cáncer, Grupos Coordinados Estables de Investigación

Reference: GC16173697BIGA

Title: Exploring Mechanisms of Resistance in Adult and Pediatric T-Acute Lymphoblastic Leukemia

IP: RIBERA SANTASUSANA, JOSEP MARIA

Period: 01/11/2016 - 31/10/2021

13.
Barcelona Endothelium Team (BET)

2016 Josep Carreras Deutsche Leukämie Stiftung, Ayudas a proyectos de investigacion

Reference: 11R/2016

Title: Enhancement of endothelial regeneration and endothelial function during GVHD

IP: CARRERAS PONS, ENRIC
Period: 01/01/2016 - 31/10/2019

15.
Myeloid neoplasms

2016 Instituto de Salud Carlos III, Proyectos de investigacion en Salud

Reference: PI16/01200

Title: Parámetros biológicos predictivos de obtención de respuesta molecular profunda y de recaída tras la suspensión del inhibidor tirosina cinasa en pacientes con Leucemia Mieloide Crónica

IP: ZAMORA PLANA, LURDES

Period: 01/01/2017 - 30/06/2021

2015 Agència de Gestió d'Ajuts Universitaris i de Recerca, FI-DGR 2016

Reference: 2016FI_B 00862

IP: ESTRADA BARRERAS, NATALIA

Period: 01/03/2016 - 28/02/2019

17.
Leukaemia Stem Cell Group

2017 Josep Carreras Deutsche Leukämie Stiftung, Ayudas a proyectos de investigación

Reference: DJCLS08/R2017

Title: Der Prolaktin Rezeptor als neues Therapie Taget bei Akuter Myeloischer Leukämie.

IP: MUÑOZ RISUEÑO, RUTH

Period: 08/08/2017 - 30/06/2021

2017 Departament de Salut, PERIS: Projects de recerca orientats a l'àmbit de la SALUT MENTAL

Reference: SLT002/16/00433

Title: Estudio post-autorización prospectivo de terapia adaptada al riesgo en la leucemia mieloide aguda y síndromes mielodisplásicos de alto riesgo: importancia del perfil genómico y de la enfermedad residual mínima en la asignación del tratamiento

IP: MUÑOZ RISUEÑO, RUTH

Period: 01/01/2017 - 31/12/2019

2016 Ministerio de Ciencia, Innovación y Universidades, Ayudas para incentivar la incorporación estable de doctores (IED)

Reference: IEDI-2016-00740

IP: MUÑOZ RISUEÑO, RUTH

Period: 01/01/2017 - 31/12/2019

2015 Ministerio de Economia y Competitividad, Programa Estatal de I+D+i Orientada a los Retos de la Sociedad

Reference: SAF2015-66721-P

Title: Estudio de la Implicación de los Receptores de Serotonina en los Procesos de Transformación Leucémica

IP: MUÑOZ RISUEÑO, RUTH

Period: 01/01/2016 - 31/12/2019

2016 Ministerio de Economia y Competitividad, Retos Colaboración

Reference: RTC-2016-5205-1

Title: Nuevo tratamiento para la leucemia mieloide aguda y los síndromes mielodisplásicos

IP: MUÑOZ RISUEÑO, RUTH

Period: 01/01/2016 - 30/06/2020

20.
Myelodysplastic syndromes

2018 Instituto de Salud Carlos III, Acciones complementarias de programacion conjunta internacional

Reference: AC18/00002

Title: An integrated European platform to conduct translational studies in myelodysplastic syndromes based on the EuroBloodNet infrastructure

IP: SOLE RISTOL, FRANCESC

Period: 01/01/2019 - 31/12/2021

2018 Fundación Científica de la Asociación Española Contra el Cáncer, Ayudas a proyectos de investigacion en cáncer TRANSCAN (Translational Research on Rare Cancers)

Reference: TRNSC18003SOLE

Title: An integrated European platform to conduct translational studies in myelodysplastic syndromes based on the EuroBloodNet infrastructure

IP: SOLE RISTOL, FRANCESC

Period: 01/12/2018 - 30/11/2021

2017 Instituto de Salud Carlos III, Proyectos de investigacion en Salud

Reference: PI17/00575

Title: Aplicación de la secuenciación masiva (NGS) en el diagnóstico y pronóstico de síndromes mielodisplasicos/neoplasias mieloproliferativas.

IP: SOLE RISTOL, FRANCESC

Period: 01/01/2018 - 31/12/2020

2016 Fundación Ramon Areces, Ayudas a la investigación

Title: Hacia la mejora del diagnóstico y tratamiento en anemias diseritropoyéticas congénitas.

IP: SOLE RISTOL, FRANCESC

Period: 08/03/2017 - 07/03/2020

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 00288

Title: Modalitat GRC (Reconegut i Consolidat).

IP: SOLE RISTOL, FRANCESC

Period: 01/01/2017 - 30/09/2021

21.
Stem cell biology, developmental leukemia and immunotherapy

2019 Fundación Científica de la Asociación Española Contra el Cáncer, Ideas Semilla AECC

Reference: IDEAS19005MENE

Title: Redirecting car t-cells to the bone marrow: improved car t-cell persistence and anti-leukemia effects while alleviating related toxicity

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/10/2019 - 30/09/2021

2018 Lady Tata Memorial Trust, Lady Tata Inernational Awards

Title: Adoptive Cellular Immunotherapy using CARCD7 NK-cells and CARCD1a T-cells for Treatment of Pediatric T-Cell Acute Lymphoblastic Leukemia.

IP: LOPEZ MILLAN, MARIA BELEN

Period: 01/09/2019 - 31/08/2020

2018 Fundació "La Caixa", Health Research 2018

Reference: HR18-00069

Title: Next-generation CAR-DOT cells for allogeneic adoptive cancer immunotherapy

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/09/2019 - 01/09/2022

2019 Fundación Uno Entre Cien Mil, VI Beca Unoentrecienmil. Fundación para la investigación en el área de la leucemia aguda infantil del 2019

Reference: 1entre100mil

Title: Towards a clinical translation of the CD1a-directed CAR for relapse/refractory cortical T-cell Acute Lymphoblastic Leukemia and Langerhans Cell Histioscytosis: feasibility, efficacy and safety

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/06/2019 - 31/05/2021

2018 European Food Safety Authority, NP/EFSA/PRAS/2018/04

Reference: NP/EFSA/PRAS/2018/04-CT1

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/02/2019 - 31/03/2020

2017 Ministerio de Economia y Competitividad, Ayudas Juan de la Cierva - Incorporación 2017

Reference: IJCI-2017-33172

IP: VINYOLES VERGES, MERITXELL

Period: 01/02/2019 - 31/01/2021

2017 Comissió Europea, Proof of Concept Grants 2018

Reference: ERC-2018-PoC-811220

Title: Therapeutic immunotherapy targeting NG2 and CD22 antigens for MLL-rearranged and MLL-germline B-cell Acute Lymphoblastic Leukemia

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/01/2019 - 30/06/2020

2017 Comissió Europea, H2020-MSCA-IF-2017

Reference: H2020-MSCA-IF-792923

IP: VELASCO HERNANDEZ, TALIA

Period: 01/01/2019 - 31/12/2020

2018 Comissió Europea, H2020-SC1-BHC-2018-2020 (Topics 2018)

Reference: 825749

Title: Childhood Leukaemia: Overcoming distance between South America and Europe Regions

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/01/2019 - 31/12/2023

2017 Ministerio de Economia y Competitividad, Retos-Colaboracion

Reference: RTC-2017-6367-1

Title: Obtención de hematíes in vitro a partir de ipscs de donantes con fenotipos eritrocitarios seleccionados y optimizados mediante edición genómica, como alternativa a los paneles de hematíes actuales

IP: MENÉNDEZ BUJAN, PABLO
Period: 01/09/2018 - 31/12/2021

2017 Ministerio de Ciencia, Innovación y Universidades, Ayudas para contratos predoctorales para la formacion de doctores (FPI)

Reference: BES-2017-080380

IP: BARONI, MATTEO LIBERO

Period: 01/07/2018 - 30/06/2022

2017 Comissió Europea, H2020-MSCA-IF-2017

Reference: H2020-MSCA-IF-795833

IP: ZANETTI, SAMANTA ROMINA

Period: 01/04/2018 - 31/03/2020

FACTS & FIGURES /
AWARDED AND ACTIVE PROJECTS

2016 Agència de Gestió d'Ajuts Universitaris i de Recerca, ajuts per a la incorporació de personal investigador postdoctoral al sistema català de ciència i tecnologia dins del programa Beatriu de Pinós (BP 2016)

Reference: 2016 BP 00048

IP: MOLINA CAMPOY, OSCAR

Period: 01/01/2018 - 31/12/2019

2017 Instituto de Salud Carlos III, Proyectos de investigación en Salud

Reference: PI17/01028

Title: Inmunoterapia celular adoptiva con CAR CD5 "síngular o dual" para tratamiento de LLA-T pediátrica e infecciones fúngicas post-transplante alogénico de progenitores hematopoiéticos

IP: BUENO UROZ, CLARA

Period: 01/01/2018 - 31/12/2020

2017 Fundación Científica de la Asociación Española Contra el Cáncer, Postdoctoral AECC

Reference: POSTD042TORR

Title: RECREACIÓN FUNCIONAL DE LLA-B t(4;11) EN CÉLULAS MADRE HEMATOPOYÉTICAS EN DISTINTOS ESTADÍOS DEL DESARROLLO MEDIANTE LA APLICACIÓN DE HERRAMIENTAS DE EDICIÓN GÉNICA

IP: TORRES RUIZ, RAUL

Period: 01/12/2017 - 30/11/2021

2017 COST, Cost Action proposals

Reference: CA16223

Title: LEukaemia GENe Discovery by data sharing, mining and collaboration

IP: MENÉNDEZ BUJAN, PABLO

Period: 26/10/2017 - 25/10/2021

2016 Departament de Salut, PERIS: Programes de recerca orientats - Medicina regenerativa

Reference: SLT002/16/00299

Title: Regeneració hematopoetica a partir de célul·les mare pluripotents.

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/04/2017 - 31/12/2019

2016 Fundación de Investigación Oncológica, Beca FERO de Investigación Oncológica Traslacional

Title: Inmunoterapia adoptativa con células T CAR-NG2 para la leucemia aguda con reordenamiento MLL.

IP: BUENO UROZ, CLARA

Period: 01/01/2017 - 30/06/2019

2016 Ministerio de Economia y Competitividad, Retos Colaboración

Reference: RTC-2016-4603-1

Title: Escalado del suministro y estudios de eficacia del indolocarbazol EC-70124 en modelos animales predictivos. (INDOLKIN)

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/01/2017 - 30/07/2019

24.
Lymphoma translational

2017 Agència de Gestió d'Ajuts Universitaris i de Recerca, Grups de Recerca de Catalunya (SGR)

Reference: 2017 SGR 00221

Title: Modalitat GRC (Consolidat). Concedit a IJC

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/01/2017 - 30/09/2021

2016 Ministerio de Economia y Competitividad, Programa Estatal de I+D+i Orientada a los Retos de la Sociedad

Reference: SAF2016-80481-R

Title: Inmunoterapia adoptiva con células T CAR-NG2 para la leucemia aguda con reordenamiento MLL

IP: MENÉNDEZ BUJAN, PABLO

Period: 30/12/2016 - 29/12/2019

2014 Comissió Europea, ERC-2014-CoG Reference: 646903

Title: Genomic, cellular and developmental reconstruction of infant MLL-AF4+ Acute Lymphoblastic Leukemia (INFANTLEUKEMIA)

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/01/2016 - 31/12/2020

2014 Heath Canada, Projects Reference: H4080-144541

Title: Pro-inflammatory bone marrow stroma in Acute Myeloid Leukemia: implication in the onset, evolution and drug resistance (Co-leader, Michael Rosu-Myles, Ottawa)

IP: MENÉNDEZ BUJAN, PABLO

Period: 01/10/2014 - 31/12/2019

2019 INTERREG POCTEFA, 3ª convocatoria de proyectos POCTEFA 2014-2020

Reference: EFA360/19

Title: Red cooperativa franco-española para el análisis de proteinopatías y el desarrollo de terapias individualizadas en cánceres hematológicos

IP: ROUÉ, GAËL

Period: 01/06/2019 - 31/05/2022

FACTS & FIGURES / **INNOVATION AND TRANSFERABILITY**

The Josep Carreras Institute is committed to knowledge transfer and assessing and searching for market opportunities in the broadest terms. As well as focusing on its own interests, it seeks to contribute to society and our country's progress.

In 2019, the results of our research in terms of innovation and transferability were as follows:

2 new patents:

- PCT/EP2020/053769 - CAR T-cells for the treatment of CD1a-positive cancer (priority date: 14/02/2019).
- PCT/EP2020/083386 - KDM subfamily 6 protein inhibitor for use in the treatment of cancer (priority date: 26/11/2019).

1 spin-off – Leukos Biotech:

- CEO: Luis Ruiz-Ávila
- Co-Founder and CSO: Ruth M. Risueño

Leukos Biotech is a spin-off of the Josep Carreras Leukaemia Research Institute that aims to find new cures for acute myeloid leukaemia (AML) and other haematological malignancies. This biopharmaceutical company was founded in 2015 as a tool to bring the research carried out by Dr. Ruth Muñoz-Risueño closer to patients.

Indeed, Leukos Biotech holds a patent licence from the Josep Carreras Leukaemia Research Institute for the use of a family of drugs and antibodies with potential for the treatment, diagnosis and prognosis of haematological malignancies, including AML. Thus, Leukos Biotech is currently developing new therapeutic strategies for targeting leukaemic stem cells, which are responsible for maintenance and relapse despite treatment.

LEUKOS BIOTECH

FACTS & FIGURES / **TEACHING AND TRAINING**

The Josep Carreras Institute offers a high-quality teaching programme for scientists and technicians interested in achieving a solid, up-to-date grounding in the field of leukaemia and malignant blood diseases. It organizes complementary training activities at all levels, from scientific conferences, seminars and technology sessions to specialized courses.

- 1 International congress
- 31 Scientific seminars
- 6 Non-scientific seminars
- 4 Training courses

In addition, the Josep Carreras Institute offers a Doctoral Degree in Haematology and a Master's Degree in Malignant Blood Diseases and participates in the teaching activities of degrees in medicine and biomedicine:

- 13 Staff linked to the University
- 10 Theses read
- 38 Current doctoral theses

As an affiliate of the University of Barcelona and the Autonomous University of Barcelona, the Josep Carreras Institute provides training for new generations of scientists, and our researchers disseminate scientific knowledge and discoveries in several biomedical and related degrees and master's courses.

FACTS & FIGURES / **COURSES AND SEMINARS**

January 2019

Inversió en empreses del sector biotech i salut: com funciona, com es seleccionen les empreses i un cas pràctic.

Speaker: Daniel Oliver i Oliver Balcells

Capital Cell and RheoDx

VI IJC Scientific Meeting 2019

Scientific Workshop

February 2019

From red blood cell deformability to next generation sequencing: a bridge for the diagnosis of rare anaemias

Speaker: Joan LLuís Vives.

Josep Carreras Leukaemia Research Institute, Spain

Uncovering direct epigenetic-metabolic connections: BRD4 and MTHFD1, how folate metabolism shapes transcription regulation

Speaker: Sara Sdelci

Gene Regulation, Stem Cells and Cancer Group Leader

CRG, Spain.

Diffuse Large B cell Lymphoma: pathogenetic and therapeutic implications from genomic analysis

Speaker: Dr. Riccardo Dalla-Favera

Professor of Pathology & Cell Biology, Professor of Microbiology & Immunology, Professor of Genetics and Development, Director, Institute for Cancer Genetics. Institute for Cancer Genetics, Columbia University, USA

Unraveling the human IgG4 antibody response in health and disease

Speaker: S. Marieke van Ham. Professor of Biological Immunology at the University of Amsterdam's Faculty of Science (FNWI), The Netherlands

March 2019

Harnessing molecular dependencies in lung cancer

Speaker: Martin Sos

Center for Integrated Oncology in Cologne

Cytogenetics and Molecular Genetics of Haematological Neoplasms Course

Course

La robòtica i les relacions afectives

Speaker: Carme Torras.

UPC, Spain.

"Sequences and beyond: a tale of expectations, challenges and deceptions"

Speaker: Dr. Ana Rojas

Computational Biology and Bioinformatics Group, CABD/CSIC, Spain.

Bioinformatics workshop: Introduction to NGS data analysis

Scientific Workshop

Speakers: VVAA.

Engineering the Immune System for Enhanced Cancer Immunotherapy

Speaker: Luis Alvarez-Vallina

Aarhus University, Aarhus, Denmark

April 2019

Cytogenetics and Molecular Genetics of Haematological Neoplasms Course

Course

Cap a on ens porta la ciència? Els reptes de la biomedicina del segle XXI

Speaker: Salvador Macip, MD, PhD

Mechansism of Cancer and Ageing Lab

Deparment of Molecular and Cell Biology University of Leicester, UK

Myotonic dystrophy: complex repeats in a complex disorder

Speaker: Darren Monckton

Professor of Human Genetics (Institute of Molecular Cell and Systems Biology)

FACTS & FIGURES /
COURSES AND SEMINARS

May 2019

Finding, understanding and exploiting transcriptional dependencies in cancer
Speaker: Johannes Zuber
IMP, Austria

Epigenetics and Lymphoma: From Knowledge to Applications
Speaker: Manel Esteller.
Josep Carreras Institute, Spain.

La historia de 150 años del Anís del Mono en Badalona
Speaker: Antonio Guillen
Director of Anís del Mono, Badalona, Spain.

Cytogenetics and Molecular Genetics of Haematological Neoplasms Course
Course

June 2019

Immunogenomics one cell at a time
Speaker: Roser Vento-Tormo
Group Leader at Wellcome Sanger Institute, UK.

Cuina de proximitat en una Estrella Michelín
Speaker: Carme Ruscalleda, Sant Pol, Spain.

July 2019

Combinar Expresión Génica y Perfil Inmunofenotípico a Escala Unicelular

Speaker: Serge Scherrer PhD

Field Applications Specialist, BDB Multiomics South Europe

Host: Francesc Solé

Structure determination of genomes and genomic domains by satisfaction of spatial restraint

Speaker: Marc Martí Renom.

Structural Genomics Group Leader Centre Nacional d'Anàlisi Genòmica - Centre for Genomic Regulation (CNAG-CRG)

Immediate and deferred epigenomic signature of neuronal activation

Course

Bionano Genomics: Next-Generation Cytogenomics: High-throughput Mapping of Structural Variation in Cancer and Genetic Disease

Speaker: Sales assistant, Bionano Genomics.

September 2019

L'assetjament al codi penal

Speaker: Sr. Artur Matamoros and David Gracia.

Mossos d'esquadra, Spain.

Multiple ways of altering the gene regulatory program in cancers: focus on transcription factors, microRNAs, and DNA methylation

Speaker: Anthony Mathelier

Computational Biology & gene Regulation Group, Group leader, Centre for Molecular Medicine Norway (NCMM), Oslo University Hospital

FACTS & FIGURES /
COURSES AND SEMINARS

October 2019

Targeting Gene Control via Pharmacologic Protein Degradation

Speaker: Georg Winter

Leader of the Chemical Biology of Oncogenic Gene Regulation Group, Ce-M-M, Research Center for Molecular Medicine of the Austrian Academy of Sciences, Austria.

Leukemia, tumor immunology and cancer therapeutics

Speaker: Laura Belver, PhD

Institute for Cancer Genetics, Columbia University Medical Center, USA

Host: Dr. Manel Esteller

Clinical Implications of Clonal Hematopoiesis

Speaker: David P, Steensma, MD

Associate Professor, Medicine, Harvard Medical School. Attending Physician, Hematologic Oncology, Dana- Farber Cancer Institute. Attending Physician, Medicine, Brigham and Women's Hospital. Dana- Farber Cancer Institute, Boston, USA

Optimized target detection in qPCR: new primer and probe chemistries for gene expression and genotyping

Speaker: Soraya Cobos

Sales Manager of IDT Integrated DNA Technologies, USA

November 2019

Young blood for old brains

Speaker: Tony Wyss-Coray

Professor, Neurology & Neurological Sciences, Stanford University School of Medicine, USA

Investigating the Functional Implications of Arginine Citrullination

Speaker: Priyanka Sharma.

Centre for Genomic Regulation, Barcelona.

DFMO and 5-Azacytidine increase M1 macrophages in the tumor microenvironment of ovarian cancer

Speaker: Dr. Cynthia Ann Zahnow, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, USA

Immunodeficient murine models for studies of healthy hematopoiesis, acute leukemia and immunotherapy

Speaker: Pablo Menéndez

Josep Carreras Leukaemia Research Institute, Spain

Precision Sequencing with Single-Cell Genomics: Resolving Heterogeneity in Blood and Solid Tumors

Speaker: Gema Fuerte, FAS,
Mission Bio, USA

New tools for a new view: RNA-protein interactions form a systems perspective

Speaker: Eneko Villanueva
Cambridge center for proteomics of the
University of Cambridge, UK

Desember 2019

Targeting the osteoblast-leukemia crosstalk as a new therapy for Acute Myeloid Leukemia

Speaker: Marta Galán Díez
Associate Research Scientist, Dept. Physiology& Cellular Biophysics
Columbia University, New York, USA

The epitranscriptome: a new era for cancer research

Speaker: Francesca Aguiló, principal investigator of AguiloLab, group of research on Epigenetics and RNA modifications. UMEA University,
Sweden.

Antigen-presenting cells, the immune response and tailored therapies

Speaker: Dr. Elodie Segura.
Principal Investigator, INSERM Research Associate, Institut Pasteur, France

Somatic mutations and clonal hematopoiesis in cardiovascular disease: commonalities with cancer

Speaker: Dr. Jose Javier Fuster
CNIC, Madrid, Spain.

FACTS & FIGURES / **INSTITUTIONAL EVENTS**

MANAGEMENT RETREAT
21 OCT 2019

The Josep Carreras Institute's Management Retreat served to create a shared vision among all staff categories within the organization. At this retreat, which was held at the Casino de Tiana, our management staff collaborated with colleagues, engaged in meaningful leadership activities and built management team excellence.

SCIENTIFIC RETREAT
4 DEC 2019

The Institute's Scientific Retreat was held at the beautiful Romanesque Castellet Castle, a UNESCO centre and the headquarters of the Abertis Foundation, and participants talked about the past, present and future of the Josep Carreras Institute.

FACTS & FIGURES / **FINANCIAL DATA**

The Institute's pioneering mixed-funding model is partially financed by the Josep Carreras Foundation. It also receives core funding from the Catalan government and is reliant on competitive funding for its research activities.

In 2019, there was a 63.11% increase in income from public funds and the provision of services. With respect to spending, this increased by 66.76% compared to the previous year.

A total of 24.18% of IJC's outlay corresponds to staffing, with a 62.20% increase compared to the previous year.

The profit for the 2019 financial year was €470.001,00, but when the depreciation of investments is taken into account the result was a loss of €496.370,65.

	2018	2019
INCOMES	**5.226.656**	**8.282.177**
Contributions from the Generalitat	1.215.944	1.785.632
Other transfers (fijc)	895.515	1.530.075
Services	274.979	808.533
Project implementation	2.444.395	3.828.160
Overheads	395.823	329.777
Operational expenses	5.203.788	7.794.444
Staffing costs	1.172.163	1.884.503
Information technologies services	52.529	100.229
Communication	870	4.717
Building maintenance	497.866	666.237
Laboratories maintenance	128.206	170.127
Research support	24.950	179.387
Project implementation	2.444.395	3.828.160
Scientific-technical services (platforms)	246.368	323.246
Biobank	11.841	14.246
Management support services	116.743	175.680
Other	328.406	312.076
Vat prorata	81.235	65.032
Expenditure on investments pending activation	58.377	50.414
Heritage	22.748	14.643
Reimbursement of subsidies and other management losses	17.091	5.747
RESULT OF THE ACTIVITY	**22.868**	**487.734**
Extraordinary result	73.503	0
Operating income	96.371	487.734
Financial performance	-35.789	-17.733
Result before amortization	60.582	470.001
Amortization	-911.943	-966.372
RESULT	**-851.361**	**-496,371**

FACTS & FIGURES / **FUNDRAISING**

This is an across-the-board aim that feeds into our research and help us raise people's awareness of leukaemia. The success of the campaigns depends on the support we receive in terms of design and media coverage. That is why companies that wish to demonstrate their commitment and alliance to the fight against leukaemia play such a key role.

Companies can become associated with one of the projects or research lines being carried out by our researchers through the Josep Carreras Leukaemia Foundation, thereby combining their strength and resources with ours through shared goals and values.

Leukaemia patients and their families are the focus of our work, with respect to their well-being and our search for a cure. For this reason, the Josep Carreras Leukaemia Research Foundation organizes Patients' Day every year with the collaboration of our researchers.

FACTS & FIGURES / **AWARDS**

Given our efficient governance, the Josep Carreras Leukaemia Research Institute is a Catalan Research Centre of Excellence and forms part of the Catalan government's current research centre network. It is also accredited by the Spanish Ministry of Health as a Health Research Centre of Excellence and by the Spanish Association Against Cancer. The Institute also holds the HR Excellence in Research Award from the European Commission.

The Spanish Ministry of Health reconfirmed the status of the campus as a Centre for Health Research Excellence in its last evaluation in 2014 and it is currently applying for renewal for 2019 onwards. IJC has subscribed the European Charter and Code of Conduct for the Recruitment of Researchers and it is in process of obtaining the HRS4R award (foreseen to have the recognition mid 2019).

FACTS & FIGURES / **INSTITUTIONS INVOLVED**

The Josep Carreras Institute strives to establish continuing cooperation agreements and aims to broaden its strategic alliances and agreements with the pharmaceutical industry and other private organizations.

The following organizations are currently associated with our Institute:

Founding members:

JOSEP CARRERAS Leukaemia Foundation

Generalitat de Catalunya Government of Catalonia

With the institutional collaboration of:

Ajuntament de Badalona

UAB Universitat Autònoma de Barcelona

Universitat de Barcelona

In scientific association with:

CLÍNIC BARCELONA Hospital Universitari

Germans Trias i Pujol Hospital

ICO Institut Català d'Oncologia

HOSPITAL DE LA SANTA CREU I SANT PAU

BANC DE SANG I TEIXITS

IMPPC Institut de Medicina Predictiva i Personalitzada del Càncer

IDIBAPS Institut d'Investigacions Biomèdiques August Pi i Sunyer

santpau Institut Investigació Biomèdica | Barcelona

IGTP

FUNDACIÓ CLÍNIC BARCELONA

With the inestimable suport of:

janssen

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Private funding:

Consortia:

Special thanks to all the staff for your outstanding work.
Individually we are strong. Together we are unstoppable!

Josep Carreras Research Institute

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The report can also be downloaded from:
http://www.carrerasresearch.org

Josep Carreras
LEUKAEMIA
Research Institute