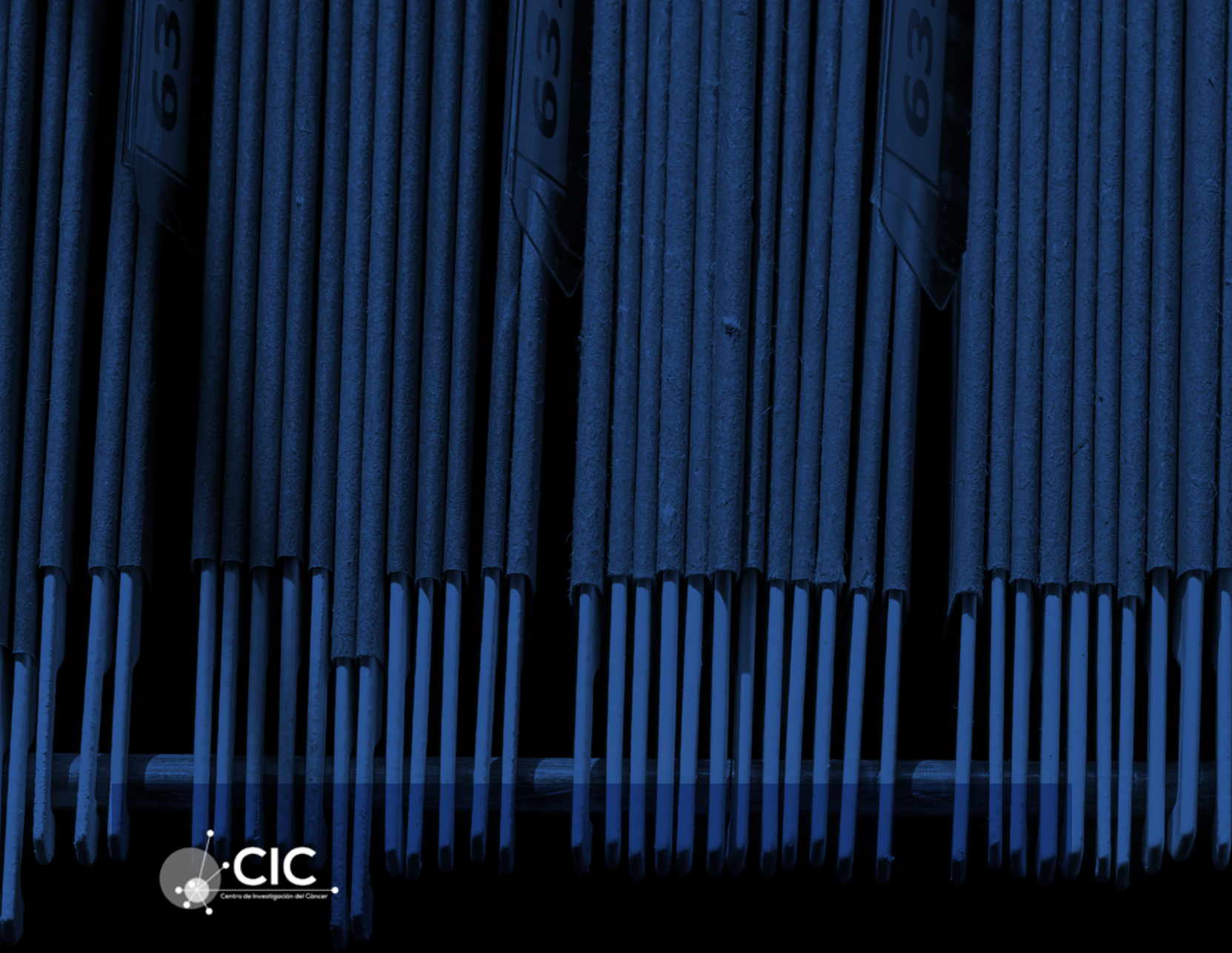
SCIENTIFIC REPORT

2020 | 2021

CIC Centro de Investigación del Cáncer

VNiVERSiDAD D SALAMANCA CAMPUS DE EXCELENCIA INTERNACIONAL

CSIC Consejo Superior de Investigaciones Científicas



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https://www.cicancer.org/scientific-report-2020-2021

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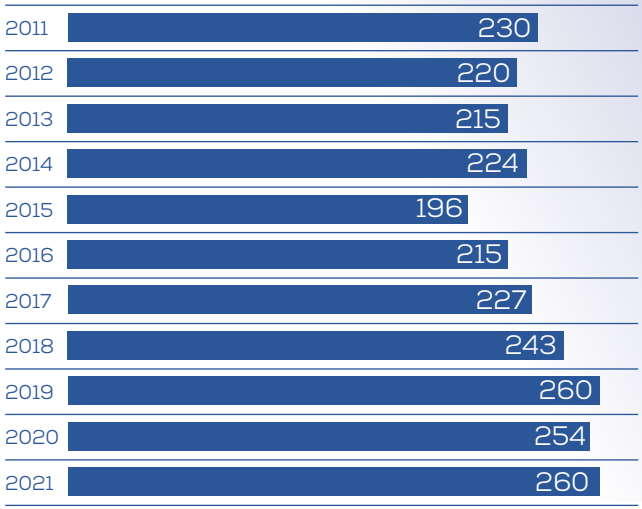
FOREWORD

This report summarizes the most relevant activities in the **CIC-IBMCC** (Cancer Research Center-Institute of Molecular and Cell Biology of Cancer of Salamanca (CSIC-USAL) throughout **the years 2020 and 2021**, a period that will be otherwise long remembered because of the deep impact caused by the **COVID-19 pandemic** on social, economic and public health activities at a global level. Of course, the pandemic also impacted greatly at the local level on the CIC IBMCC by forcing us to reorganize our regular day-to-day activities during this period in order to safeguard the health of all our researchers and workers while at the same time keeping focus on achieving the scientific objectives of our Strategic Research Plan. However, despite the difficulties and thanks to the resilience and effort of our researchers and supporting staff, and the efficient implementation and use of new communication technologies and virtual research platforms and applications, we have been able to **successfully maintain most of our research and training activities and goals** during this period. In this regard, I want to express my deepest appreciation and thanks to our scientific and technical support personnel, whose commitment and hard work in front of unfavorable circumstances has made it possible for the CIC-IBMCC to achieve its scientific goals and to maintain its national and international reputation during this period. I also want to send my sympathy and condolences to all members of our Center who have suffered losses in family and friends as a result of the COVID-19 pandemic.

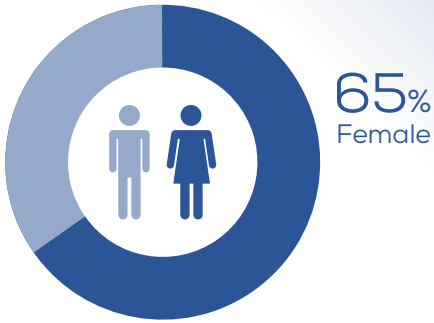
Our previous scientific report already mentioned that, after external international evaluation of our Strategic Plan (SP) 2018-2021, the CIC-IBMCC had just received accreditation

TOTAL STAFF CIC-IBMCC 2011-2021



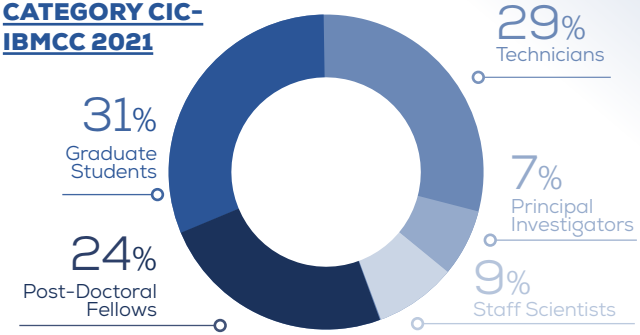
as the first "**Center of Research Excellence**" recognized in Castilla y León and was awarded a grant of €2,100,000 in order to support efforts to improve our international competitiveness, research excellence, and outreach in the field of cancer research for the period 2018-2022. The **implementation of our new SP during 2020-21** has involved, in particular: **(i)** the full reorganization of all research structures of our center around two complementary Research Programs: the Molecular Mechanisms of Cancer Program (MMC) and the Research Program Translational and Clinical Cancer (TCRC); **(ii)** the renewal of our External Scientific Advisory Board (ESAB) to incorporate new external international researchers, two of them women; **(iii)** our accreditation with an Excellence in Research Award (HRA) from the European Commission in order to make our center more attractive for researchers financed with EU funds, thus facilitating recruitment, incorporation and stabilization of new talent in our center; or **(iv)** the renewal of the Quality and PRL certifications covering our services and socio-sanitary activities, during the period 2020-2021. We hope that all the improvements recently achieved under our accreditation as a regional Excellence Center in Castilla y Leon will provide a strong foundation helping us in future to achieve accreditation in a national call for "Severo Ochoa" Centers of Excellence.

AVERAGE DISTRIBUTION BY GENDER CIC-IBMCC 2021

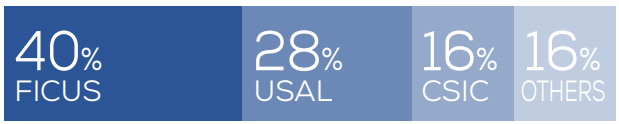


DISTRIBUTION BY AREAS CIC-IBMCC PERSONNEL 2021

DISTRIBUTION BY PROFESSIONAL CATEGORY CIC-IBMCC 2021



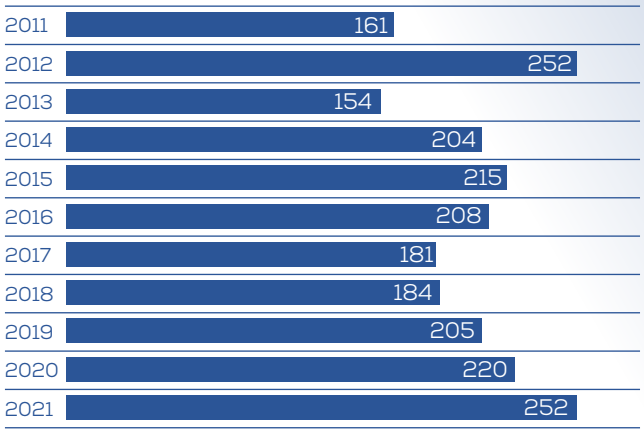
DISTRIBUTION BY INSTITUTIONS PERSONNEL CIC-IBMCC 2021



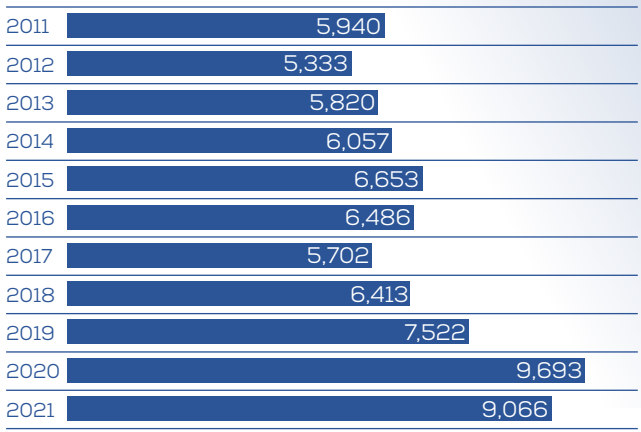
Regarding our **research staff**, it is worth highlighting at this point the significant **rejuvenation of the scientific roster of our institute** that started at the end of 2019 with the incorporation of three young researchers (**Dr. Sandra Blanco, Dr. Esther Castellano and Dr. Miguel Vicente-Manzanares**) and has continued with the more recent incorporation, in September 2021, of three new CSIC Senior Scientists including **Dr Antoni Hurtado** (from University of Oslo (Norway) and Hospital Clínic/University of Barcelona), **Dr. Mattias Drösten** (from CNIO, Madrid), and **Dr. David Santamaría** (from European Institute of Chemistry and Biology in Bordeaux, France). In parallel to the incorporations *via* CSIC, **Dr. Jacques J.M. van Dongen** (from Immunology Dept of Leiden University, and the beneficiary of an ERC Advanced Grant from the European Commission) also joined the CIC IBMCC on September 2021 as a senior PI supported by a contract underwritten by FICUS. It is clearly apparent that all these new incorporations increase our scientific excellence and international competitiveness and also provide significant hope for the future renewal and continuity of our center. On the other hand, two CIC PIs left our Center at the end of 2021: **Dr. Juan Jesús Cruz** (CIC Lab 14, Head of Oncology at the University Hospital of Salamanca), who reached retirement age; and **Dr. Felipe X. Pimentel Muiños** (CIC Lab18), who transferred his CSIC position to CIB, CSIC, in Madrid. On behalf of everyone at the CIC-IBMCC, I would like to convey to both of them our deepest gratitude and recognition for their work, friendship and dedication over the years, and wish them the best for the future.

Taking into consideration the incorporations and departures of PIs during these two years, in December 2021 the CIC-IBMCC was made up of **25 research groups**, 19 of them led by R4 Senior PIs and 6 of them led by R3 researchers. In addition, our center also holds **5 Core Units**, **5 Clinical Diagnosis Units** and **9 Research Support Units**. The following pages in this report contain updated descriptions of the composition and function of our Research Units, Core & Diagnostic Units, and Support Units for the years 2020-21. Consistent with our status as a Joint institute ("**Instituto Mixto**") of the University of Salamanca (**USAL**) and the Spanish National Research Council (**CSIC**) whose activity is also supported by the Cancer Research Foundation at the University of Salamanca (**FICUS**), approximately 44% of our scientific staff were formally affiliated with either USAL or the CSIC, while about 40% held employment contracts underwritten by FICUS. The remaining 16% of the staff working at the CIC IBMCC corresponds to researchers supported by institutions affiliated with ISCIII, such as CIBERONC or IBSAL.

CIC-IBMCC PUBLICATIONS 2011-2021



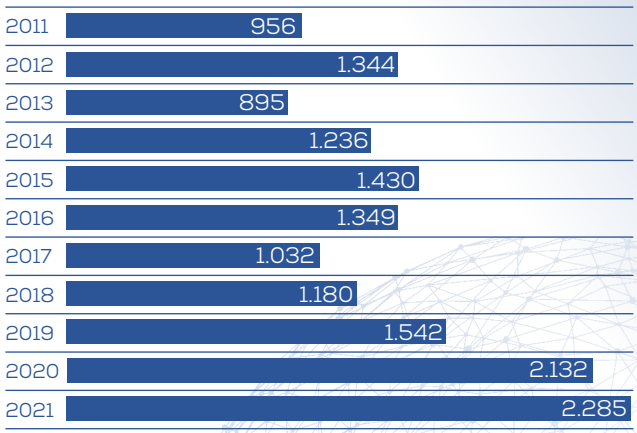
CIC-IBMCC IF/PAPER 2011-2021



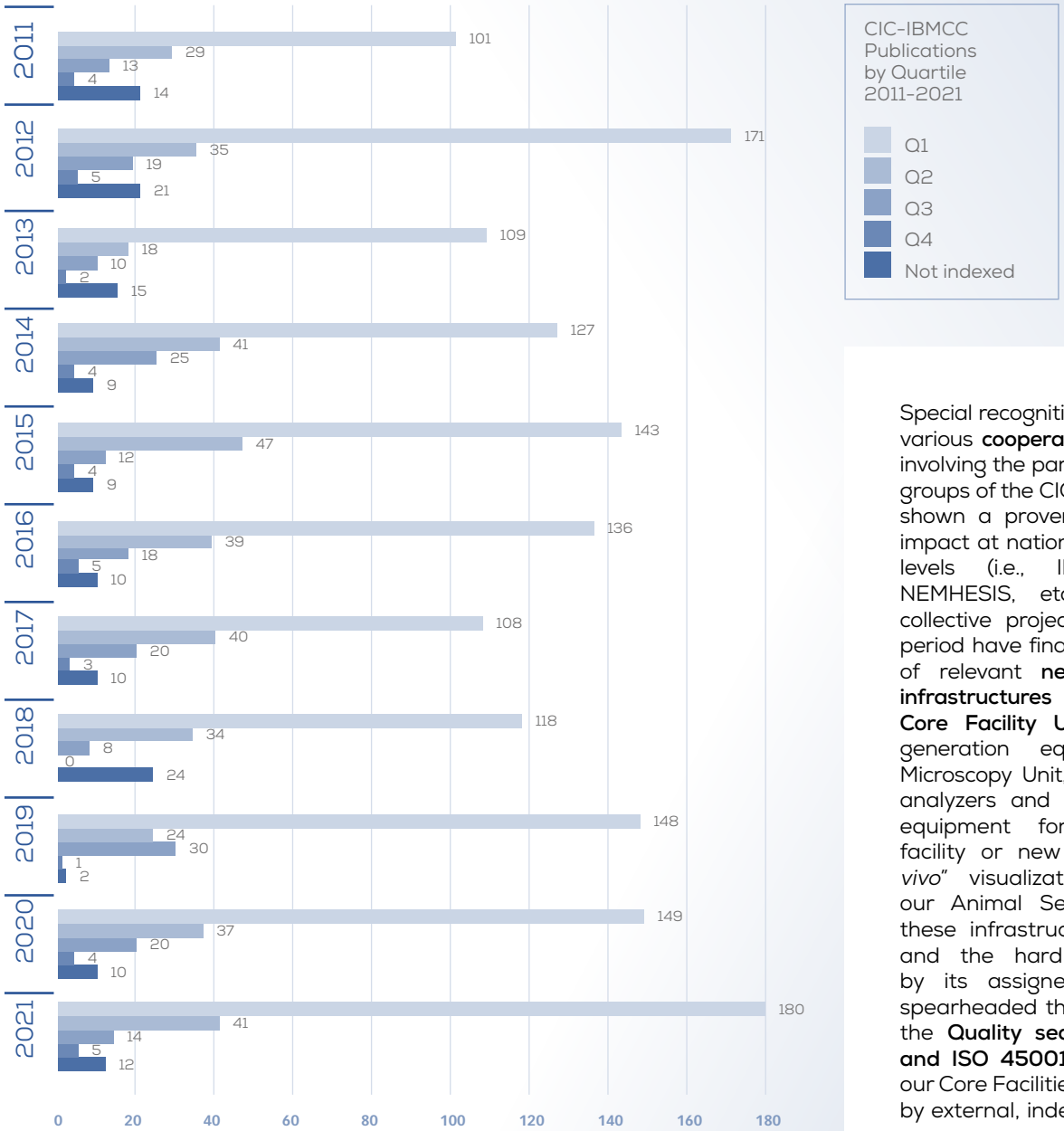
Regarding **scientific productivity**, during this two-year period the CIC-IBMCC researchers have authored **472 original articles** related to different fields of cancer research that were published in 183 different international journals. **329** of the aforementioned articles were published in journals ranked in the first quartile (**Q1**), and **149** articles in journals ranked in the first decile (**D1**) of their corresponding area of knowledge. **125** of those articles were published in journals with an impact factor greater than 10. Remarkably, our overall scientific production during the pandemic years 2020-2021 represents a notable **growth over previous years with regards to the number and quality of publications as well as average impact factor** (9.29) per article during this period.

As for **external funds** obtained by scientists working at the CIC IBMCC, it is worth to mention at this point the **198 research projects that were active during this period** and were coordinated or participated by members of our Center. 90% of our projects came from competitive calls, with 78% of them being financed by public funds and the remaining 22% supported by private sources. Of these active projects, **119 were actually awarded within 2020-2021** and amounted to more than **13 million euros.** 10% of this amount corresponds to support from international sources, 28% was financed by national agencies, 40% was related to regional funds, and the remaining 22% was financed by foundations, non-profit entities, and/or contracts with private companies.

CIC-IBMCC IMPACT FACTOR 2011-2021



CIC-IBMCC PUBLICATIONS BY QUARTILE 2011-2021



Special recognition is due here to the various **cooperative clinical projects,** involving the participation of multiple groups of the CIC IBMCC, which have shown a proven, important clinical impact at national and international levels (i.e., IDIAL_NET, ECRIN, NEMHESIS, etc). Likewise, other collective projects held during this period have financed the acquisition of relevant **new equipment and infrastructures for our shared Core Facility Units,** including last generation equipment for our Microscopy Unit, new metabolomics analyzers and mass spectrometry equipment for our Proteomics facility or new equipment for "*in vivo*" visualization of tumors in our Animal Service Unit. Indeed, these infrastructure improvements and the hard work contributed by its assigned personnel have spearheaded the recent renewal of the **Quality seals (ISO 9001:2015 and ISO 45001:2018)** awarded to our Core Facilities and Support Units by external, independent evaluation

Certification

Awarded to

FUNDACIÓN DE INVESTIGACIÓN DEL CÁNCER DE LA UNIVERSIDAD DE SALAMANCA

CAMPUS MIGUEL DE UNAMUNO, CENTRO DE INVESTIGACIÓN DEL CÁNCER - 37007 - SALAMANCA - ESPAÑA

Bureau Veritas Certification certifies that the Management System has been audited and found to be in accordance with the requirements of standard:

STANDARD

ISO 9001:2015

Scope of certification:

RESEARCH SUPPORT SERVICES, CORE FACILITIES: PROTEOMICS UNIT, GENOMICS UNIT, CLEANING AND STERILIZATION UNIT, MICROSCOPY UNIT, RADIOACTIVITY UNIT, DIAGNOSTIC MOLECULAR PATHOLOGY UNIT.

Certificate Number:	ES126220-1
Original approval date:	13-10-2006
Certification/Renovation Audit:	08-06-2021
Expiry date of previous cycle:	15-08-2021
Effective date:	15-12-2021
Certificate expiration date:	15-08-2024

This certificate is valid, subject to the general and specific terms and conditions of certification services

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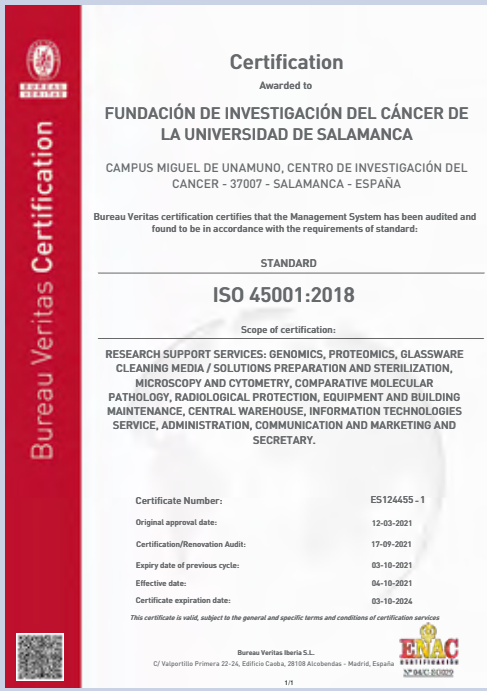

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STANDARD

ISO 45001:2018

Scope of certification:

RESEARCH SUPPORT SERVICES: GENOMICS, PROTEOMICS, GLASSWARE CLEANING MEDIA / SOLUTIONS PREPARATION AND STERILIZATION, MICROSCOPY AND CYTOMETRY, COMPARATIVE MOLECULAR PATHOLOGY, RADIOLOGICAL PROTECTION, EQUIPMENT AND BUILDING MAINTENANCE, CENTRAL WAREHOUSE, INFORMATION TECHNOLOGIES SERVICE, ADMINISTRATION, COMMUNICATION AND MARKETING AND SECRETARY.

Certificate Number:	ES124455-1
Original approval date:	12-03-2021
Certification/Renovation Audit:	17-09-2021
Expiry date of previous cycle:	03-10-2021
Effective date:	04-10-2021
Certificate expiration date:	03-10-2024

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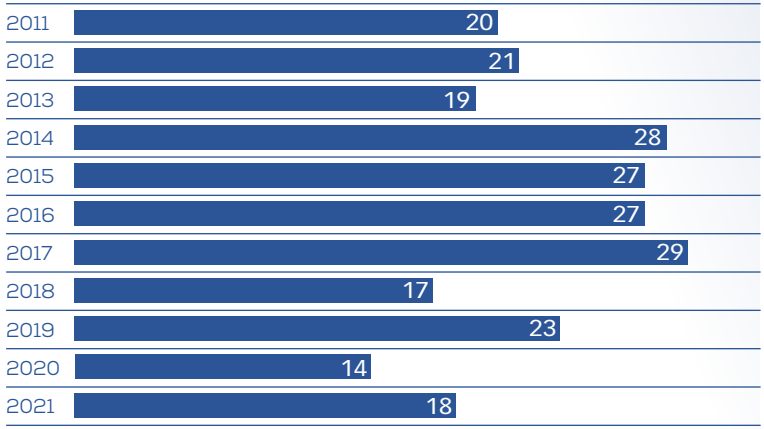
agencies. Finally, regarding transfer of research results we may also mention the **6** families of **patents** licensed by researchers from our center to different Spanish and international companies or the **15 collaborative agreements** signed with biotechnological and biopharmaceutical companies during this two-year period.

We have also dedicated special efforts during 202-21 in order to improve the scientific quality and the effective **internationalization of our academic programs** (master and PhD) aimed at training our scientific and technical personnel. In spite of all the difficulties inherent to the ongoing Covid-19 crisis, during this period we were able to progressively implement the exclusive use of the **English language** in our Master program and all other scientific activities of our Center (web, seminars, communications, etc) and we also generated various videos and booklets in this language with **information about the research and training activities** of the CIC IBMCC (www.cicancer.org/training/master-degree). We have also entered multi-campus collaborations in order to **join 2 international master programs**, namely the **Coimbra group Life Sciences master program in Cancer Biology** (connecting the CIC-IBMCC Cancer Program with the universities of Montpellier (France), Würzburg (Germany), zu Koln (Cologne, Germany), Turku (Finland), Abo Akademi (Finland), Vilnius (Lithuania), Tartu (Estonia), Coimbra (Portugal), Pavia (Italy) and Barcelona (Spain); and the International Master Program on **"Health and Wellness"** of the **PEC2U Program/European campus of University Cities** (2021-2023) coordinated by the University of Poitiers (France) and involving Turku (Finland) , Coimbra (Portugal), Iasi (Romania), Pavia (Italy), Jena (Germany) and the CIC-IMBCC-University of Salamanca).

THESES PER YEAR CIC-IBMCC 2011-2021



A total of **32 Doctoral Theses** (PhD) directed by CIC-IBMC scientists were presented and successfully defended at our Center during this period. Our yearly **Cancer Seminar Series program**, involving 50 different national and international speakers, was also maintained during 2020-21, mostly under online format due to the Covid pandemic.

Communication and outreach activities directed to the outside scientific community as well as to patients, society and the general public are also important goals for an integral, comprehensive cancer research center like ours. In this regard, the CIC-IBMCC has continued to sponsor during this period the "**Doctores Diz Pintado Award**" which, after 11 annual editions, is already recognized as the most coveted award recognizing the excellence of the most outstanding cancer researcher younger than 45 in Spain. The awardees for 2020 and 2021 were, respectively, **Dr. Iñaki Martín-Subero** (IDIBAPS, Barcelona) and **Dr. José M. C. Tubio** (CIMUS, Santiago de Compostela), two of the most relevant and recognized young cancer scientists at the current Spanish and international cancer scene.

At this point, I would like to mention that **on February 2021 the CIC IBMCC was evaluated by the Scientific Committee of our national State Research Agency (AEI)** regarding the execution of our 2018-2022 Strategic Plan, receiving a score of 172 points out of 200. Among other relevant entries from the committee´s report we may emphasize here the following: **(i)** *"The Center has very limited core funding and therefore relies on external sources. In this context, the productivity is certainly excellent"*. **(ii)** In this situation, **"***an increase in institutional funding would contribute greatly to facilitating the capitalization of the gains"*. **(iii)** *"The proposals included in SP 2018-2021 for increasing international leadership seems sensible, although it faces with the reality of being competitive enough in the international arena to recruit top talent, given the salary limitations at the public sector"*. Certainly, these **general conclusions from the AEI report are in complete agreement with the claims that we have repeatedly included in all our scientific reports of previous years,** where we always highlighted the **need for a definite and stable economic support from our sponsoring institutions** to cover the costs of regular operations (building maintenance, security, administration, etc.) in our Center if we wanted to maintain the center's competitiveness and its ability to keep first-rate scientists in our staff or to attract new, young talented researchers to our Salamanca cancer Center.

In this context, there are a number of specific lines of action that our Center need/must take I order to overcome these challenges in the coming years. **First**, we need **to implement our new Strategic Plan 2022-2025** including **(i)** new focus on molecular mechanisms involved in early cancer development, and its translation into early cancer diagnosis and intervention, **(ii)** reinforcement/ expansion of our comprehensive cancer research lines to boost translation of research results into clinical practice, **(iii)** extension of the scope of our research programs to foster development and validation of novel targeted therapies and immunotherapy and **(iv)** integration into strong research networks with clinicians and the pharmaceutical industry geared towards development and testing of new therapies, novel drug design and screening platforms, and industry partnerships focused on early treatment intervention and prevention of cancer. **Second**, to fulfill the specific obligation posed by the Escalera de Excelencia of CyL, our Center should also apply to the **incoming national calls for Severo Ochoa Centers of Excellence** in order to enable the execution and financing of the aforementioned objectives in our new Strategic Plan.

I want to conclude this foreword by expressing our gratitude to our **External Scientific Advisory Board** that has always provided scientific guidance and adequate steering to our research work, and also to all outside **sponsors and anonymous donors** who have helped our Center during the past two years. I am persuaded that adding up all these external contributions to the internal efforts of our scientific and technical staff will permit the CIC-IBMCC to continue its success producing high quality scientific research in the field of oncology for years to come.

Eugenio Santos
Director

2 ORGANIZATION

SUMMARY

The Centro de Investigación del Cáncer-Instituto de Biología Molecular y Celular del Cáncer of Salamanca (CIC-IBMCC) was initiated in 2000 as a joint research center between the University of Salamanca (USAL) and the Spanish National Scientific Council (CSIC) and adopted a research structure similar to the US Comprehensive Cancer Centers.

With this approach, we aimed at the rapid transfer of results to patients by putting together basic, translational, and clinical research groups and offer distinctive features over other Spanish research centers:

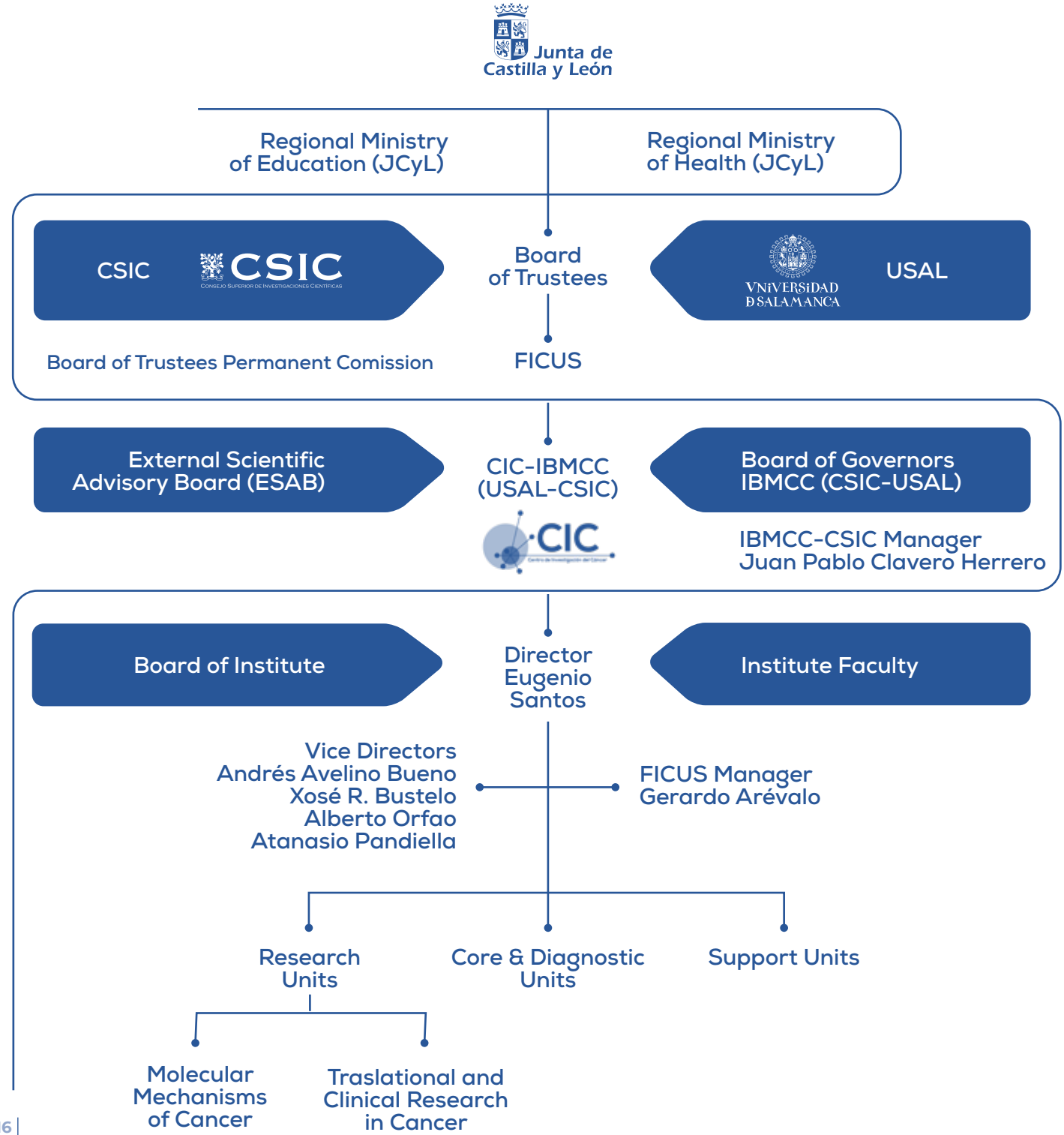
- A monographic focus on multidisciplinary cancer research.
- Close connection with the Salamanca University Hospital and nationwide hospitals.
- The development of patient-oriented diagnostic units, new treatments, and diagnostic resources.
- Implementation of services to facilitate access of new technologies to external stakeholders.
- Interest in translating research developments into patents, collaboration with biopharmaceutical companies, and spin-offs.
- Extensive cancer-related training programs.

The governing bodies of the CIC-IBMCC are: (i) the Governing Committee composed of two representatives of the CSIC and two representatives of the USAL (ii) the Board of the Institute, consisting of the director, Vice-Directors, manager, principal investigators of the institute, a representative of the scientific staff, and a representative of the technical and support staff (iii) the Director, appointed by the Presidents of the CSIC and the Rector of the Salamanca University according the proposal of Faculty Board of the Institute, (iv) four Vice-Directors as proposal of the director of the center, (v) the Center Manager, responsible for budget management, economic, and administrative personnel, (vi) the Faculty Board, a consultative body that is integrated by all PIs and representatives of the scientific, technical, and training staff and finally (vii) the External Scientific Advisory Board.

In addition to this common structure to most research centers, the CIC-IBMCC has the Foundation for Cancer Research at the University of Salamanca (FICUS), which (i) contributes to flow in the center of scientific activity through the recruitment of scientific, technical and administrative, (ii) serves as a bridge between agency activities performed by the CIC-IBMCC and society, channeling funds and sponsorships provided by individuals, private companies and non-governmental organizations to the center, (iii) facilitate the rapid transfer of results obtained by researchers to R+D and finally (iv) promotes research excellence through the promotion of periodic evaluation of the research carried out by an external scientific committee. The FICUS has a Board of Trustees presided by the Rector of the University of Salamanca and the President of CSIC, joined representatives of the University of Salamanca, the CSIC and representatives of the Regional ministries of Education and Health of the Junta de Castilla y León that evaluates and approves major organizational changes at the center, the FICUS Director, who exercises the legal and institutional representation of the Institute and the functions of scientific management and the FICUS External Scientific Advisory Board (ESAB), an independent advisory body to the Foundation and CIC-IBMCC, composed by renowned external scientists with expertise in cancer research that advises and supports the FICUS Board of Trustees and the Scientific Director.

The overall organization of our research is structured around two mutually complementary Research Programs (RP) (i) Molecular Mechanisms of Cancer (MMC) Program and (ii) Translational And Clinical Research In Cancer (TCRC). Together, both Programs cover essential areas of cancer research, including basic, translational and clinical research. They also include multiple experimental models that cover gene characterization, genome-wide high-throughput techniques (sequencing, transcriptomics profiling, proteomics, metabolomics, multi-omics), cellular models, animal models, and clinical models (patient-derived xenografts, primary cancer samples). Topics currently covered include genomics, signal transduction, metastasis, cell signaling, chromosomal stability, apoptosis, autophagy, systems biology, bioinformatics, diagnostics, riskstratification/prognostics, drug testing, and clinical trials.

To catalyze the implementation of the current 2018- 2022 Strategic Program (SP) of CIC-IBMCC-FICUS a management structure has been implemented (i) Designation of a SP Director to coordinate all activities linked to the SP, (ii) Designation of a Program Manager to help in the day-to-day execution of the SP and the outreach activities of the Center (iii) establishment several Committees (Research Program, Training and Core Facility And Infrastructures Committees and finally (v) Core Facilities & Services and Support Units.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Xosé R. Bustelo
Alberto Orfao
Atanasio Pandiella
FICUS Manager
Gerardo Arévalo
Research Units
Core & Diagnostic Units
Support Units
Molecular Mechanisms of Cancer
Traslational and Clinical Research in Cancer

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D. Javier González Benito

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Hospital Clinic /IDIBAPS, Barcelona

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University Hospital La Princesa / CNIC, Madrid

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Hospital 12 Octubre /CNIO, Madrid

Dr. Anne Ridley
Bristol University (United Kingdom)

Dr. Eugenio Santos
Director of Institute of Molecular Biology and Cancer (IBMCC)

RESEARCH UNITS

MOLECULAR MECHANISMS OF CANCER PROGRAM

Epitranscriptomics and cancer
Sandra Blanco Benavente

Roles of dynamic ubiquitylation and deubiquitylation of replisome components at Replication forks
Andrés Avelino Bueno Nuñez
Maria Sacristán Martín

Role of RHO GTPase-regulated pathways in cancer: molecular mechanisms and therapeutic opportunities
Xosé R. Bustelo

Tumour-Stroma Signaling
Esther Castellano Sánchez

RAS signaling and lung cancer
Matthias Drosten (from September 2021)

Signaling by human chromatin kinases in cancer and neurodegenerative diseases
Pedro Alfonso Lazo-Zbikowski Taracena

Chromosome Segregation and Human Disease
Alberto Martín Pendás

Structural Biology of Cell Adhesion and Signaling
José María de Pereda Vega

Unconventional autophagy in health and disease
Felipe X. Pimentel Muiños

Quantitative control of RAS signaling output
David Santamaria Velilla (from September 2021)

GTPases and cancer. RAS mediated signaling
Eugenio Santos

Tumor biophysics
Miguel Vicente Manzanares

TRANSLATIONAL AND CLINICAL RESEARCH IN CANCER PROGRAM

Oncohematology
Marcos González Díaz

Familial and Hereditary Cancer. Early onset colorectal cancer
Rogelio González Sarmiento

Receptor inhibitors and CDK4 inhibitors
Antoni Hurtado Rodríguez (from September 2021)

Immunology and cancer
José Alberto Orfao de Matos Correia e Vale

Breast and ovarian cancer
Atanasio Pandiella Alonso

Molecular and genetic determinants of cancer susceptibility, evolution and treatment response
Jesús Pérez Losada

Bioinformatics and functional genomics
Javier De Las Rivas

Experimental Therapeutics and Translational Oncology Program: Stem Cells, Cancer Stem Cells and Cancer
Isidro Sánchez-García

CORE FACILITIES & SERVICES

Genomics
Scientific Coordinator: Xosé R. Bustelo

Proteomics
Scientific Coordinator: Xosé R. Bustelo

Microscopy
Scientific Coordinators: Alberto Martín Pendás / Miguel Vicente-Manzanares

Bioinformatics
Scientific Coordinator: Javier De Las Rivas

Cytometry
Scientific Coordinator: José Alberto Orfao de Matos Correia e Vale

Cytogenetics
Scientific Coordinator: Jesús María Hernández Rivas

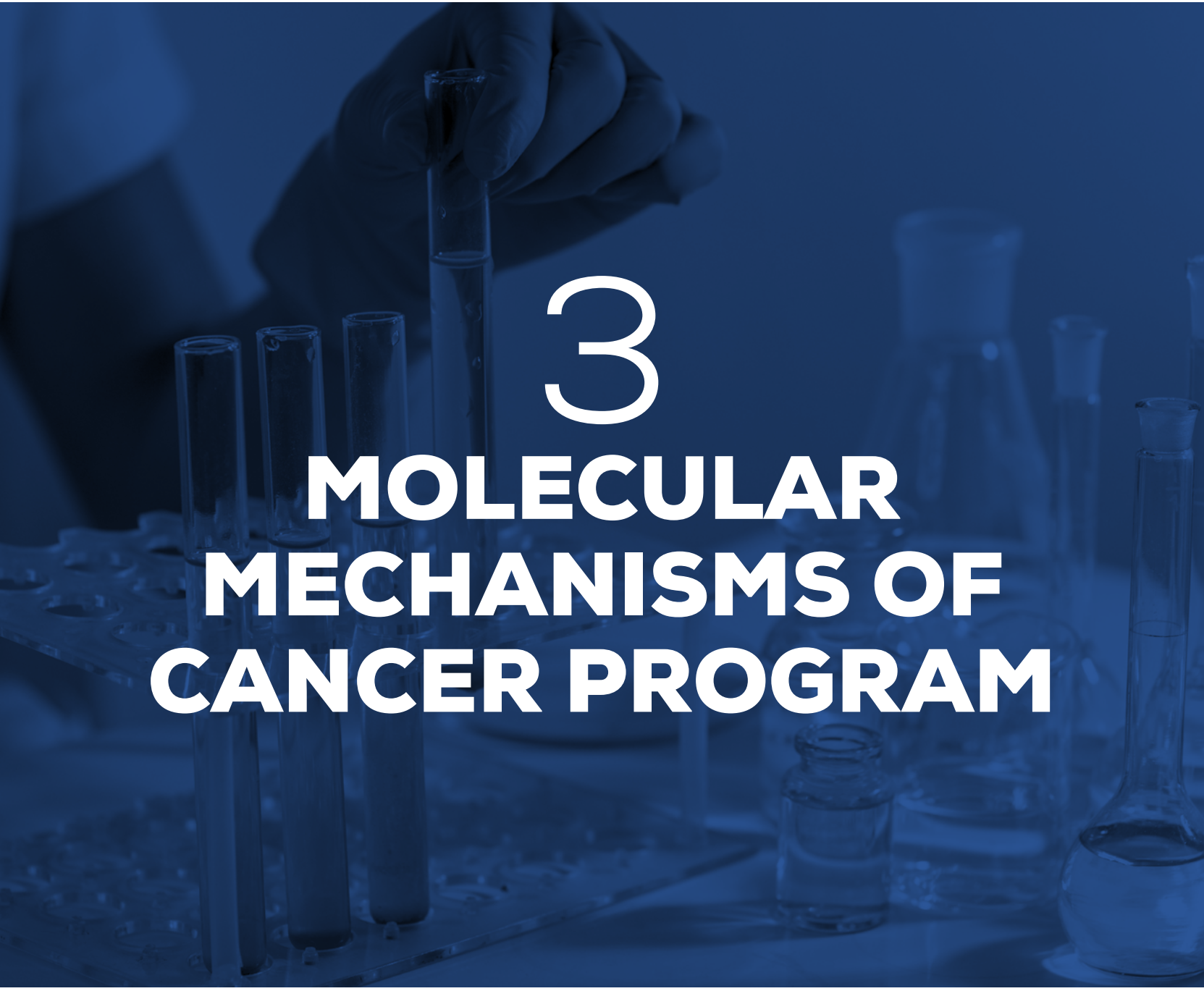
Molecular Biology
Scientific Coordinator: Marcos González Díaz

Comparative Molecular Pathology
Scientific Coordinator: Mª del Carmen García Macías

Hereditary Cancer & Genetic Counselling
Scientific Coordinators: Rogelio González-Sarmiento / Emilio Fonseca

SUPPORT UNITS

- FICUS Manager
- Secretary
- IBMCC-CSIC Manager
- IBMCC-CSIC Paymaster
- Communication & Marketing
- Administration
- Equipment & Building Maintenance
- Quality Control & Risk Prevention
- Central Warehouse & Radiological Protection
- Glassware and Media Sterilization
- Information Technologies Service (IT)



3 MOLECULAR MECHANISMS OF CANCER PROGRAM

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DESCRIPTION

Basic scientists in this program aim at characterizing new oncogenic drivers, signaling elements, and pathobiological programs that participate in the origin, malignant progression, and therapeutic responsiveness of a variety of tumor subtypes. To this end, they use a multifaceted approach composed of in silico analyses, genomics, proteomics, genetically-modified mice, and cell models such as cell lines, organoids, and patient-derived xenografts. These analyses also allow the identification and validation of new drug targets as well as the design of new biomarkers and other diagnostic tools.

During this period, we had the opportunity to expand the Program with the incorporation of three new members: Esther Castellano (CSIC Tenured Scientist), Matthias Drosten (CSIC Tenured Scientist), and David Santamaría (CSIC Research Staff Scientist). Matthias and David focus their research on the regulation and role of RAS oncogenes in cancer. Esther's work aims at dissecting the interactions between cancer and stromal cells during tumor initiation and progression. Those three groups also work on the identification of new drug candidates in those signaling and biological processes. We welcome them to the Program and the CIC faculty!

TEAM LEADER
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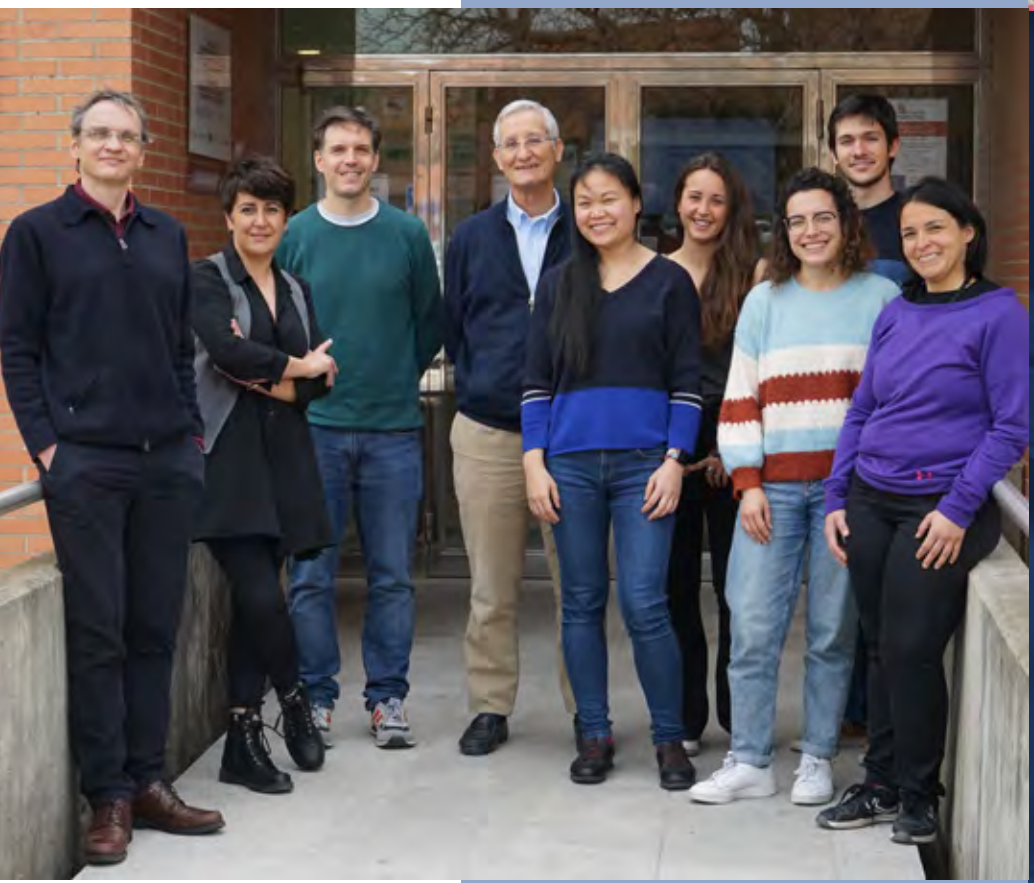

RESEARCH TEAM

SENIOR RESEARCHER
Alberto Fernández Medarde

POSTDOCTORAL
Fernando Calvo Baltanás
Rósula García Navas

PREDOCTORAL
Rocío Fuentes Mateos
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TECHNICIAN
Nuria Calzada Nieto

MASTER STUDENT
Pablo Rodríguez Ramos
Nerea Hongfen Vidaña Bedera

LABORATORY 1

GTPASES AND CANCER. RAS MEDIATED SIGNALING

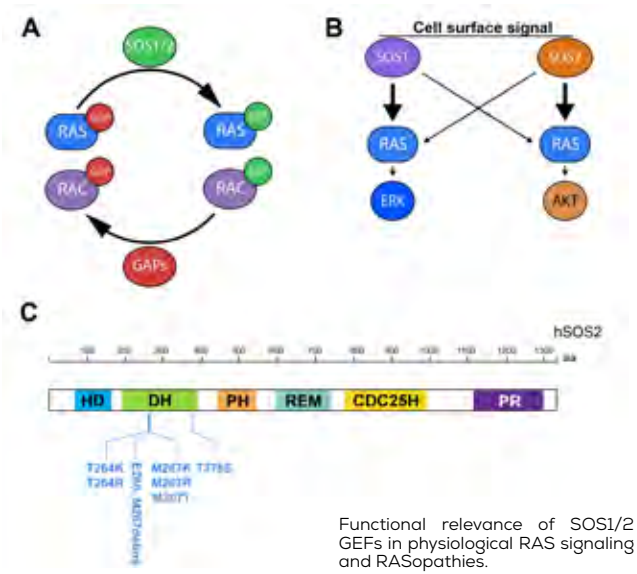
RESEARCH SUMMARY

During this period, the research activity our group was centered on studying the mechanisms of activation of cellular RAS proteins by guanine nucleotide exchange factors (GEF) and ascertaining the specificity/redundancy of the different RAS and RAS-GEF isoforms in various physiological and/or tumoral processes. Our experimental approaches have involved phenotypic and mechanistic analyses, at both the systemic and the cellular level, of various murine KO models for RAS (H-RAS, N-RAS, K-RAS), SOS (SOS1, SOS2) and GRF (GRF1, GRF2) genes and isoforms participating in RAS-MAPK signaling pathways, with an aim at characterizing their functional specificity/redundancy in a variety of normal and pathological processes including cancer in particular. Overall, our observations have been instrumental to identify potential biomarkers and/or therapy targets and novel antitumor drugs that are functionally relevant for RAS-driven tumorigenesis.

Our studies of the GRF family members have demonstrated the differential functionality of GRF1 and GRF2 uncovering specific roles of GRF1 in pancreatic beta cells and neurosensory and photoreception processes. We have also described specific functional roles of GRF2 in T-cell signaling, substance-addiction behavior, control of nuclear migration required for development and function of retinal cone photoreceptors, and control of stem cell density and onset of differentiation during adult neurogenesis.

The analysis of various KO mouse models for the SOS1 and SOS2 family members has demonstrated the functional prevalence of SOS1 over SOS2 regarding the control of cellular proliferation and viability, as well as a direct mechanistic link between SOS1 and the control of mitochondrial dynamics, metabolism and redox homeostasis. We have also demonstrated that SOS1 plays a critical role in tumorigenic processes, including chemically-induced skin carcinogenesis and bcr-abl-driven leukemogenesis. We also described recently a specific functional role of SOS2 in control of epidermal stem cell homeostasis. Finally, we have also identified novel anthraquinone, small-molecule inhibitors of the GEF activity of purified SOS proteins that might be potentially useful in the future as therapeutic tools for RAS-driven cancer treatment.

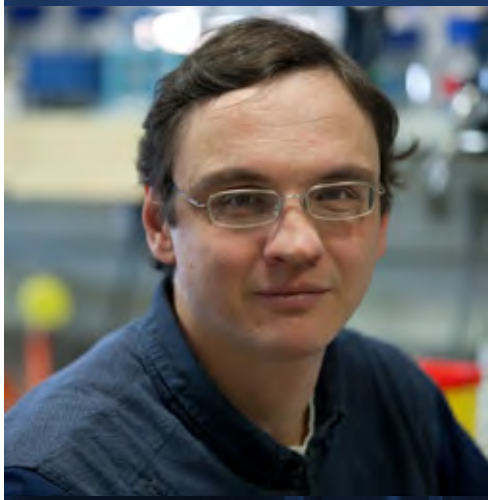
Regarding the functional specificity of RAS family members, our work characterizing HRAS/NRAS double-KO animals has uncovered essential roles of HRAS and NRAS in control of the process of prenatal and perinatal lung maturation, and has also clarified the mechanistic contributions of each of these RAS isoforms to modulation of the process of differentiation of various lung cell lineages that are essential structural and functional components of this respiratory organ.



Functional relevance of SOS1/2 GEFs in physiological RAS signaling and RASopathies.

SENIOR RESEARCHER

MECHANISMS OF RAS ACTIVATION AND THEIR USE AS THERAPEUTIC TARGETS



SENIOR RESEARCHER
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RESEARCH SUMMARY

The latest research goals of Alberto Fernández Medarde lay on the screening of compound libraries to search for inhibitors of Ras activation, analysis of the effect of this inhibition "in vitro" and "in vivo" and their possible application for cancer and developmental disease treatment, through toxicity studies and disease evolution in mice. He is also involved in a second line of research, which focus on RasGRF role in sensory development.

STRATEGIC OBJECTIVES

i. Screening of Compound libraries and a collection of animal venoms to find Ras-GEF inhibitors.

ii. Analysis of Ras-GEF inhibitors in the inhibition of cell growth and Ras activation in Ras WT and mutant tumoral cell lines.

iii. Toxicity of Ras-GEF inhibitors on adult mice and effects of the compounds on Ras activation "in vivo".

iv. Effect of Ras-GEF inhibitors on tumor development/growth in mice cancer models.

v. Use of KRas mutant lung cancer organoids for the screening of inhibitors of tumor growth.

vi. Improve the detection of Ras activity in cells and tissues.

vii. Analysis of RasGRF2 physiological role in olfaction.

MAIN LINES OF RESEARCH

1. Screening of Ras activation inhibitors (major).
2. Analysis of RasGRF2 role in olfaction (minor).
3. Study of RasGRF1 role in lens formation and myopia (minor).

GOALS ACHIEVED

- Finding of the molecular alterations responsible for the defects in memory formation of the RasGRF1 KO mice.
- Discovery of a role for RasGRF1 in two steps of light perception: photoreception and light refraction at the lens.
- Description of the RasGRF1-Pttg1 relationship in pancreatic β-cells.
- Disclosing the role of RasGRF2 in binge drinking and alcohol preference.
- Screening of two compound libraries and selection of four Ras-GEF inhibitors.
- Analysis of the effect of the Ras-GEF inhibitors on the growth of cancer cell lines. Three out of four compounds showed activity towards pancreatic cancer cell lines and only two of them against lung cancer cell lines.
- Analysis of the toxicity of the Ras-GEF inhibitors. Two of the compounds are highly toxic and are removed from the study. Only one compound inhibits growth of pancreatic cancer cell lines and is not toxic. We will follow our studies with this compound.

FUTURE GOALS

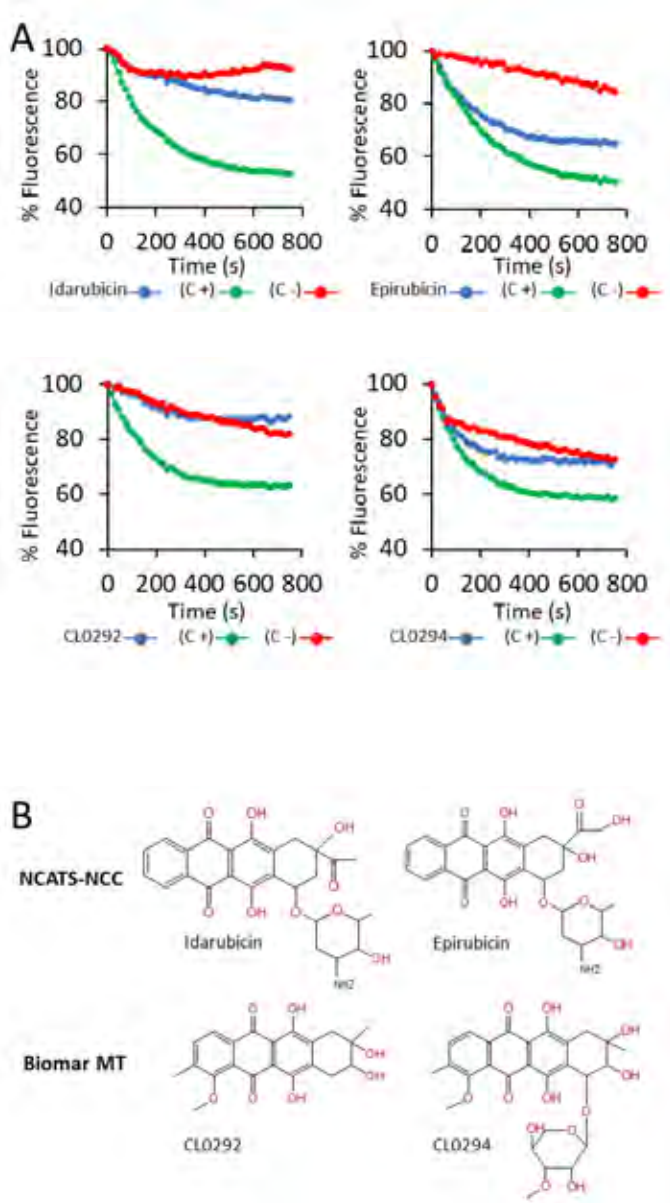
a) Analysis of RasGRF1 and RasGRF2 in odor detection.

b) New screening of inhibitors of the RasGEF exchanger activity using a new compound libraries. Detection of specific inhibitors of SOS2 GEF activity.

c) Preclinical studies using mice models of cancer with Ras-GEF inhibitors. Effect on tumor growth and metastasis formation.

d) Generation of lung cancer organoids and screening of molecules capable of blocking organoid growth.

e) Generation of molecular probes for detection of Ras activation.



Anthraquinone inhibitors of SOS1 GEF activity. (A) Fluorescence tracings og GEF assays in the absence (green, positive control C+) or the presence (blue) of the indicagtd compounds (10 μM) selected in the screening. **(B)** Chemical structures of compounds assayed and selected in screenings of the NIH-NCATS library and the Biomar MT library

PUBLICATIONS

- **SOS GEFs in health and disease.** *Baltanás FC, Zarich N, Rojas-Cabañeros JM, Santos E.* **Biochim Biophys Acta Rev Cancer. 2020 Dec;1874(2):188445. doi: 10.1016/j.bbcan.2020.188445**. PMID: 33035641. Review. **IF: 10.680 / D1**

- **Functional Specificity of the Members of the Sos Family of Ras-GEF Activators: Novel Role of Sos2 in Control of Epidermal Stem Cell Homeostasis.** *Baltanás FC, Mucientes-Valdivieso C, Lorenzo-Martín LF, Fernández-Parejo N, García-Navas R, Segrelles C, Calzada N, Fuentes-Mateos R, Paramio JM, Bustelo XR, Santos E.* **Cancers (Basel). 2021 Apr 29;13(9):2152. doi: 10.3390/cancers13092152.** PMID: 33946974. **IF:6.639/Q1**

- **Ras GEF Mouse Models for the Analysis of Ras Biology and Signaling.** *Fernández-Medarde A, Santos E.* **Methods Mol Biol. 2021;2262:361- 395. doi: 10.1007/978-1-0716-1190-6_23.** PMID: 33977490. **IF: NI 6.639/Q1 .**

- **40 Years of RAS-A Historic Overview.** *Fernández-Medarde A, De Las Rivas J, Santos E.* **Genes (Basel). 2021 May 1;12(5):681. doi: 10.3390/genes12050681.** PMID: 34062774 Review. **IF:4.096 / Q2**

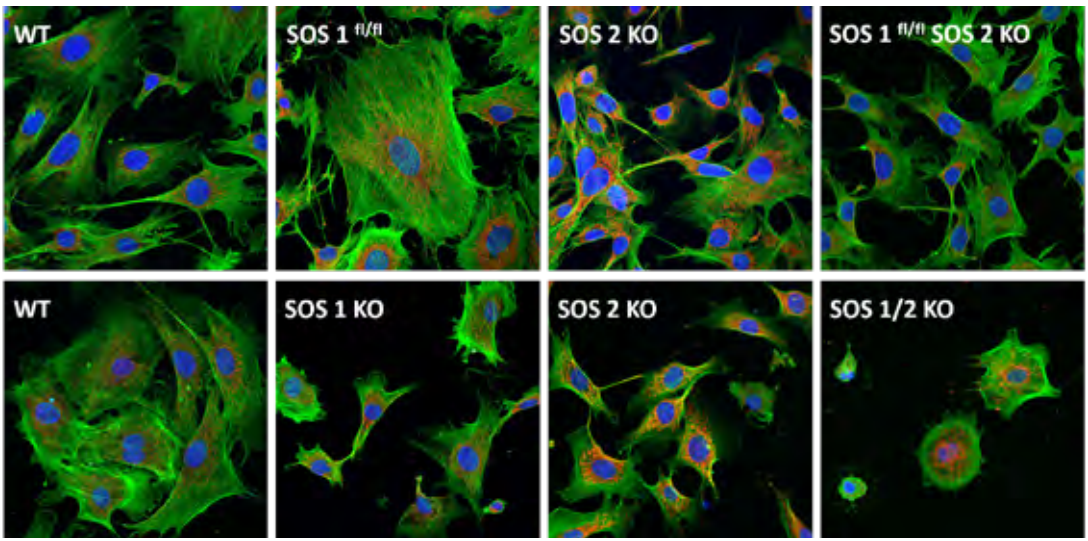
- **Critical requirement of SOS1 RAS-GEF function for mitochondrial dynamics, metabolism, and redox homeostasis.** *García-Navas R, Liceras-Boillos P, Gómez C, Baltanás FC, Calzada N, Nuevo-Tapioles C, Cuezva JM, Santos E.* **Oncogene. 2021 Jul;40(27):4538-4551. doi: 10.1038/s41388-021-01886-3.** PMID: 34120142.**IF:9.867 / D1**

- **SOS2 Comes to the Fore: Differential Functionalities in Physiology and Pathology.** *Baltanás FC, García-Navas R, Santos E.* **Int J Mol Sci. 2021 Jun 21;22(12):6613. doi: 10.3390/ijms22126613.** PMID: 34205562. Review. **IF:5.923/Q1**

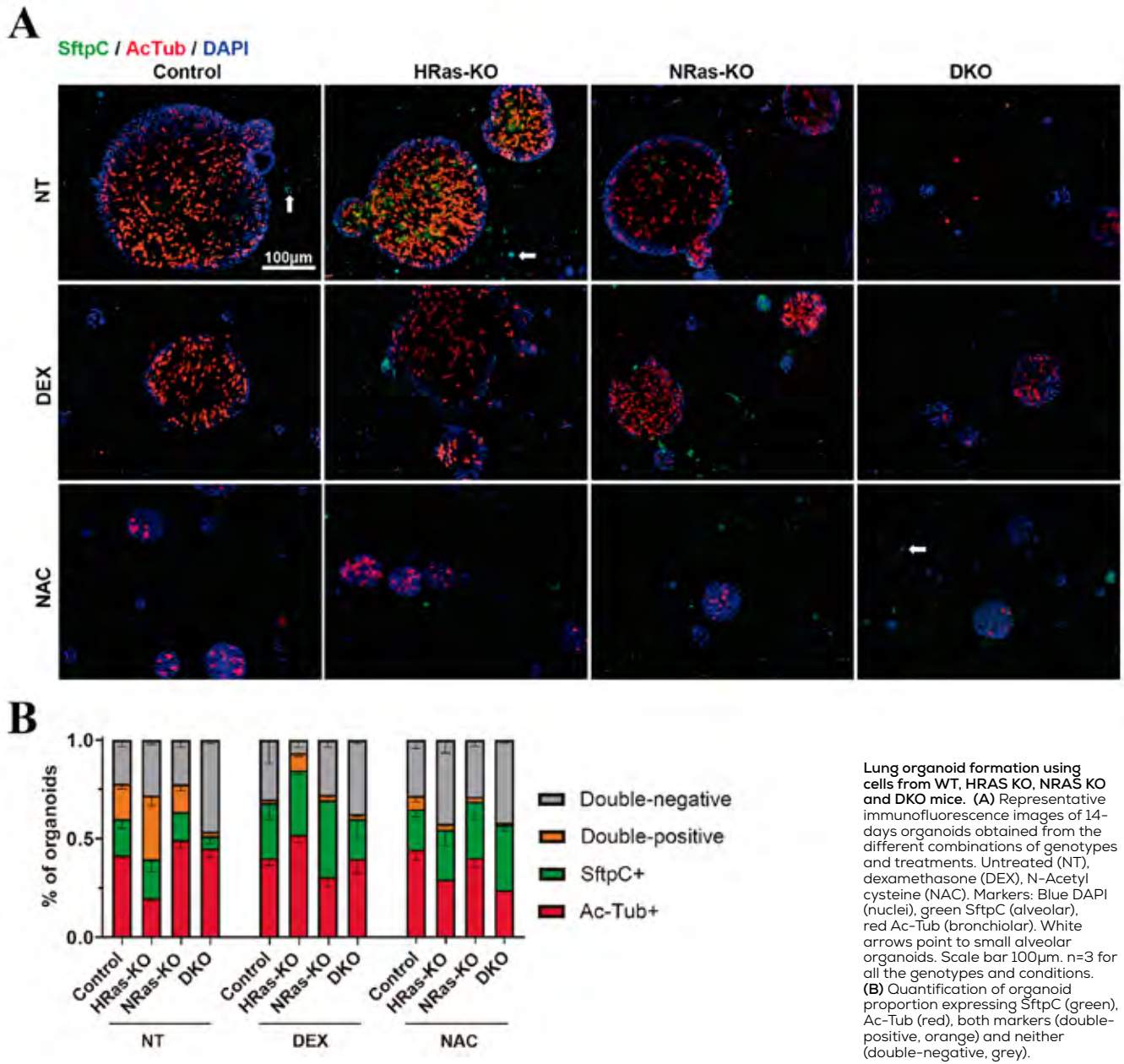
- **Anthraquinones as Inhibitors of SOS RAS-GEF Activity.** *Fernández-Medarde A, Fuentes-Mateos R, García-Navas R, Juan AO, Sánchez-López JM, Fernández-Medarde A, Santos E.* **Biomolecules. 2021 Jul 30;11(8):1128. doi: 10.3390/biom11081128**. PMID: 34439794. **IF:4.879/Q2**

- **The reversed intra- and extracellular pH in tumors as a unified strategy to chemotherapeutic delivery using targeted nanocarriers.** *Pérez-Herrero E, Fernández-Medarde A.* **Acta Pharm Sin B. 2021 Aug;11(8):2243-2264. doi: 10.1016/j.apsb.2021.01.012. Epub 2021 Jan 24.** PMID: 34522586. **IF:11.614 / D1**

- **The Childhood-Onset Neurodegeneration with Cerebellar Atrophy (CONDCA) Disease Caused by AGTPBP1 Gene Mutations: The Purkinje Cell Degeneration Mouse as an Animal Model for the Study of this Human Disease.** *Baltanás FC, Berciano MT, Santos E, Lafarga M.* **Biomedicines. 2021 Sep 4;9(9):1157. doi: 10.3390/biomedicines9091157.** PMID: 34572343. **IF: 6.081 /Q1**



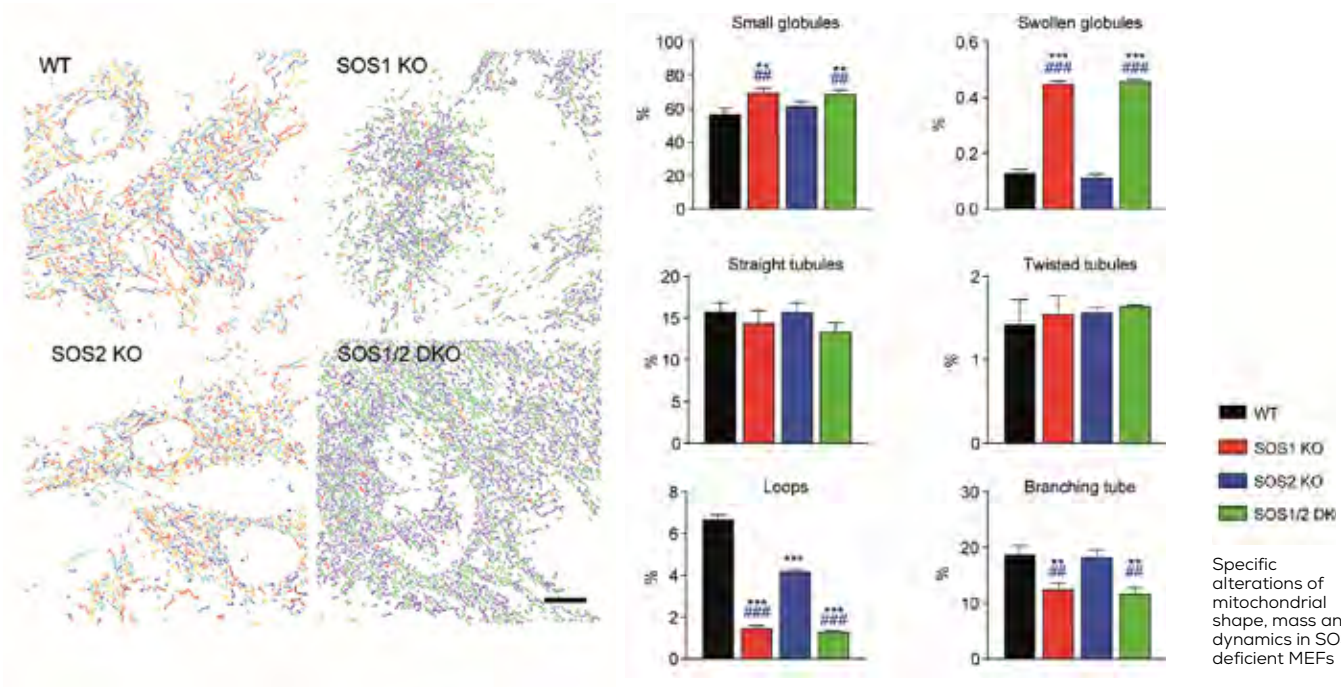
Immunofluorescence imaging of immortalized Mouse Embryonic Fibroblasts (MEFs) by confocal microscopy. Morphological differences regarding cytoskeleton (Phaloidin, green) and mitochondria (TOMM40, red) can be observed among the different SOS protein genotypes in the absence (top) or presence (bottom) of Tamoxifen.



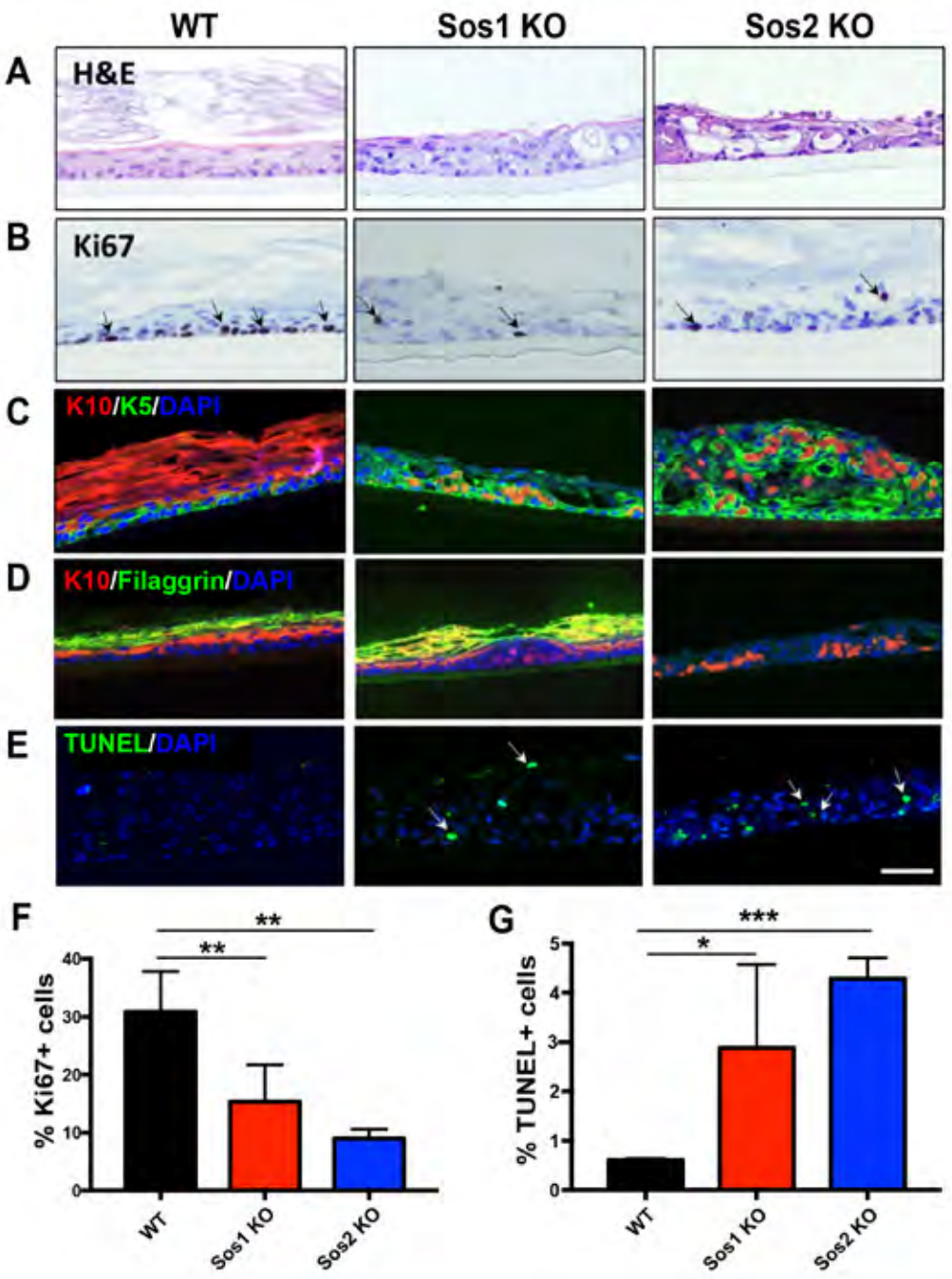
Lung organoid formation using cells from WT, HRAS KO, NRAS KO and DKO mice. (A) Representative immunofluorescence images of 14-days organoids obtained from the different combinations of genotypes and treatments. Untreated (NT), dexamethasone (DEX), N-Acetyl cysteine (NAC). Markers: Blue DAPI (nuclei), green SftpC (alveolar), red Ac-Tub (bronchiolar). White arrows point to small alveolar organoids. Scale bar 100µm. n=3 for all the genotypes and conditions. **(B)** Quantification of organoid proportion expressing SftpC (green), Ac-Tub (red), both markers (double-positive, orange) and neither (double-negative, grey).

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Especificidad funcional y caracterización de RAS-GEFS de las familias SOS y GRF como biomarcadores o dianas terapéuticas en cáncer (SA264P18)	Eugenio Santos	Regional Government of Castilla y León	2018-2020	120.000,00 €
Medicina de precisión: Los activadores GEF de la familia SOS como dianas terapéuticas en tumores dependientes de Ras (CIVP19A5942)	Eugenio Santos	Ramón Areces Foundation	2019-2021	129.357,00 €
Análisis de vías de señalización implicadas en activación de proteínas Ras por activadores GEF de las familias SOS y GRF: Mecanismos, biomarcadores y dianas terapéuticas en cáncer y otras patologías (PI19/00934)	Eugenio Santos	Carlos III Health Institute	2020-2022	292.820,00€
Single and dual SOS1/SOS2 inhibition (BI-3406): evaluation of therapeutic effects and toxicity (#56458)	Eugenio Santos	Boehringer Ingelheim RCV GmbH & Co	2021-2023	200.000,00€



Specific alterations of mitochondrial shape, mass and dynamics in SOS1-deficient MEFs



Functional redundancy of SOS1 and SOS2 in the formation of 3D pseudoepidermis

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Natalia Fernández-Parejo
Sonia G. Gaspar

TECHNICIAN
Antonio Luis Abad de Blas

LABORATORY 2

ROLE OF RHO GTPASE-REGULATED PATHWAYS IN CANCER: MOLECULAR MECHANISMS AND THERAPEUTIC OPPORTUNITIES

RESEARCH SUMMARY

Our lab is mostly interested on the characterization of the role of Rho GTPases in cancer. To this end, we utilize a multifaceted approach based on in silico analyses of Pan-Cancer data as well as signaling, cellular biology, and genetics techniques to: (i) Understand how Rho GTPase-regulated pathways mediate the origin and malignant progression of different tumor types. (ii) Pinpoint the key signaling elements and pathobiological programs that regulate those malignant processes, focusing on those that offer new therapeutic opportunities. (iii) Validate them using knock-in, knockout and gene-edited mouse models as well as patient derived xenografts. (iv) Developing gene signatures that could facilitate a better classification, stratification, and diagnosis of cancer patients.

Following this general philosophy, during these two years we have made a number of key milestones. Firstly, using knock-in mice, primary epithelial cells, and patient-derived cells, we demonstrated that one of the upstream regulators of Rac1 and RhoA GTPases (designated as Vav2) plays critical roles in the development and subsequent maintenance of the malignant properties of both skin cancer and head and neck squamous cell carcinomas. This process is mediated by a Vav2- and Rac1–RhoA-dependent biological program that, via the stimulation of transcriptional factors such as c-Myc and Yap/Taz, leads to the acquisition of highly undifferentiated, stem cell-like features by the cancer cells. This work also led us to identify diagnostic gene signatures and therapeutic vulnerabilities for these tumor types (Lorenzo-Martín et al., Nat Commun 2020 & Cancers 2020).

Secondly, we could demonstrate using a "pharmaco-mimetic" knock-in mouse model for Vav2 that the partial inhibition of the catalytic activity of this protein is sufficient to block the foregoing tumorigenic processes. Interestingly, these anti-tumorigenic effects could be obtained without the induction of any overt collateral effect on healthy tissues. Hence, these results demonstrated for the first time in the field that the inhibition of these upstream regulators of Rho GTPases is a therapeutically viable option (Lorenzo-Martín et al., Oncogene 2020).

Thirdly, by using a combination of catalytic gain- and loss-of-function mouse models for Vav2, we could demonstrate during this period that the catalysis-dependent pathways of this protein play critical roles in the regulation of skeletal muscle mass and the implication of that tissue in proper

glucose clearance. These analyses also shed light into hitherto unknown crosstalk between skeletal muscle and adipose tissue that are essential to maintain metabolic homeostasis at the whole organism level (Rodríguez-Fdez et al., Nat Commun 2020).

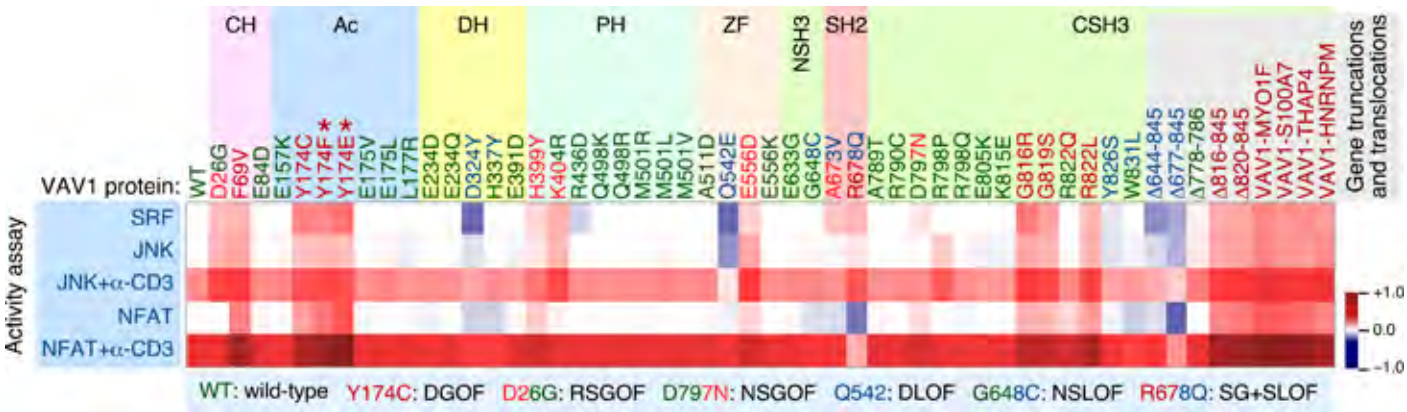
Last, but not least, we also discovered during this period that Vav1 acts as an oncogenic driver in peripheral T cell lymphoma (PTCL). This protein, like Vav2, acts both as an activator of Rho GTPases and as an adaptor protein. In this latter capacity, Vav1 can work as a protumorigenic factor or as a tumor suppressor protein. By cataloguing 51 *VAV1* mutations found in cancer patients, we found that most of them represent pathogenic variants. Furthermore, we found that all these mutations can be classified in five functional subclasses depending upon the type of deregulation induced in the downstream signaling branches. These data suggest that patients might exhibit quite different clinical features and therapeutic susceptibilities depending on the *VAV1* mutant subclass present in their tumors. Using adoptive T cell transfer experiments, we could demonstrate that the strongest *VAV1* mutant subclass promotes per se the development of PTCL when expressed in CD4+ lymphocytes. Interestingly, these tumors are quite similar to the human counterparts in terms of cellular features and gene expression programs. We have also identified therapeutic vulnerabilities in these tumors, some of them actionable, that could be of interest to treat patients in the near future. This is quite relevant in this case, given the low survival rates usually exhibited by PTCL patients (Robles-Valero et al., EMBO J 2021). In connection with this work, we also identified during this period new regulatory layers for Vav1 that contribute to modulate its normal and oncogenic signaling output (Rodríguez-Fdez et al., Cells 2020).

We would also like to highlight results obtained from collaboration with other colleagues during this period. This work led us to inroads in new drugs targeting Rho GTPase pathways (González et al., Front Cell Dev Biol 2020) as well as in other signaling processes important for a variety of tumors such as melanoma (Colón-Bolea et al., Mol Biol Cell 2020) and those originating from the skin (Baltanás et al., Cancers 2021; Rico-Leo et al., Stem Cells 2021), prostate (Shahrouzi et al., Cancers 2020), and lung (Nacarino-Palma et al., Cancers 2021).

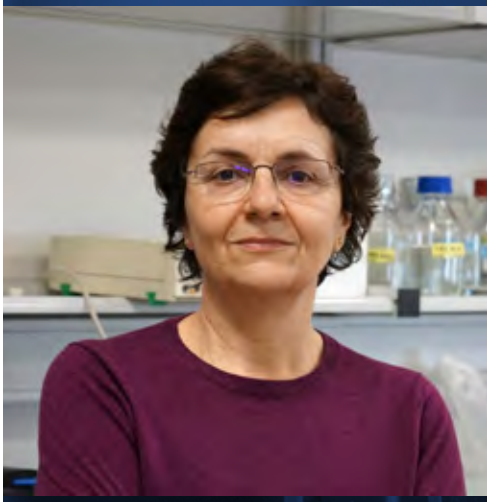
Outside these scientific outputs, we would also like to pinpoint the generous funding obtained through the highly competitive La Caixa Foundation Health Call at the end of 2020 that, from now on, will allow us to go deeper into the mechanisms of action of a new protumorigenic factor for PTCL.

Academically, we continued our coordination tasks associated with the CIC Strategic Plan, the Molecular Mechanisms of Cancer Program of our Center, and the Mechanisms of Tumor Progression of the CIBERONC. We have also been at the core of the coordination of the CSIC Cancer Hub, a new initiative aiming at knitting collaborative efforts among all the CSIC scientists working in the cancer field (patients, hospitals, companies, etc.).

So, despite all the efforts made by the Covid-19 to stop us, we managed to move on during these dire pandemic times.



Hierarchical histogram showing biological activities of VAV1 mutants found in tumors. (Robles-Valero et al., EMBO J 2021)



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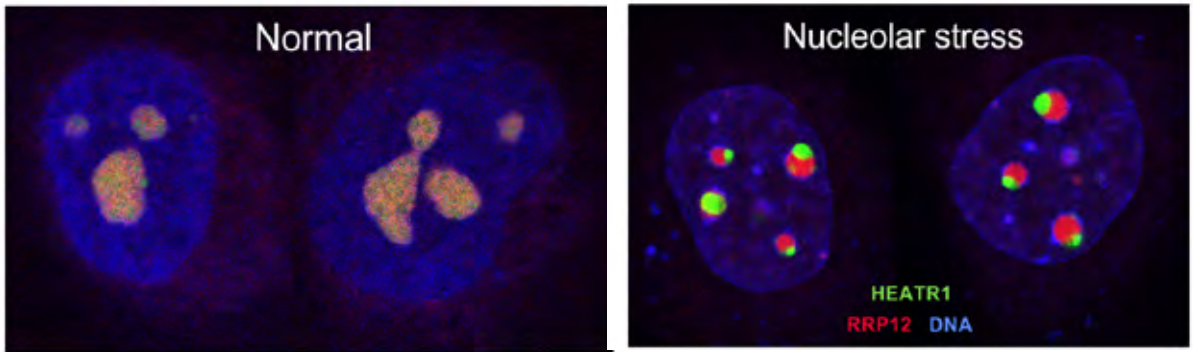
SENIOR RESEARCHER

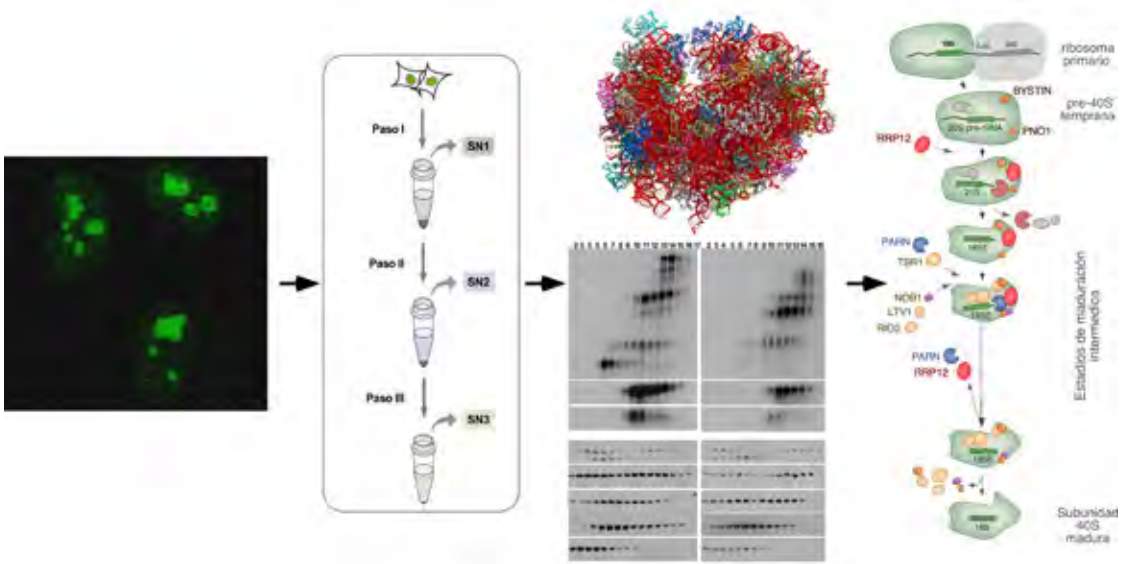
REGULATION OF RIBOSOME SYNTHESIS IN NORMAL AND CANCER CELLS

RESEARCH SUMMARY

Our group has investigated some steps of the ribosome synthesis pathway that were not well-characterized in human cells. In the past two years we developed new reagents and techniques to study the ribosome precursors formed in the inner regions of the nucleolus. One notable achievement has been the development of a new fractionation method that allows the purification and compositional analyses of intermediate nucleolar preribosomes. Using this method, we defined the functions of several factors that are essential for the assembly of the small ribosomal subunit and, most importantly, we dissected a maturation step of this subunit that is mediated by a ribonuclease and is specific to human cells. Our new techniques and results have been published in two articles in the journals Nature Communications and RNA Biology. Other lines of research carried out by the group (ongoing work) include the molecular detailing of 40S subunit synthesis defects that cause Diamond-Blackfan anemia, and the functional characterization of ribosome assembly factors and rRNA modifying enzymes that show specific regulation in cancer cells.



Microscopy analysis of cervix-cancer (HeLa) cells growing normally (upper panel) and after treatment with actinomycin D (lower panel). Segregation of nucleolar proteins HEATR1 and RRP12 can be used to monitor the induction of nucleolar stress by drug treatments.



Genetics, cell-biology, biochemistry and structural-biology approaches are combined to unveil the molecular details of ribosome maturation in normal and cancer cells

PUBLICATIONS

- **Identification of distinct maturation steps involved in human 40S ribosomal subunit biosynthesis.** *Nieto B, Gaspar SG, Moriggi G, Pestov DG, Bustelo XR, Dosil M.* **Nat Commun. 2020 Jan 9;11(1):156. doi: 10.1038/s41467-019-13990-w.** PMID: 31919354. **IF:14.919 / D1**

- ***In Silico* Analysis of the Age-Dependent Evolution of the Transcriptome of Mouse Skin Stem Cells.** *Lorenzo-Martín LF, Bustelo XR* **Cells. 2020 Jan 9;9(1):165. doi: 10.3390/cells9010165.** PMID: 31936599. **IF:6.600 / Q2**

- **Lysine Acetylation Reshapes the Downstream Signaling Landscape of Vav1 in Lymphocytes.** *Rodríguez-Fdez S, Fernández-Nevado L, Lorenzo-Martín LF, Bustelo XR.* **Cells. 2020 Mar 4;9(3):609. doi: 10.3390/cells9030609.** PMID: 32143292. **IF:6.600 / Q2**

- **Computational and in vitro Pharmacodynamics Characterization of 1A-116 Rac1 Inhibitor: Relevance of Trp56 in Its Biological Activity.** *González N, Cardama GA, Chinestrad P, Robles-Valero J, Rodríguez-Fdez S, Lorenzo-Martín LF, Bustelo XR, Lorenzano Menna P, Gomez DE.* **Front Cell Dev Biol. 2020 Apr 15;8:240. doi: 10.3389/fcell.2020.00240.** PMID: 32351958. **IF:6.684 / Q1**

- **Vav2 pharmaco-mimetic mice reveal the therapeutic value and caveats of the catalytic inactivation of a Rho exchange factor.** *Lorenzo-Martín LF, Rodríguez-Fdez S, Fabbiano S, Abad A, García-Macías MC, Dosil M, Cuadrado M, Robles-Valero J, Bustelo XR.* **Oncogene. 2020 Jul;39(28):5098-5111. doi: 10.1038/s41388-020-1353-x.** PMID: 32528129. **IF:9.867 / D1**

- **HERC Ubiquitin Ligases in Cancer.** *Sala-Gaston J, Martinez-Martinez A, Pedrazza L, Lorenzo-Martín LF, Caloto R, Bustelo XR, Ventura F, Rosa JL.* **Cancers (Basel). 2020 Jun 22;12(6):1653. doi: 10.3390/cancers12061653.** PMID: 32580485. **IF: 6.639 / Q1**

- **Drug Vulnerabilities and Disease Prognosis Linked to the Stem Cell-Like Gene Expression Program Triggered by the RHO GTPase Activator VAV2 in Hyperplastic Keratinocytes and Head and Neck Cancer.** *Lorenzo-Martín LF, Menacho-Márquez M, Bustelo XR.* **Cancers (Basel). 2020 Sep 3;12(9):2498. doi: 10.3390/cancers12092498.** PMID: 32899210. **IF: 6.639 / Q1**

- **Genomic and Functional Regulation of TRIB1 Contributes to Prostate Cancer Pathogenesis.** *Shahrouzi P, Astobiza I, Cortazar AR, Torrano V, Macchia A, Flores JM, Niespolo C, Mendizabal I, Caloto R, Ercilla A, Camacho L, Arreal L, Bizkarguenaga M, Martinez-Chantar ML, Bustelo XR, Berra E, Kiss-Toth E, Velasco G, Zabala-Letona A, Carracedo A.* **Cancers (Basel). 2020 Sep 11;12(9):2593. doi: 10.3390/cancers12092593.** PMID: 32932846. **IF: 6.639 / Q1**

- **VAV2 signaling promotes regenerative proliferation in both cutaneous and head and neck squamous cell carcinoma.** *Lorenzo-Martín LF, Fernández-Parejo N, Menacho-Márquez M, Rodríguez-Fdez S, Robles-Valero J, Zumalave S, Fabbiano S, Pascual G, García-Pedrero JM, Abad A, García-Macías MC, González N, Lorenzano-Menna P, Pavón MA, González-Sarmiento R, Segrelles C, Paramio JM, Tubío JMC, Rodrigo JP, Benitah SA, Cuadrado M, Bustelo XR.* **Nat Commun. 2020 Sep 22;11(1):4788. doi: 10.1038/s41467-020-18524-3.** PMID: 32963234IF: **14.919 / D1**

- **RAC1 induces nuclear alterations through the LINC complex to enhance melanoma invasiveness.** *Colón-Bolea P, García-Gómez R, Shackleton S, Crespo P, Bustelo XR, Casar B.* **Mol Biol Cell. 2020 Dec 1;31(25):2768-2778. doi: 10.1091/mbc.E20-02-0127.** PMID: 33026942. **IF: 4.138 / Q3**

- **Vav2 catalysis-dependent pathways contribute to skeletal muscle growth and metabolic homeostasis.** *Rodríguez-Fdez S, Lorenzo-Martín LF, Fernández-Pisonero I, Porteiro B, Veyrat-Durebex C, Beiroa D, Al-Massadi O, Abad A, Diéguez C, Coppari R, Nogueiras R, Bustelo XR.* **Nat Commun. 2020 Nov 16;11(1):5808. doi: 10.1038/s41467-020-19489-z.** PMID: 33199701. **IF:14.919 / D1**

- **Functional Specificity of the Members of the Sos Family of Ras-GEF Activators: Novel Role of Sos2 in Control of Epidermal Stem Cell Homeostasis.** *Baltanás FC, Mucientes-Valdivieso C, Lorenzo-Martín LF, Fernández-Parejo N, García-Navas R, Segrelles C, Calzada N, Fuentes-Mateos R, Paramio JM, Bustelo XR, Santos E.* **Cancers (Basel). 2021 Apr 29;13(9):2152. doi: 10.3390/cancers13092152.** PMID: 33946974. **IF:6.639 / Q1**

- **Distinct Roles of Vav Family Members in Adaptive and Innate Immune Models of Arthritis.** *Conde J, Fernández-Pisonero I, Cuadrado M, Abad A, Robles-Valero J, Bustelo XR.* **Biomedicines. 2021 Jun 19;9(6):695. doi: 10.3390/biomedicines9060695.** PMID: 34205377. **IF: 6.081 / Q1**

- **Aryl hydrocarbon receptor controls skin homeostasis, regeneration, and hair follicle cycling by adjusting epidermal stem cell function.** *Rico-Leo EM, Lorenzo-Martín LF, Román ÁC, Bustelo XR, Merino JM, Fernández-Salguero PM.* **Stem Cells. 2021 Dec;39(12):1733-1750. doi: 10.1002/stem.3443.** PMID: 34423894. **IF:6.277 / Q1**

- **Loss of Aryl Hydrocarbon Receptor Favors K-RasG12D-Driven Non-Small Cell Lung Cancer.** *Nacarino-Palma A, Rejano-Gordillo CM, González-Rico FJ, Ordiales-Talavero A, Román ÁC, Cuadrado M, Bustelo XR, Merino JM,*

Fernández-Salguero PM. **Cancers (Basel). 2021 Aug 13;13(16):4071. doi: 10.3390/cancers13164071.** PMID: 34439225. **IF: 6.639 / Q1**

- **Efficient fractionation and analysis of ribosome assembly intermediates in human cells.** *Nieto B, Gaspar SG, Sapio RT, Clavaín L, Bustelo XR, Pestov DG, Dosil M.* **RNA Biol. 2021 Oct 15;18(sup1):182-197. doi: 10.1080/15476286.2021.1965754.** PMID: 34530680. **IF:4.652 / Q2**

- **New Functions of Vav Family Proteins in Cardiovascular Biology, Skeletal Muscle, and the Nervous System.** *Rodríguez-Fdez S, Lorenzo-Martín LF, Fabbiano S, Menacho-Márquez M, Sauzeau V, Dosil M, Bustelo XR.* **Biology (Basel). 2021 Sep 1;10(9):857. doi: 10.3390/biology10090857.** PMID: 34571735. **IF:5.079 / Q1**

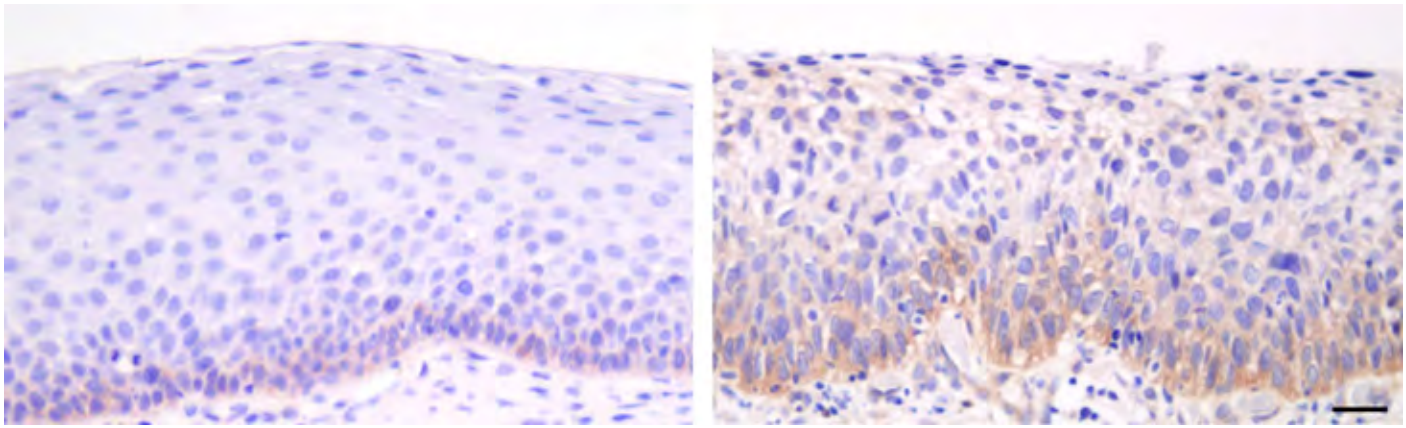
- **Cancer-associated mutations in VAV1 trigger variegated signaling outputs and T-cell lymphomagenesis.** *Robles-Valero J, Fernández-Nevado L, Lorenzo-Martín LF, Cuadrado M, Fernández-Pisonero I, Rodríguez-Fdez S, Astorga-Simón EN, Abad A, Caloto R, Bustelo XR.* **EMBO J. 2021 Nov 15;40(22):e108125. doi: 10.15252/embj.2021108125.** PMID: 34617326. **IF:11.598 / D1**

- **Rho GTPases in Skeletal Muscle Development and Homeostasis.** *Rodríguez-Fdez S, Bustelo XR.* **Cells. 2021 Nov 2;10(11):2984. doi: 10.3390/cells10112984.** PMID: 34831205. **IF:6.600 / Q2**

OTHER PUBLICATIONS & BOOK CHAPTERS

- **Inteligencia artificial en medicina genómica del cáncer: el proyecto Pan-Cáncer y otros estudios ómicos. In "La inteligencia artificial en el campo de la salud. Un nuevo paradigma: aspectos clínicos, éticos y legales".** *Bustelo, X.R. (2021)* **Fundación Merk Salud. ISBN 978-84-18568-02-2. Link descarga:** https://www.fundacionmercksalud.com/wp-content/uploads/2021/02/DIGITAL_MONOGRAFIA-26_INTELIGENCIA-ARTIFICIAL_FINAL-1.pdf

- **Challenge 1. Cancer. In Challenges in Biomedicine & Health, Volume 4, CSIC.** *Durán, R.V., Bustelo, X.R., and Nieto, M.A. (2021).* I**SBM 978-84-00-10744-4 (volume 4, print), 978-84-00-10745-1 (volume 4, online). 978-84-00-10736-9 (whole collection, print), 978-84-00-10734-5 (whole work, online)**



Histological sections showing Vav2 expression (brown color) in normal and hyperplastic oral epithelium (Lorenzo-Martín et al. Nat Commun 2020)

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Function, diagnostic value and pharmacological inhibition of R-Ras2, a new oncogenic driver (GC16173472GARC)	Xosé R. Bustelo	Spanish Association against Cancer	2016-2022	1,200,000.00 €
Center for Biomedical Research in Oncology (CB16/12/00351)	Xosé R. Bustelo	Carlos III Health Institute	2017-2022	480,000.00 €
Funding to support the strategic plan of the Salamanca Cancer Research Center (CLC-2017-01)	Xosé R. Bustelo	Castilla y León Autonomous Government	2018-2022	2,100.000.00 €
Rho GTPase exchange factors: Friends or foes in cancer? (RTI2018-096481-B-100)	Xosé R. Bustelo	Spanish Research State Agency	2019-2022	370,000.00 €
Cell and Systemic Interactions between cancer and metabolic signaling (RED2018-102379-T)	Xosé R. Bustelo	Spanish Research State Agency	2020-2022	20,500.00 €
Early Cancer Research Initiative Network on MBL (ECRIN-M3)	Coordinator: Alberto Orfao	AECC-Cancer Research UK-IACR Accelerator Award Program	2020-2024	1,565,658.88 €
A new functional paradigm for RHOA gene mutations in peripheral T cell lymphoma: functional and clinical implications (HR20-00164).	Xosé R. Bustelo	La Caixa Foundation	2021-2023	498,300.00 €
A new functional paradigm for loss-of-function gene mutations in peripheral T cell lymphoma (CSI145P20).	Xosé R. Bustelo	Castilla y León Autonomous Government	2021-2023	264,000.00 €
CSIC Cancer Hub (202120E046)	Xosé R. Bustelo	Spanish National Research Council	2021-2023	350,000.00 €
New roles of driver genes in peripheral T cell lymphoma (PI20/01724)	Javier Robles-Valero	Carlos III Health Institute	2021-2023	80,000.00 €
Molecular processes involved in formation of human ribosomes	Mercedes Dosil	Spanish Research State Agency	2021-2023	132,000.00 €

OTHER ACTIVITIES & RELEVANT FACTS

Leadership activities

2001-Present ***Director***
Genomics and Proteomics Unit, Centro de Investigación del Cáncer

2014-Present ***Vice-Director***
Centro de Investigación del Cáncer

2017-Present ***Coordinator***
Mechanisms of Tumor Progression Program
Centro de Investigación Biomédica en Red de Cáncer (CIBERONC)

2017-Present ***Member of the Executive Committee***
CIBERONC

2018-2022 ***Director, Strategic Plan***
Centro de Investigación del Cáncer/ Cancer Research Center, CSIC-University of Salamanca, Salamanca, Spain

2019-2020 ***President***
Spanish Association for Cancer Research / Asociación Española de Investigación sobre el Cáncer

2021-2022 ***Past-President***
Spanish Association for Cancer Research / Asociación Española de Investigación sobre el Cáncer

2021-2022 ***Vice-President***
Spanish Federation of Medical Oncology Societies / Federación de Sociedades Españolas de Oncología

2021-Present ***Co-Coordinator***
CSIC Cancer Hub

Editorial Boards

- *Front. Immunol.* (since 2010)
- *Small GTPases* (since 2011)
- *Encyclopedia of Signaling Molecules* (since 2012)
- *Front. Cell Develop. Biol.* (since 2015)
- *Clin. Transl. Oncol.* (since 2017)
- *Skins* (since 2020)
- *Curr. Opin. Cell Biol.* (since 2020).

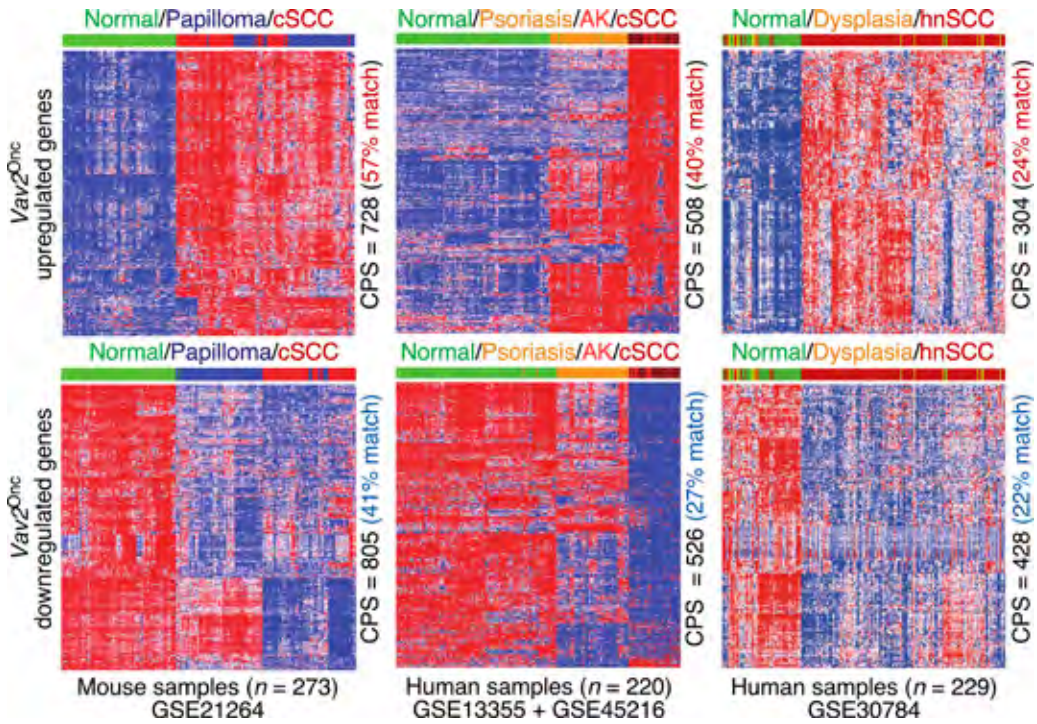
Ad hoc Scientific Committees

- European Science Foundation College of Expert Reviewers (2019-2021)
- IDIBELL Career Evaluation Panel (2020)
- Coordinator, Study Section for Axencia de Avaliación para a Calidade do Sistema Universitario de Galicia / Agency for the Control of the Quality of the Galician University System, Program for the Consolidation of Competitive Research Units (Galician autonomous government, Galicia, Spain, 2020)
- *Selection Committe*
  Professorship in Biochemistry, Medicine School, University of Basel, Switzerland (2021)
- *Lead Speaker and Member, Expert Review Panel*
  CancerResearch UK Discovery Research Committee, UK (2021)
- *Evaluation Commitee of CERCA Centers (IMIM)*
  CERCA (Centers of Research of Catalonia), Catalonia, Spain (2021)
- Member of Evaluation Committee
  Josep Baselga Fellowship, FERO (2021)

Scientific Committees

- ***External Scientific Committee***
  Santiago University Hospital Health Research Institute (Santiago of Compostela, Spain, 2008-2021)

- ***External Scientific Committee***
  Marqués de Valdecilla Hospital Research Institute (Santander, Spain, 2009-Present)
- ***President and Member of the External Scientific Committee***
  La Princesa Hospital Health Research Institute (Madrid, Spain, 2009-Present)
- ***Kærtor Foundation Scientific Committee***
  (2017-Present) Kærtor Foundation
- ***Scientific Committee***
  17th ASEICA International Congress (2020)
- ***President and Member of the External Scientific***
  Committee (2020-Present)
  Institut Hospital del Mar d'Investigacions Mèdiques and Parc de Salut Mar (Barcelona, Spain)
- ***External Scientific Committee*** (2020-Present)
  Centro de Investigacións Biomédicas (CINBIO), University of Vigo (Vigo, Galicia, Spain)
- ***Scientific Committee***
  V Trobada d'Investigadors i Investigadores en Càncer Ciutat d'Alcoi, 2021
- ***Scientific and OrganizingCommittee***
  2nd ASPIC-ASEICA International Meeting on Current Trends of Precision Medicine in Cancer (2021)
- ***External Advisory Board***
  Krasko Research SL (2021-present)



Conservation of Vav2-dependent expression signatures in human cutaneous papilloma and squamous cell carcinoma samples (Lorenzo-Martin et al., Nat Commun 2020).

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LABORATORY 4

SIGNALING BY HUMAN CHROMATIN KINASES IN CANCER AND NEURODEGENERATIVE DISEASES

RESEARCH SUMMARY

Our laboratory is studying the role that the human chromatin kinase VRK1 plays in the regulation of chromatin dynamics in the context of cancer and neurodegerative diseases such as spinal muscular atrophy or amyotrophic lateral sclerosis.

The regulation and coordination of epigenetic chromatin remodeling is associated to different functional states of chromatin, in physiology and pathology. In this context, the nuclear chromatin kinase VRK1 is a candidate for this coordinating role of histone epigenetic modifications by signaling to all pathways implicated, from DNA condensation/relaxation, transcription and replication, all requiring a dynamic chromatin reorganization. Altered chromatin remodeling underlies cancer and neurological diseases. In our group we are studying the steps that constitute the novel signaling pathways where the human chromatin kinase VRK1 is involved in the regulation of epigenetic modifications, participate in biological processes such as the DNA-damage response linking cancer and neurodegenerative diseases.

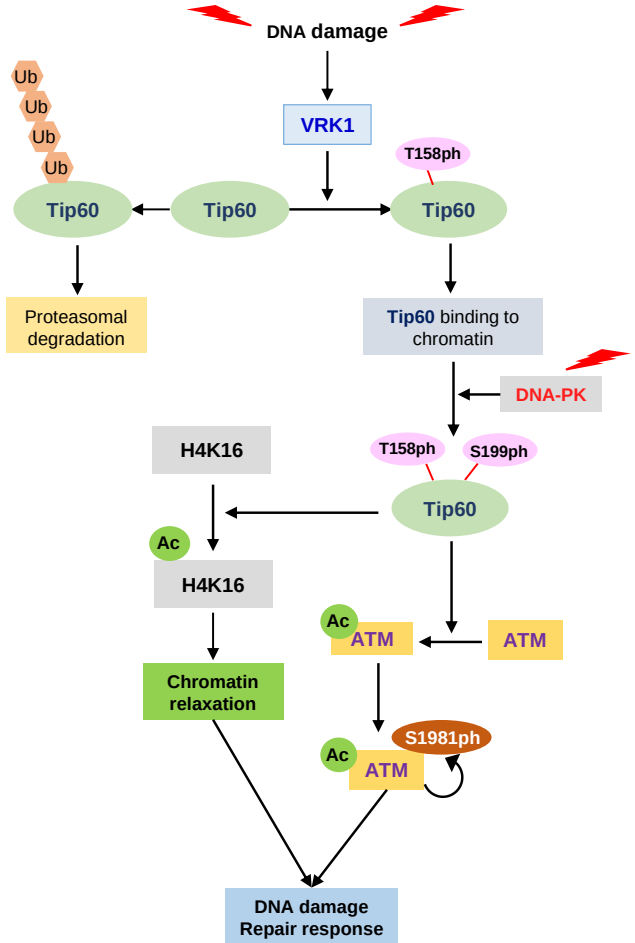
Genome stability is essential for the maintenance of species, but at the same time, genetic variation is necessary for their evolution. Therefore, in all species there are several mechanisms aiming to protect DNA from genetic damage of endogenous or exogenous origin. DNA repair mechanisms have to function in all these different cellular contexts. Endogenous DNA damage is a consequence of the biological properties of cells, and includes oxidative stress, replication errors, transcriptional errors or metabolism of DNA, to which cells are continuously exposed. Alternatively, exogenous factors such as ultraviolet light, ionizing radiation or drugs (chemicals) also cause DNA damage to which exposure is frequently transient. The DNA damage has many different forms, single or double strand breaks, nucleotide or base modifications.

Chromatin remodelling underlines all biological processes of the genome. The dynamic reorganization of chromatin requires several different, or alternative, epigenetic modifications of histones, which include acetylation, methylation, ubiquitination and phosphorylation. Different combinations of these epigenetic marks are associated with the compaction or relaxation of chromatin, and its biological functions including transcription, replication, differentiation, telomere protection, genome stability and DNA damage and repair at the right place and time. Each individual cell has to remodel its chromatin to adjust to its particular functional situation. This dynamic chromatin remodelling involves at least four different enzyme activities, which includes writers such as lysine acetyl transferases (KAT) and methyl transferases (KMT),

as well as erasers such as lysine deacetylases (HDAC) and demethylases (KDM). All of them are an active target for pharmacological development in cancer. The transition from one epigenetic histone modification to another requires the coordination of the two, or four, enzymes implicated, depending on the specific lysine. This transition implicates four different enzymes that need to be coordinated. However, the coordination of these activities and their functional organization is unknown. The balance among these alternative histone epigenetic modifications is likely to be regulated by phosphorylation in Ser or Thr residues in nucleosomal histones, as well as by the regulation of the enzymes implicated in these modifications.

DNA repair requires a sequential remodeling of chromatin to allow for the different and consecutive steps in each repair pathway, which includes protection of damaged DNA, recognition of the type of lesion, recruitment of specific repair mechanisms, ligation of DNA ends, and restoration to its normal chromatin organization. After DNA damage, in addition to the DNA lesion, the initial effect is a local distortion of an altered chromatin, which is the initiating event to trigger the cascade of DNA repair processes. As organisms increased in their complexity, new regulatory elements are necessary not only to coordinate different functions in DDR, but also to adjust to their much more complex and dynamic structure of chromatin. Therefore, new regulatory mechanisms that integrate and coordinate basic processes are necessary. In this context, new regulatory elements have evolved from preexisting proteins. A candidate for this role must be a chromatin protein with a reversible enzymatic activity. In this context, among the 518 kinase of the human kinome, vaccinia-related kinase-1 (VRK1/NHK1) is a potential candidate for this role because of its association to chromatin.

Alterations in genes associated to DNA-damage responses (DDR) are usually manifested either as cancer predisposition genes/tumor suppressors as well as associated to neuropathology, as is the case of NBS1, ATM or XPC. Alterations in DDR genes linked to cancer also cause neurodegenerative syndromes, such as ataxias, Nijmegen-breakage syndrome or xeroderma pigmentosum among others. When DNA damage repair fails, in cells with division potential, mutations accumulate and can lead to cancer. In non-dividing neurons, these genes protect neurons from DNA-damage caused by oxidative stress due to their very high oxygen consumption. Neuronal oxidative stress can lead to the accumulation of DNA damage, and can be a



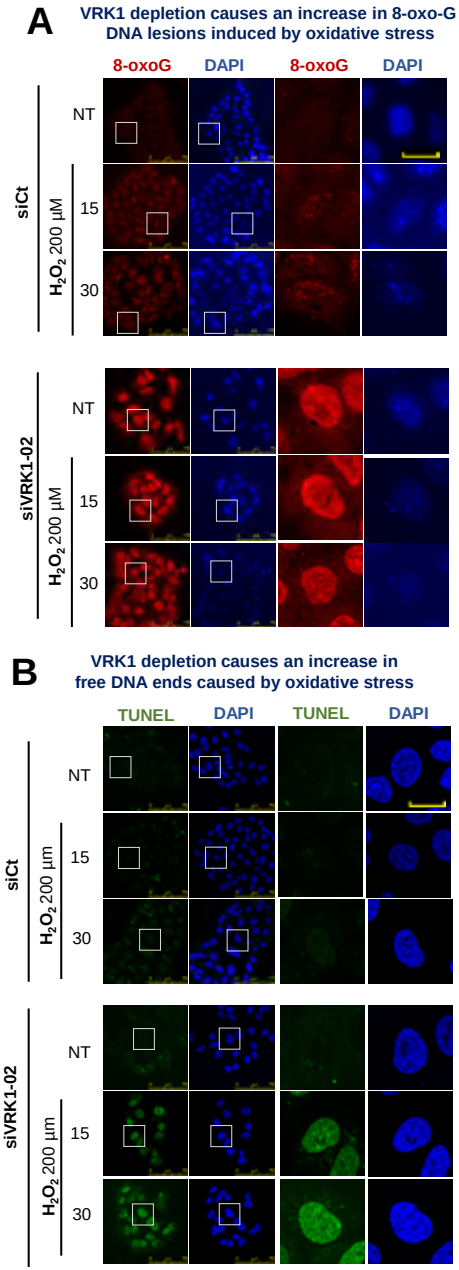
Sequential cooperation of VRK1 and DNA-PK in the activation of Tip60 in the response to DNA damage.

pathogenic mechanism for deterioration of neurological functions associated to aging. Neurons are non-dividing cells, in which homologous recombination is not functional, but are continually exposed to oxidative DNA damage, and DNA lesions will have to be repaired in the absence of replication. VRK1 neuro pathogenic variants cause heterogeneous syndromes affecting the motor-neuron due to a functional insufficiency as reported by our group.

VRK1 is a sensor of chromatin alteration and its activity is regulated by interaction with nucleosomal histones.

Chromatin in interphase has a very large size and DNA lesions can occur at any place, heterochromatin and euchromatin, which are likely to have a different sensitivity to DNA damage. Alterations of DNA by strand-breaks or chemical modifications, such as oxidation, alkylation, or intercalation among others, will alter the chromatin organization by introducing a local distortion, which is a likely initiating event for triggering the complex processes of DNA repair. However, responding to DNA damage requires the coupling of a local aberrant chromatin distortion to a signal transduction system, probably mediated by a nuclear chromatin kinase. Early sensors mechanism of DNA damage must fulfill some basic requirements, be a nuclear enzyme that interacts with basic chromatin components in nucleosomes, and be a capable of an immediate signaling reaction that is also reversible. In this context, a kinase, such as VRK1, is a very suitable candidate for this role. A requirement for a sensor kinase is that its activation is independent of the type of DNA damage and therefore is not associated to any particular type of DNA damage. In this latter case, the kinase involved will participate in specific steps of a particular DNA damage response, as is the case for ATM, ATR or DNA-PK in the response to double-strand DNA breaks. In DDR, the kinase activity of VRK1 increases tenfold after induction of DNA damage, independently of its type, which includes pyrimidine dimers caused by ultraviolet light, single-strand DNA breaks caused by hydroxyurea treatment, or double-strand DNA breaks induced by either doxorubicin or ionizing radiation. Acting upstream of ATM and DNA-PK. Pharmacological targeting of VRK1 might be an alternative approach in cancer therapies based on synthetic lethality, which combines targeting different components in DDR, either by mutations or pharmacologically.

In our laboratory, we have demonstrated that targeting VRK1 can led to development of novel therapeutic anti-cancer strategies based on synthetic lethality, which reduces the exposure to high doses of drugs and reduces the development of drug resistance. In the context of neurodegenerative diseases, we have identified and characterized several new VRK1 variants that are associated to amyotrophic lateral sclerosis (ELA), spinal muscular atrophy (SMA) and distal neuromotor diseases such as Charcot-Marie-Tooth or spastic paraplegia. This has led to the identification of c common pathogenic mechanism based on the disruption of Cajal bodies, which are regulated by VRK1.



VRK1 depletion facilitates on the generation of oxidative stress lesions, formation of 8-oxoGuanine (Left) and DNA single strand breaks labeled detected by TUNEL assays (right)

PUBLICATIONS

- **VRK1 (Y213H) homozygous mutant impairs Cajal bodies in a hereditary case of distal motor neuropathy.** *Marcos AT, Martín-Doncel E, Morejón-García P, Marcos-Alcalde I, Gómez-Puertas P, Segura-Puimedon M, Armengol L, Navarro-Pando JM, Lazo PA.* **Ann Clin Transl Neurol. 2020 May;7(5):808-818. doi: 10.1002/acn3.51050**. PMID: 32365420. **IF: 4.511 / Q2**

- **Novel Dominant KCNQ2 Exon 7 Partial In-Frame Duplication in a Complex Epileptic and Neurodevelopmental Delay Syndrome.** *Lazo PA, García JL, Gómez-Puertas P, Marcos-Alcalde Í, Arjona C, Villarroel A, González-Sarmiento R, Fons C.* **Int J Mol Sci. 2020 Jun 23;21(12):4447. doi: 10.3390/ijms21124447.** PMID: 32585800. **IF: 5.923 / Q1**

- **VRK1 Phosphorylates Tip60/KAT5 and Is Required for H4K16 Acetylation in Response to DNA Damage.** *García-González R, Morejón-García P, Campillo-Marcos I, Salzano M, Lazo PA.* **Cancers (Basel). 2020 Oct 15;12(10):2986. doi: 10.3390/cancers12102986.** PMID: 33076429. **IF: 6.639 / Q1**

- **The human VRK1 chromatin kinase in cancer biology.** *Campillo-Marcos I, García-González R, Navarro-Carrasco E, Lazo PA.* **Cancer Lett. 2021 Apr 10; 503:117-128. doi: 10.1016/j.canlet.2020.12.032.** PMID: 33516791. **IF:8.679 / D1**

- **Pathogenic convergence of CNVs in genes functionally associated to a severe neuromotor developmental delay syndrome.** *García-Hernández JL, Corchete LA, Marcos-Alcalde Í, Gómez-Puertas P, Fons C, Lazo PA.* **Hum Genomics. 2021 Feb 8;15(1):11. doi: 10.1186/s40246-021-00309-4.** PMID: 33557955 **IF: 4.639 / Q2**

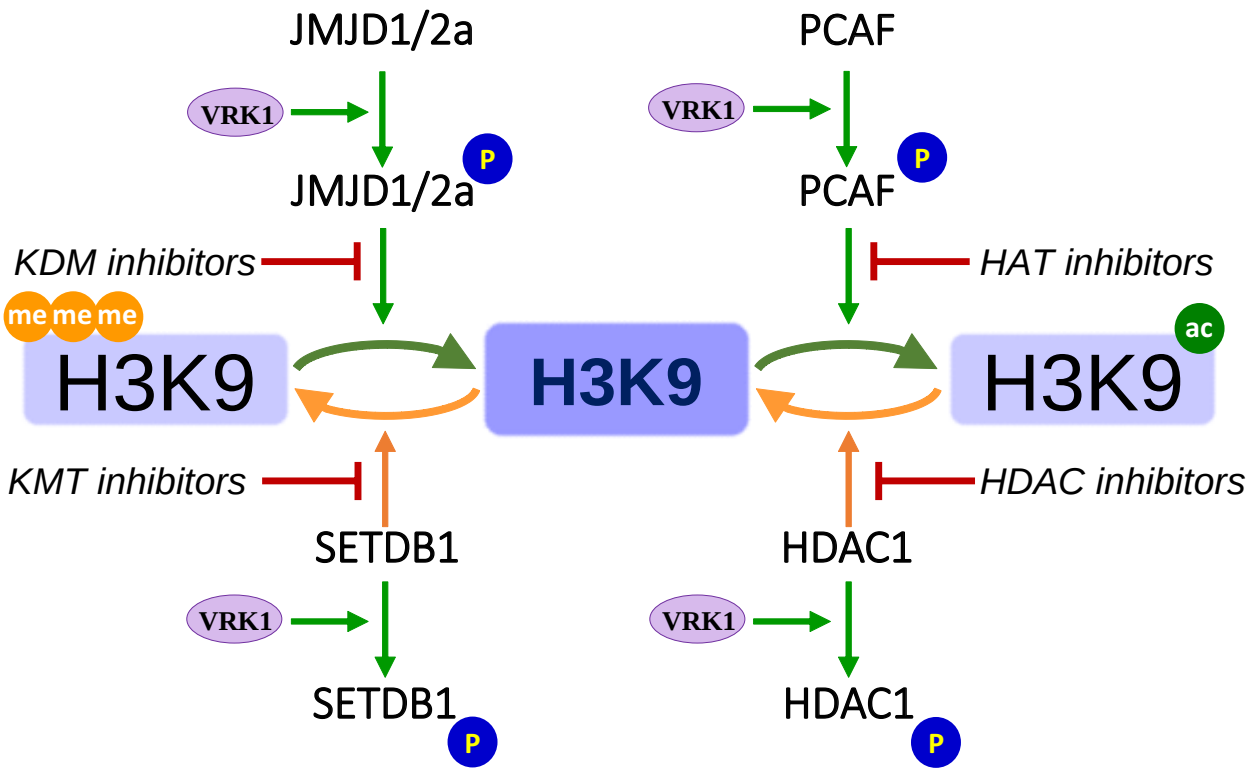
- **VRK1 Depletion Facilitates the Synthetic Lethality of Temozolomide and Olaparib in Glioblastoma Cells**. *Navarro-Carrasco E, Lazo PA.* **Front Cell Dev Biol. 2021 Jun 14; 9:683038. doi: 10.3389/fcell.2021.683038.** PMID: 34195200. **IF:6.684 / Q1**

- **Dysfunctional Homozygous VRK1-D263G Variant Impairs the Assembly of Cajal Bodies and DNA Damage Response in Hereditary Spastic Paraplegia.** *Morejon-Garcia P, Keren B, Marcos-Alcalde I, Gomez-Puertas P, Mochel F, Lazo PA.* **Neurol Genet. 2021 Sep 2;7(5):e624. doi: 10.1212/NXG.0000000000000624.** PMID: 34504951. **IF: 3.485 / Q2**

- **Lysine Methyltransferase Inhibitors Impair H4K20me2 and 53BP1 Foci in Response to DNA Damage in Sarcomas, a Synthetic Lethality Strategy.** *Campillo-Marcos I, Monte-Serrano E, Navarro-Carrasco E, García-González R, Lazo PA.* **Front Cell Dev Biol. 2021 Sep 3; 9:715126. doi: 10.3389/fcell.2021.715126.** PMID: 34540832. **IF:6.684 / Q1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Funciones de la quinasa VRK1 humana en la patogénesis del cáncer y enfermedades neurodegenerativas (SAF2016-75744-R)	Pedro A. Lazo-Zbikowski	Spanish Ministry of Economy & Competitiveness	2017-2019	314,600.00 €
RedINC: Spanish network of the International Nucleome Consortium (COST COST Action "International Nucleome Consortium" (INC) CA18127) (RED2018-102801-T)	Pedro A. Lazo-Zbikowski	Ministry of Science and Innovation / State Research Agency	2019-2022	25,000.00 €
Manipulación de la estabilidad genómica como estrategia de letalidad sintética en oncología (CSI264P20)	Pedro A. Lazo-Zbikowski	Regional Government of Castilla y León	2020-2023	172,000.00 €
Regulación por VRK1 de remodelación de cromatina en la patogénesis del cáncer y neurodegeneración (PID2019-105610RB-I00)	Pedro A. Lazo-Zbikowski	Ministry of Science and Innovation / State Research Agency	2020-2023	276,000.00 €



Role of the coordinating role played by VRK1 in the transition of epigenetic modification of histone H3 from a repressive state (methylation) to and activation state (acetylation) of gene transcription.

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Borja Miguel López
Óscar Monteagudo García

STUDENTS
Soña Gubová
Barbara Castellanos García

LABORATORY 5A

EPITRANSCRIPTOMICS AND CANCER

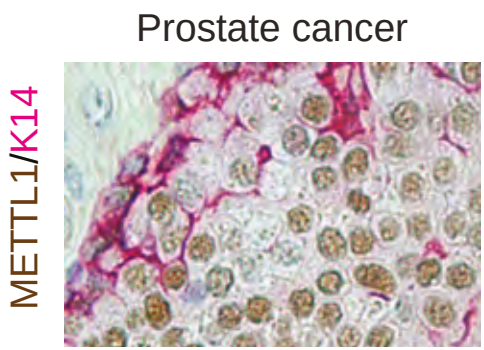
RESEARCH SUMMARY

RNA modifications are beginning to define a novel layer of biological complexity that is becoming widely appreciated as the epitranscriptome. To date over 170 known chemical modifications are known in RNA and emerging evidence is revealing that post-transcriptional modifications mediate regulation of gene expression and protein translation efficiency and accuracy. Our main interest is to decipher novel epitranscriptomic mechanisms affecting human disorders, with special focus on cancer and other degenerative diseases. We seek to understand how RNA modifications regulate self-renewal, differentiation, growth, survival and invasion processes in normal and malignant cells.

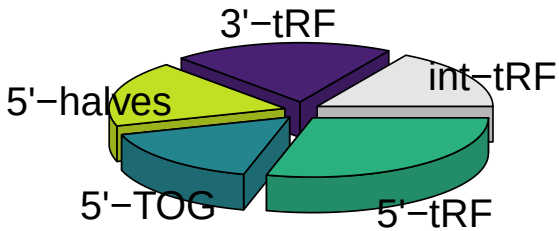
To this aim, we combine state-of-the-art transcriptome-wide sequencing methods, with biochemical methods, mouse models, human cancer cell lines, stem cell cultures, patient samples and 3D culture models to study the role of post-transcriptional modifications such as RNA methylation in tissue and cancer stem cell functions, development and cancer initiation, progression, metastasis and therapy tolerance development.

Our aims:

1 We have shown that RNA modifications are novel regulators of gene expression at the protein synthesis level, which in turn regulate cellular processes. In particular we have shown that m5C on transfer RNA (tRNAs) can regulate their processing into small non coding RNAs (ncRNAs)-derived tRNA fragments, which in turn regulate the translation machinery favouring the expression of stress response and migration genes, and



Immunohistochemistry for METTL1 (brown) and K14 (red, basal cells) in human prostate cancer. Scale bar represents 50 µm.



Percent of differentially expressed tRNA-derived fragments identified in METTL1 KO cells versus control (WT) cells. tRNA fragments with log^2 fold change >2, and p-value < 0.05 are represented. 3' tRNA-derived fragments (3'-tRFS), Int-tRFs span the interior of the mature tRNA sequence, 5' tRNA-derived fragments start at -10 to +10 of tRNA start site, and 5'TOGs are containing a 5' terminal oligoguanines.

thus regulating those processes in tissue homeostasis and disease. m5C dynamic deposition is fundamental for metabolic regulation and cell cycle progression. Now we aim to characterize the role of RNA modifications, "writers", "erasers" and "protein readers" in the regulation of tissue homeostasis in normal development. Characterize their functional role in cellular processes including proliferation, self-renewal, differentiation, migration or adaptation to microenvironment changes or stress stimuli.

2 Emerging evidence implicates a key role for non-mutational stress resistance mechanisms such as epigenetics and epitranscriptomics underlying the survival of residual cancer cells. Unlike DNA epigenetics with only one major chemical modification known, over 170 chemical modifications of RNA are known to compose "the epitranscriptome". Their function remains still widely unknown, however they are emerging as modulators of self-renewal, differentiation, stress responses and their alterations are associated to cancer. Now we aim to identify the epitranscriptome in disease and determine the impact of aberrant deposition in cancer and in neurodegenerative diseases. Define and characterize genomic or transcriptional alterations of RNA modifying enzymes including "writers", "erasers" and "protein readers" in several tumour types.

3 Cancer is a highly heterogeneous and dynamic disease that arises from the integrated dysregulation of different cellular processes including metastasis or immunity responses. The information regarding the connection between the epitranscriptome and tumour microenvironment epithelial–mesenchymal transition (EMT), metastasis or cancer immune-suppressive regulation is limited, however recent data suggest that could be an interesting target for the treatment of tumours. The recent observations require the detailed exploration of the mechanism by which metastasis and cancer immune-suppressive activity are regulated by RNA modifying proteins and the therapeutic potential. Thus our objective is to identify critical RNA modifying proteins that regulate the crosstalk of tumour cells with the micro-environment to find therapeutical strategies to influence metastasis or cancer-associated immune responses.

4 The fast evolving knowledge we have acquired on the role of the epitranscriptome in homeostasis and diseases is mainly due to our current capacity of detecting RNA modifications at single nucleotide resolution. To date few RNA modifications are being explore mainly due to the lack of high throughput detection methods that allow us the identification of novel modifications. Thus we aim to develop novel high throughput RNA modifications detection methods to then discover the epitranscriptomic landscape in health and disease.

5 Discovering the molecular function of modified RNAs are key to understand their role in physiology and pathology. We aim to determine the fate of RNA modified RNAs applying RNA sequencing, proteomic and microscopy approaches.

6 Determine the therapeutic potential of the manipulation of the epitranscriptome in cancer cells. Development of small molecule inhibitors of RNA modifying enzymes that are altered in cancer.

PUBLICATIONS

- **Emerging roles of novel small non-coding regulatory RNAs in immunity and cancer.** *Rosace D, López J, Blanco S.* **RNA Biology. 2020 Mar 18:1-18. doi: 10.1080/15476286.2020.1737442**. PMID: 32186461. **IF:4.652 / Q2**

- **Glia Crosstalk in Neuroinflammatory Diseases.** *Sevilla A, Bernaus A, Blanco S.* **Frontiers in Cellular Neuroscience. 2020 Jul 29;14:209. doi: 10.3389/fncel.2020.00209. eCollection 2020.** PMID: 32848613. **IF:5.505 / Q1**

- **The role of m6A, m5C and Y in cancer. Novel therapeutic opportunities.** *Nombela P, Miguel-López B, Blanco S.* **Mol Cancer. 2021 Jan 18;20(1):18. doi: 10.1186/s12943-020-01263-w.** PMID: 33461542 **IF: 27.401 / D1**

- **A therapy PUSh for GBM.** *Morón-Calvente V, Blanco S.* **Nat Cancer. 2021 Sep;2(9):876-878. doi: 10.1038/s43018-021-00255-z.** PMID: 35121866. **IF: NI**

OTHER PUBLICATIONS & BOOK CHAPTERS

- **Genome and Epigenetics.** *Montoliu L, Rada-Iglesias A; Domínguez A et al.* **Libro Blanco CSIC 3 (2020). Publisher Consejo Superior de Investigaciones Científicas (España). Doi: http://dx.doi.org/10.20350/digitalCSIC/12650.**
- **Challenges in Biomedicine and Health.** *Mario Delgado, María Moros, Raúl V Durán, Xosé R Bustelo, M Ángela Nieto, Joaquín Arribas, Sandra Blanco, et al.* **Libro Blanco CSIC 4 (2020). Publisher Consejo Superior de Investigaciones Científicas (España). Doi: http://dx.doi.org/10.20350/digitalCSIC/12651.**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Post-transcriptional modifications and processing of RNA in cancer stem cells. (SAF2016-78667-R.)	Sandra Blanco	Ministry of Science and Innovation	2016-2020	168,000.00 €
Post-transcriptionally modified RNAs as regulators of growth and survival in cancer. (LABAE19040BLAN)	Sandra Blanco	Spanish Association against Cancer Scientific Foundation (FCAECC)	2019-2023	300,000.00 €
Evaluación de los procesos postranscripcionales que regulan procesos de auto-renovación en células madre de cáncer de próstata	Sandra Blanco	Carlos III Health Institute (Proteored)	2020	5,000.00 €
Papel funcional de las modificaciones post-transcripcionales ribosómicas en cáncer de próstata. (FS/25-2019)	Domenico Rosace	Solorzano Foundation	2020	1,721.00 €
Papel de la epitranscriptómica y su implicación en la metástasis y la respuesta inmune en cáncer. (PID2019-111692RB-I00)	Sandra Blanco	Ministry of Science and Innovation	2020-2023	217,000.00 €
Using the epitranscriptome of non-coding RNAs to improve human epidermal stem cell therapeutics. (CIRA-2020-78)	Abdulrahim Abdulrahman Sajini	Competitive Internal Research Award 2020 Khalifa University	2020-2024	70,000.00 €
Identificación de mecanismos epitranscriptómicos que regulan la respuesta inmunitaria tumoral a nivel de célula única	Sandra Blanco	Leonardo Grant Program BBVA Foundation	2021-2023	40,000.00 €
Alteraciones en los patrones de pseudouridilación de ARN en cáncer de próstata.(FS/36-2020).	Mª Paz Nombela Blanco	Solorzano Foundation	2021	1,854.91 €

OTHER ACTIVITIES & RELEVANT FACTS

Participation in Consortiums

- Participating member of the EPITRAN Cost Action CA16120 - European Epitranscriptomics Network (2017-2121).
- Participating Member of the Spanish Network on Prostate Cancer Uroncomol - (2019-2021).

Peer Review Experience

- Ad Hoc Referee for FRS (Belgium Research Council), MRC (British Medical Research Council), ANR (French Research Agency), AEI (Agencia Española de Investigación), ERC (European Research Council),

Examiner at Thesis dissertations:

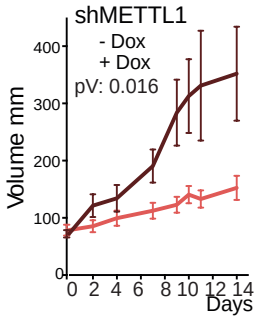
- Mª Rosario Prados Carvajal, January 2020, University of Seville. "Crosstalk between DNA end resection and RNA metabolism.
- Marta Rodríguez Escribá, 2020, University of Barcelona. "Role of tRNA modifications in the synthesis of the extracellular matrix".
- Margalida Rosselló Tortella, December 2021, University of Barcelona. Epigenetic Regulation of tRNA Biology in Cancer

Outreach

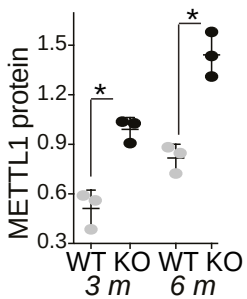
- 11th Feb 2020. Woman and girl in Science Talk given in Valladolid Science Museum, event: 'Ellas son ciencia: vidas dedicadas a la investigación, historias con personalidad'.
- 14th Feb 2020. Woman and girl in Science Talk given in Secondary School (IES, Martínez Uribarri, Salamanca).
- April 2020. Podcast at Ciencia.es. https://cienciaes.com/entrevistas/2020/04/19/arn-y-vida/
- Nov 2020. Opening and exhibition of Con Ciencia Con Arte at Colegio Fonseca - University of Salamanca. An initiative that joins artist and scientist, organized and coordinated by S Blanco and funded by FGCSCI. Keynote Speaker: Javier Armentia, Director of Planetario de Pamplona. https://concienciaconarte.csic.es/
- Feb/Mar 2021. Organizing committee for Conócelas initiative (ASEICAMujer), coordinator in Castilla y León and Castilla La Mancha areas. https://view.genial.ly/6009742faafdee12655bf91f./ https://www.cicancer.org/science-society/cic-news/conocelas.
- 11th Feb 2021. Canal 8 Magazine Bierzo. Entrevista 11F. https://youtu.be/sD8X-5rmYZg
- 18th Feb 2021. La Central Divulga at La Fábrica de Luz Museo de Energía Ponferrada. Dissemination talk Cómo ser científica y no morir en el intento. https://www.youtube.com/watch?v=vSWULOM-Nu4
- 19th Mar 2021. Coloquio mujer e investigación de la USAL. Presented by the Chancellor of the University of Salamanca and the President of the Senate Pilar Llop. https://www.youtube.com/watch?v=5Z6cR3PN_ul
- July 2021. Campus Científico. An activity dedicated to train during a week the future generation of scientist.
- Oct-Nov 2021. Opening and exhibition of Con Ciencia Con Arte at Museum of Energy – The light Factory Ponferrada. http://www.lafabricadeluz.org/es/agenda/eventodetalle/947/-/con-ciencia-con-arte

Teaching

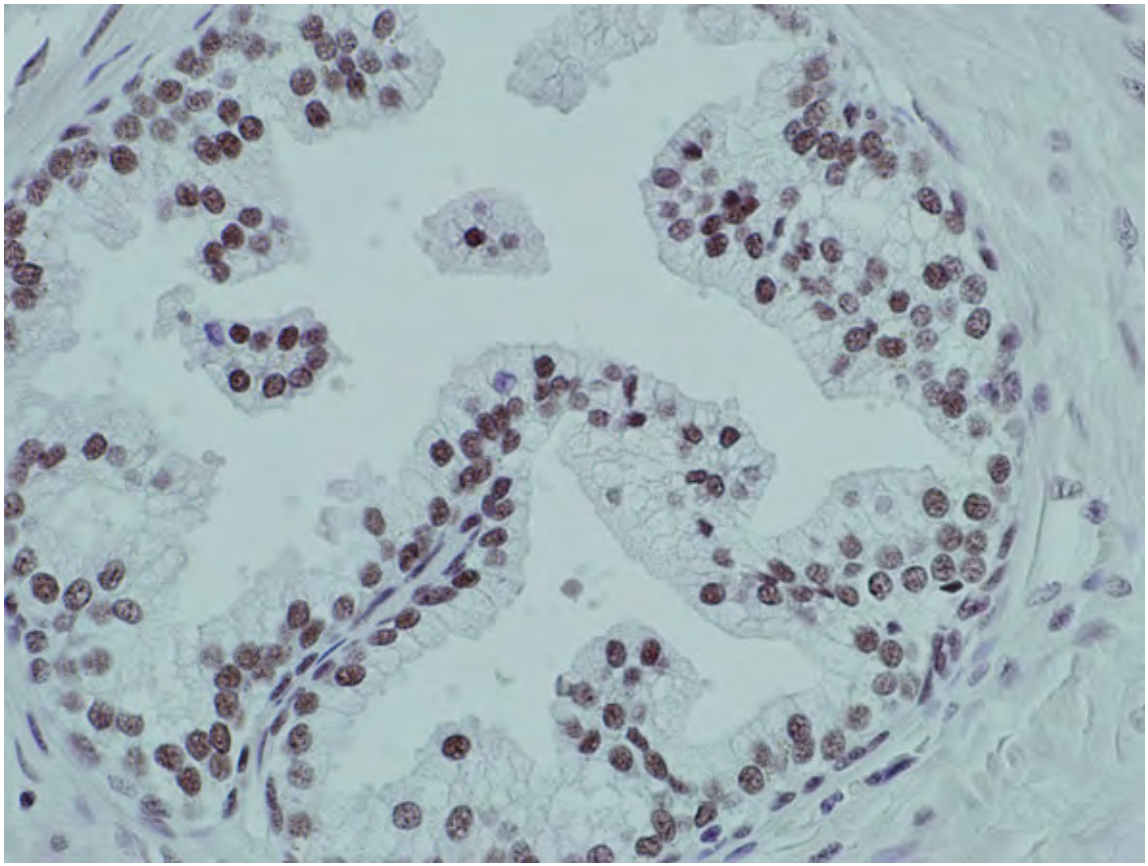
- Lecturer at Communication and dissemination strategies in cancer research subject. MSc Biology and Clinic of Cancer. Academic year 2020-2021.



Tumour growth of xenografted PC3 *METTL1 KD* and control (WT) cells in athymic nude mice. Mean ± SEM are represented (n=10, each genotype).



Mettl1 expression in prostate tumors from *PtenKO* mice at 3 (at tumour initiation) and 6 moths (invasive carcinoma) of age compared to wild-type mice (WT) at same ages.



METTL3 staining in human prostate

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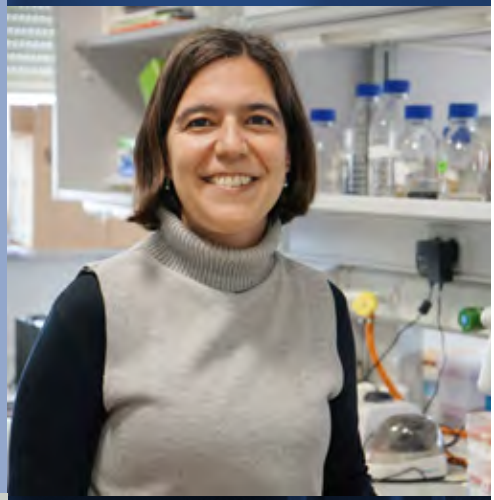


RESEARCH TEAM

POSTDOCTORAL
Cristina Cuesta

PREDOCTORAL
Víctor Manuel Pérez
Marta Alcón
Cristina Arévalo
Cristian Morillo

STUDENTS
Alejandro Rosell
Belén Martínez
Mario Rodríguez

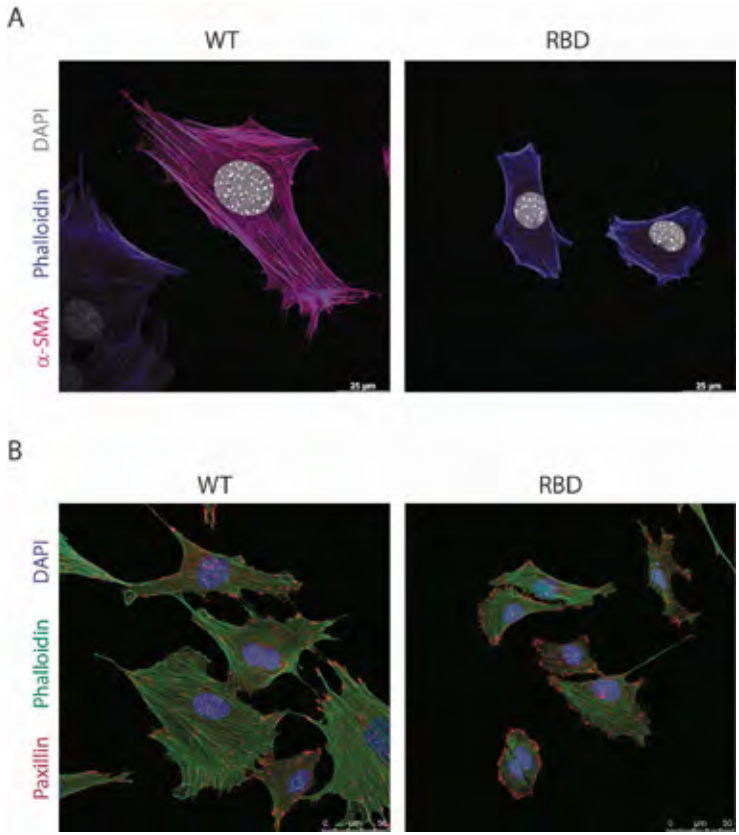
LABORATORY 5B

TUMOUR-STROMA SIGNALING

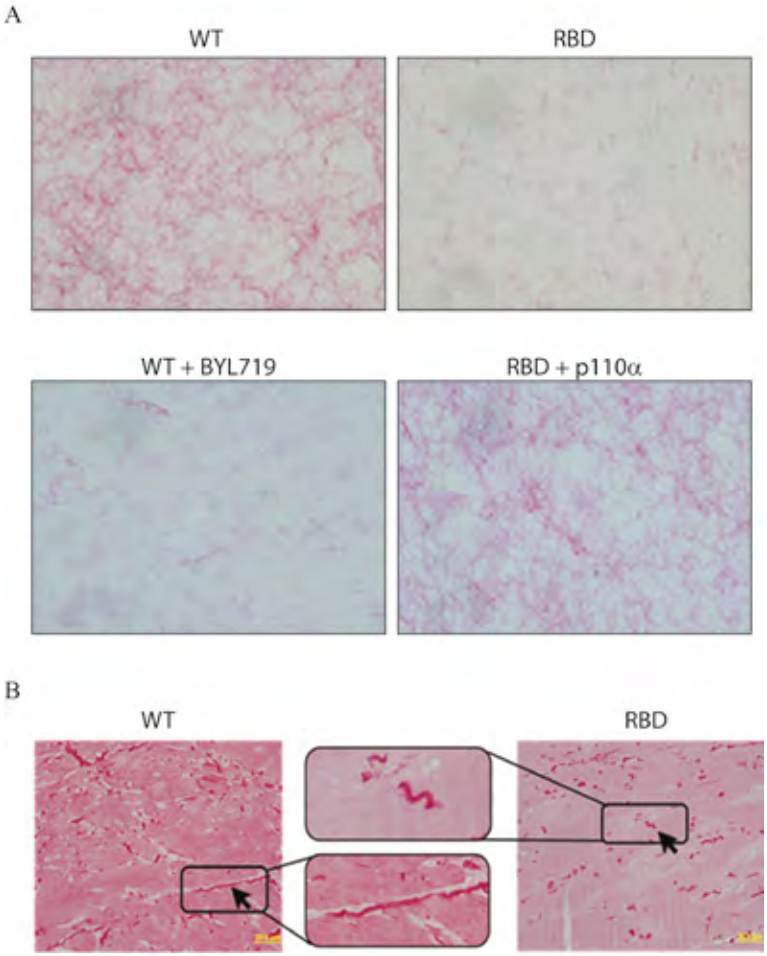
RESEARCH SUMMARY

Our lab aims to understand how oncogenic RAS proteins drive cancer development by regulating the interplay between tumour cells and their microenvironment in lung cancer. Interactions between tumoral cells and the surrounding stroma are essential to maintain tumour growth and cancer progression. These interactions provide proliferative and migratory advantages that help tumour development and progression. RAS oncogenes are key players in the initiation and development of cancer, but little is known about how RAS signalling can modulate the stroma to support tumour progression. Identifying the key molecules required for RAS-dependent tumour-stroma crosstalk is fundamental to better understand the biology of RAS-driven lung cancer.

During this period, our group focused on understanding the role that RAS binding to PI3K plays in the activation and function of cancer associated fibroblasts (CAFs) to generate a tumour microenvironment that is tumour-growth permissive, using animal and cellular models of KRAS-driven lung cancer. CAFs are essential during tumour growth since they are able to: 1) affect the behaviour of cancer cells by exerting trophic functions and favouring motility; 2) shape the reactivity of other stromal cells by promoting recruitment and modulating physical and functional interactions; 3) modify structural features of the tumour microenvironment by promoting acidification and secreting proteins that remodel the extracellular matrix (ECM); 4) escort and promote survival of cancer cells while in the bloodstream, enabling colonization of metastatic sites and 5) modulate response to chemotherapeutic agents.



Disruption of RAS binding to PI3K impairs formation of stress fibres and focal adhesions in TGF-β activated fibroblasts. Representative immunofluorescence (IF) images showing formation of (A) stress fibres and (B) focal adhesion points in TGF-β activated fibroblasts. Results suggest that TGF-β activated fibroblasts lacking RAS-PI3K interaction (RBD) present a decrease in stress fibre formation and in the number of focal adhesion points.



Collagen remodelling is decreased in TGF-β activated fibroblasts lacking RAS binding to PI3K. (A) Representative images of collagen gels remodelled by TGF-β activated fibroblasts. Fibroblasts were allowed to remodel the gels for 24 h. Results showed that disruption of RAS binding to PI3K in fibroblasts (RBD) decreases formation of thicker collagen fibres. Treatment with BYL719, a p110α inhibitor, leads to similar defects in collagen remodelling than those observed in RBD fibroblasts and reintroduction of a functional p110α in RBD cells rescues collagen remodelling. Collagen is visualized by Red Sirius staining. **(B)** TGF-β activated fibroblasts resuspended in matrigel were injected in the flanks of C57BL/6 mice and were allowed to remodel the matrigel for 10 days. Plugs were collected and Red Sirius staining was performed. WT fibroblasts were able to form long, thick, linear collagen fibres, whereas RBD fibroblasts formed shorter and curlier collagen fibres.

Our analysis of the role of RAS-PI3K binding in the activation of CAFs has demonstrated that transition from normal fibroblasts to CAFs depends on this signalling pathway, since its abrogation in fibroblasts prevents expression of typical CAF markers, impairs cytoskeletal reorganization and morphological changes linked to the CAF phenotype and affects their mechanotransduction properties. In addition, RAS activation of PI3K in CAFs is necessary for the secretion of different components of the ECM and for remodelling of existing components. Regarding the later, RAS-PI3K regulates: i) fibre orientation of existing components; ii) expression and function of matrix metalloproteases; iii) collagen processing proteins. These changes modify the physical and chemical properties of the tumour ECM, influencing intra-tumoral signalling, transport, metabolism and immunogenicity.

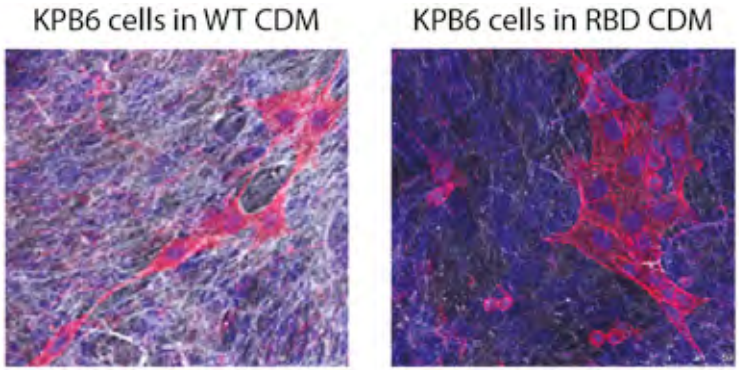
Our data suggests that the role of RAS-PI3K signalling goes beyond regulation of CAF function, since its alteration in CAFs affects other cells in the tumour microenvironment. We found that the behaviour of different tumour cells harbouring mutations in KRAS is altered when co-cultured with CAFs deficient in RAS-PI3K signalling or when grown in decellularized ECM created by these CAFs. Similarly, functionality, morphology and migration of macrophages is impaired when seeded in the ECM scaffold created by CAFs lacking RAS binding to PI3K. Future work will be aimed at better understanding the molecular pathways governing these changes, as well as generating more complex co-culture models involving three cellular components of the TME and the ECM scaffold created by these CAFs.

In order to analyse the functional role of RAS-PI3K in CAFs in vivo we recently generated an inducible knock-in murine model in which RAS-PI3K can be disrupted only in fibroblasts. Initial characterization of this model allowed us to validate our *in vitro* data, although further analysis of this complex model is required to fully understand the role of RAS-PI3K in CAFs during tumour growth and establishment of the metastatic niche

PUBLICATIONS

- **The Crossroads between RAS and RHO Signaling Pathways in Cellular Transformation, Motility and Contraction.** *Soriano O, Alcón-Pérez M, Vicente-Manzanares M, Castellano E.* **Genes (Basel). 2021 May 27;12(6):819. doi: 10.3390/genes12060819.** PMID: 34071831. **IF:4.096 / Q2**

- **The Importance of Being PI3K in the RAS Signaling Network.** *Cuesta C, Arévalo-Alameda C, Castellano E.* **Genes (Basel). 2021 Jul 19;12(7):1094. doi: 10.3390/genes12071094.** PMID: 34356110. **IF:4.069 / Q2**



Composition and structure of ECM regulates tumor cell behaviour. Lung cancer cells (KP86) were seeded in decellularized CDMs formed by TGF-β activated WT or RBD fibroblasts. Data shows that tumor cells seeded in WT-derived CDMs acquire a mesenchymal phenotype, however they retain the epithelial phenotype when seeded in RBD-derived CDMs.

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Efficacy of the BTK inhibitor Acalabrutinib in a preclinical model of lung cancer	Esther Castellano	Acerta Pharma Ltd.	2017-2022	250,000.00€
Explore the therapeutic effect of Acalabrutinib (ACP-196) in combination with Stat3 inhibitor (AZD9150) in KRAS-driven lung tumour growth	Esther Castellano	Acerta Pharma Ltd.	2018-2022	50,000.00€
Targeting RAS-PI3K signalling to re-educate the stroma of RAS mutant lung cancers (RTI2018-099161-A-I00)	Esther Castellano	Spanish Ministry of Economy and Competitiveness	2019-2021	157,000.00€
Actualización del equipo existente de micro-tomografía por Rayos-X para imagen in-vivo (EQC2019-006712-P)	Esther Castellano	Ministry of Science and Innovation	2020	105,000.00€

CONFERENCES MEETINGS & SCIENTIFIC COURSES

- RAS binding to PI3K controls CAF function and tumour extracellular matrix dynamics to promote lung tumour progression. EACR-AACR. https://www.aacr.org/meeting/eacr-aacr-aspic-tumor-microenvironment-2020/continuing-medical-education/ (March 2020)

- Exploring the role of RAS signalling in the remodelling of the tumour microenvironment of KRAS-driven lung cáncer. The RAS Initiative https://ncifrederick.cancer.gov/events/conferences/RasSymposium/ (May 2021)

- Understanding the role of RAS signaling in the tumor microenvironment of KRAS-driven lung cancer. SEBBM https://congresosebbm.barcelona2021.es/ (July 2021)

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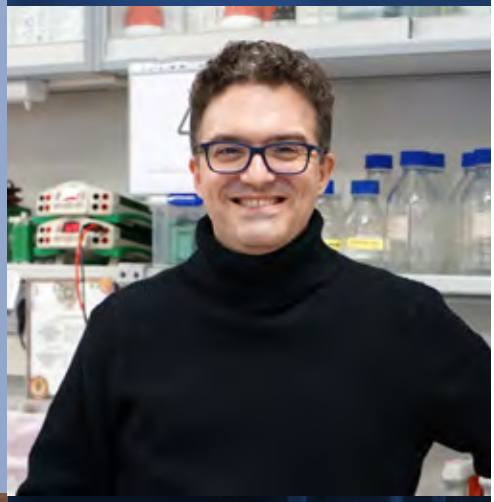

RESEARCH TEAM

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María Millán Salanova
Gloria Asensio Juárez
Marina Garrido Casado

TECHNICIAN
Olga Arjona Soriano

LABORATORY 6

TUMOR BIOPHYSICS

RESEARCH SUMMARY

During this period, the group has focused its activities on analyzing the mechanisms that control force generation in cells and developing new models and approaches to different aspects of the mechanics of the immune response.

In 2020, we published a pivotal study in Current Biology demonstrating the existence of a novel mechanism that regulates myosin II function by controlling its assembly in cells. This mechanism consists of the inhibition of myosin II assembly by phosphorylation of free RLC in Tyr155. This phosphorylation is executed by Tyr kinases of the EGFR family as well as Src. These stimuli, which promote protrusion and directional migration; and adhesion dynamics, respectively, inhibit myosin II activation at the leading edge not only by promoting the inactivation of assembled myosin II via phosphorylation of RLC in Ser19 (this mechanism is currently under investigation); but also by preventing the actual assembly of myosin II at the front. This is a landmark discovery that constitutes a completely novel mode of myosin regulation and force generation.

In the same direction, recent work from the lab have identified new protein kinases involved in specific aspects of myosin II regulation. This work, still in development, identifies myosin II as a target of mitotic and apoptotic kinases, contributing to the delineation of the myosin interactome and its role in the regulation of shape changes during cell migration and metastatic transformation.

Other activities in the lab have focused on studying the function of myosin II isoforms in T cell activation. One study submitted for publication demonstrates that low-expression myosin isoforms crucially regulate T cell activation and proliferation in response to immune challenge.

In a parallel effort in collaboration with the group of Prof. Henry Higgs (Dartmouth College, NH) that is also under consideration, we have demonstrated that low-expression myosin II isoforms also regulate actin assembly in response to calcium influx as well as mitochondrial dynamics. Combined, these two studies represent a quantitative advance that combines high-end quantitative mass spectrometry and cutting edge cell biology to demonstrate the crucial role of underrepresented myosin II isoforms in cellular events crucial for cell division, energy production and proliferative responses upon specific stimulation or driven by oncogenic transformation.

A novel aspect of our research is that we are characterizing the dynamics, behavior and impact on contraction of diverse GTPases of the Rho superfamily in migrating tumor cells. To undertake this sub-project, we are developing novel imaging tools and microscopy modes that will allow us to interrogate the localization and function of diverse GTPases and oncogenic mutations at a single-molecule level. Part of this work is being developed in collaboration with the groups of Prof. X. R. Bustelo and Eugenio Santos.

Regarding translational aspects, we are collaborating with Prof. Rogelio González (CIC/IBSAL) to determine the effect of novel mitotic inhibitors in tubulin dynamics. We are characterizing the cross-talk between microtubules and microfilaments during the response to treatment with anti-mitotics.

Finally we have begun unraveling the role of Myh9 (myosin IIA gene) mutations in human platelet disease and beyond. Using CRISPR/Cas9, we have generated diverse lines containing mutant myosin IIA variants, which are being studied in terms of molecular dynamics and function in specific lineages involved in the pathogenesis of MYH9 diseases.

As part of our commitment to the development of a basic immunology program at the CIC, we are collaborating with the groups of Alberto Orfao and Julia Almeida under the umbrella of the ECRIN-M3 program. This research program aims at developing new diagnostic and therapeutic approaches to the treatment of CLL and MBL. We are interested in the development of immunosuppression in CLL and MBL patients. To undertake this, we aim to study the activation of T cells in patients suffering from these diseases using a combination of traditional immunological methods and single-cell sequencing. This project has been severely delayed due to the COVID-19 pandemic.

Finally, we have initiated a collaboration with the group of Dr. J.C. Gallego-Gómez at the University of Antioquia (Colombia), in which we interrogate the ability of Dengue virus proteins to trigger morphological modifications in different cell types, mainly through the regulation of contraction, the activation of the Abl kinase and the onset of epithelial-mesenchymal transition.

PUBLICATIONS

- **Meeting Report - Workshop 'Actin-based mechanosensation and force generation in health and disease'**. *Polesskaya A, Vicente-Manzanares M.* **J Cell Sci. 2020 Mar 17;133(6):jcs244319. doi: 10.1242/jcs.244319**. PMID: 32184275. **IF: 5.285 / Q2**

- **Tyrosine Phosphorylation of the Myosin Regulatory Light Chain Controls Non-muscle Myosin II Assembly and Function in Migrating Cells**. *Aguilar-Cuenca R, Llorente-González C, Chapman JR, Talayero VC, Garrido-Casado M, Delgado-Arévalo C, Millán-Salanova M, Shabanowitz J, Hunt DF, Sellers JR, Heissler SM, Vicente-Manzanares M.* **Curr Biol. 2020 Jul 6;30(13):2446-2458.e6. doi: 10.1016/j.cub.2020.04.057.** PMID: 32502416. **IF: 10.834 / D1**

- **Linking the Landscape of MYH9-Related Diseases to the Molecular Mechanisms that Control Non-Muscle Myosin II-A Function in Cells.** *Asensio-Juárez G, Llorente-González C, Vicente-Manzanares M.* **Cells. 2020 Jun 12;9(6):1458. doi: 10.3390/cells9061458.** PMID: 32545517. **IF:6.600 / Q2**

- **Differential miRNAs in acute spontaneous coronary artery dissection: Pathophysiological insights from a potential biomarker.** *Lozano-Prieto M, Adlam D, García-Guimaraes M, Sanz-García A, Vera-Tomé P, Rivero F, Cuesta J, Bastante T, Baranowska-Clarke AA, Vara A, Martin-Gayo E, Vicente-Manzanares M, Martín P, Samani NJ, Sánchez-Madrid F, Alfonso F, de la Fuente H.* **EBioMedicine. 2021 Apr;66:103338. doi: 10.1016/j.ebiom.2021.103338.** PMID: 33866193. **IF:8.143 / Q1**

- **The Crossroads between RAS and RHO Signaling Pathways in Cellular Transformation, Motility and Contraction.** *Soriano O, Alcón-Pérez M, Vicente-Manzanares M, Castellano E.* **Genes (Basel). 2021 May 27;12(6):819. doi: 10.3390/genes12060819**. PMID: 34071831 **IF:4.096 / Q2**

- **Booster Effect of a Natural Extract of Polypodium leucotomos (Fernblock®) that Improves the UV Barrier Function and Immune Protection Capability of Sunscreen Formulations.** *Aguilera J, Vicente-Manzanares M, de Gálvez MV, Herrera-Ceballos E, Rodríguez-Luna A, González S.* **Front Med (Lausanne). 2021 Jun 2;8:684665. doi: 10.3389/fmed.2021.684665.** PMID: 34150816. **IF:5.093 / Q1**

- **Nonmuscle Myosin II Regulation Directs Its Multiple Roles in Cell Migration and Division.** *Garrido-Casado M, Asensio-Juárez G, Vicente-Manzanares M.* **Annu Rev Cell Dev Biol. 2021 Oct 6;37:285-310. doi: 10.1146/annurev-cellbio-042721-105528.** PMID: 34314591. **IF: 13.827/D1**

- **An Integrated View of Virus-Triggered Cellular Plasticity Using Boolean Networks.** *Alfaro-García J, Granados-Alzate MC, Vicente-Manzanares M, Gallego-Gómez JC.* **Cells 2021, 10(11), 2863 https://doi.org/10.3390/cells10112863** PMID: 34831086. **IF: 6.60/Q1**

OTHER PUBLICATIONS & BOOK CHAPTERS

- **The Crossroads between RAS and RHO Signaling Pathways in Cellular Transformation, Motility and Contraction.** *Soriano O, Alcón-Pérez M, Vicente-Manzanares M, Castellano E.* **Genes (Basel). 2021 May 27;12(6):819. doi: 10.3390/genes12060819.** PMID: 34071831. **IF:4.069 / Q2**

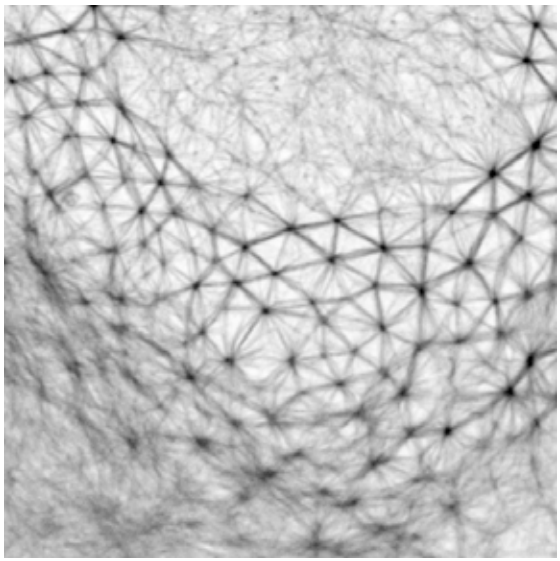
- **The Importance of Being PI3K in the RAS Signaling Network.** *Cuesta C, Arévalo-Alameda C, Castellano E.* **Genes (Basel). 2021 Jul 19;12(7):1094. doi: 10.3390/genes12071094.** PMID: 34356110. **IF:4.069 / Q2**

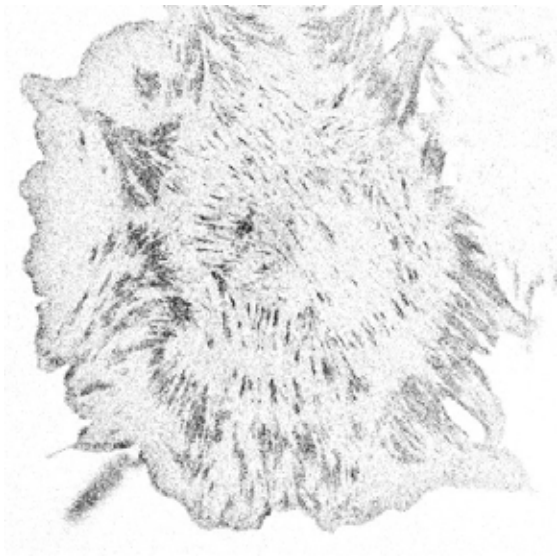
GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Control biofísico de la metástasis en melanoma mediante dispositivos bio-sintéticos (IDEAS VICE18018)	Miguel Vicente-Manzanares	Spanish Association against Cancer Semilla Program	2018-2020	20,000.00 €
Control de la heterogeneidad y evasión inmune tumoral por la mecánica tisular y la generación de fuerzas intracelulares (SAF2017-84708-R)	Miguel Vicente-Manzanares	Spanish Ministry of Economy and Competitiveness	2018-2021	170,000.00 €
Early Cancer Research Initiative Network on MBL (ECRIN-M3) PIs: Miguel Vicente-Manzanares, Julia Almeida, 8+	Coordinator: Alberto Orfao	FCAECC-CRUK-AIRC Accelerator Award Program	2020-2024	1,565,658.88 €
Determinantes mecánicos y químicos de generación de fuerza intracelular en la migración leucocitaria, división celular y canceres linfáticos (PID2020-116232-I00)	Miguel Vicente-Manzanares	Ministry of Science and Innovation	2021-2024	240,000.00 €

OTHER ACTIVITIES & RELEVANT FACTS

- March 2021 – The PI has become the Editor in Chief of European Journal of Cell Biology (Elsevier)





STED nanoscopy is allowing our group to reveal actomyosin dynamics with unprecedented temporal and spatial resolution. Images are stills from FLIM-STED movies imaging Myh9, a crucial component of the actomyosin machinery in human osteosarcoma cells.

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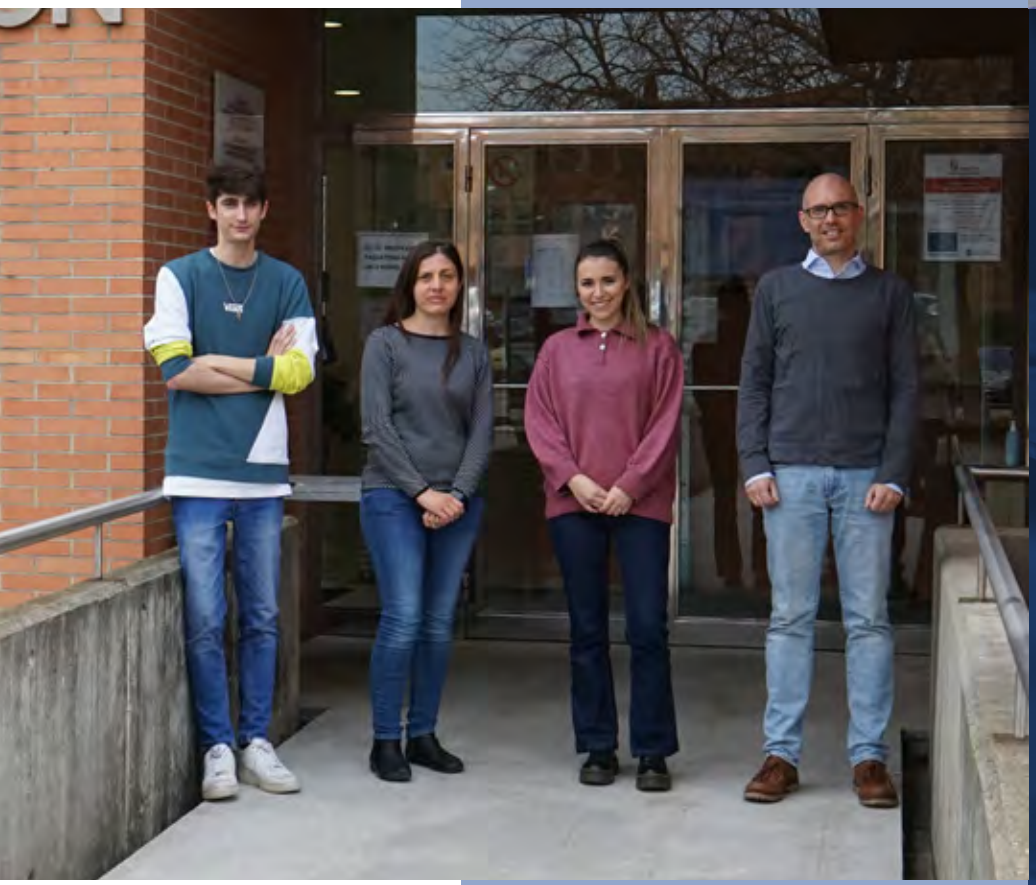

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STUDENT
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LABORATORY 7A

RAS SIGNALING AND LUNG CANCER

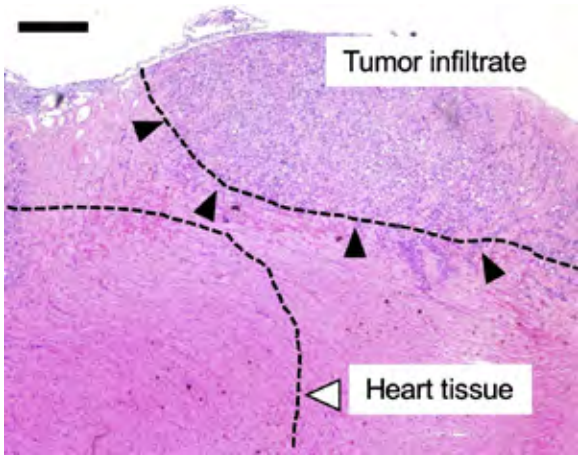
(from September 2021)

RESEARCH SUMMARY

Lung cancer is the leading cause of cancer-related deaths both in Spain and worldwide, and the low 5-year-survival rate of less than 20% has barely improved over the last decades. Research in our laboratory focuses on the identification of mechanisms leading to the formation of lung cancer to take advantage of this knowledge to develop novel therapeutic strategies with special emphasis on tumors driven by mutations in *KRAS*.

Although it was known for a long time that approximately one quarter of these tumors are driven by mutations in *KRAS*, researchers have failed to develop a selective therapy against KRAS for decades. Yet, 2021 witnessed approval of the first KRAS-selective inhibitor to treat these tumors. However, this inhibitor only targets one of the multiple *KRAS* mutations which is present in around 40% of all *KRAS*-mutant lung cancers, although these tumors almost invariably become resistant to the inhibitor at one point. Therefore, the urgent need for the development of alternative strategies for *KRAS*-mutant lung cancers remains unchanged.

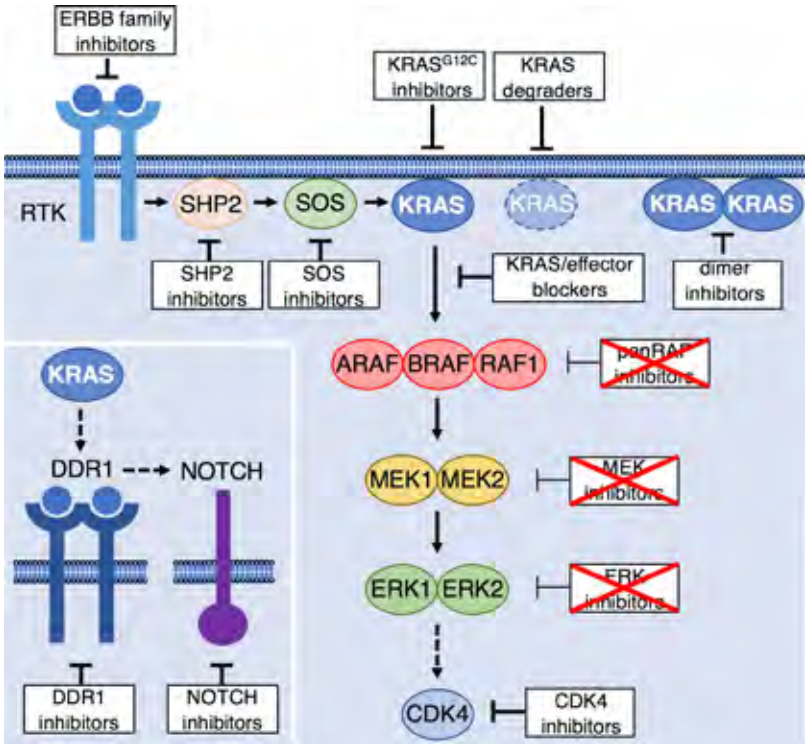
Previous work from our group and other laboratories has clearly emphasized the role of the RAF/MEK/ERK (MAPK) effector pathway in *KRAS*-mutant lung tumor formation and maintenance. Unfortunately, tempering with this KRAS effector pathway produces significant toxicities, possibly due to the requirement for MAPK signaling in normal homeostasis. Yet, to overcome this limitation, identification of novel targets that are downstream of the canonical MAPK pathway may be equally effective in tumor control and could cause significantly less toxicity. Previously, we have shown that the repressor CIC plays an important role downstream of the KRAS/MAPK signaling pathway in vivo in tumor formation as well as drug resistance.



Heart metastasis from a KRAS4AG12V-driven lung tumor (from Salmón et al., PNAS 2021).

Our laboratory will thus aim at the identification and validation of novel molecular targets for the treatment of lung cancer driven by *KRAS* oncogenes with special emphasis on those targets that may help to overcome resistance to targeted therapies directed against KRAS or its downstream effectors such as CIC. To identify and validate these targets, we will employ a wide variety of techniques including genetic screens and sophisticated mouse models. We will especially focus on these research goals:

1. Identification and validation of novel targets for KRAS-driven lung cancer with special emphasis on genetic programs activated by mutant KRAS in lung tumor cells.
2. Understanding how KRAS shapes the tumor microenvironment to pinpoint novel therapeutic strategies.
3. Characterization of resistance mechanisms to selective inhibition of KRAS or its MAPK effector pathway with the goal of developing additional therapeutic options for patients experiencing resistance.
4. Exploring and validating the role of the repressor CIC as a major effector of KRAS-driven lung cancer growth. In addition, CIC has also been implicated in resistance to KRAS inhibition, thus making it even more relevant to understand the link between KRAS and CIC in lung cancer.
5. Characterization of the general tumor suppressor role of CIC in lung adenocarcinomas as well as other tumor types.



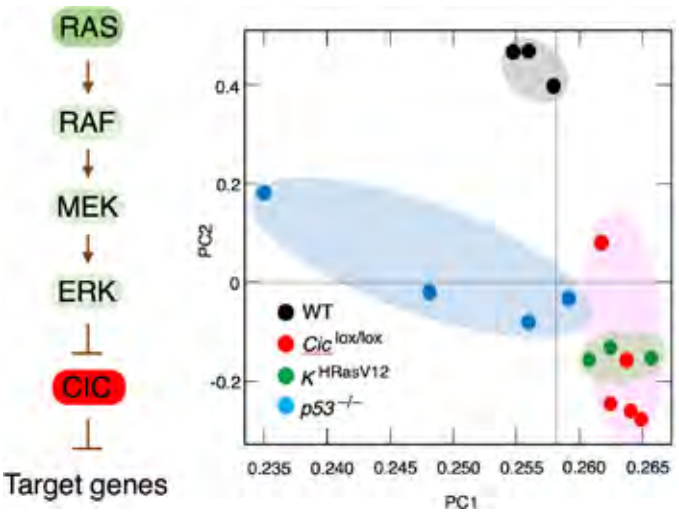
Strategies to target KRAS in cancer (from Drosten and Barbacid, Mol Oncol 2021)

PUBLICATIONS

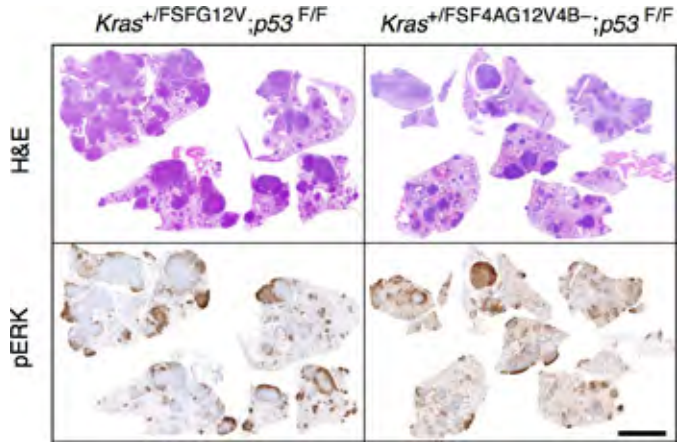
- Targeting KRAS mutant lung cancer: light at the end of the tunnel. *Drosten M, Barbacid M.* **Mol Oncol 2021 Dec 23 doi: 10.1002/1878-0261.13168.** PMID: 34951114. **IF 6.603 / Q1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Implication of the repressor CIC in KRAS-driven lung tumor formation and resistance to targeted therapies (PID2020-116705RB-I00)	Matthias Drosten	Ministry of Science and Innovation	2021-2024	217,800.00 €
Linking KRAS oncogene signaling and the tumor microenvironment: mechanistic implications and therapeutic opportunities (LABAE211678DROS)	Matthias Drosten	Spanish Association against Cancer (AECC)	2021-2024	300,000.00 €



The repressor CIC as a gatekeeper of RAS signaling in development and cancer. Left: Regulation of CIC repressor activity by RAS/MAPK signaling. Right: Similarity of transcriptional profiles of T-ALL driven by RAS activation or CIC inactivation (from Simón-Carrasco et al, Genes Dev 2017)



Lung tumor formation by KRAS^{G12V}and KRAS4A^{G12V} (from Salmón et al., PNAS 2021)

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LABORATORY 8

REGULATION OF REPLISOME COMPONENTS AT REPLICATION FORKS

RESEARCH SUMMARY

The genome must be completely and faithfully replicated during S-phase before it is segregated into the progeny to ensure genomic stability. Cells are constantly exposed to the threat of endogenous and exogenous DNA damage, a major source of genomic instability and, in multicellular organisms, a driving force for cancer. Cells are particularly sensitive to damage during DNA replication because the stringent nature of replicative DNA polymerases cannot accommodate damaged bases and, consequently, DNA synthesis is blocked with potential deleterious effects. To cope with base damage during DNA replication all three domains of life have evolved damage tolerance mechanisms that allow them to circumvent DNA lesions allegedly to ensure coordinated and timely progression of replication forks. Tolerance to DNA damage is based on translesion DNA synthesis (TLS), a bypass mechanism that allows cells to overcome the potentially lethal effects of confronting DNA base lesions that impede progression of replicative DNA polymerases. DNA Damage Tolerance, or DDT, has been misleadingly known as a post-replicative repair mechanism. However, DDT is not a repair tool as DNA lesions are only circumvented as a consequence of using DNA templates containing damaged bases.

The identification of specialized, evolutionary conserved but alternative DNA polymerases with the ability to use damaged templates and effectively bypass lesions, was a landmark discovery indicating the existence of a mechanism to tolerate DNA damage. These enzymes, termed TLS DNA polymerases, are potentially mutagenic as they accommodate templates with bulky lesions, lack proofreading activity, are low-fidelity and, therefore, error-prone. An alternative mechanism of DDT exists, which is based on template switching (TS), an error-free mechanism that involves sister-strand pairing. TS was first described in prokaryotes as an error-free post-replicative repair mechanism involved in filling-in gaps left behind replication forks. TS plays a not yet fully understood role in replication all throughout the evolutive scale.

The proliferating cell nuclear antigen (PCNA) has a central role in DNA replication. Moreover, it also constitutes a central DNA scaffold for the recruitment of a plethora of components involved in both tolerance and response to DNA damage mechanisms. In eukaryotes, DDT mechanisms are mediated by ubiquitylation of this essential replication factor PCNA, a key processivity factor for polymerases during DNA synthesis. Monoubiquitylation of Lys164 of PCNA (ubPCNA^{K164}) promotes TLS-mediated error-prone translesion synthesis. Further Lys^{63}-linked polyubiquitylation of mono-ubPCNA^{K164} triggers the error-free mechanism based on TS. The prevailing view is that PCNA^{K164} is ubiquitylated in a DNA damage-dependent manner. Therefore, it is believed that not such modification (ubPCNA^{K164}) occurs in cells during unchallenged S-phase in most organisms except in fission yeast and Xenopus.

Although the evolutionary conserved mechanism of PCNA ubiquitylation is well understood, the deubiquitylation of ubPCNA remains uncharacterized. Our group is interested in understanding the role and, therefore, the biological significance of ubPCNA deubiquitylation in yeast models. Our working hypothesis is that Ubiquitin-specific proteases, or PCNA-DUBs, revert PCNA ubiquitylation to prevent excessive translesion synthesis (TLS) on replicating chromatin. This hypothesis predicts that both branches of the DNA damage tolerance pathway, TLS-DNA polymerases sampling on replicating DNA and template switching during S-phase, would be limited at forks by PCNA deubiquitylation.

Research Aims

Given the tremendous impact that PCNA-DUBs ubiquitin-proteases may have in genomic stability, the major aim of our research group is to understand in depth the replication fork-coupled mechanism down-regulating DDT events through PCNA deubiquitylation.

Despite recent progress in the DNA damage tolerance field, a number of important questions remain open. We want to address what we consider the most appealing questions in the field to gain a clear understanding of what is in full the role of PCNA-DUBs at sites of nascent DNA. Particularly, we want to address the following questions:

1. Is the control of DDT at replication forks asymmetric and, consequently, divergent in leading and lagging strands?
2. Is leading strand DNA synthesis at forks permissive for the error-prone branch of DDT?
3. What is the molecular nature of the template switching events at forks prevented by PCNA-DUBs?

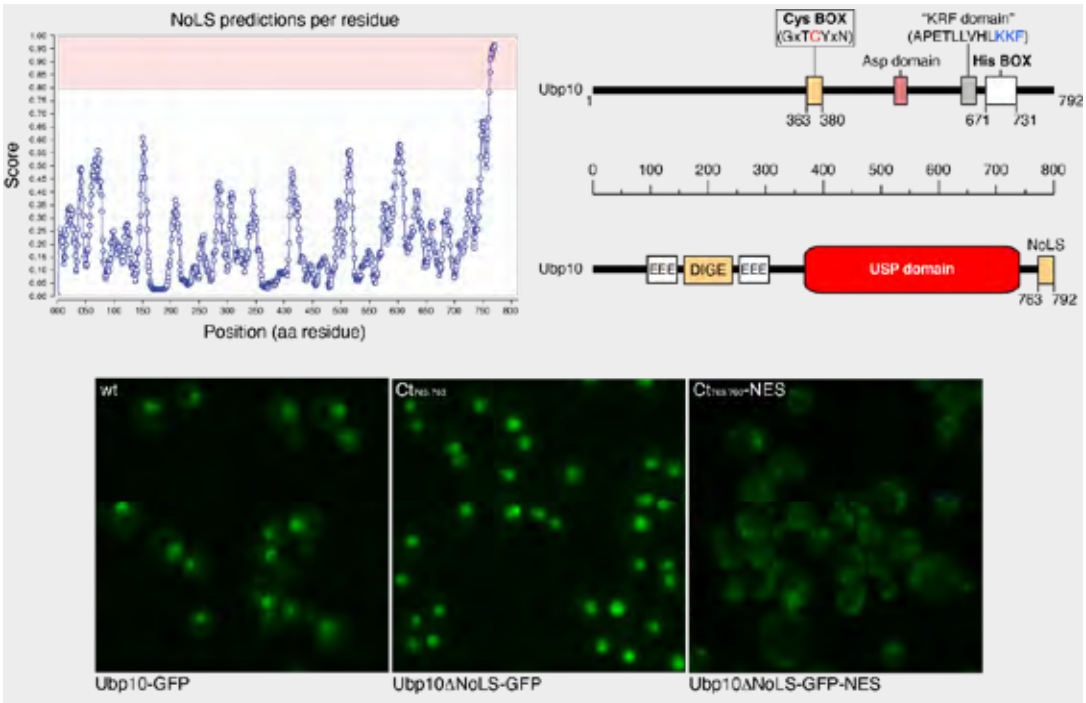
Goals Achieved

1. Smooth and timely progression through S-phase in eukaryotic cells requires $PCNA^{K164}$ deubiquitylation.
2. Ubp10 and Ubp12 budding yeast ubiquitin proteases remove ubiquitin from $PCNA^{K164}$ with discrete chain preferences.
3. Replication fork association of Ubp10, but not Ubp12, depends on PCNA binding to lagging strands.
4. PCNA-DUBs Ubp10 and Ubp12 counteract template-switching events and Rev1, a key translesion synthesis adaptor, binding to replication forks.

Future Goals

I. Analysis of additional ubiquitin-proteases involved in PCNA deubiquitylation.

II. Testing asymmetry in DNA Damage Tolerance regulation at replication forks.



One of the research targets in the lab is the S.cerevisae UBP10 gene that encodes a nuclear (mainly nucleolar) protein with a role as a PCNA deubiquitylase (or PCNA-DUB)

III. Analysis of non-canonical small Y-shaped replication intermediates accumulating at stalled forks in ubp10 and ubp10 ubp12 mutants.

Specific Objetives

a. Testing interactions in vivo of PCNA-DUBs with replisome components.

The goal is to identify the interactome of PCNA-DUBs at active replication forks using the isolation of proteins on nascent DNA (iPOND)-method coupled with mass spectrometry. We will validate that PCNA-DUBs are Replisome components during normal and perturbed S-phase. Identifying proteins that interact with PCNA-DUBs and their posttranslational modifications is an additional key element to understanding how the genome is replicated every cell division cycle. One effective experimental approach to analyse systematically the components, as well as their modifications, of the replisome progression complex is the iPOND method. The purification and identification by mass spectrometry of proteins on newly synthesized DNA using iPOND will allow us to extend the study of the potential temporal association of PCNA-DUBs with replication forks and also to confirm that they are functional components of the replisome as we hypothesized.

b. eSPAN asymmetry test for PCNA-DUBs and TLS-polymerases.

eSPAN is a strand-specific analysis based on the enrichment and Sequencing of Protein-Associated to Nascent DNA. eSPAN measures the relative amounts of proteins at nascent leading and lagging strands of DNA replication forks in a step-wise procedure involving chromatin immunoprecipitation of a protein of interest (bait) followed by the enrichment of protein-associated nascent DNA through BrdU immunoprecipitation. The key part is that the isolated ssDNA is then subjected to strand-specific sequencing allowing detection of proteins enriched at leading or lagging strand of nascent DNA. We plan to test asymmetry of *PCNA-DUBs and TLS DNA-polymerases* at forks by a strand-specific analysis based on eSPAN.

PUBLICATIONS

- **PCNA Deubiquitylases Control DNA Damage Bypass at Replication Forks.** *Álvarez V, Frattini C, Sacristán MP, Gallego-Sánchez A, Bermejo R, Bueno A.* **Cell Rep. 2019 Oct 29;29(5):1323-1335. e5. doi: 10.1016/j.celrep.2019.09.054.** PMID: 31665643. **IF:9.423 / D1**
- **Working on Genomic Stability: From the S-Phase to Mitosis.** *Ovejero S, Bueno A, Sacristán MP.* **Genes (Basel). 2020 Feb 20;11(2):225. doi: 10.3390/genes11020225.** PMID: 32093406. **IF:4.096 / Q2.**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Mechanisms of Genome Protection During Replication (SA103P20)	Andrés Avelino Bueno	Regional Government of Castilla y León	2020-2023	264,000.00€
A Comprehensive Molecular Analysis of PCNA Deubiquitylation at Replication Forks (PID2019-109616GB-100)	Andrés Avelino Bueno	Ministry of Science and Innovation	2020-2024	181,500.00€

OTHER ACTIVITIES & RELEVANT FACTS

- Andrés Avelino Bueno is the current director of the *Consolidated Research Unit nº252* (Junta de Castilla y León), award renewed in 2020.

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LABORATORY 9

CHROMOSOME SEGREGATION AND HUMAN DISEASE

RESEARCH SUMMARY

The gametogenesis is among the most complex and highly regulated differentiation programmes that make use of a unique reductional division or meiosis to give rise to highly specialized cells: the gametes. The oocytes and spermatozoa thus generated are the most genetically (meiotic haploid products), epigenetically (epigenetic erasure and histone replacement), and morphologically (oocytes and sperm) distinctive cells of an adult organism and are essential for the continuity of life. At present, we are far from understanding the genetic basis of mammalian gametogenesis and the molecular mechanisms underlying its pathological condition, infertility. Our main objective is to expand our current knowledge of the "fertility loci kit" (coding and non-coding) and the mechanism by which these molecules are essential to carry out gametogenesis/reproduction. We are also interested to understand the causative role of the miss-expression of these proteins in several human tumors and the involvement of the meiotic DNA repair machinery in the genome diploidization process that occur after transformation of tumor cells. To do that we make use of a combination of forward and reverse genetic approaches using the mouse as a model via genome edition.

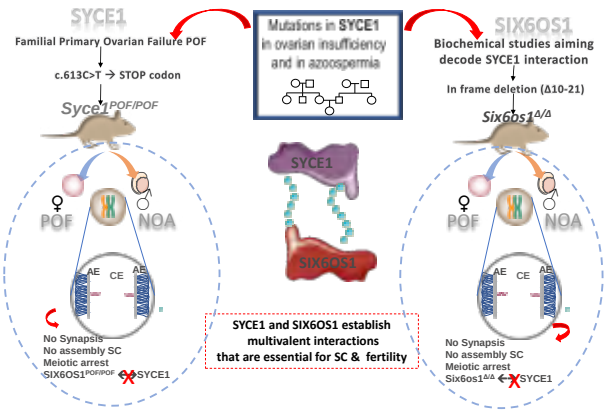
During the last years, the research group have identified and characterized RAD21L, a new α-kleisin of the cohesin complex located in the axial elements (AE) of the synaptonemal complex (SC) that is essential for synapsis and DNA repair in spermatocytes but not in mouse oocytes. This study challenges REC8 being the only meiotic α-kleisin in mammals, and suggests that the existence of two meiotic α-kleisins explains why yeast, but not Rec8-/- mice, do not assemble their AEs. We have validated this hypothesis by showing that double Rec8-/- and Rad21L-/- mice do not assemble their AEs. Given the relevance of cohesins in mouse meiosis, we addressed their role in human fertility. By exome sequencing of a family with Premature Ovarian Failure (POF), we identified a deletion disrupting the STAG3 gene. By mouse modeling, we stablished a causal relationship between cohesins and human infertility. Although, males in the family with mutations in STAG3 were heterozygous (fertile), we predicted that human males with STAG3-deficiency would show meiotic arrest with Non-Obstructive Azoospermia (NOA), and proposed that NOA and POF are the same disease. Owing to the existence of natural genetic variants affecting meiotic recombination, we have characterized an anonymous locus from GWAS studies of human fertility (rs1254319). We showed this locus encodes a novel protein of the synaptonemal

complex (SIX6OS1) that interacts with the central element protein 1 (SYCE1). Mice lacking SIX6OS1 are defective in synapsis and infertile. Accordingly, SIX6OS1 is essential for the processing of intermediate recombination nodules. Moreover, we have shown that these multivalent interactions between SYCE1 and SIX6OS1 are essential for synapsis and, interestingly, are disrupted in several human infertilities.

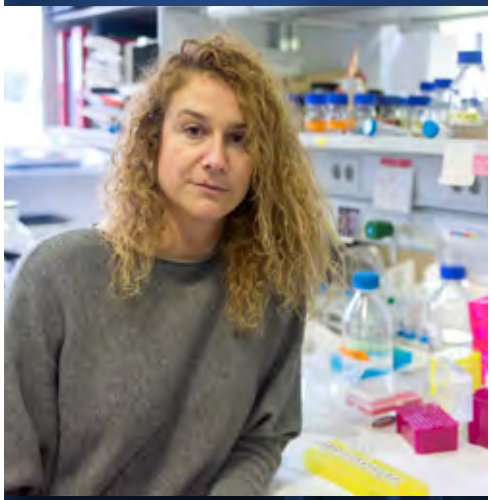
We have also studied the ubiquitin proteasome system (UPS) and its controversial implication in mammalian fertility through the USP26 protease as well as dissected this pathway of protein degradation by the testicular-specific proteasome (spermatoproteasome, PSMA8). PSMA8 is localized and depends on the central region of the (SC). Consequently, PSMA8-/- mice exhibit alterations in the proteostasis of key meiotic players that leads to apoptotic spermatocytes. We have also contributed to studying the role of the protease Separase in DNA repair through the proteolysis of cohesin RAD21 and its role in the protection of mammalian cells against oncogenic transformation both *in vitro* and in vivo.

More recently and already during the period 2020-2021, we have identified a human family with mutations in a gene encoding a new meiotic recombination protein called HSF2BP. The new meiotic protein localized to the recombination nodules at the chromosome axes and plays its function through an anonymous interactor called C19ORF57/BMRE1 which is complexed to BRCA2/PALB1/RPA. Humanized mice show defects in meiotic recombination with a significan decrease in the number of crossing-overs whereas null mutants are meiotic arrested and infertile.

During this period, finally, we have identified (collaboration) a new inhibitory mechanism for Separase through the complex formed by Shugoshina-2-Mad2 acting like a pseudo-substrate.



A missense in HSF2BP causing primary ovarian insufficiency affects meiotic recombination by its novel interactor C19ORF57/BRME1



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PUBLICATIONS

- **Securin-independent regulation of separase by checkpoint-induced shugoshin-MAD2.** *Hellmuth S, Gómez-H L, Pendás AM, Stemmann O.* **Nature. 2020 Apr;580(7804):536-541. doi: 10.1038/s41586-020-2182-3.** PMID: 32322060. **IF:49.962 / D1**

- **HDAC11 is a novel regulator of fatty acid oxidative metabolism in skeletal muscle.** *Hurtado E, Núñez-Álvarez Y, Muñoz M, Gutiérrez-Caballero C, Casas J, Pendás AM, Peinado MA, Suelves M.* **FEBS J. 2021 Feb;288(3):902-919. doi: 10.1111/febs.15456**. PMID: 32563202. **IF:5.542 / Q1**

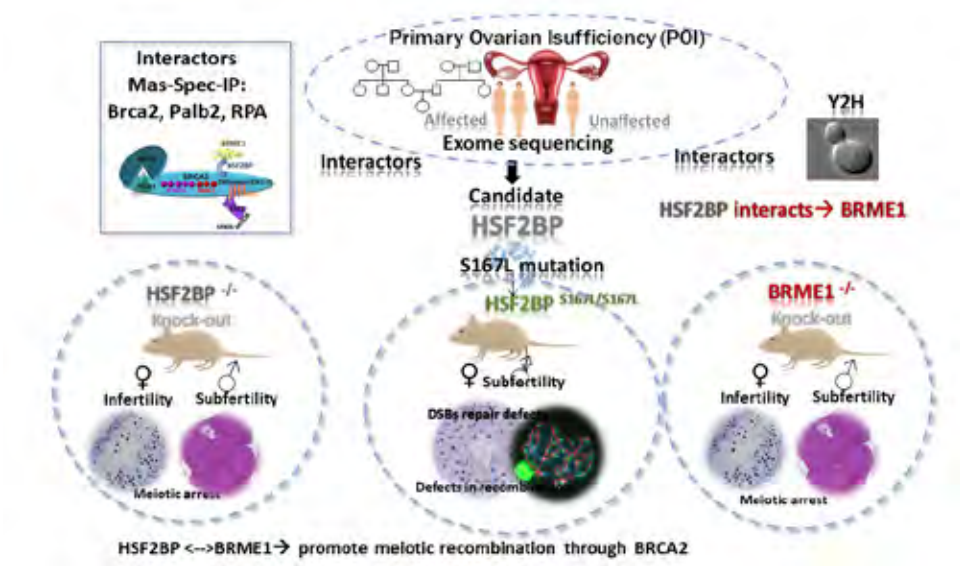
- **Loss of HDAC11 accelerates skeletal muscle regeneration in mice.** *Núñez-Álvarez Y, Hurtado E, Muñoz M, García-Tuñon I, Rech GE, Pluvinet R, Sumoy L, Pendás AM, Peinado MA, Suelves M.* **FEBS J. 2021 Feb;288(4):1201-1223. doi: 10.1111/febs.15468**. PMID: 32602219 **IF:5.542 / Q1**

- **Meiotic chromosome synapsis depends on multivalent SYCE1-SIX6OS1 interactions that are disrupted in cases of human infertility.** *Sánchez-Sáez F, Gómez-H L, Dunne OM, Gallego-Páramo C, Felipe-Medina N, Sánchez-Martín M, Llano E, Pendas AM*, Davies OR*.* **Sci Adv. 2020 Sep 2;6(36):eabb1660. doi:10.1126/sciadv.abb1660.** PMID: 32917591. **IF:14.143 / D1**

- **BRCA2 binding through a cryptic repeated motif to HSF2BP oligomers does not impact meiotic recombination.** *Ghouil R, Miron S, Koornneef L, Veerman J, Paul MW, Le Du MH, Sleddens-Linkels E, van Rossum-Fikkert SE, van Loon Y, Felipe-Medina N, Pendas AM, Maas A, Essers J, Legrand P, Baarends WM, Kanaar R, Zinn-Justin S, Zelensky AN.* **Nat Commun. 2021 Jul 29;12(1):4605. doi: 10.1038/s41467-021-24871-6.** PMID: 34326328. **IF:14.919 / D1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Mecanismos moleculares de la segregacion cromosomica y la gametogenesis	Alberto Martín Pendás	Ministry of Science and Innovation	2021-2023	340,000.00 €
Análisis in vivo de los mecanismos de inhibición de serparasa y su implicación en la segregación cromosómica.	Alberto Martín Pendás	Regional Government of Castilla y León	2021-2023	172,000.00 €



HSF2BP is mutated in POI and signals through its new interactor BRME1

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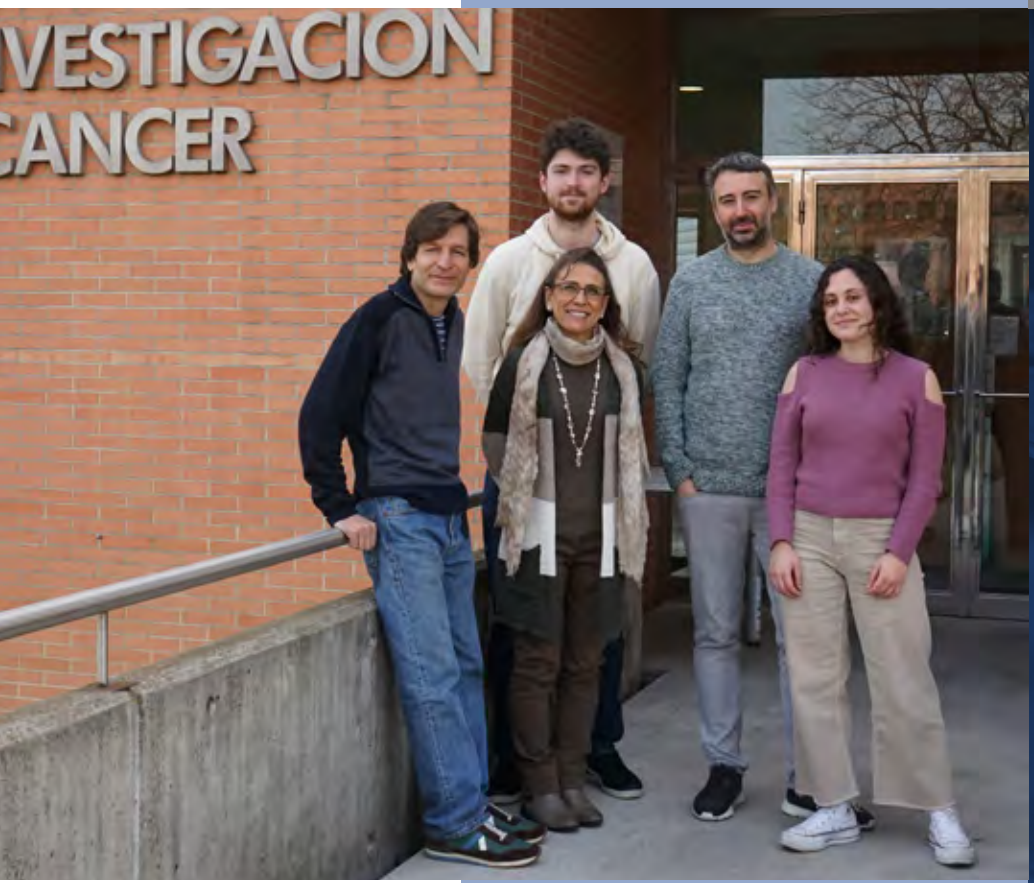

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STUDENT
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LABORATORY 10

NOVEL RAS REGULATORS IN CANCER & HOMEOSTASIS

(from September 2021)

RESEARCH SUMMARY

We use mouse models and patient derived cell lines to characterize new signalling pathways and oncogenic functions that govern the onset and progression of lung adenocarcinoma (LUAD) as well as the development of therapy resistance in the clinic. We have a particular interest in deciphering novel molecular mechanisms that regulate the initiation, intensity and duration of the RAS-ERK signalling output. Quantitative differences affecting the activity of this pathway are an essential feature controlling cancer growth and response to treatment to targeted agents. Our work has identified a key role of KRAS membrane-clustering in this process. Our immediate goal is to understand the molecular basis underlying this feature and to functionally characterize yet unknown protein factors required to assemble a KRAS-dependent signalling platform on the inner plasma membrane. As a whole, this approach may identify novel therapeutic targets with low toxicity and potential clinical applicability in LUAD.

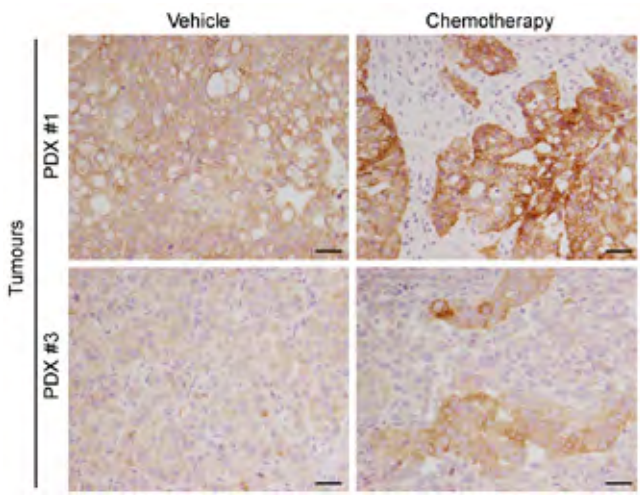
Indeed, in collaboration with Dr. Chiara Ambrogio (MRC, Torino, Italy) we provided the first biological evidence suggesting that KRAS monomers on the cell membrane are functionally inert and that dimerization is an essential requirement for the activation of downstream signalling and the establishment of an oncogenic output. Mounting evidences indicate that KRAS dynamics at the inner cell membrane are an important regulatory node controlling its activity both in health and disease. These observations potentially identify KRAS dimerization as a novel therapeutic target for the treatment of KRAS driven cancers.

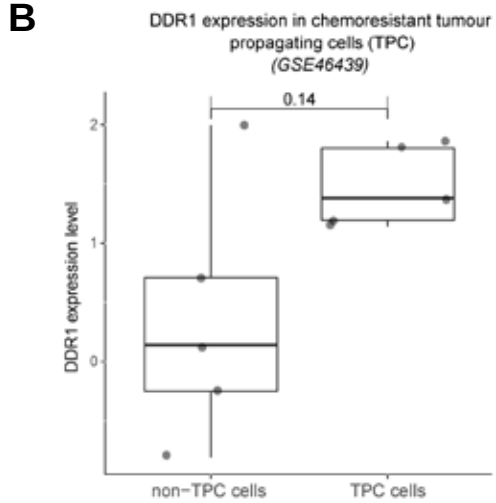
We are currently optimizing the conditions to identify and characterize structural co-factors that are required for the formation and/or stabilization of KRAS-dimers and the signalling clusters that depend on them. We are implementing FLIM/FRET and single-molecule localization microscopy approaches (SPT) to follow the stability and membrane trajectories of KRAS-containing complexes. Also, we are using protein-specific localized crosslinking (based on amber suppression) to identify new membrane interactors of KRAS using cross-linking/mass spectrometry. Finally, in collaboration with Stéphanie Cabantous (CRCT, Toulouse), we are using a flexible fluorescent cellular system compatible with high-throughput approaches that will be key to monitor and quantify KRAS dimerization in cells. This will be key not only to validate by gain & loss of function experiments the candidates identified in our crosslinking approach but also for the identification of compounds preventing KRAS dimerization.

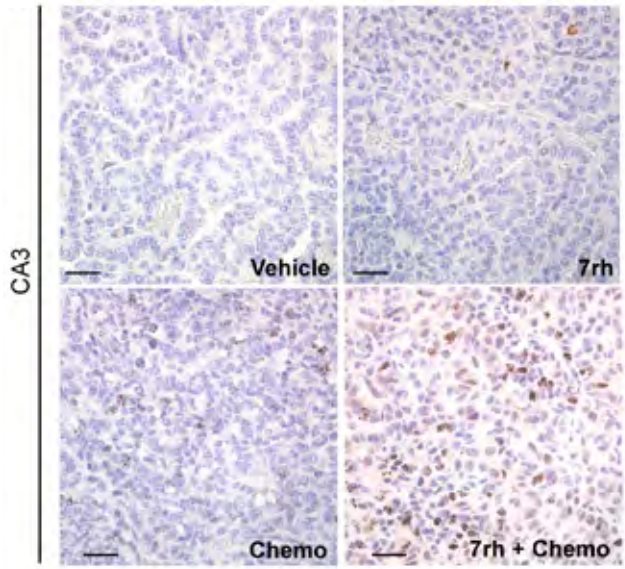
We also have an interest in understanding how fluctuations affecting the RAS-ERK (MAPK pathway) signalling influence cancer transformation and progression. We have developed a genetic cellular system that provides the right selective pressure and used it to perform an unbiased identification of novel regulators of the MAPK transcriptional output by Crispr/Cas9. Likewise, we are interrogating publicly available LUAD datasets to identify recurrent transcriptional changes that correlate with MAPK quantitative output and that may help identify novel regulators of the pathway. We hope this combined approach will contribute to elucidating new control mechanisms with cancer relevance. In this respect, we are combining established cell lines as well as patient derived xenografts from paired biopsies pre- & post-treatment to study the central role of MAPK output in the onset of adaptive resistance to therapy. We are concentrating on targeted therapies currently applied in the clinic based on combinations of drugs targeting RAF & MEK (BRAF mutant LUAD) as well as more recent KRAS specific inhibitors. We are using these models to investigate potential vulnerabilities acquired during the onset of drug resistance.

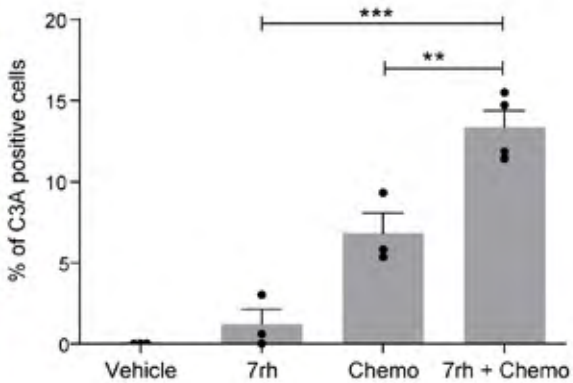
GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Caracterización de la función y potencial terapéutico de los complejos de KRAS en membrana (PID2020-116824RB-I00)	David Santamaría	Ministry of Science and Innovation / State Research Agency	2021-2024	278,300.00 €









A) Crl:NU-Foxn1nu mice implanted with KRAS-mutant PDX were treated with either vehicle or standard chemotherapy based on cisplatin (3 mg/kg) and paclitaxel (20 mg/kg) administered i.p. every 5 days for 3 weeks (n=6). After necropsy, tumour samples were fixed and analyzed for DDR1 expression by immunostaining. Clones showing high DDR1 expression are observed in the chemotherapy-treated tumours. Scale bar: 50 µm. B) Differential DDR1 expression in chemoresistant tumour propagating cells (TPCs) vs. the tumour bulk population (non-TPC). Gene expression data was obtained from GSE46439. Wilcoxon's test P value is indicated above the box plots. C) Left: representative immunostaining of the apoptotic marker active caspase-3 (C3A) in sections obtained from mice harbouring $KRas^{G12V}$ endogenous lung tumours (n=6 mice per group) following the indicated treatments (note 7rh is a DDR1 kinase inhibitor). Scale bar: 50 µm. Right: quantification of C3A+ cells. Data were analyzed using 1-way ANOVA followed by Bonferroni's multiple comparison test and shown as the mean ± SEM. $^{**}P < 0.01$, $^{***}P < 0.001$.

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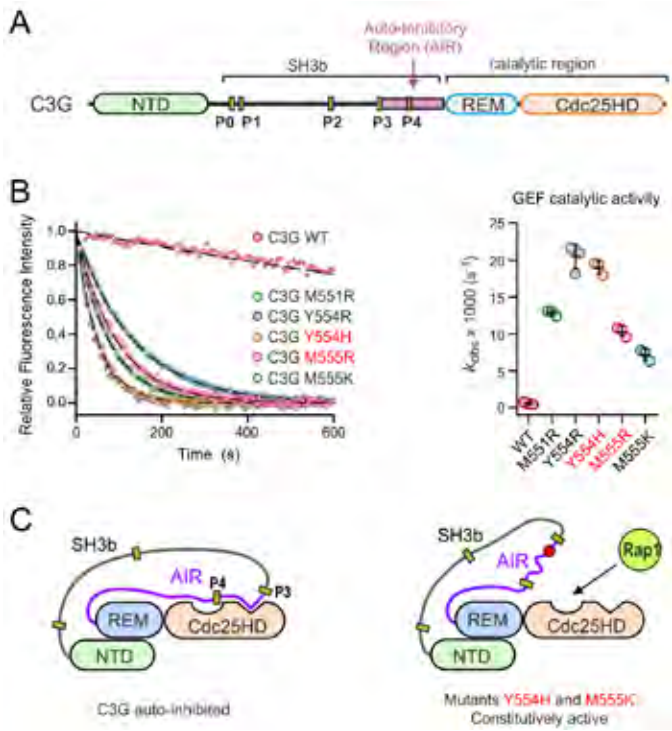
LABORATORY 17

STRUCTURAL BIOLOGY OF CELL ADHESION AND SIGNALING

RESEARCH SUMMARY

Integrins are a family of receptors found on the cell surface, which mediate adhesion to the extracellular matrix and other cells. Alterations in cell adhesion are linked to a variety of human diseases including coagulation disorders, skin blistering diseases, and cancers of various types. Our research aims to understand the structural and mechanistic basis of the assembly and regulation of integrin adhesion complexes, as well as of signaling pathways that regulate integrin function. In our work we apply multidisciplinary approaches that include complementary structural biology methods and quantitative biophysical and biochemical techniques.

During this period we have studied the mechanisms that regulate the human protein C3G (also known as RapGEF1). C3G is a guanine nucleotide exchange factor (GEF) that stimulates integrin-mediated cell adhesion through the activation of the small GTPase Rap1. C3G has a modular structure. The carboxy-terminal catalytic region of C3G consists of a Ras exchange motif (REM) domain and a Cdc25 homology domain (Cdc25HD); the latter is directly responsible of the activation of Rap1. C3G also has two non-catalytic regions: the amino-terminal domain (NTD) and the central SH3-binding (SH3b) domain. The SH3b domain contains four proline-rich motifs (PRMs) that are binding sites for some proteins with SH3 domains, such as Crk adaptor proteins. The GEF activity of C3G is tightly regulated; in resting conditions C3G has low GEF activity. We have characterized the mechanisms of autoinhibition of



Autoinhibition of C3G and deregulation by disease-linked point mutations. (A) Schematic representation of the domain structure of C3G. The central SH3b region contains five Pro-rich motifs (P0 to P4). (B) Measurement of the GEF activity of C3G over Rap1. (left) Nucleotide dissociation kinetics catalyzed by C3G wild type (WT) and the indicated point mutants. (right) Dissociation rate constants (k_{obs}) calculated from the analysis of the kinetics. The higher values observed for C3G mutants reveal that they are in constitutively active states. (C) Model of autoregulation of C3G that illustrates the two intramolecular interactions NTD/REM and AIR/Cdc25HD identified in our work (left). We have showed that somatic missense mutations Y554H and M555K detected in non-Hodgkin's lymphomas disrupt the AIR/Cdc25HD autoinhibitory contact and cause constitutive activation of C3G (right).

C3G. We have shown that a segment of the SH3b domain binds directly to the catalytic Cdc25H domain and blocks the GEF activity; hence we named that regulatory segment as the autoinhibitory region or AIR. Within the AIR we have identified two segments. The initial part is sufficient and necessary for binding to the Cdc25HD, but it does not block the GEF activity. A second part of the AIR is necessary for inhibiting the GEF activity of the Cdc25HD, but this segment is not sufficient for stable binding. Therefore, the mechanisms of the Cdc25HD autoinhibition by the AIR operates as a lock-and-lid; the second part of the AIR acts as a lid that blocks the catalytic site and the first part of the AIR works as a latch that fixes the lid.

C3G is activated in response to stimuli that cause tyrosine phosphorylation of proteins. Upon stimulation C3G is recruited by Crk adaptor proteins to phospho-sites on the plasma membrane where C3G is phosphorylated by tyrosine kinases. We have shown that both binding of Crk and tyrosine phosphorylation of C3G independently cause partial activation of C3G and that combination of the two stimuli is required for strong activation of C3G. We have shown that binding of CrkL to the third PRM of C3G displaces the AIR/Cdc25HD autoinhibitory interaction and stimulates the GEF activity.

We have identified three residues in the AIR that are essential for maintaining the AIR/Cdc25HD interaction. Individual mutation of any of these residues in full length C3G caused constitutive activation of C3G *in vitro* and in cells. The activation of C3G by single point mutations has been a key finding because it suggested that single nucleotide variants in the gene coding for C3G could induce deregulation. In fact we identified two somatic missense mutations described in non-Hodgkin's lymphomas (Y554H and M555K) that cause constitutive activation of C3G. We have shown that these mutations induce abnormal activation of Rap1 and integrin LFA-1 in Ba/F3 cells. The deregulation of C3G by missense mutations that we have identified represents a novel mechanism for the acquisition of aberrant Rap1 signaling during the evolution of tumors; which might promote the progression and dissemination of tumors.

Our future goal is to better understand the impact of the deregulation of C3G caused by missense mutations in hematopoietic malignancies. We also aim at elucidating the mechanisms of physiological activation of C3G and the structural basis of C3G autoinhibition and activation.

PUBLICATIONS

- **A mutation in p62 protein (p. R321C), associated to Paget's disease of bone, causes a blockade of autophagy and an activation of NF-kB pathway.** *Usategui-Martín R, Gestoso-Uzal N, Calero-Paniagua I, De Pereda JM, Del Pino-Montes J, González-Sarmiento R.* **Bone. 2020 Apr;133:115265. doi: 10.1016/j.bone.2020.115265.** PMID: 32036052. **IF: 4.398 / Q2**

- **Analysis of gene variants in the GASH/Sal model of epilepsy.** *Díaz-Casado E, Gómez-Nieto R, de Pereda JM, Muñoz LJ, Jara-Acevedo M, López DE.* **PLoS One. 2020 Mar 13;15(3):e0229953. doi: 10.1371/journal.pone.0229953. eCollection 2020**. PMID: 32168507. **IF: 3.240 / Q2**

- **Mechanisms of autoregulation of C3G, activator of the GTPase Rap1, and its catalytic deregulation in lymphomas.** *Carabias A, Gómez-Hernández M, de Cima S, Rodríguez-Blázquez A, Morán-Vaquero A, González-Sáenz P, Guerrero C, de Pereda JM.* **Sci Signal. 2020 Sep 1;13(647):eabb7075. doi: 10.1126/scisignal.abb7075.** PMID: 32873726. **IF: 8.192 / Q1**

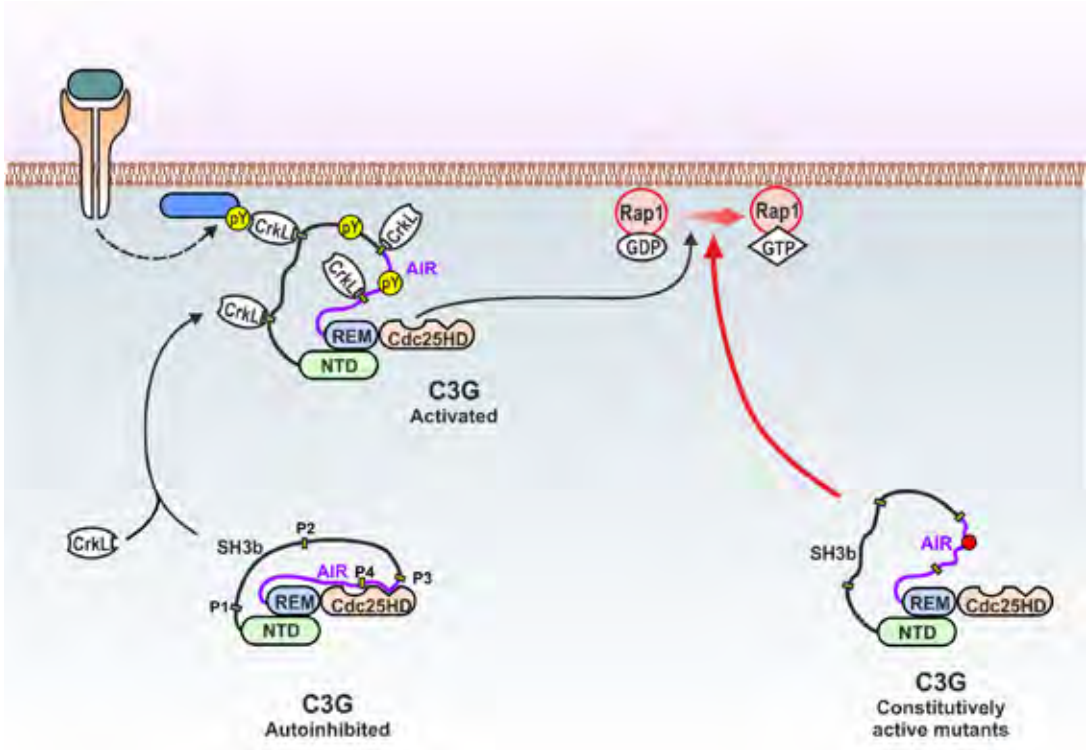
- **C3G self-regulatory mechanism revealed: implications for hematopoietic malignancies.** *Carabias A, Guerrero C, de Pereda JM.* **Mol Cell Oncol. 2020 Dec 1;8(1):1837581. doi: 10.1080/23723556.2020.1837581.** PMID: 33553598. **IF: NI**

- **EGFR-dependent tyrosine phosphorylation of integrin ?4 is not required for downstream signaling events in cancer cell lines.** *Te Molder L, Kreft M, Heemskerk N, Schuring J, de Pereda JM, Wilhelmsen K, Sonnenberg A.* **Sci Rep. 2021 Apr 21;11(1):8675. doi: 10.1038/s41598-021-88134-6.** PMID: 33883672. **IF: 4.380 / Q1**

- **Regulation of hemidesmosome dynamics and cell signaling by integrin α6β4.** *Te Molder L, de Pereda JM*, Sonnenberg A** **J Cell Sci. 2021 Sep 15;134(18):jcs259004. doi: 10.1242/jcs.259004.** PMID: 34523678. **IF: 5.285 / Q2**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Structural and mechanistic basis for the activation of Crk-C3G-Rap1 signaling and its regulation in diseases	Jose M de Pereda	Ministry of Science and Innovation	2020-2023	108,900.00 €
Papel de C3G en tumores hematopoyéticos y en angiogénesis mediada por plaquetas. Evaluación de su uso como diana terapéutica (SA078P20)	Carmen Guerrero Arroyo	Regional Government of Castilla y León	2020-2023	172,000.00 €
New connections - A novel cytoskeletal linkage that connects cell matrix adhesions to intermediate filaments	Benjamin Goult	The Royal Society, International Exchanges	2018-2020	12,000.00 £



Physiological activation of C3G and impact of catalytic deregulation. Prior to stimulation, C3G is in the cytoplasm in an autoinhibited conformation. C3G is activated in response to signals that result in tyrosine phosphorylation. C3G is recruited to the signaling sites by the adaptor protein CrkL that binds to the Pro-rich motifs of C3G and to phospho-Tyr sites. Next, the autoinhibition of C3G is released by combined action of tyrosine phosphorylation and binding of CrkL. Constitutively point mutants of C3G, such as those detected in non-Hodgkin's lymphomas, bypass the phosphorylation and CrkL dependent activation mechanisms and cause aberrant Rap1 signaling.

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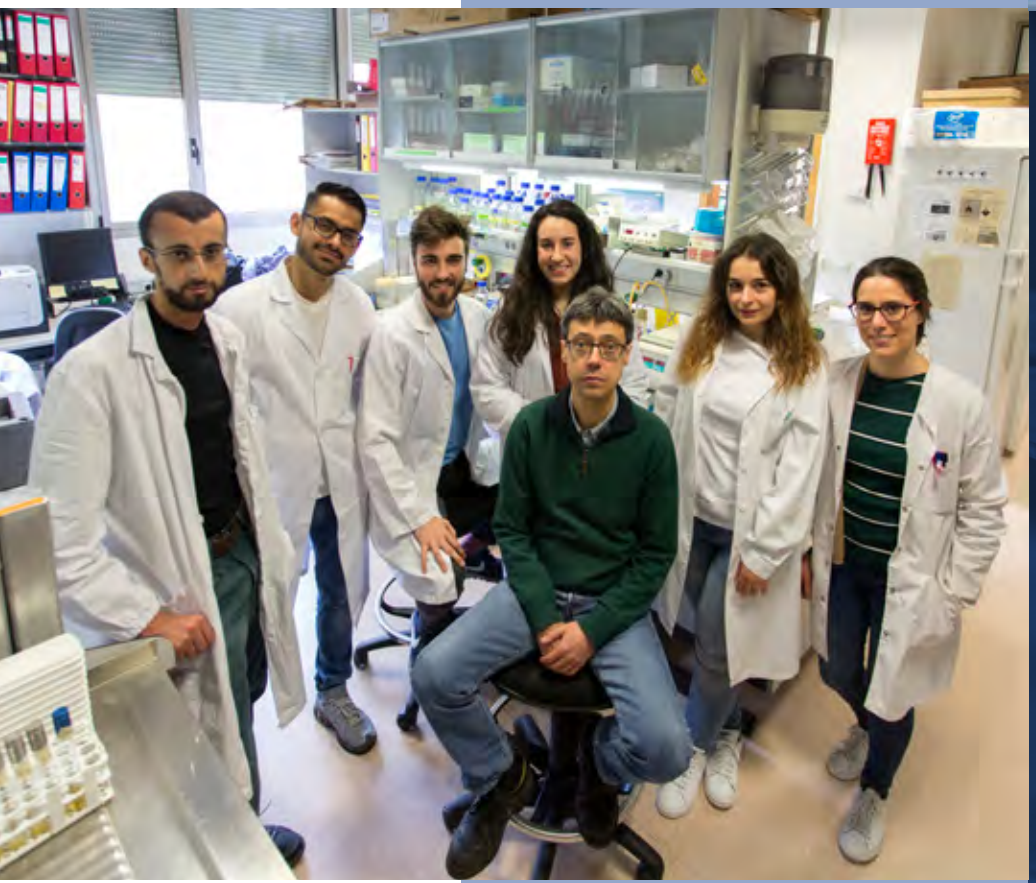

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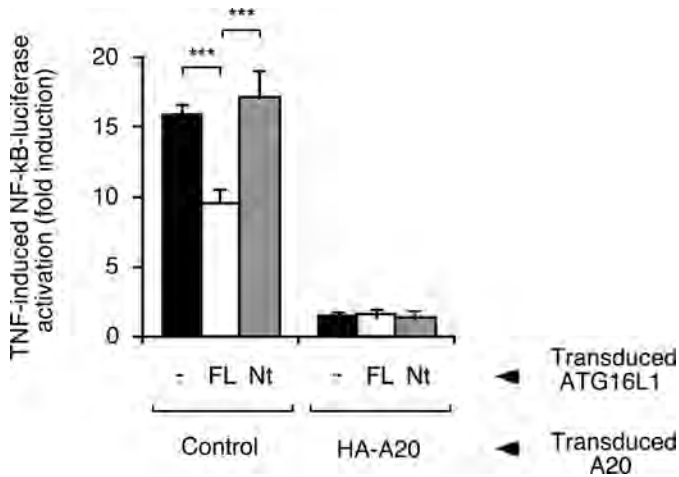
LABORATORY 18

UNCONVENTIONAL AUTOPHAGY IN HEALTH AND DISEASE

RESEARCH SUMMARY

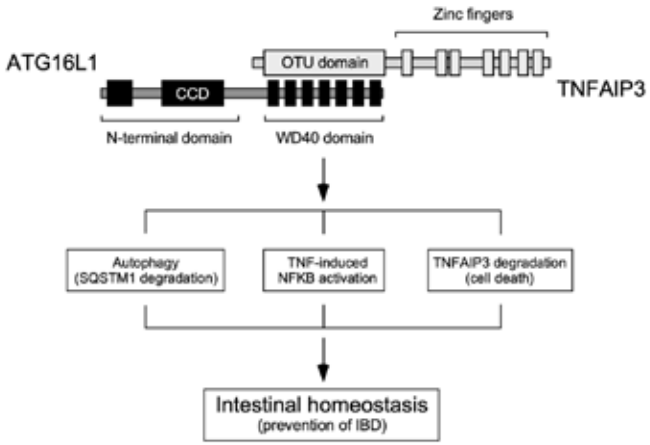
The main focus of our laboratory is the study of unconventional forms of autophagy and the implications that this growing collection of processes may have in human disease.

In its most canonical version, autophagy is a catabolic process that promotes degradation of cytoplasmic components for metabolic homeostasis and quality control. This phenomenon involves sequestration of the items to be degraded into double membrane vesicles that become labeled with the autophagic marker LC3 and fuse with lysosomes for degradation of their contents. Due to well-established roles in stress management and quality control, autophagy is widely viewed as a mechanism that helps maintain a healthy cellular homeostasis. However, in the last few years a number of atypical forms of autophagy have been described where either autophagy itself or the molecular machinery that regulates this process play biological roles that seem unrelated to the canonical activities originally described. The molecular mechanisms governing these novel functions are largely unknown.



Our interest in unconventional autophagy comes from our previous characterization of the autophagic activity induced by the transmembrane protein TMEM59. This molecule activates an atypical autophagic process where its own single membrane vesicles become labeled with LC3 and are more efficiently targeted for lysosomal degradation, a phenomenon that seems to be involved in the innate defense against invading microorganisms. TMEM59 directly engages the canonical autophagic mediator ATG16L1 through a minimal aminoacid motif present in its intracellular domain. Notably, a polymorphic allele of ATG16L1 (T300A) that increases the risk of suffering Crohn's disease alters the ability of ATG16L1 to bind TMEM59, raising the idea that at least part of the pathological features caused by the T300A allele may be due to dysfunctions in the normal biology of TMEM59 or other proteins with a similar activity. Therefore, identification of autophagic regulators that function through a TMEM59-like mechanism may point to the molecular and cellular activities whose alteration increases susceptibility to disease.

In our laboratory we are trying to identify such molecules, study the common mechanisms that they utilize to trigger autophagy and analyze their functional relevance in a variety of unconventional processes where the autophagic machinery has been involved. These processes range from the secretion of leaderless proteins, regulation of vesicle trafficking or control of innate and adaptive immunity. Since many of these events are tightly linked to physiopathological processes like inflammation, immune responses or microbial infections, their detailed characterization holds substantial interest in human health. We are also exploring how the normal activity of these molecules may be altered by the ATG16L1-T300A allele to favor disease onset. We are using animal models lacking the relevant molecules to confirm their relevance in disease and possible value as therapeutic targets.



PUBLICATIONS

- **Unconventional WD40 domain-dependent role of ATG16L1 in the regulation of IL10R (interleukin 10 receptor) endocytosis, trafficking and signaling.** *Villamuera R, Fernández-Cabrera A, Serramito-Gómez I, Terraza-Silvestre E, Taouil R, Pimentel-Muiños FX.* **Autophagy. 2021 Sep;17(9):2639-2641. doi: 10.1038/s41467-019-09667-z.** PMID: 34251955. **IF: 16.016 / D1**

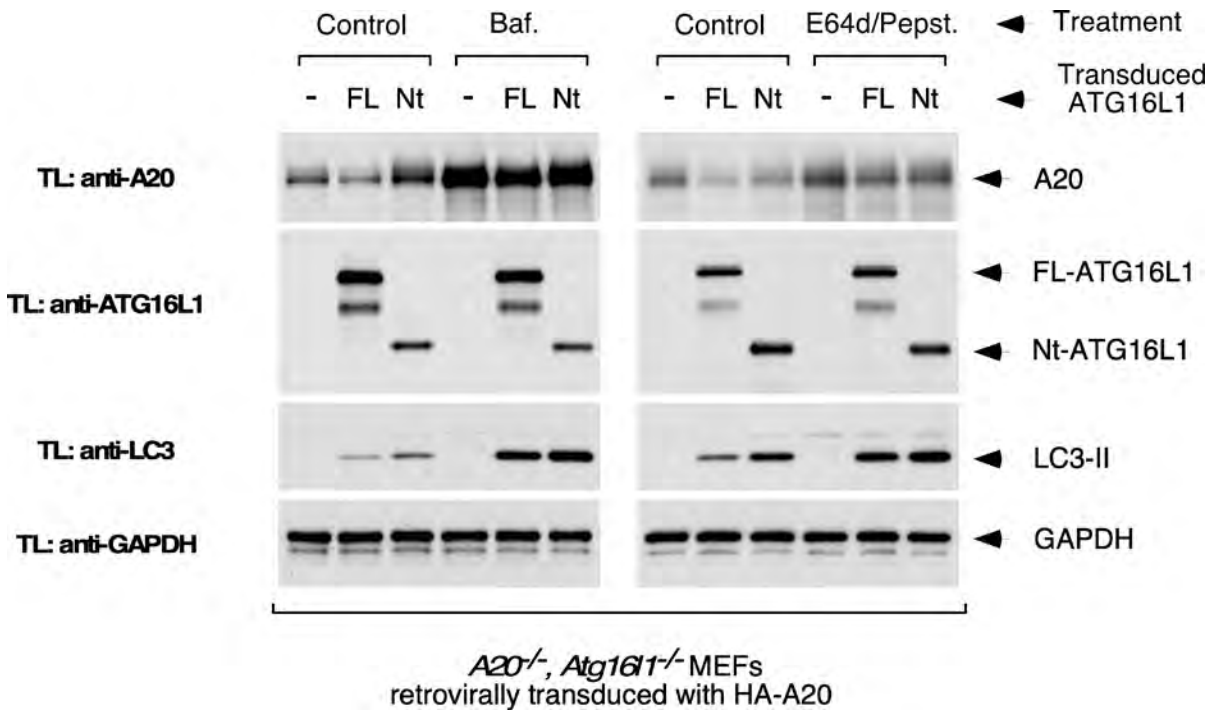
- **Regulation of cytokine signaling through direct interaction between cytokine receptors and the ATG16L1 WD40 domain.** *Serramito-Gómez I, Boada-Romero E, Villamuera R, Fernández-Cabrera A, Cedillo JL, Martí-Regalado A, Carding S, Mayer U, Powell PP, Wileman T, García-Higuera I, Pimentel-Muiños FX.* **Nat. Commun. 2020 Nov 20;11(1):5919. doi: 10.1038/s41467-020-19670-4.** PMID: 33219218. **IF: 14.919 / D1**

OTHER PUBLICATIONS & BOOK CHAPTERS

- **Autophagy in the grastrointestinal system and cross talk with microbiota. In: "Autophagy in health and disease"**. *Pimentel-Muiños FX. Rothermel BA and Diwan A (eds).* **Academic Press, London (UK)**; 321-330, 2022.

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Mechanisms and manipulation of immunogenic cell death (IDEAS18093PIME)	Felipe X. Pimentel Muiños	Spanish Association against Cancer	2019-2022	20,000.00 €
Nuevas actividades del regulador autofágico ATG16L1 y su relevancia en patología (SAF2017-88390-R)	Felipe X. Pimentel Muiños	Ministry of Economy and Competiveness	2018-2020	205,700.00 €



4

TRANSLATIONAL AND CLINICAL RESEARCH IN CANCER PROGRAM

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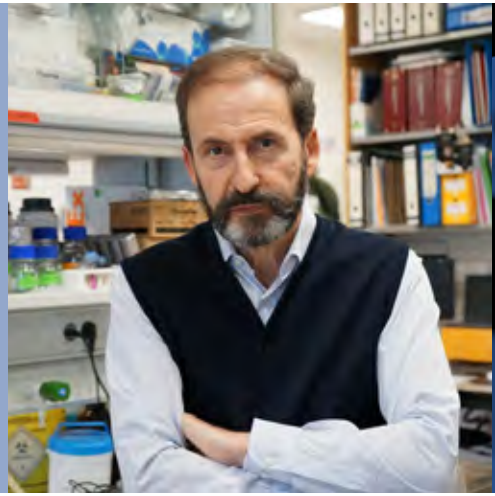

DESCRIPTION

This Research Program is composed of groups interested in the direct translation of results from the lab to the bench side. To this end, they work on the validation of drug targets, the design of new therapeutic avenues based on single and combinatorial therapies, the understanding of therapeutic resistance and posttreatment recurrence, and the genomic characterization of tumors during both pre- and post-treatment windows. They are also engaged in an extensive number of clinical trials. This Program also has support groups that enable robust Bioinformatics and System Biology analyses. In addition, they benefit from other health-related initiatives coordinated by our Center such as the Castilla-León Regional Tumor BioBank, the Familiar Cancer Detection Unit, and the Molecular Diagnostic Unit.

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LABORATORY 11

IMMUNOLOGY AND CANCER

RESEARCH SUMMARY

The research activity of this area focuses on the relationship between the immune response and cancer, as well as on the study of malignancies derived from cells of the immune system, such as leukemias and lymphomas. Among other areas, it relates with improved diagnosis and classification of leukemias and lymphomas, as well evaluation of treatment effectiveness during follow-up via detection of low numbers of therapy-resistant malignant cells, i.e. detection of «minimal residual disease» (MRD).

As the various types of hematological malignancies resemble their normal counterparts, combined studies of normal hematopoietic cells and their malignant counterparts are essential to support the unraveling of oncogenic events that induce deregulation of cellular processes and malignant transformation, including the potential role of immune responses and the immune system in controlling and/or promoting malignant transformation and expansion of neoplastic cells. Therefore, this research field combines cellular, genetic and molecular studies on normal and malignant hematopoiesis, including the immune responses associated with cancer development and control. Translation of the obtained information into novel diagnostics has high priority for this group.

Immunophenotyping is one of the primary bases for the diagnosis, classification and treatment monitoring of hematological malignancies. In the last years, large technological improvements have been achieved in this field, which have allowed a more rational panel design (i.e. more sensitive and specific) for the study of leukemias and lymphomas; however, in parallel, they have led to an increased complexity of flow immunophenotypic data, since no new tools have been developed to ease data interpretation. In order to address the complexity and subjectivity of analysis of flow cytometry data, it is also an essential research activity of our group to design, develop and validate high throughput systems and tools for the automated and standardized flow cytometry data analysis, for the diagnostic (screening), classification, prognostic evaluation and treatment monitoring of hematological malignancies, and to translate these new automated tools to clinical settings.

A more recent research activity of our group –closely related with the one referred above, focused on studying normal hematological/immune cells– is to develop and implement sensitive and specific approaches by multiparametric flow cytometry, to measure and monitor immune responses after immunotherapy (i.e. after antitumor immunotherapy).

OBJECTIVES:

The general aim of this program is based on the fact that the oncogenic events that induce deregulation of cellular processes in hematological malignancies may translate into aberrant protein patterns displayed by malignant cells, which could be useful from the clinical point of view, for diagnosis, classification, prognosis evaluation and treatment monitoring in patients suffering from hematological malignancies. In the same line, understanding of the role of the (normal) immune system on different malignancies/clonal disorders, through the analysis of the interactions between tumor cells and the immune microenvironment, could constitute the basis for novel immunotherapeutic strategies in the near future, and can help design strategies for monitoring the immune system after (antitumor) immunotherapy.

SENIOR RESEARCHER

PHENOTYPIC AND MOLECULAR CHARACTERIZATION OF SYSTEMIC MASTOCYTOSIS

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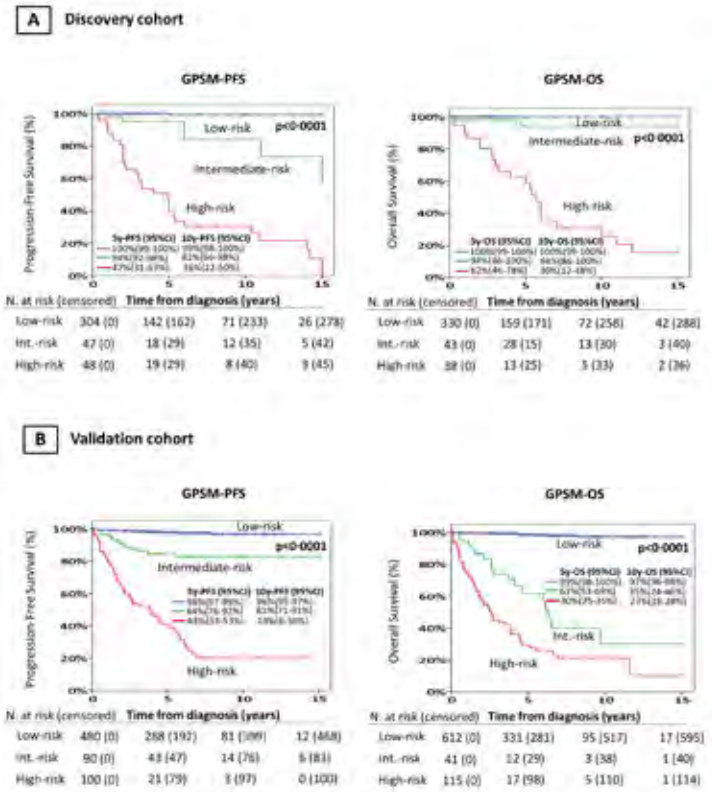
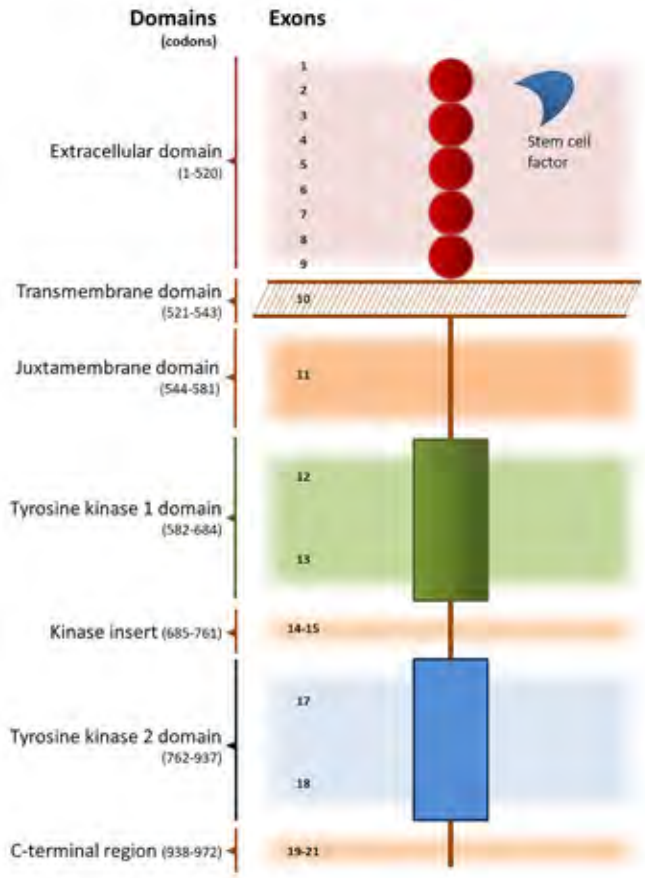
RESEARCH SUMMARY

Systemic mastocytosis (SM) are orphan diseases, indolent in most patients (ISM) that can progress to aggressive forms (ASM). Pathologic mast cells (MC) displayed particular immunophenotypes and functions with a potential immunomodulatory role over other cell types of the innate and/or adaptive immune responses of the SM patients. Objective: to clarify whether such immune interactions could have any role on the clinic-biological features and progression of the disease and to identify the potential molecular patterns associated to the severity and evolution of SM. Lines of research and challenges: 1) Transcriptomics and genomics of purified MC to identify molecular pathways altered in ASM vs ISM. 2) Detailed immune characterization of the different cell compartments of the innate and adaptive immune responses to know their potential role on the clinic-biological features of SM. 3) Identification of somatic and/or germinal genetic variants responsible for the malignant transformation associated to the *KIT* D816V mutation in myeloid neoplasia, using as a model the transformation from ISM to ASM, and to evaluate the potential clinical utility of the genetic markers detected in the prognostic stratification of the SM patients; and 4) Analysis of the potential correlation between immunophenotype, molecular events, functional profiles, clinical data and environmental features in order to define their utility as diagnostic/prognostic biomarkers and/or as potential therapeutic targets.



Progression-free survival (PFS) (left panels) and overall survival (OS) (right panels) Kaplan-Meier estimates of SM patients stratified according to the newly proposed global prognostic scores for SM (GPS_M).



Schematic representation of the kit receptor

SENIOR RESEARCHER

CHRONIC LYMPHOID NEOPLASMS: FACTORS INVOLVED IN ONTO-PATHOGENESIS AND TRANSFORMATION OF PRELEUKEMIC CONDITIONS INTO CLONAL/MALIGNANT DISEASES

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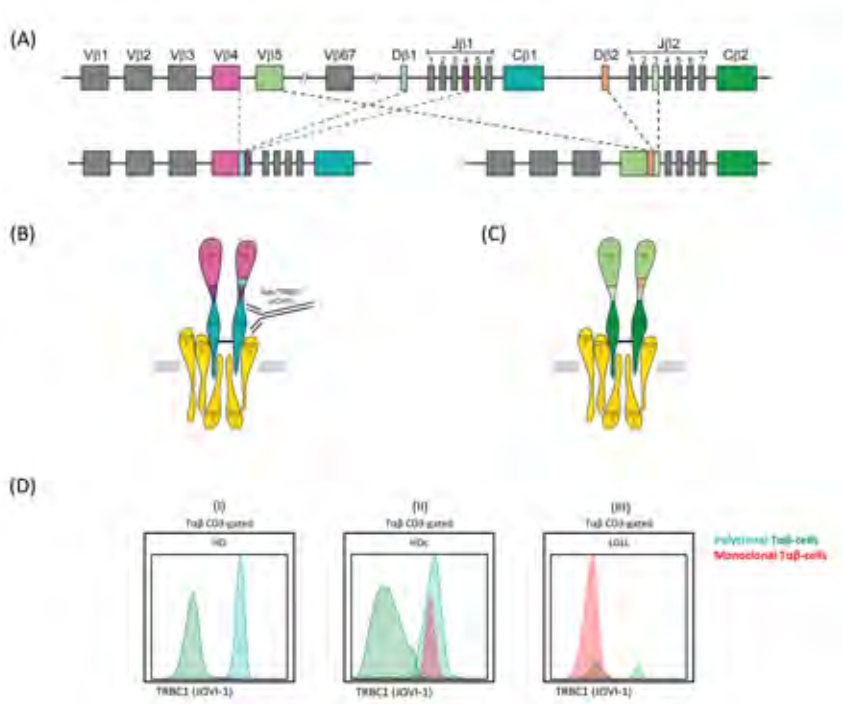
RESEARCH SUMMARY

Her research is focused on "Immunology and Cancer" applied to hematological malignancies (leukemias and lymphomas) derived from mature T/NK and B cells (chronic lymphoproliferative disorders, from the onto-pathogenesis to clinical settings, these latter including their potential application in diagnosis –particularly early diagnosis-, classification and treatment monitoring of these neoplasms). Major research activities: i) the identification of mechanisms involved in the transformation/evolution of reactive to clonal and malignant conditions (i.e. the early stages of cancer, both prior to the onset of the disease and before recurrence after therapy), ii) phenotypic, genetic/molecular and functional characterization of these cells and iii) its translation to diagnosis, classification and treatment monitoring of these neoplasms; iv) biological characterization of their normal (T/NK- and B-) cell counterparts; and v) role of the immune system in the control and progression of the disease, with special focus on hematological

malignancies. As a consequence of its scientific activity, the team led by Almeida has published 20 international scientific papers in the last 6 years, from which 85% are Q1, with a mean impact factor of 6.7, and registered 2 licensed patents, for a total production of 133 articles in international indexed scientific journals (PI H-index of 41 with >5,000 citations). Almeida is a member of the EuroFlow Consortium (European collaborative group) since its creation in 2006, which aims at standardization and automation in flow cytometry, to improve current flow cytometry strategies applied to the diagnosis, classification and monitoring after treatment of patients with hematological malignancies; specifically, she is the responsible person for the design and development of the T- and NK-cell CLPD panels. More recently (2018-19), she has contributed to an in depth characterization of distinct compartments of normal blood immune cells, such as monocytes (J Allergy Clin Immunol 2019), CD4+ T cells (Frontiers in Immunology 2020) and their alterations in tumor-associated (secondary) immune deficiencies (Haematologica 2018 and Leukemia 2018), and has contributed to the feasibility of applying automated strategies for reproducible analysis by flow-cytometry (J. Immunol Methods 2019); also, she has shown for the first time the potential role of an activated (though defective) immune system in promoting progression to leukemic stages from earlier pre-tumor conditions (Haematologica 2018 and Leukemia 2018), and the finding that monoclonal B lymphocytosis (a pre-tumor condition) is also very frequent in non-Western populations (Haematologica 2019).

In the near future, her activities will focus on in-depth analyses of the onto-pathogenic factors involved in chronic B-cell leukemia, and early detection and (potential) intervention (at monoclonal B lymphocytosis stages).



Schematic representation of TRB gene rearrangement and interpretation of the TRBC1 antibody (JOVI-1 clone)-based flow cytometry approach: (A) Mutually exclusive TRBC selection during TRB gene rearrangement in the thymus; (B,C) Representation of the two resulting TRB complex structures, composed of either the TRBC1 (B) or the TRBC2 (C) proteins, and specific binding of the anti-TRBC1 antibody to TRBC1 but not to TRBC2; (D) Illustrative histograms of TRBC1 staining of blood Tαβ-cells.

SENIOR RESEARCHER

IMMUNOTECHNOLOGY, NANOTECHNOLGY, AND PROTEOMICS APPROACHES FOR BIOMARKER AND DRUG DISCOVERY IN CANCER AND IMMUNOPATHOLOGIES

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RESEARCH SUMMARY

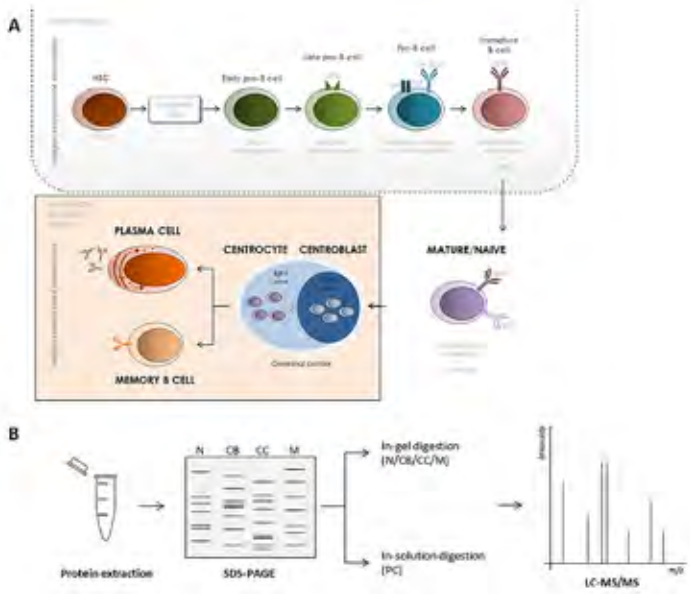
Immunotherapies that train or stimulate the inherent immunological systems to recognize, attack & erradicate tumor cells with minimal damages to healthy cells have demonstrated promising clinical responses. Recently, a huge progress has been experienced in two main Immuno-Onco-Therapy (IO) areas: Chimeric Antigen Receptor (CAR-T cells) & Immune modulation by blocking suppressive Immune Check-points (IC). Although IO has demonstrated exciting clinical responses, they are some limitations: high cost, efficacy restricted to certain patients subsets, biomarkers for patient stratification, resistant to IO, dose-limiting-auto-immune effects like cytokine release syndrome... Despite that Immune Checkpoint Inhibitors (ICI) has revolutionize the management of cancer, by increasing the immune response towards tumors, already in the clinical setting; however, it is still required active investigation because the low responses and some patients are primary unresponsive to develop ulterior resistance to these drugs (primary & acquire resistance). Nowadays, there are several clinical trials which promotes the combination of ICIs with other onco-therapeutic strategies: ablative cancer treatments

(radiotherapy, chemotherapy,...) that cause tumoral cell death in an immunogenic way. The Immunogenic Cell Death (ICD) enhances immune stimulatory or subvert immune suppressive effects for the activation, proliferation, T cells tumor infiltration to synergize with current ICI therapies. Hence, it is necessary to decipher molecular basis of anti-tumor immune response to design the optimal IO combination[x]. The anti-tumor immune response consists of key steps: i.-Antigen released from tumoral cells are captured by antigen-presentation cells (APCs). ii.-Danger Associated Molecular Patterns (DAMPs) such as pro-inflammatory cytokines and factors released by dying tumoral cells signal APCs maturation. iii.-Activated APCs present Tumor Associated Antigens (TAAs) on MHC-I & MHC-II to T cells, resulting in the activation of effector T cells against tumor-specific-antigens. iv.-Activated effector T cells traffic to and infiltrate tumor bed where they specifically recognized tumoral cells through integration between T-cell receptor (TCR) and MHC-I bound cognate antigen and kill tumor cells. v.-Tumor death cells release TAAs to increase the breadth and depth to the immune response in subsequent revolutions of cycle.

Thus, there is a potential mechanism of combined benefits of TOT based on Nanomedicines and Immunotherapy based on ICIs. Because Nanomedicines allow learning from biology and nanotechnology to design approaches that can address some of the challenges in IO: i.-Enabling the combination of molecular targeted therapies with immunotherapies which could be pharma- and biologically compatible; ii.-Early monitoring of efficacy of immunotherapies; iii.-Personalizing an immune response to a patient´s tumor.

Then, the main goal of our group to design and validate a immunoproteogenomics strategy, in order to perform ortogonal verification of the panel of biomarkers useful in combination of targeted onco-therapy and immune-checkpoint inhibitors to improve the therapeutic scheme. This immunoproteogenomic methodology is based on the systematic integration of next generation genomic, transcriptomic, proteomics and immune monitoring (in array format) that allows ortogonal validation of biomarkers (in haematological and solid tumors) in order to promote a rapid translation into the clinic. In particular, we are focused on:

1. Establish correlation between somatic mutations and cell signaling pathways by proteogenomics.
2. Inter-relationship of Characterization of TCR sequences and HLA immunopeptidomes.
3. Design and development of methods for the proteomic quantification of proteins and their encoded proteoforms according to genomic alterations and immunpeptidomes.
4. Identify differential tumor associated antigen (TAAs) profiles according to altered protein profiles and immunopeptidomes.
5. Immune monitoring in high-density array for the rapid and simultaneous determination soluble components of immune response and immunogenic cell death.



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- **Frequency and prognostic impact of blood-circulating tumor mast cells in mastocytosis.** *Henriques A, Muñoz-González JI, Sánchez-Muñoz L, Matito A, Torres-Rivera L, Jara-Acevedo M, Caldas C, Mayado A, Pérez-Pons A, García-Montero AC, Álvarez- Twose I, Orfao A.* **Blood. 2021 Sep 9:blood.2021012694. doi: 10.1182/blood.2021012694.** PMID: 34496018. **IF: 23.629 / D1**

- **Anti-TRBC1 Antibody-Based Flow Cytometric Detection of T-Cell Clonality: Standardization of Sample Preparation and Diagnostic Implementation.** *Muñoz-García N, Lima M, Villamor N, Morán-Plata FJ, Barrena S, Mateos S, Caldas C, Balanzategui A, Alcoceba M, Domínguez A, Gómez F, Langerak AW, van Dongen JJM, Orfao A, Almeida J.* **Cancers (Basel). 2021 Aug 30; 13(17):4379. doi: 10.3390/cancers13174379.** PMID: 34503189. **IF: 6.639 / Q1**

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- **Inter-laboratory analytical validation of a next-generation sequencing strategy for clonotypic assessment and minimal residual disease monitoring in Multiple Myeloma.** *Medina A, Jiménez C, Puig N, Sarasquete ME, Flores-Montero J, García-Alvarez L, Prieto-Conde I, Chillón C, Alcoceba L, González-Calle V, Gutiérrez NC, Jacobsen A, Vigil E, Hutt K, Huang Y, Orfao A, González M, Miller J, García-Sanz R.* **Archives of pathology & laboratory medicine. doi: 10.5858/arpa.2021-0088-OA.** PMID: 34619755. **IF: 5.534 / Q1**

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- **Overcoming resistance to immunotherapy in advanced cutaneous squamous cell carcinoma.** *García-Sancha N, Corchado-Cobos R, Bellido-Hernández L, Roman-Curto C, Cardenoso-Álvarez E, Pérez-Losada J, Orfao A, Canueto J.* **Cancers, 13(20): 5134. doi: 10.3390/cancers13205134.** PMID: 34680282. **IF: 6.639 / Q1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Red Transfonteriza de Innovacion en Diagnóstico Precoz de Leucemia para un Envejecimiento Saludable IDIAL-NET. POCTEC-INTERREG (Portugal-España)	Alberto Orfao	European Union	2019-2022	993,570.25 €
PERISCOPE: PERtussIS Correlates of Protection Europe". HORIZON2020: Innovative Medicines Initiative IMI2/OUT/2016/01402	Alberto Orfao	European Union /Bill & Melinda Gates Foundation	2016-2022	138,000.00 €
Early Cancer Research Initiative Network on Monoclonal B lymphocytosis (ECRIN-M3)	Alberto Orfao	CRUK–AIRC-FCAECC Accelerator Award Call	2020-2025	1,565,658.88 €
Innovative CAR cell therapy platforms (INCAR)	Alberto Orfao	CRUK–AIRC-FCAECC Accelerator Award Call	2018-2023	963,418.97 €
Monitorización simultánea de celulas leucémicas y del sistema inmune circulantes en leucemia aguda linfoblástica de precursores B del adulto mediante NGF de >25 colores: impacto pronóstico (PI19/01183)	Alberto Orfao	Carlos III Health Institute	2020-2022	309,457.50 €
Grupo de Investigación del CIBER de Cáncer CB16/12/00400 (CIBERONC)	Alberto Orfao	Carlos III Health Institute	2017-2020	389,620.00 €
Impacto de la linfocitosis B monoclonal y del estado del sistema inmune en el desarrollo y evolución de la infección COVID-19 en adultos (COV20-00386)	Alberto Orfao	Carlos III Health Institute	2020-2021	106,017.00 €
Análisis secuencial de la respuesta inmune en la infección COVID-19 vs gripe estacional: valor predictivo de la sintomatología y grado de gravedad de la enfermedad, y del nivel de inmunización humoral (SA109P20)	Alberto Orfao	Regional Government of Castilla y Leon	2021-2023	264,000.00 €
Red Transfonteriza de Innovacion en Diagnóstico Precoz de Leucemia para un Envejecimiento Saludable IDIAL-NET. POCTEC-INTERREG (Portugal-España)	Manuel Fuentes García	Carlos III Health Institute	2020-2022	184,750.35 €
Detección múltiplex de alta sensibilidad y rapidez de biomarcadores séricos de daño pulmonar agudo, síndrome de distress respiratorio y perfil antigénico de COVID19 y SARS-CoV-2 (COV20EDU/00187)	Manuel Fuentes García	Carlos III Health Institute & Regional Government of Castilla y Leon	2019-2021	164,500.00 €
Red Temática Española de Descubrimiento de Fármacos (REDEFAR). (SAF2017-90913-REDT)	Manuel Fuentes García	Spanish Ministry of Economy and Competitiveness	2018-2021	45,000.00€
Plataforma de Recursos Biomoleculares y Bio-Informáticos PRB3 (PT17/0019/0023)	Manuel Fuentes García	Carlos III Health Institute	2018-2021	123,750.00€
Identificación y validación mediante inmunoproteogenómica de biomarcadores útiles en diagnóstico y evolución de la Leucemia Linfoide Crónica célula B (PI17/01930)	Manuel Fuentes García	Carlos III Health Institute	2018-2021	120,000.00€
Modulación de la respuesta del sistema inmune en mastocitosis sistémica: papel del micro-medioambiente celular y potencial asociación a la progresión clínica de la enfermedad (PI19/01166)	Andrés C. García Montero	Carlos III Health Institute	2020-2022	98,010.00 €

PROJECT	PI	GRANT	TIME	FUNDING
Biobancos y biomodelos (PT20/00085)	Andrés C. García Montero	Carlos III Health Institute	2021-2023	237,600.00 €
Identificación de factores involucrados en la ontopatogenia de la leucemia linfática crónica y de parámetros asociados a riesgo de transformación maligna en fases pre-leucémicas". subproyecto PI17/00399	Julia Almeida	Carlos III Health Institute	2018-2022	112,530.00 €
Citometría de flujo de última generación para acercarnos al conocimiento de las neoplasias de linfocitos T y NK maduros: implicaciones en la clasificación diagnóstica (PI20/01346)	Julia Almeida	Carlos III Health Institute	2021-2023	105,270.00 €

OTHER ACTIVITIES & RELEVANT FACTS

- External member (elected unanimously) of the "Conselho Geral" of the University of Coimbra (Coimbra, Portugal), since February 8, 2021.
- Editor of the monographic issue "Immunophenotyping of leukemia and lymphoma" of the journal Cancers, January 2021.
- Member of the jury for the Doctoral Thesis of Doña Maria del Carmen Martin Sierra (Arguente; Universidade de Aveiro, Portugal, 2020).
- Member of the scientific committee of the 10th Congress of the Portuguese Society of Clinical Pathology (SPPC). Porto (Portugal), February 2020.

OTHER PUBLICATIONS & BOOK CHAPTERS

- **Deciphering Intracellular Signaling Pathways in Tumoral Pathologies.** *Landeira-Viñuela A, Juanes-Velasco P, Góngora R, Hernández AP, Fuentes M.* **Methods Mol Biol. 2021; 2344: 211-226. doi: 10.1007/978-1-0716-1562-1_15.** PMID: 34115362.
- **Systematic and Rational Design of Protein Arrays in Noncontact Printers: Pipeline and Critical Aspects.** *Juanes-Velasco P, Landeira-Viñuela A, Hernandez AP, Fuentes M.* **Methods Mol Biol. 2021; 2344: 9-29. doi: 10.1007/978-1-0716-1562-1_2.** PMID: 34115349.

PATENTS

PATENT REFERENCE	TITLE	INVENTORS	PRIORITY DATE
EP21382687.8	In vitro method for the prognosis of patients suffering from sepsis	Ángela Patricia Hernández García, Pablo Juanes Velasco, Alicia Landeira Viñuela, Rafael Góngora y Manuel Fuentes	26/07/2021

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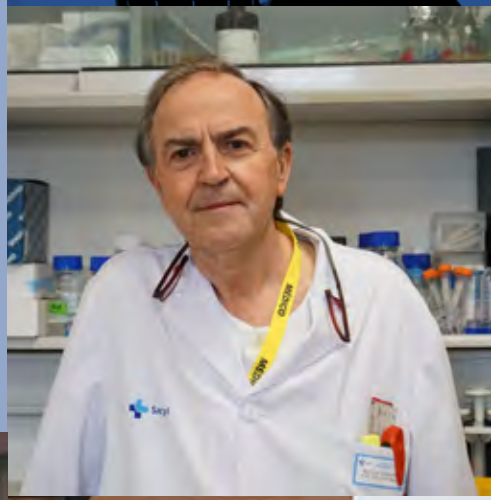

LABORATORY 12

ONCOHEMATOLOGY

RESEARCH TEAM

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Jesús María Hernández Rivas

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Mauro Lorenzo Mohamed
Igor de la Torre Loizaga
Ana Marín Quilez
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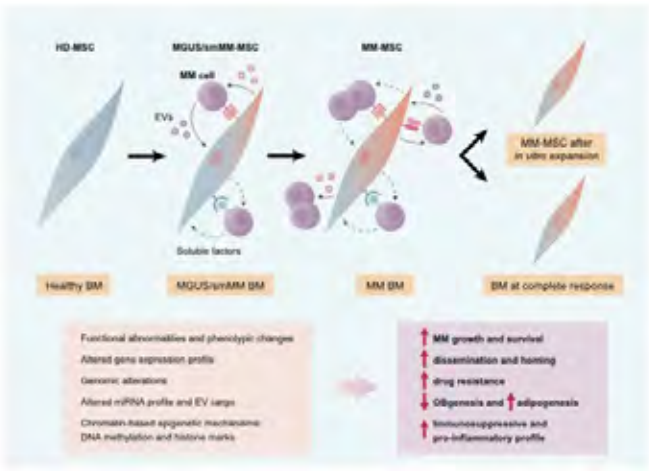
Mariem Lachaal
Maritza Cruz Hernández
Ivan Maldonado Campos

RESEARCH SUMMARY

Prof González's group is characterized by its translational research, which stems from the interaction between laboratory 12 at the Cancer Research Center and the Hematology Department of the University Hospital of Salamanca. This interaction has been very fruitful, not only because of the number of scientific publications, but also, because of the achieved diagnostic and therapeutic advances for patients. Although the interest of the group involves all haematological malignancies, a special focus has been put on multiple myeloma (MM), acute myeloid leukemia (AML) / myelodisplastic syndromes (MDS) and chronic lymphoproliferative disorders (CLL) / lymphomas.

STRATEGIC OBJECTIVES

1. To deepen into the knowledge of the tumor clone through multiparametric studies (phenotypic, cytogenetic, molecular and functional) with the final goal of identifying novel prognostic markers.



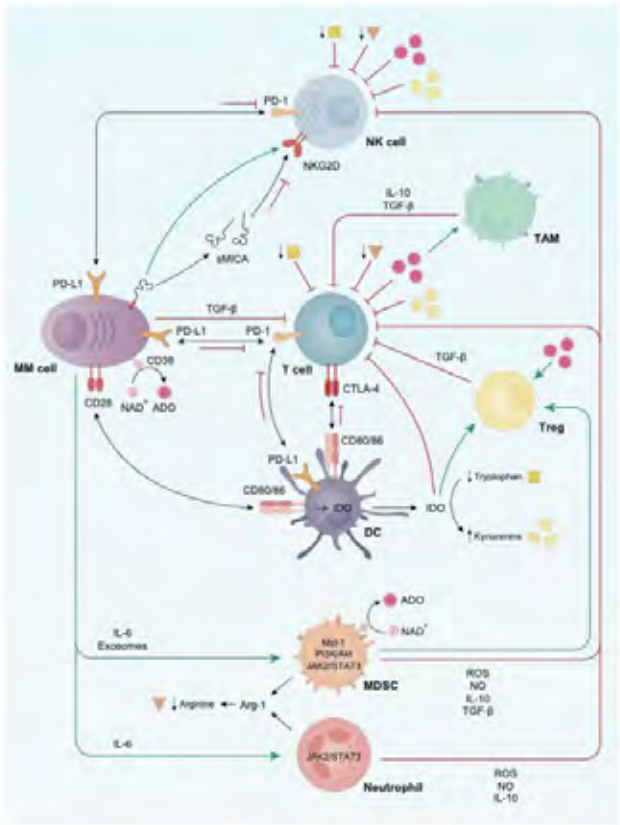
Hypothetical transition from HD-MSCs to myeloma MM-MSCs mediated by interaction with MMcells. Interaction of MGUS and smMM plasma cells with MSCs is considered an initiating event. Direct contact of myeloma cells and MSCs, together with soluble factors (dashed arrows) and EVs (solid arrows) induce various layers of modifications in MSCs (phenotypic, gene expression, genomic, miRNA, and epigenetic), contributing to the transition from HD- to MM-MSCs and to myeloma pathology. Epigenetic modifications may be responsible for maintenance of MM-MSC features in absence of myeloma cell interactions. doi: 10.3390/cancers13112542

2. Development of diagnostic tools applicable to clinical practice. Standardization and validation of Next Generation Sequencing and Next Generation Flow techniques to be implemented in routine therapeutic monitoring. Development of new-generation Multiplarameter Flow Cytometry and NGS, and their applicability in diagnosis and in detection of Minimal Residual Disease.
3. To evaluate potential antitumoral targets to design novel therapeutic strategies in the preclinical setting that could be quickly translated into the clinic.

MAIN LINES OF RESEARCH

The lines, based on the strategic objectives, are divided into four main research areas:

1. OncoHaematologic Molecular Cytogenetics
   - Molecular cytogenetics and genomic arrays in haematological malignancies.
   - Analysis of the tumor transcriptome and exome.
   - Study of the functional status of p53 in multiple myeloma and its impact on therapeutic response and patient survival
   - Investigation of RNA splicing and its regulation in multiple myeloma
   - Protein biomarker discovery and validation using capillary electrophoresis with immunoassay (ProteinSimple)
2. Molecular Biology and Immunopathology
   - Study of genomic expression and mutations in genes associated with cancer: clinico-biological correlations.
   - Immunophenotypic and molecular markers for the detection of minimal residual disease.
   - Analysis of genetic polymorphisms: role on etiopathogenesis and prognosis.
   - Study of antigenic receptors for B & T lymphocytes: applications in the diagnosis and etiopathogenesis of lymphoproliferative disorders.



Schematic representation of the main immune system alterations described in MM patients. Briefly, T and NK cells are inhibited through both soluble factors and cell-to-cell contacts with either myeloma cells or other immune cell populations. Black arrows refer to receptor-ligand union, green arrows stand for activation whereas red bar-headed lines indicate inhibition.

doi: 10.3390/cancers13061353

3. Cell Therapy and Transplantation
   - Study of hematopoiesis and bone marrow microenvironment in hematological disorders.
   - Clinical investigation in haematopoietic transplantation. Novel procedures and complications.
   - Analysis of Extracellular Vesicles in haematological diseases and EICH

4. Novel Therapies in hematological malignancies
   - Preclinical development of targeted antitumor drugs and immunotherapies
   - Intrinsic and bone marrow microenvironment-mediated mechanisms of drug resistance
   - Phase I/II/III clinical trials with experimental agents

ACHIEVED GOALS

Among the main achieved goals in the last years, we can highlight: a) Our group has described the prognostic value of several cytogenetic and molecular abnormalities in MM, NHL, MDS or CLL, and we have also significantly contributed to the whole sequencing of the genome of CLL. b) Establishment of the prognostic impact of MRD by flow cytometry (International Reference). c) In the field of novel antitumoral drugs, our group has identified novel agents and combinations, which has allowed the leadership of our group in several clinical trials (phase I/II and phase III for registration), including participation in intenational clinical trials on CAR T-cells in both DLBCL and MM.

FUTURE CHALLENGES

- To deepen into the genomic mechanisms responsible for the development of haematological neoplasms and mechanisms of tansformation into a more aggressive disease. Evaluation of clonal heterogeneity and identification of the ancestor clonogenic cell.
- To identify and characterize the tumor stem cells and to gain further insights into the role of the tumour microenvironment.
- To analyze the mechanisms responsible for the development of drug-resistance.
- Analysis of new immunotherapeutic approaches: check-point inhibitors, CAR (Chimeric Antigenic Receptor) T-cells and NK-cells, BAR (B-cell Antigenic Receptor) T-cells.
- Identification of synthetic lethal vulnerabilities in multiple myeloma: construction of isogenic cell lines for MMSET, c-MAF, MAFB or c-MYC and genome-scale CRISPR-Cas9 knockout screening.

SENIOR RESEARCHER

GENETICS IN ONCOHEMATOLOGY

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RESEARCH SUMMARY

Our group has an extensive experience on the most advanced technological approaches in biomedicine, such as next-generation sequencing and CRISPR genome editing. Our aim is the integration of the data obtained in the different research lines to provide more personalized treatments, specifically:

- To analyze the mechanisms responsible for the development of drug-resistance using high-throughput CRISPR/Cas9 technology by generating new leukemia-derived cell lines and animal models harboring specific mutations and reproducing the genomic heterogeneity seen in haematological malignancies.
- To use Big Data to deliver information that will help improve the care of patients with hematologic malignancies. This will be achieved by gathering, integrating and analysing anonymous patient data from several high-quality sources, thereby defining clinical endpoints and outcomes that will be assessed by all key stakeholders. This will facilitate and improve decision making for policy makers and physicians alike to help them choose the right treatment for the right patient at the right time.

Among the main achieved goals in the last years, we can highlight the description of the prognostic value of several cytogenetic abnormalities in MM, MDS, ALL, CML, MPD, HD or CLL, and our significant contribution to the sequencing of the genome of CLL. Furhermore, the presence of mutations and chromosomal alterations in hematopoietic progenitors in CLL has also been analyzed and the processes of clonal evolution underlying clinical progression of CLL patients have been analyzed by whole-exome sequencing. We have also shown that the combined use of traditional sequencing and massive sequencing to detect mutations in splicing

genes can improve diagnosis in patients with MDS with ring sideroblasts. Our group has also participated in the publication of a guide for the clinical application of NGS in patients with MDS and CMML made by the Spanish Group of Myelodysplastic Syndromes (GESMD).

Additionally, we have also described new relevant mutations found in congenital thrombopathies in colaboration with the Hemostasis and Thrombosis Unit from the University Hospital of Salamanca. The group has also been involved in several international projects related to expression microarrays (MILE), genomic microarrays (EuGESMA), next generation sequencing (IRON, ELAN, NGS-PTL, NEMHESYS), and big data and personalized medicine (HARMONY, HARMONY PLUS, ONC-NGS and SYNTHERAPY). Our group has published more than 260 papers in international scientific journals, has directed 38 research projects and 20 doctoral theses.

Chronic myeloid leukemia (CML) is a malignant hemopathy arising from a specific chromosomal translocation which activates the ABL protooncogene. Unlike other carcinogenic processes, where accumulative mutations transform the normal cell into a malignant cell, the CML is triggered and maintained by this single oncogenic event. Thus, when ABL remains inactivated by drugs, disease progression is prevented, and patients remain asymptomatic. This is the base of the current CML treatment, the inhibition of ABL with specific drugs, such as imatinib, which has improved the survival of patients. However, this treatment is not successful in all patients and 25% of them become refractory by acquiring resistant mutations. Besides, it must be administered continuously to maintain ABL oncogene silenced or inactive. Nowadays, with the emergence of CRISPR technology to induce knock-out mutations in a targeted manner, we could definitively treat this disease abrogating ABL at genetic level. The objective of our group has been focusing on inducing knock-out mutations (indels triggering frameshift mutations) in the ABL coding sequence breaking their reading phase. Our previous work has shown that it is possible, both *in vitro* and in vivo assays. In addition, we have shown as CRISPR abolishes the tumor process and returns the hematopoietic multipotent capacity to the leukemic stem cell. These studies are providing proof of-principle for genome editing in CML patients. However, the methodology should be refined since a definitive cure would require the exclusive selection of those stem cells with a non-functional ABL. The goal of this project is to develop the technology that allows us to edit the BCR / ABL oncogene while providing us with a system for its selection.

Chromosome 11q22.3 deletion -del(11q)- is one of the most common cytogenetic alterations in chronic lymphocytic leukemia (CLL), which defines a high-risk subgroup of patients characterized by a rapid disease progression, impaired responses to chemotherapy-based regimes and reduced survival. The size of this deletion is variable and it can encompass hundreds of genes, being specifically ATM and BIRC3 suggested to have a role in CLL pathogenesis, since loss-of-function mutations of ATM or BIRC3 preferentially occur in del(11q) cases. This complete dysfunction of ATM or BIRC3 proteins has been shown to aggravate the outcome of del(11q) patients. However, the biological determinants by which the co-occurrence of these abnormalities drives CLL progression, clonal evolution and therapy response are largely unexplored. In addition, other concomitant genetic abnormalities have also been described in del(11q) patients, although their role in the prognosis of this specific subgroup of CLLs has not been established. In order to shed light into these aspects, during this period, our group has implemented a high-throughput sequencing approach to characterize the mutational landscape of a high-risk cohort of del(11q) CLL patients and in parallel, we have applied the CRISPR/Cas9 genome-editing system to generate novel *in vitro* and in vivo models recapitulating the biology of del(11q) as well as concurrent mutations in ATM, BIRC3 or other genes. These models, in combination with ex vivo primary CLL cultures from genetically matched patients, have made possible to gain a deeper understanding into the role of ATM and BIRC3 in del(11q) clonal evolution, as well as to define novel therapeutic vulnerabilities of these high-risk subgroups of CLL patients.

Within the research lines of the HARMONY Project (Big Data for Blood Cancer), in which the laboratory collaborates, we can highlight the analysis of sequencing data (NGS) and clinical data to discover patterns and insights that can improve current medical protocols. One of the lines of research is focused on analysing the co-occurrence of genetic lesions in patients with AML that affect the patient's evolution. A presentation of the combined impact of $DNMT3^{mut}$ and $RAD21^{mut}$ has been accepted at the ASH 2021 congress, as well as other presentation of a predictive machine learning research tool to predict the risk of relapse after first remission in AML patients treated without allogeneic haematopoietic stem cell transplantation.

SENIOR RESEARCHER

BONE MARROW MICROENVIRONMENT IN MULTIPLE MYELOMA AND BONE LESIONS

SENIOR RESEARCHER
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RESEARCH SUMMARY

Our group has focused on the study of the role of the bone marrow microenvironment in the pathology of multiple myeloma (MM) and in the development of bone lesions associated to this disease. We have also been involved in preclinical studies of targeted agents with an anti-myeloma effect and/or being beneficial on osteolytic lesions. More recently, we have become engaged in evaluating the mechanism of action of monoclonal antibodies against MM, identifying mechanisms of resistance to current anti-myeloma therapies and exploring the role of extracellular vesicles in the biology of the disease.

LINES OF RESEARCH AND STRATEGIC OBJECTIVES

1) To study the interactions of myeloma cells and the bone marrow microenvironment (mesenchymal stromal cells, immune cells, role of extracellular vesicles).

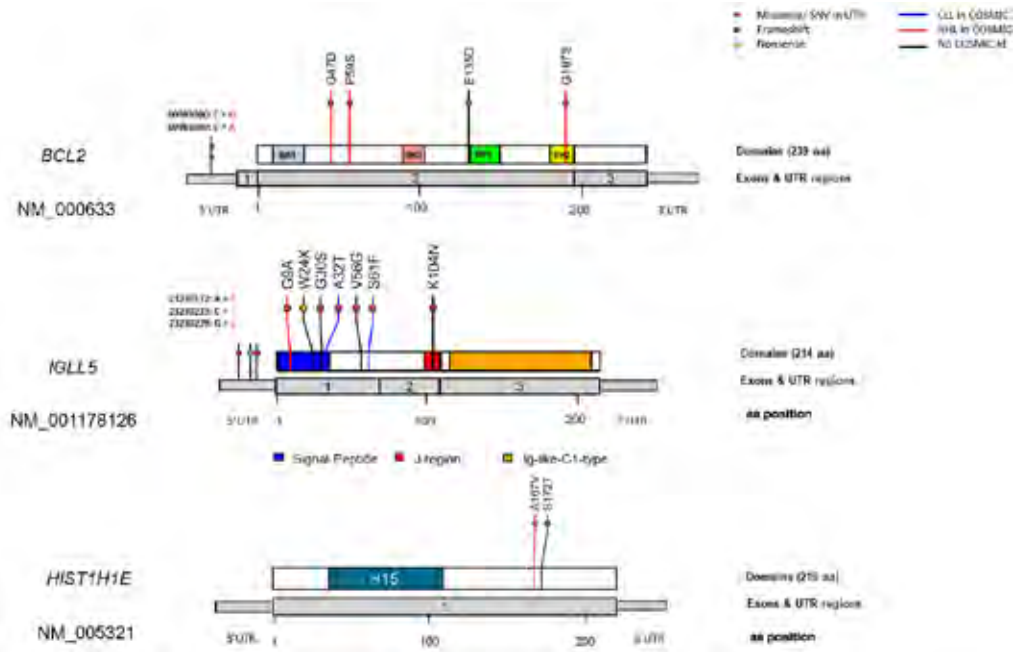
2) To assess the efficacy and mechanism of action of new targeted agents and their combinations with anti-myeloma or bone anabolic/anti-resorptive effects.

3) To characterize the efficacy and mechanism of action *(in vitro and in vivo models)* of immunotherapeutic agents in monotherapy and in combination with standard agents in multiple myeloma.

4) To decipher intrinsic and bone marrow microenvironment-mediated mechanisms of resistance to anti-myeloma agents.

FUTURE CHALLENGES

- To develop appropriate *in vivo* models for the characterization of immunotherapeutic agents and their effect on the bone marrow microenvironment.
- To identify mechanisms by which the bone marrow microenvironment mediates therapeutic resistance and survival to myeloma cells.
- To implement genome-wide screenings for the search of MM intrinsic mechanisms of resistance to therapeutic agents.
- To explore the potential biomarker value of circulating vesicles from myeloma patients.



Schematic representation of BCL2, IGLL5 and HIST1H1E mutations. Positions of coding mutations are indicated according to the aminoacid change at the protein level; positions of UTR mutations are indicated according to the nucleotide change in the DNA sequence (GRCh37/hg19 genome); with respect to the UTR regions, only BCL2 and IGLL5 UTR regions were covered in the sequencing analysis. Number of cases are denoted by circles in each mutation line and the color of the circles indicates the mutation subtype (missense, frameshift and nonsense). Mutations identified in the COSMIC database in non-Hodgkin lymphomas (NHL) are represented with red lines; mutations reported in the COSMIC database in CLL are indicated with blue lines; all other mutations are shown in black. Aa, aminoacid.

PUBLICATIONS

- **Daratumumab is a safe and effective rescue therapy for multiple myeloma patients who relapse after allo-HSCT.** *González-Rodríguez AP, López-Corral L, Fajardo DFM, González-Huerta AJ, Palomo P, Bermúdez A, Ripa TZ, Santos-Díaz P, González-Muñiz S, Zanabilli J, Ubieto AJ, de Arriba F, Arnao-Herraiz M, Sordo-Bahamonde C, López-Soto A, González S, Rosiñol L, Mateos MV.* **Bone Marrow Transplant. 55(2):461-463, 2020 doi: 10.1038/s41409-019-0525-1.** PMID: 30988379. **IF: 5.483 / Q1**

- **Daratumumab-based regimens are highly effective and well tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies.** *Mateos MV, Spencer A, Nooka AK, Pour L, Weisel K, Cavo M, Laubach JP, Cook G, Iida S, Benboubker L, Usmani SZ, Yoon SS, Bahlis NJ, Chiu C, Ukropec J, Schecter JM, Qin X, O' Rourke L, Dimopoulos MA.* **Haematologica. 105 (2): 468-477, 2020. doi: 10.3324/haematol.2019.217448.** PMID: 31221782. **IF: 9.941 / D1**

- **Preclinical evaluation of the simultaneous inhibition of MCL-1 and BCL-2 with the combination of S63845 and venetoclax in multiple myeloma.** *Algarín EM, Díaz-Tejedor A, Mogollón P, Hernández-García S, Corchete LA, San-Segundo L, Martín-Sánchez M, González-Méndez L, Schoumacher M, Banquet S, Kraus-Berthier L, Kloos I, Derreal A, Halilovic E, Maacke H, Gutiérrez NC, Mateos MV, Paíno T, Garayoa M, Ocio EM.* **Haematologica. 105(3): e116-e120, 2020. doi: 10.3324/haematol.2018.212308.** PMID: 31320555. **IF: 9.941 / D1**

- **Genomic analysis of a familial myelodysplasia/acute myeloid leukemia and inherited RUNX1 mutations without a pre-existing platelet disorder.** *Prieto-Conde MI, Labrador J, Hermida G, Alonso S, Jiménez C, García-Álvarez M, Medina A, Balanzategui A, Alcoceba M, Sarasquete ME, Puig N, González V, Gutiérrez NC, García-Sanz R, González-Díaz M, Chillón MDC.* **Leuk Lymphoma. 61(1):181-184, 2020 doi: 10.1080/10428194.2019.1648801.** PMID: 31385734. **IF: 3.280 / Q3**

- **Influence of donor type, stem cell source and conditioning on outcomes after haploidentical transplant for lymphoma - a LWP-EBMT study.** *Bazarbachi A, Boumendil A, Finel H, Castagna L, Dominietto A, Blaise D, Diez-Martin JL, Tischer J, Gülbas Z, Wallet HL, Corral LL, Mohty M, Koc Y, Yakoub-Agha I, Schmid C, El Cheikh J, Arat M, Forcade E, Dreger P, Rocha V, García GG, Chalandon Y, Ferra C, Orvain C, Robinson S, Montoto S, Sureda A.* **Br J Haematol.;188(5):745-756, 2020. doi: 10.1111/bjh.16182.** PMID:31498883 **IF: 6.998 / Q1**

- **Efficacy of bortezomib to intensify the conditioning regimen and the graft-versus-host disease prophylaxis for high-risk myeloma patients undergoing transplantation.** *Caballero-Velázquez T, Calderón-Cabrera C, López-Corral L, Puig N, Marquez-Malaver F, Pérez-López E, García-Calderón C, Rosso-Fernández CM, Caballero Barrigón D, Martín J, Mateos MV, San Miguel J, Pérez-Simón JA; European Myeloma Network.* **Bone Marrow Transplant.; 55(2):419-430, 2020. doi: 10.1038/s41409-019-0670-6.** PMID: 31551517. **IF: 5.483 / Q1**

- **A New Next-Generation Sequencing Strategy for the Simultaneous Analysis of Mutations and Chromosomal Rearrangements at Dna Level in Acute Myeloid Leukemia Patients.** *Prieto-Conde MI, Corchete LA, García-Álvarez M, Jiménez C, Medina A, Balanzategui A, Hernández-Ruano M, Maldonado R, Sarasquete ME, Alcoceba M, Puig N, González-Calle V, García-Sanz R, Gutiérrez NC, González-Díaz M, Chillón MC.* **J Mol Diagn.; 22(1):60-71, 2020. doi: 10.1016/j.jmoldx.2019.08.002.** PMID: 31605801. **IF: 5.568 / Q1**

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- **Benchmarking of survival outcomes following haematopoietic stem cell transplantation: A review of existing processes and the introduction of an international system from the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE).** *Snowden JA, Saccardi R, Orchard K, Ljungman P, Duarte RF, Labopin M, McGrath E, Brook N, de Elvira CR, Gordon D, Poirel HA, Ayuk F, Beguin Y, Bonifazi F, Gratwohl A, Milpied N, Moore J, Passweg J, Rizzo JD, Spellman SR, Sierra J, Solano C, Sanchez-Guijo F, Worel N, Gusi A, Adams G, Balan T, Baldomero H, Macq G, Marry E, Mesnil F, Oldani E, Pearce R, Perry J, Raus N, Schanz U, Tran S, Wilcox L, Basak G, Chabannon C, Corbacioglu S, Dolstra H, Kuball J, Mohty M, Lankester A, Montoto S, Nagler A, Styczinski J, Yakoub-Agha I, de la Tour RP, Kroeger N, Brand R, de Wreede LC, van Zwet E, Putter H.* **Bone Marrow Transplant. 55(4):681-694, 2020. doi: 10.1038/s41409-019-0718-7.** PMID: 31636397. **IF: 5.483 / Q1**

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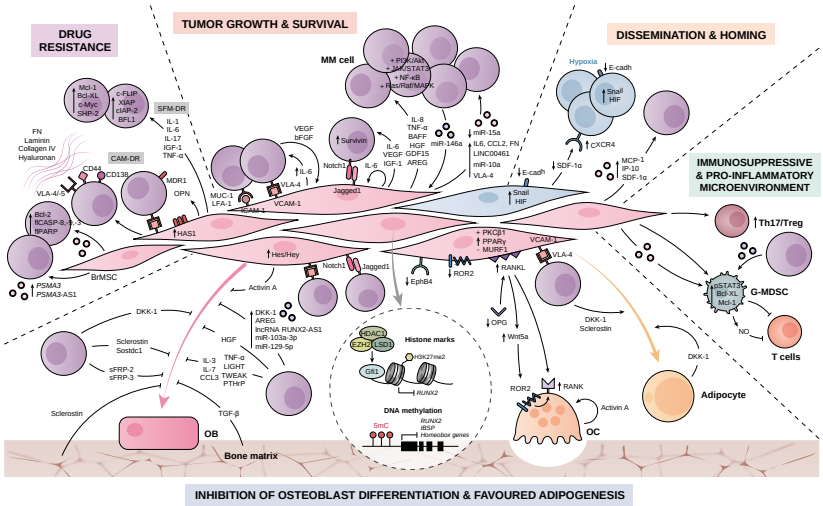

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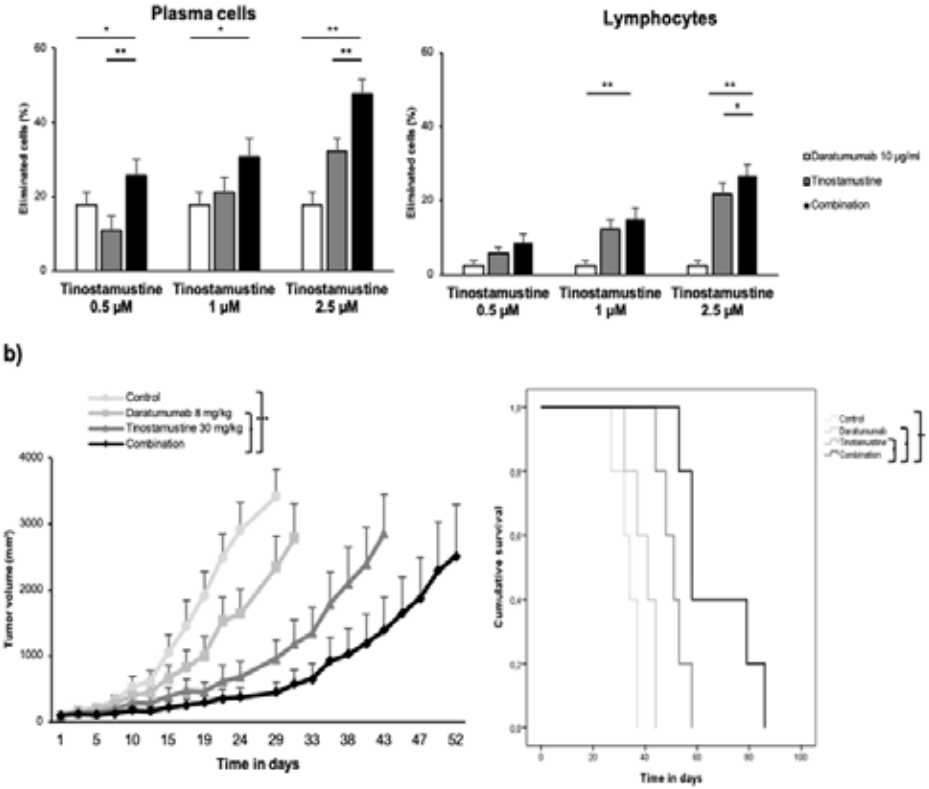

a) Effect of the combination of tinostamustine + daratumumab for 24 hours in ex vivo cultures of bone marrow samples from MM patients. Each bar shows mean + SEM (n=10). *p<0.05 and **p<0.01 by the Kruskal-Wallis test and Dunn's post hoc tests. b) Tinostamustine + daratumumab treatment delayed the growth of human plasmacytomas and prolonged mice survival. *p<0.05, "*p<0.01 and ***p<0.001 by one-way analysis of variance (ANOVA) and Dunn's post-hoc test.

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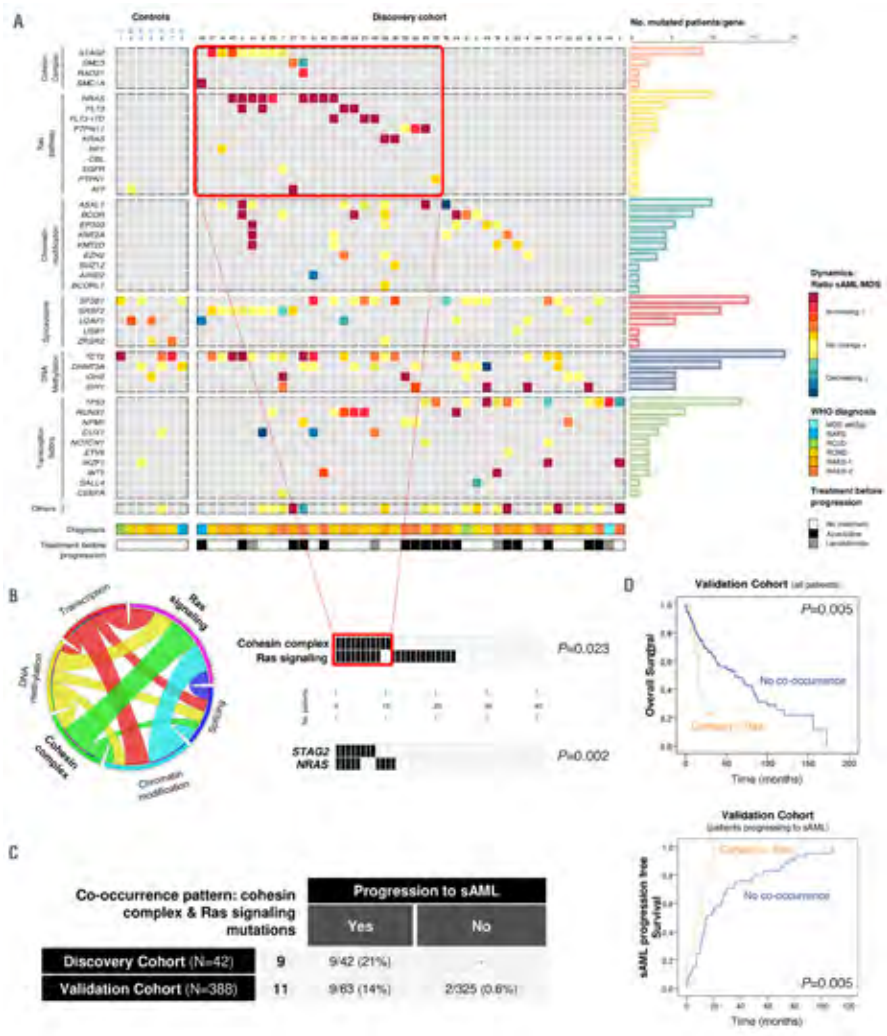

Dynamics of gene mutations in the myelodysplastic syndromes to secondary acute myeloid leukemia progression axis. (A) Comprehensive landscape of mutational dynamics in the discovery and control cohorts. Genes are grouped by cellular functions and are represented in rows; each column represents a patient. Dynamics are represented by a color gradient: red/orange for newly acquired/increasing mutations, yellow for stable mutations, and blue/green colors for decreasing mutations. (B) Co-occurrence of cohesin complex and Ras signaling mutations in the discovery cohort. Circos plot of statistically significant associations between mutations detected in the discovery cohort, grouped by functional pathways. Graphs represent patients with mutations in the cohesin complex and Ras signaling, and the most frequently mutated genes in these pathways, STAG2 and NRAS, showing a statistically significant association (P=0.023 and P=0.002, respectively). (C) Incidence of this co-occurrence pattern in the discovery and validation cohorts. The table contains the number of patients with the combination of cohesin and Ras signaling mutations in the discovery and validation cohorts and an indication of whether they evolved to secondary acute myeloid leukemia (sAML). (D) Prognostic impact of the co-occurring mutations in the cohesin complex and Ras pathway. Kaplan-Meier curves for overall survival and sAML progression-free survival in patients bearing co-occurring cohesin and Ras pathway mutations in the entire validation cohort. VAF: variant allele frequency; LR: low-risk; HR: high-risk; NS: not significant; *P<0.05. (doi: 10.3324/haematol.2020.248807).

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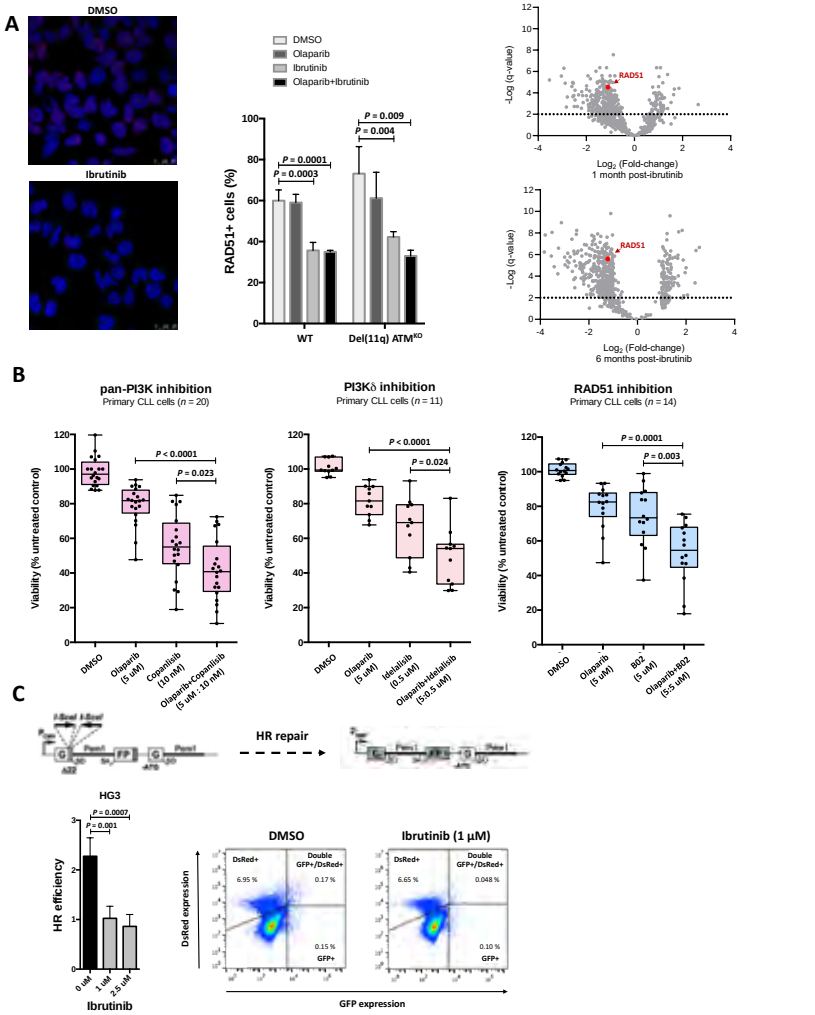

Effects of ibrutinib in RAD51-mediated HR repair in CLL. a Left panel: representative images and quantification of the number RAD51-positive cells 6 h after irradiation (2 Gy) in HG3WT and HG3-del(11q) ATMKO clones. Cells were pretreated for 24 h with 5 μM olaparib, 1 μM ibrutinib or the drug combination. Data are represented as the mean values +/- SD of three independent experiments. Cells were scored RAD51 + when five or more foci were formed. At least 100 cells per experiment were counted. Right panel: volcano plots of transcripts changes comparing 1- (top) and 6-month (bottom) post-ibrutinib initiation vs. pretreated longitudinal samples in 14 CLL patients. RAD51 expression is significantly downregulated in samples after 1 month and 6 months of ibrutinib therapy. Log2 of fold-changes (treatment vs. control) are shown in x axis and statistical significance (-log10 of q value) is shown in y axis. RNA-seq data were previously generated in Landau et al. b Primary CLL cells were seeded in co-culture with HS-5 bone marrow stromal cells, 1.5 μg/mL CpG and 50 ng/mL IL-2 and treated with the indicated drugs and doses for 5 days. Normalized surviving fraction is expressed relative to untreated cells. Data are presented as the mean +/- SD. c Upper panel displays a representation of the HR-reporter plasmid adapted from Seluanov et al. Lower-left panel represents the HR repair efficiency as calculated by dividing the number of GFP + cells of the totality of positive transfected DsRed + cells. Data represent mean +/- SD of three independent experiments. Right panel displays representative plots of the HR efficiency of HG3 treated with DMSO or ibrutinib (1 μM). (doi: 10.1038/s41375-020-0714-3)

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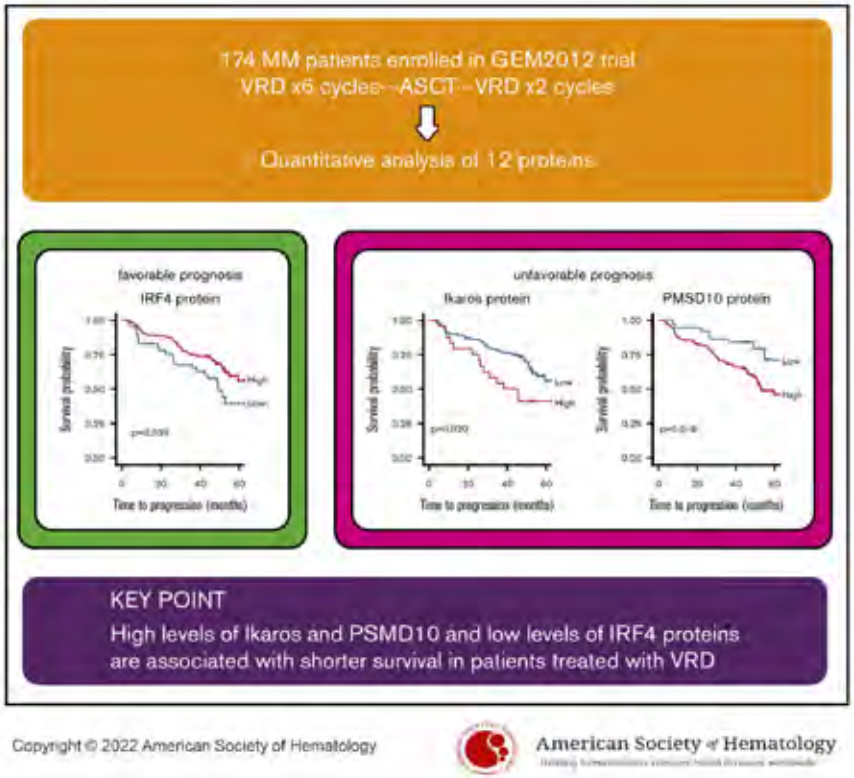

Quantitative expression of Ikaros, IRF4, and PSMD10 proteins predicts survival in VRD-treated patients with multiple myeloma

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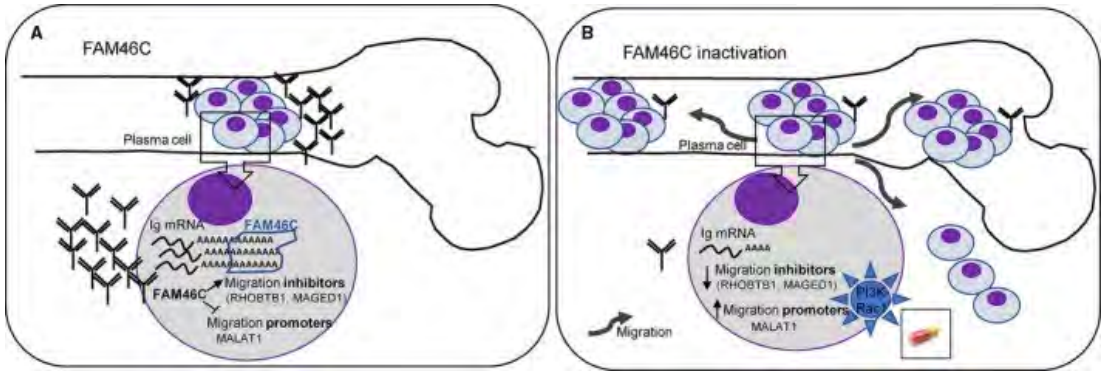
- **Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenstrom's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study.** *Buske C, Tedeschi A, Trotman J, García-Sanz R, MacDonald D, Leblond V, Mahe B, Herbaux C, Matous JV, Tam CS, Heffner LT, Varettoni M, Palomba ML, Shustik C, Kastritis E, Treon SP, Ping J, Hauns B, Arango-Hisijara I, Dimopoulos MA.* **J Clin Oncol. 2021 Oct 4:JCO2100838. doi: 10.1200/JCO.21.00838.** PMID: 34606378. **IF: 44.544 / D1**

- **Interlaboratory Analytical Validation of a Next-Generation Sequencing Strategy for Clonotypic Assessment and Minimal Residual Disease Monitoring in Multiple Myeloma.** *Medina A, Jiménez C, Puig N, Sarasquete ME, Flores-Montero J, García-Álvarez M, Prieto-Conde I, Chillón C, Alcoceba M, González-Calle V, Gutiérrez NC, Jacobsen A, Vigil E, Hutt K, Huang Y, Orfao A, González M, Miller J, García-Sanz R.* **Arch Pathol Lab Med. 2021 Oct 7. doi: 10.5858/arpa.2021-0088-OA.** PMID: 34619755. **IF: 5.534 / Q1**

- **Reference Values to Assess Hemodilution and Warn of Potential False-Negative Minimal Residual Disease Results in Myeloma.** *Puig N, Flores-Montero J, Burgos L, Cedena MT, Cordón L, Pérez JJ, Sanoja-Flores L, Manrique I, Rodríguez-Otero P, Rosiñol L, Martínez-López J, Mateos MV, Lahuerta JJ, Bladé J, San Miguel JF, Orfao A, Paiva B.* **Cancers (Basel). 2021 Sep 30;13(19):4924. doi: 10.3390/cancers13194924.** PMID: 34638406. **IF: 6.639 / Q1**

- **Prognostic significance of FLT3-ITD length in AML patients treated with intensive regimens.** *Castaño-Bonilla T, Alonso-Dominguez JM, Barragán E, Rodríguez-Veiga R, Sargas C, Gil C, Chillón C, Vidriales MB, García R, Martínez-López J, Ayala R, Larrayoz MJ, Anguita E, Cuello R, Cantalapiedra A, Carrillo E, Soria-Saldise E, Labrador J, Recio I, Algarra L, Rodríguez-Medina C, Bilbao-Syeiro C, López-López JA, Serrano J, De Cabo E, Sayas MJ, Olave MT, Sánchez-García J, Mateos M, Blas C, López-Lorenzo JL, Lainez-Gonzalez D, Serrano J, Martínez-Cuadrón D, Sanz MA, Montesinos P.* **Sci Rep. 2021 Oct 20;11(1):20745. doi: 10.1038/s41598-021-00050-x.** PMID: 34671057. **IF: 4.380 / Q1**

- **External Evaluation of Population Pharmacokinetic Models of Imatinib in Adults Diagnosed with Chronic Myeloid Leukaemia.** *Corral Alaejos Á, Zarzuelo Castañeda A, Jiménez Cabrera S, Sánchez-Guijo F, Otero MJ, Pérez-Blanco JS.* **Br J Clin Pharmacol. 2021 Oct 27. doi: 10.1111/bcp.15122.** PMID: 34705297. **IF: 4.340 / Q2**



Schematic representation of the functional consequences of FAM46C inactivation. A, *FAM46C* is up-regulated during PC differentiation to increase antibody production by extending the poly(A) tail of Ig mRNAs. B, Inactivation of the ncPAP reduced Ig poly(A) tail length, the amount of Ig mRNAs and, consequently, the Ig protein levels. Moreover, the lack of FAM46C increases the migratory ability of MM cells, which might explain the role of this gene as a tumour suppressor. The increased rate of migration after *FAM46C* knockout depended on PI3K-Rac1 activation. Therefore, patients with FAM46C mutations could benefit from PI3K or Rac1 inhibitors.

OTHER PUBLICATIONS & BOOK CHAPTERS

- **Hematología: Manual Básico Razonado (5ª edición).** San Miguel JF, Sánchez-Guijo F. **Barcelona, Elsevier, 2020. 336 páginas. ISBN: 978-84-9113-453-4.**
- **Síndromes linfoproliferativos. Cap 12 Book: Hematología. Manual básico razonado (5ª edición).** M González Díaz. Eds: JF San Miguel, F M Sánchez-Guijo. **Editorial Elservier España, SA, pp 139-154. 14-febrero-2020; ISBN-13: 978-8491134534.**
- **Manual para el control y tratamiento de los pacientes con leucemia mieloide crónica** Sánchez-Guijo Martín F. **ISBN: 978-84-09-24696-0**.
- **Discontinuación del tratamiento** Sánchez-Guijo F. **Book: Manual para el control y tratamiento de los pacientes con leucemia mieloide crónica. Cap. 14 Grupo Español de LMC (GELMC). Editado por MFAR, Barcelona, 2020. Págs: 154-159. ISBN: 978-84-09-24696-0.**
- **Nuevos fármacos y perspectivas terapéuticas en la leucemia mieloide crónica.** Sánchez-Guijo F, Steegmann JL. **Book: Manual para el control y tratamiento de los pacientes con leucemia mieloide crónica. Cap. 15. Grupo Español de LMC (GELMC). Editado por MFAR, Barcelona, 2020. Págs: 160-167. ISBN: 978-84-09-24696-0.**
- **Guía de linfomas 2020-FUCALHH.** Marcos González, M. Dolores Caballero, Ramón García-Sanz, Norma C. Gutiérrez, Alejandro Martín. Coordinadora MJ Peñarrubia. **ISBN: 978-84-09-17278-8.**
- **Guía clínica:** Marcos González, Miguel Alcoceba. **Guía Nacional de Leucemia Linfática Crónica y Linfoma Linfocítico 2020. ISBN: 978-84-09-20746-6**.
- **Guía clínica: Hematoguía Mieloma.** M. Victoria Mateos, Verónica González de la Calle, Noemí Puig**. Grupo de Estudio de Gammapatías Monoclonales de Castilla y León. 2020. Versión 4.1. SEHH. https//www.sehh.es/recursos/2020/09/27.**
- **Guía clínica: Guía de Mieloma Múltiple.** M. Victoria Mateos, Norma C. Gutiérrez, Noemí Puig. **Grupo Español de Mieloma (GEM). Con el aval científico de la Sociedad Española de Hematología y Hemoterapia (SEHH) y PETHEMA. Luzán 5 Health Consulting. S.A. 2021; ISBN: 978-84-18420-91-7.**
- **Guía de Práctica Clínica de GELTAMO para el tratamiento de pacientes con Linfoma de Hodgkin.** Ramón García-Sanz. **ISBN: 978-84-09-11251-7.**
- **¿Cómo se diagnostica la leucemia linfocítica crónica?.** *A. Navarro Bailón, M. Baile González & M. González Díaz.* **Book: «50 preguntas clave en leucemia linfocítica crónica» - SEHH. Eds: Javier de la Serna Torroba y José Ángel Hernández Rivas. ISBN: 978-84-17670-82-5.**
- **Fotoaféresis extracorpórea en el tratamiento de la enfermedad injerto contra receptor. Guía de práctica clínica.** Lucia López-Corral. **ISBN: 978-84-09-09563-6.**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Providing the right care to the right patient with MyeloDysplastic Syndrome at the right time (MDS-RIGHT)	María Diez Campelo (IECSCYL)	European Union	2015-2020	35,145.00 €
Restoring tissue regeneration in patients with visceral graft versus host disease (RETHRIM)	Fermín Sánchez-Guijo Martín (Nodo 6)	European Union	2015-2021	314,850.00 €
Función valor diagnóstico e inhibición farmacológica de R-RAS2, un nuevo "driver" oncogénico.	Mª Dolores Caballero Barrigón (Grupo 3)	Spanish Association against Cancer (AECC)	2016-2021	197,500.00 €
Modelo integrado de citometría y ultrasecuenciación de nueva generación para desvelar la patogénesis de la leucemia mieloblástica aguda y definir nuevos criterios de respuesta (PI16/00517)	Jesús San Miguel (Coordinator) / Mª Carmen Chillón (PI)	Carlos III Health Institute (ISCIII)	2017-2021	163,350.00 €
Red de Investigación Cooperativa (RETIC) de Terapia Celular (TerCEL) (RD16/0011/0015)	Fermín Sánchez-Guijo Martín	Carlos III Health Institute (ISCIII)	2017-2021	222,925,00 €
Centro en Red de Medicina Regenerativa y Terapia Celular de Castillla y León	Fermín Sánchez-Guijo Martín	Regional Governement of Castilla y Leon (JCyL)	2017-2021	110,000.00 €
Hematologic tumours: diagnosis and therapeutic precision innovations and assessment of their usefulness in controlled clinical trials (clinical trials and usual practice) (CB16/12/00233)	Marcos González Díaz	Carlos III Health Institute (ISCIII)	2017-2022	149,400.00 €
HARMONY" Program: Topic 4 "Development of an outcomes-focused data platform to empower policy makers and clinicians to optimize care for patients with hematologic malignancies" (Innovative Medicines Initiative, "H2020-JTI-IMI2" Big Data for Better Outcomes)	Jesús Mª Hernández Rivas	European Union	2017-2021	2,200,000.00 €
Caracterización de los SMD de bajo riesgo sin sideroblastos en anillo: de las CPH a las vesículas extracelulares circulantes (PI17/01741)	María Diez Campelo	Carlos III Health Institute (ISCIII)	2018-2020	197,230.00 €
Plataforma de unidades de investigación clínica y ensayos clínicos	Mª Victoria Mateos Manteca	Cardiovascular Health Institute	2018-2020	120,450.00 €
Study of the functional status of p53 in multiple myeloma and its impact on therapeutic response and patient survival.	Norma C. Gutierrez Gutierrez	Spanish Association against Cancer (AECC)	2018-2020	60,000.00 €
Estudio de los pacientes con trastornos plaquetarios hereditarios mediante secuenciación del exoma y edición del ADN por CRISPR/CAS9 (PI17/01996)	Jose María Bastida	Carlos III Health Institute (ISCIII)	2018-2020	128,018.00 €
Non-invasive diagnostics and monitoring of MRD (minimal resudual disease) and clonal evolution of Waldenström´s macroglobulemira (FIL_BIOWM)	Ramón García Sanz	International Waldenstrom´s Macroglobulinemia Foundation (IWMF)	2018-2020	100,000.00 €
Mutational landscape of follicular lymphoma at late relapse, early failure and histological transformation (PROYE18020BEA)	Ramón García Sanz	Spanish Association against Cancer (AECC)	2018-2021	100,000.00 €
Study of the functional status of p53 in multiple myeloma and its impact on the therapeutic response and patient survival	Norma C Gutiérrez Gutiérrez	Spanish Association against Cancer (AECC)	2018-2021	60,000.00 €
Valoración de cereales integrales para el desarrollo de alimentos de carácter inmunomodulador dirigidos a pacientes oncohematológicos	Mª Dolores Caballero Barrigón	Spanish Ministry of Science and Innovation	2018-2022	223,850.00 €

PROJECT	PI	GRANT	TIME	FUNDING
Early detection and intervention: understanding the mechanism of transformation and hidden resistance of incurable hematological malignancies	Marcos González Díaz	Spanish Association against Cancer (AECC)	2018-2023	269,052.00 €
Centro en Red de Medicina Regenerativa y Terapia Celular de Castillla y León	Mercedes Garayoa Berrueta (Nodo CIC)	Regional Governement of Castilla y Leon (JCyL)	2019-2020	164,000.00€
Multiparametric evaluation of the effects of midostaurin and HDM201 on human bone marrow-derived mesenchymal stromal cells	Fermín Sánchez-Guijo Martín	Novartis Pharmaceuticals	2019-2020	33,000.00 €
Evaluación de estrategias de sensibilización a tratamientos inmunoterápicos en Mieloma Múltiple (ref. PI18/01600)	Teresa Paíno	Carlos III Health Institute (ISCIII)	2019-2021	87,120.00 €
Caracterizacion y seguimiento del sistema inmune en pacientes mayores con MM tratados dentro del ensayo GEM2017FIT: tratando de personalizar el tratamiento para maximizar la respuesta. (PI18/01673)	Mª Victoria Mateos Manteca	Carlos III Health Institute (ISCIII)	2019-2021	209,330.00 €
Macroglobulinemia de Waldenstrom: identificación de la célula clonogénica e implicaciones en su diagnóstico y monitorización. (PI18/01866)	Ramón García Sanz	Carlos III Health Institute (ISCIII)	2019-2021	220,000.00 €
SYNtherapy. Synthetic Lethality for Personalized Therapy-based Stratification in Acute Leukemia (ERAPERMED2018-275)	Jesús Mª Hernández Rivas	European Union ERAPERMED/ ISCIII	2019-2021	199,999.00 €
Identificación de marcadores pronósticos/predictores de recaída/progresión precoz en linfoma folicular (PI18/00410)	Mª Dolores Caballero Barrigón	Carlos III Health Institute (ISCIII)	2019-2021	135,520.00 €
Caracterizacion Molecular de Hemofilia (Sobi19/001)	Jose Ramon González Porras	Sobi Laboratories	2019-2021	20,000.00 €
Perfil genómico integrado DNA/RNA como estrategia para el diagnóstico de la leucemia mieloblástica aguda. Monitorización molecular de EMR mediante técnicas de alta sensibilidad (PI18/01946)	Marcos González Díaz	Carlos III Health Institute (ISCIII)	2019-2021	209,088.00 €
Caracterización molecular de subpoblaciones celulares en macroglobulinemia de Waldenström para identificar la célula clonogénica: implicaciones en el diagnóstico, tratamiento y monitorización (PI18/01866)	Ramón García Sanz (PI) / M. Eugenia Sarasquete (co-PI)	Carlos III Health Institute (ISCIII)	2019 -2021	304,678.00 €
Minimal residual disease in patients with non-Hodgkin's lymphoma using imaging and molecular biology techniques: total metabolic volume, tumor glycolysis and circulating tumor DNA (GLD18/00063.)	Ramón García Sanz	Gilead Sciences, S.L.U.	2019-2021	49,829.00 €
Estudio genómico y funcional de la concurrencia de alteraciones genéticas y de la resistencia a fármacos en pacientes de leucemia linfática crónica mediante modelos celulares y animales	Jesús Mª Hernández Rivas	Carlos III Health Institute (ISCIII)	2019-2021	135,520.00 €
Medicina personalizada en la Leucemia Aguda Linfoblástica. Uso clínico de las tecnologías de secuenciación masiva. (SA271P186)	Jesús Mª Hernández Rivas	Carlos III Health Institute (ISCIII)	2019-2021	120,000.00 €
Cell therapy for knee osteoarthritis. Comparison of treatments with autologous and allogenic mesenchymal stromal cells in a multicenter controlled randomized clinical trial (ARTROCEL)	Fermín Sánchez-Guijo Martín	Carlos III Health Institute (ISCIII)	2019-2022	767,962.00 €
Contrato Miguel Servet tipo II (CPII18/00028)	M. Eugenia A. Sarasquete	Carlos III Health Institute (ISCIII)	2019-2022	91,125.00 €

PROJECT	PI	GRANT	TIME	FUNDING
Caracterización fenotípica y genética de la infiltración de médula ósea en pacientes con linfoma difuso de células B grandes (GRS 2035/A/19)	Alejandro Martín	Regional Health Management. Regional Governement of Castilla y Leon	2020	13,320.00 €
Monitorización de la respuesta al tratamiento del linfoma de Hodgkin mediante ADN circulante tumoral (GRS 2037/A/19)	Ramón García Sanz	Regional Health Management. Regional Governement of Castilla y Leon	2020	15,840.00 €
Caracterización haplotípica, genotípica y alélica de polimorfismos implicados en la regulación de la actividad de células NK en pacientes con leucemia mieloblástica aguda (GRS 2080/A/19)	Francisco Boix	Regional Health Management. Regional Governement of Castilla y Leon	2020	13,140.00 €
Estudio multicéntrico para la caracterización clinicomolecular de los "rare bleeding disorders" (FUCALHH20/001)	José Mª Bastida Bermejo	Hematology & Hemotherapy Foundation of Castilla y Leon (FUCALHH)	2020	6,000.00 €
Estandarización y validación de un papel diagnóstico integrado de secuenciación masiva en el manejo asitencial de la leucemia linfática crónica: mutaciones genéticas, alteracieones del número de copias e hipermutación somática de IGH. (GRS 2036/A/19)	Marcos González Diaz	Regional Health Management. Regional Governement of Castilla y Leon	2020	14,400.00 €
Caracterización biológica de los pacientes con linfoma difuso de células B grandes (LDCBG) doble-hit MYC/BCL2 de Castilla y León (FUCALHH19/001)	Miguel Alcoceba Sánchez	Hematology & Hemotherapy Foundation of Castilla y Leon (FUCALHH)	2020	6,000.00 €
Caracterización de las alteraciones genéticas en linfoMa difuso de células B grandes con doble /triple translocación MYC y BCL2 y/o BCL6 en pacientes de Castilla y León (FS/24-2019)	Miguel Alcoceba Sánchez	Solorzano Foundation	2020	1,822.00 €
Generación de modelos murinos mediante CRISPR/Cas9 para el análisis de la patogenicidad de las alteraciones germinales de RUNX1 y su relación con el riesgo de desarrollar leucemia aguda en los pacientes con trastorno plaquetario congénito (GRS2061/A/19)	Jose Mª Bastida Bermejo	Regional Health Management. Regional Governement of Castilla y Leon	2020	17,000.00 €
Elaboración de un Modelo de Datos armonizados bajo el standard OMOP para la recogida y gestión de información de los pacientes Covid-19 (GRSCOVID23/A/20)	Jesús Mª Hernández Rivas	Regional Health Management. Regional Governement of Castilla y Leon	2020	7,371.00 €
Análisis por secuenciación masiva de las mutaciones, productos de fusion y variaciones en el numero de copias de las leucemias agudas linfoblásticas de linaje B (GRS2062/A/19)	Jesús Mª Hernández Rivas	Regional Health Management. Regional Governement of Castilla y Leon	2020	14,940.00 €
Búsqueda de biomarcadores proteicos predictores de la respuesta al venetoclax en hemopatias malignas (GRS 2058/A/19)	Norma C Gutierrez Gutierrez	Regional Health Management. Regional Governement of Castilla y Leon	2020-2021	15,840.00 €
Aplicación de las redes sociales Twitter e Instagram como herramientas docentes para la enseñanza de la genética clínica	Jesús Mª Hernández Rivas	Salamanca University	2020-2021	700.00 €
Contrato Postdoctoral de Perfeccionamiento Sara Borrell (CD19/00030)	Cristina Jiménez	Carlos III Health Institute (ISCIII)	2020-2022	80,598.00 €

PROJECT	PI	GRANT	TIME	FUNDING
Estudio de mecanismos de resistencia intrínsecos o mediados por elementos de microambiente de la médula ósea a agentes antimieloma múltiple (PI19/01384)	Mercedes Garayoa	Carlos III Health Institute (ISCIII)	2020-2022	240,790.00 €
Evaluación dinámica de las células mesenquimales, las vesículas extracelulares y el sistema inmune en pacientes críticos de cuidados intensivos: de la fisiopatología al potencial tratamiento (PI19/01455)	Fermín Sanchez-Guijo Martín	Carlos III Health Institute (ISCIII)	2020-2022	171,820.00 €
Investigación de las funciones de las ciclinas d en la patogenia del mieloma múltiple y de su significado pronóstico (PI19/00674)	Norma C Gutierrez Gutierrez	Carlos III Health Institute (ISCIII)	2020-2022	157,000.00 €
NEMHESYS: "NGS Establishment in Multidisciplinary Healthcare Education SYStem. PROYECTO ERASMUS+. 612639-EPP-1-2019-1-ES-EPPKA2-KA	Jesús Mª Hernández Rivas	European Union	2020-2022	176,720.00 €
Contrato PFIS: Contrato Predoctorales de Formación en Investigación en Salud (FI19/00320)	Ramón García Sanz	Carlos III Health Institute (ISCIII)	2020 -2023	82,400.00 €
ctDNA evaluation in the BRESELIBET trial	Ramón García-Sanz	Geltamo / Takeda	2020-2023	322,000.00 €
Resistance mechanisms of molecular targeted therapies in mantle cell lymphoma (RESTMCL)(299/C/2019 - MARATO19/002)	Silvia Beá, Ramón García Sanz	La Marató TV3 Foundation	2020-2023	100,000.00 €
Aplicación de la secuenciación del exoma para el diagnóstico de los pacientes con trastornos plaquetarios congénitos y edición del ADN por CRISPR/CAS9 en modelos animales.	José Mª Bastida Bermejo	Mutua Madrileña Foundation	2020-2023	100,000.00 €
Towards precision medicine in myeloma: search for predictive biomarkers, overcoming resistance end finding new therapeutic targets oriented to molecular subtypes (PROYE20047GUTI)	Norma C Gutiérrez Gutiérrez	Spanish Association against Cancer (AECC)	2020-2023	300,000.00 €
Harmony Plus. Healthcare alliance for resourceful medicines effective against neoplasms in hematology – PLUS. HARMONY PLUS (945406)	Jesús Mª Hernández Rivas	European Union-Innovative Medicines Initiative	2020-2023	11,882,669.00 €
Análisis genómico y functional de las mutaciones, productos de fusion y varaciones en el número de copias, mediante secuenciació masiva y estudios in-vitro e in-vivo: implicaciones en leuceia aguda linfoblástica de linaje B(LAL-B)	Jesús Mª Hernández Rivas	Regional Governement of Castilla y Leon	2020-2023	264,000.00 €
TranspoCART: a multicenter, first-in-human, phase I/II clinical trial with transposon-based CD19-specific CART cells in patients with CD19+ R/R ALL.	Lucia López Corral	Carlos III Health Institute (ISCIII)	2020-2024	1,173,150.00 €
Estudio de los mecanismos moleculares implicados en la transformación de los síndromes mielodisplásicos a leucemia aguda mieloblástica (GRS 2155/A/2020)	Maria Diez Campelo	Regional Health Management. Regional Governement of Castilla y Leon	2021	16,000.00 €
Caracterización del linfoma folicular a nivel de célula única (single-cell) en diferentes estadios de maduración de la célula B tumoral (FUCALHH20/002)	Miguel Alcoceba	Hematology & Hemotherapy Foundation of Castilla y Leon (FUCALHH)	2021	6,000.00 €
Desarrollo preclínico de "CAR-T cells" en el Hospital Universitario de Salamanca (GRS 2182/A/20)	Fermín Sánchez-Guijo Martín	Regional Health Management. Regional Governement of Castilla y Leon	2021	15,880.00 €

PROJECT	PI	GRANT	TIME	FUNDING
Enfermedad Mínima Residual en el linfoma de Hodgkin mediante biopsia líquida y técnicas de imagen: determinación del impacto pronóstico (GRS 2272/A/20)	Ramón García Sanz	Regional Health Management. Regional Governement of Castilla y Leon	2021	15,260.00 €
Papel de la arginasa en la inmunosupresión en el Mieloma Múltiple: estudio de la combinación del inhibidor de arginasa INCB001158 con el anticuerpo monoclonal daratumumab (GRS 21707A/2020)	Mª Victoria Mateos Manteca	Regional Health Management. Regional Governement of Castilla y Leon	2021	16,700.00 €
Valoración de la utilidad de la heparina en el pronóstico y tratamiento de los pacientes con enfermedad grave por Covid 19 (GRS Covid 13/A/20)	José Ramón González Porras	Regional Health Management. Regional Governement of Castilla y Leon	2021	3,078.00 €
Estudio multicéntrico para la caracterización clínico-molecular de las coagulopatías hereditarias en Castilla y León (GRS 2147/ A7 20)	José Ramón González Porras	Regional Health Management. Regional Governement of Castilla y Leon	2021	17,300.00 €
Estudio del exoma completo y detección de variaciones en el número de copias mediante secuenciación masiva de última generación para el diagnóstico de pacientes con trastorno plaquetario congénito.	José Mª Bastida Bermejo	Regional Health Management. Regional Governement of Castilla y Leon	2021	17,700.00 €
Identificacion de marcadores clínico-biológicos predictores de supervivencia en linfoma difuso de células B grandes tras terapia CART (GRS2237/A/20)	Mª Dolores Caballero Barrigón	Regional Health Management. Regional Governement of Castilla y Leon	2021	17,700.00 €
Monitorización de la respuesta en pacientes con linfoma difuso de célula B grande sometidos a inmunoterapia con CAR-T mediante técnicas de imagen (PET/TC) y biopsia líquida (GRS 2271/A/20)	Alejandro Martín	Regional Health Management. Regional Governement of Castilla y Leon	2021	17,200.00 €
Estudio de variaciones inmunogenéticas en genes HLA y KIR para su validación como factores predictivos y de pronóstico en pacientes con COVID-19 (GRS COVID 70/A/20)	Francisco Boix	Regional Health Management. Regional Governement of Castilla y Leon	2021	7,297.00 €
Evaluación de marcadores genéticos pronósticos mediantes análisis del excoma completo en pacientes con linfoma primario mediastínico de células B grandes diagnosticados en Castilla y León. (GRS 2290/A/20)	Marcos González Diaz	Regional Health Management. Regional Governement of Castilla y Leon	2021	17,000.00 €
Estudio del valor pronóstico de genes relacionados con la autofagia en leucemia aguda linfobástica de linaje B (LAL-B)	Inmaculada Serramito Gómez	Solorzano Foundation	2021	1,918.00 €
Terapia génica en leucemia mieloide crónica mediante CRISPR-CAS9: Correción y Selección de Células Hematológicas	Ignacio García-Tuñón Llanio	Solorzano Foundation	2021	1,951.00 €
Estudio de los mecanismos moleculares que subyacen al envejecimiento y las neoplasias hematológicas: hematopoyesis clonal de potencial indeterminado (CHIP)	Mónica del Rey	Solorzano Foundation	2021	2,004.00 €
Identificación de los genes implicados en la resistencia a fármacos en leucemia linfática crónica mediante screening a escala genómica con la tecnología de edición genética CRISPR/Cas9.	Ana Eugenia Rodríguez Vicente	Salamanca University	2021	3,000.00 €
Análisis de la concurrencia de alteraciones genéticas en pacientes de leucemia linfática crónica mediante secuenciación masiva y generación de modelos celulares	Ana Eugenia Rodríguez Vicente	Solorzano Foundation	2021	1,577.00 €

PROJECT	PI	GRANT	TIME	FUNDING
Genomics and Personalized Medicine for all though Artificial Intelligence in Haematological Diseases (GENOME4ALL)	María Díez Campelo	European Union	2021-2022	154,000.00 €
UMBRELLA PROJECT: Unified platform for a Better integral Evaluation of Myelodysplastic Syndromes in Spain	María Diez Campelo	Carlos III Health Institute (ISCIII)	2021-2023	225,665.00 €
Abordaje multiómico y screening mediante CRISPR/Cas9 para la identificaci ón de vulnerabilidades y resistencias terapéuticas en leucemia linfática crónica de riesgo intermedio-alto	Jesús M. Hernández Rivas/Ana Eugenia Rodríguez Vicente	Carlos III Health Institute (ISCIII)	2021-2023	274,670.00€
Optimization of treatment with Belantamab Mafodotin (GSK2857916) in multiple myeloma: study of new pharmacological combinations and identification of resistance mechanisms	Teresa Paíno	GlaxoSmithKline (GSK)	2021-2025	193,820.00 €
Towards New Efficacy Paradigms in Newly Diagnosed Multiple Myeloma (NDMM) Patients: A Phase III GEM/ PETHEMA Trial Project Comparing the Current International Standard VRD [VRD (X 6) + Plus Transplant and Consolidation (VRDx2)] Vs. an Extended VRD (x18 Cycles) Including also Transplant, and Early Redirecting of 1st Line to Alternative Therapy if Unfavorable Response Kinetic is Observed (GCB)	Juan José Lahuerta (IP), M. Victoria Mateos (co-IP)	Spanish Association against Cancer (AECC)	2021-2027	300,000.00 €

OTHER ACTIVITIES & RELEVANT FACTS

- **Marcos González Díaz.** Consolidated Research Unit "Biología molecular y celular en hemopatías", Castilla y León code UIC 155. Director. 2015-present
- **Marcos González Díaz**. Recognized Investigation Group (GIR) at the University of Salamanca "Cellular and Molecular Biology in hemopathies". Principal Investigator. 2018-present
- **Mª Dolores Caballero Barrigón.** Consolidated Research Unit: "Linfomas y trasplante", Castilla y León code UIC 265. Director. 2018-present
- **Norma C Gutiérrez Gutiérrez.** Consolidated Research Unit in HUSAL (Salamanca): "Mieloma Múltiple", Castilla y León code UIC 110. Director. 2015-present
- **Fermín Sánchez-Guijo Martín**. Consolidated Research Unit, Castilla y León code UIC 116. Director. 25/05/2018-01/06/2024
- **Fermín Sánchez-Guijo Martín.** Recognized Investigation Group (GIR) at the University of Salamanca "Cellular Therapy and Regenerative Medicine". Principal Investigator. 1/08/2021-present
- **Fermín Sánchez-Guijo Martín.** Member of Executive Board from the "Worldwide Network for Blood and Marrow Transplantation" (WBMT). 01/04/ 2021-present.
- **Fermín Sánchez-Guijo Martín.** Elected Vicepresident from the International Society for Cellular Therapy (ISCT), Europe Region 2021-2023.
- **Fermín Sánchez-Guijo Martín.** Member of the Scientific Committee for Evaluation of Cellular Therapy Clinical Trials in Humans from the National Transplant Orgnaization (ONT). 2017-present.
- **Fermín Sánchez-Guijo Martín.** Member of the Committee of Experts from the Spanish Ministry of Health for The use of CAR **Therapy** at the National Health System, 01/01/ 2019-present.
- **Fermín Sánchez-Guijo Martín.** Member of the Committee of Experts for the Transplant of Hematopoietic Stem Cell Progenitors of the National Transplant Organization, on behalf of the Spanish Society of Hematology and Hemotherapy. 01/04/2021-present.

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LABORATORY 13

EXPERIMENTAL THERAPEUTICS AND TRANSLATIONAL ONCOLOGY: STEM CELLS, CANCER STEM CELLS AND CANCER

RESEARCH SUMMARY

Our group is mainly interested in two main areas:

1. Genetic predispostion and B-ALL development – deciphering the mechanisms responsible for clonal evolution with the aim of leukemia prevention.

2. Epigenetic priming in cancer initiation

1 GENETIC PREDISPOSTION AND B-ALL DEVELOPMENT – DECIPHERING THE MECHANISMS RESPONSIBLE FOR CLONAL EVOLUTION WITH THE AIM OF LEUKEMIA PREVENTION

Leukemia accounts for a third of all cancers in children and its incidence has increased in the last 20 years. Recent results have shown that around 5% of healthy children carry a preleukemic clone. These preleukemic cells can persist for years, without harm for the individual and it is the exposure to an oncogenic environment, which provides the necessary selection pressure for the leukemia outgrowth. However, these oncogenic environments are not known. Recently, our group has discovered for the first time the causal relationship between childhood B-cell leukemia (B-ALL) and exposure to natural infections, implying that B-ALL may be a preventable cancer. The need for the clarification how genetic predisposition and exposure to infection act synergistically in B-ALL development is one of the current major goals and challenges in Oncology. Preclinical models of childhood B-ALL have been an essential unmet need to prevent the occurrence of this disease. These mouse models have anticipated the second hit in childhood B-ALL and they will be used by our research team as the basis for understanding the molecular mechanisms that govern the development of B-ALL as a result of natural infection exposure. The conceptual and mechanistic insights obtained in this experimental system represent an entirely novel strategy and the results of these endeavours will inform approaches for preventing childhood B-ALL.

2 EPIGENETIC PRIMING IN CANCER INITIATION

Recent evidence from hematopoietic and epithelial tumors revealed that the contribution of oncogenes to cancer development is mediated mainly through epigenetic priming of cancer-initiating cells, suggesting that genetic lesions that initiate the cancer process might be dispensable for the posterior tumor progression and maintenance. Epigenetic priming may remain latent until it is later triggered by endogenous or environmental stimuli. Our group study the impact of epigenetic priming in cancer development and in the development of new therapeutic approaches.

PUBLICATIONS

- **The Second Oncogenic Hit Determines the Cell Fate of ETV6-RUNX1 Positive Leukemia.** *Rodríguez-Hernández G, Casado-García A, Isidro-Hernández M, Picard D, Raboso-Gallego J, Alemán-Arteaga S, Orfao A, Blanco O, Riesco S, Prieto-Matos P, García Criado FJ, García Cenador MB, Hock H, Enver T, Sanchez-Garcia I, Vicente-Dueñas C.* **Front Cell Dev Biol. 2021 Jul 15;9:704591. doi: 10.3389/fcell.2021.704591.** PMID: 34336858. **IF: 6.684 / Q1**

- **An immune window of opportunity to prevent childhood B cell leukemia.** *Cobaleda C, Vicente-Dueñas C, Sánchez-García I.* **Trends Immunol. 2021 May;42(5):371-374. doi: 10.1016/j.it.2021.03.004.** PMID: 33773925 **IF: 16.687 / D1**

- **Infectious triggers and novel therapeutic opportunities in childhood B cell leukaemia.** *Cobaleda C, Vicente-Dueñas C, Sanchez-Garcia I.* **Nat Rev Immunol. 2021 Sep;21(9):570-581. doi: 10.1038/s41577-021-00505-2.** PMID: 33558682. **IF: 53.106** / D1

  This article has been highlighted in:
  + Human Immunology News Vol. 9.05 - 9 February, 2021
  + Hematopoiesis News-page 5 of 61-Science News, 2021

- **Cell Fate Decisions: The Role of Transcription Factors in Early B-cell Development and Leukemia.** *Fischer U, Yang JJ, Ikawa T, Hein D, Vicente-Dueñas C, Borkhardt A, Sánchez-García I.* **Blood Cancer Discov. 2020 Nov;1(3):224-233. doi: 10.1158/2643-3230.BCD-20-0011.** PMID: 33392513. **IF:NI**

- **Inhibition of inflammatory signaling in Pax5 mutant cells mitigates B-cell leukemogenesis.** *Isidro-Hernández M, Mayado A, Casado-García A, Martínez-Cano J, Palmi C, Fazio G, Orfao A, Ribera J, Ribera JM, Zamora L, Raboso-Gallego J, Blanco O, Alonso-López D, De Las Rivas J, Jiménez R, García Criado FJ, García Cenador MB, Ramírez-Orellana M, Cazzaniga G, Cobaleda C, Vicente-Dueñas C, Sánchez-García I.* **Sci Rep. 2020 Nov 5;10(1):19189. doi: 10.1038/s41598-020-76206-y.** PMID: 33154497. **IF: 4.380 / Q1**

- **Conditional expression of HGAL leads to the development of diffuse large B-cell lymphoma in mice.** *Raboso-Gallego J, Casado-García A, Jiang X, Isidro-Hernández M, Gentles AJ, Zhao S, Natkunam Y, Blanco O, Domínguez V, Pintado B, Alonso-López D, De Las Rivas J, Vicente-Dueñas C, Lossos IS, Sanchez-Garcia I.* **Blood. 2021 Apr 1;137(13):1741-1753. doi: 10.1182/blood.2020004996.** PMID: 33024996. **IF: 23.629 / D1**

- **An intact gut microbiome protects genetically predisposed mice against leukemia.** *Vicente-Dueñas C, Janssen S, Oldenburg M, Auer F, González-Herrero I, Casado-García A, Isidro-Hernández M, Raboso-Gallego J, Westhoff P, Pandyra AA, Hein D, Gössling KL, Alonso-López D, De Las Rivas J, Bhatia S, García-Criado FJ, García-Cenador MB, Weber APM, Köhrer K, Hauer J, Fischer U, Sánchez-García I*, Borkhardt A*.* **Blood. 2020 Oct 29;136(18):2003-2017. doi: 10.1182/blood.2019004381.** PMID: 32911536. **IF: 23.629 / D1**

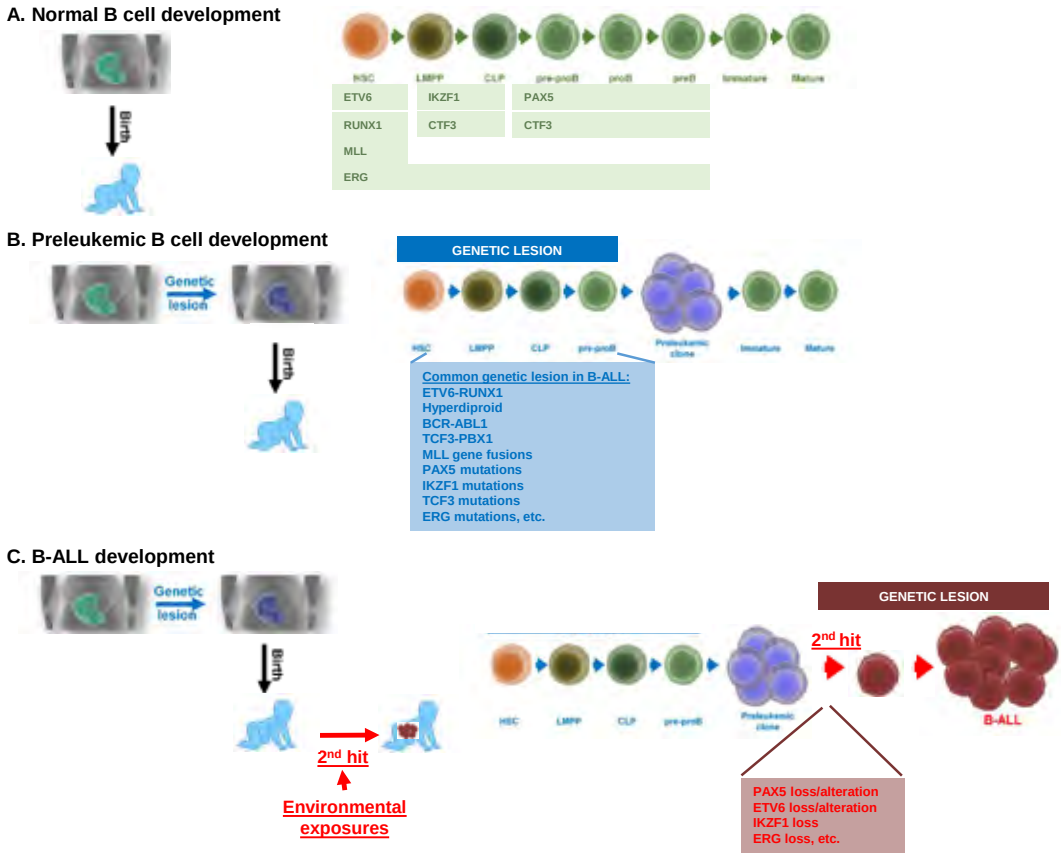
  This article has been highlighted in:
  + Cancer Discovery_Research Watch: The Gut Microbiome Dictates Whether Predisposed Mice Develop Leukemia. Cancer Discov. 2020 Nov;10(11):1625. doi: 10.1158/2159-8290.CD-RW2020-139.
  + Blood: Anindita Roy. A "gut feeling" about precursor B-ALL. Blood (2020) 136 (18): 1995–1996.
  + Blood: selected to be featured in Blood Podcast in Season 1, Episode 44 on Thursday, October 29.

- **Lineage Decision-Making within Normal Haematopoietic and Leukemic Stem Cells.** *Brown G, Sánchez L, Sánchez-García I.* **Int J Mol Sci. 2020 Mar 24;21(6):2247. doi: 10.3390/ijms21062247.** PMID: 32213936. **IF: 5.924 / Q1**

- **Editorial: Epigenetic Reprogramming and Cancer Development.** *Brown G, Vicente-Dueñas C, Sánchez-García I.* **Front Cell Dev Biol. 2020 Jan 28;8:12. doi: 10.3389/fcell.2020.00012. eCollection 2020.** PMID: 32047749. **IF: 6.684/Q1**

PATENTS

PATENT REFERENCE	TITLE	INVENTORS	PRIORITY DATE
EP20382923.9	Methods and compositions for the treatment of hematologic malignancies	Sánchez García, Isidro; Vicente Dueñas, Carolina	23/10/2020



Genetic vulnerability of B-ALL preleukemic clones. A) Transcriptional regulation determines normal B cell development. A network of transcriptional and epigenetic regulatory circuits drives the normal differentiation of HSCs to mature B cells in a stepwise, tightly regulated, process. **B)** A first oncogenic hit, usually acquired in utero, such as a chromosomal translocation that generated a chimeric protein (for example, ETV6-RUNX1 or TCF3-PBX1) or a mutation in a key developmental gene (such as *PAX5*, *IKAROS* and *ERG*), arises in early haematopoietic or B cell development. This will occur in a large number of healthy newborns (›5%, without taking into account inherited predisposition), and will introduce a vulnerability through the generation and expansion of a preleukemic B cell clone which nevertheless allows normal B cell development to take place; carriers are therefore clinically silent. **C)** Most children carrying this alteration will never develop B-ALL but, in a small percentage of cases, given certain conditions (such as environmental exposures), a preleukemic clone will acquire a second hit, therefore giving rise to a full-blown B-ALL. Only after these additional secondary genetic alterations have occurred (usually also affecting genes involved in normal B cell development), will a full-blown B-ALL develop. HSC: Hematopoietic Stem Cell; LMPP: Lymphoid-primed MultiPotential Progenitor; CLP: Common Lymphoid Progenitor.

GRANTS FOR RESEARCH IN PROGRESS

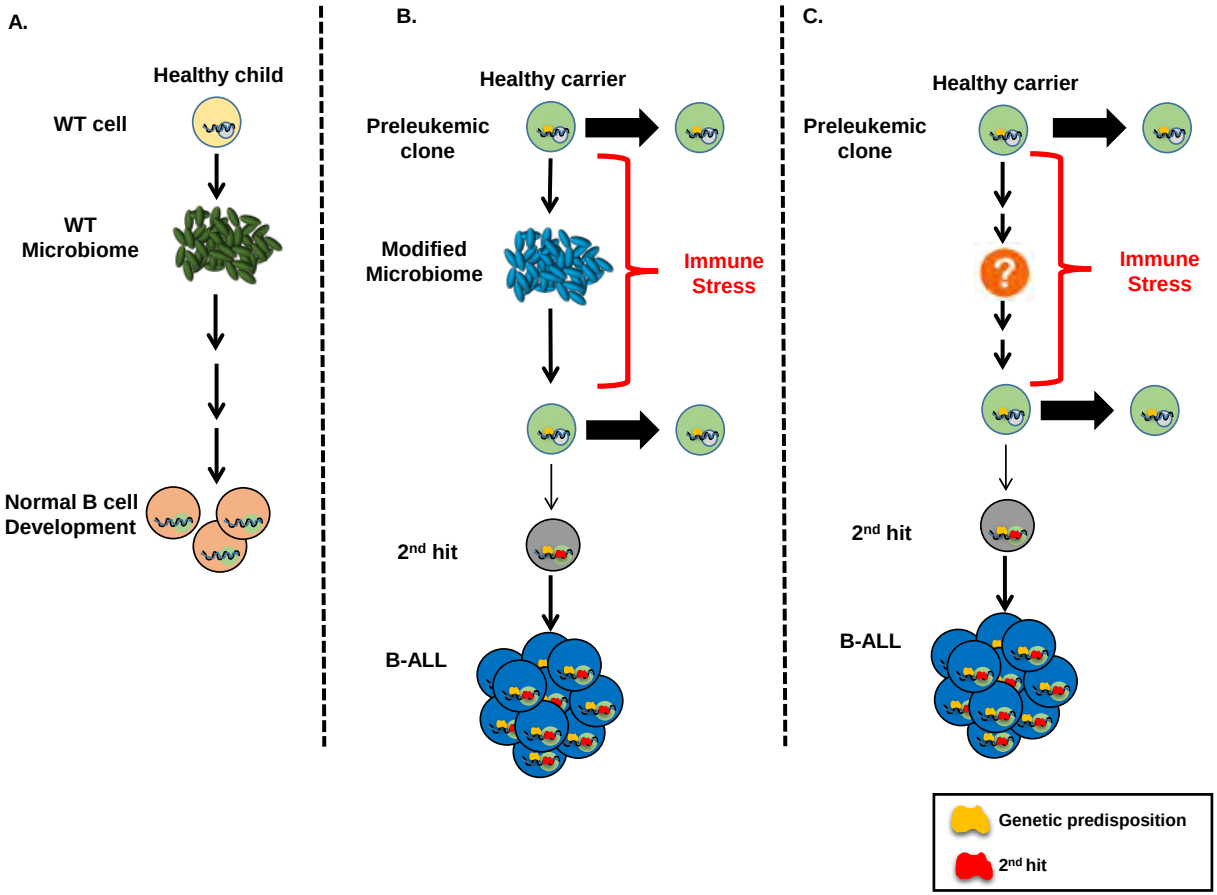
PROJECT	PI	GRANT	TIME	FUNDING
Nuevas aproximaciones terapéuticas para la prevención de la leucemia aguda infantil (CSI234P18)	Isidro Sánchez-García	Regional Government of Castilla and León	2018-2021	120.000,00€
Infectious trigger in childhood pB-ALL – deciphering the mechanisms responsible for clonal evolution with the aim of leukemia prevention (RTI2018-093314-B-100)	Isidro Sánchez-García	Spanish Ministry of Science, Research and Universities	2018-2021	290,400.00 €
Influence of low dose radiation on the Leukemia development in genetic predisposition in a mouse model	Arndt Borkhardt & Isidro Sánchez-García	German Federal Office for Radiation Protection (*BfS*)-Germany	2019-2022	280,000.00€
Identification and functional analyses of germline and somatic mutations predisposing children in Spain to acute lymphoblastic leukemia	Manuel Ramírez-Orellana & Isidro Sánchez-García	UnoEntreCienMil Foundation	2019-2021	540,000.00€
Detection of preleukemic clones and modulation of clonal progression in infection induced acute lymphoblastic leukemia	Arndt Borkhardt & Isidro Sánchez-García	German Carreras Leukemia Foundation	2020-2022	299,800.00 €
Examination of the occurrence of leukemia in predisposed animal models exposed to magnetic fields	Isidro Sánchez-García	German Federal Office for Radiation Protection (*BfS*)-Germany.	2020-2023	237,644.00 €
La pandemia causada por el virus SARS-COV-2 y su implicación en la génesis de la leucemia infantil	Isidro Sánchez-García	Regional Government of Castilla and León	2021-2023	172.000,00€
Infectious triggers and novel therapeutic opportunities in childhood B cell leukemia (PREVENT).	César Cobaleda / Manuel Ramírez-Orellana/ Isidro Sánchez-García	Spanish Association against Cancer Foundation (FCAECC)	2021-2026	1.119.500,00 €

OTHER ACTIVITIES & RELEVANT FACTS

- 2012-present. CANC-15 group Director of IBSAL (Salamanca Institute for Biomedical Research)
- 2015-present. UIC-17 Director of Castilla y León

Main talks at Scientific Meetings and Research Centers

- 25th EHA Congress Frankfurt, Germany, June 11-14, 2020.
- IARC Section of Environment and Radiation-10-year anniversary Virtual Symposium. Wednesday 16th September 2020, Lyon (France).
- XIII Simposium bases biológicas del cáncer e innovación terapéutica. May 25-27, 2021 (Salamanca)
- The 27th "Club Hématopoïèse et Oncogenèse" (CHO [Hematopoiesis and Oncogenesis Club]) CHO meeting September 29 - October 2; 2021 in Giens (Var, France).



A unified model for childhood B-ALL development. The first event is the presence of a genetic lesion (either congenital or generated de novo) leading to the development of a preleukemic clone. In the absence of such lesion (A), development takes place normally, and in the context of a normal microbiome. The preleukemic clone can, however (B) shape the gut microbiome and lead to the appearance of a modified microbiome whose characteristics are determined by the nature of the driver genetic lesion. Still, in the absence of an immune stress, this preleukemic clone doesn't progress to give rise to leukemia. However, in the presence of an immune stress (caused for example by delayed-exposure to common infections, antibiotic treatment, exposure to low-dose ionizing radiation, etc.) it might happen that, in a reduced number of occasions, an immune evasion takes place where a cell with a second hit takes advantage of the effects of this immune stress to escape to immune control and lead to leukemic development. The percentage of conversion to full-blown leukemia is highly dependent on the specific first genetic hit, both in human patients and in mouse models, but is always much less than the number of cases where preleukemic cells remain in this state and do not progress to 2nd hit and B-ALL. Finally, since we still don't know the mechanistic basis of the influence of the microbiome on the acquisition of the 2nd hit, or in the pre-cancerous clonal expansion, we must bear in mind that the alteration in the gut microbiome associated with the genetic predisposition seen in mice (Pax5+/- and ETV6-RUNX1+) might however not play a role in the transformation of preleukemic clones, and then there might be cases (C) where such progression takes place via microbiome-independent mechanisms.

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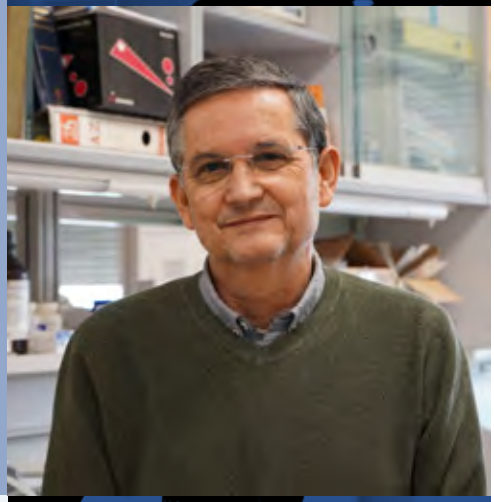

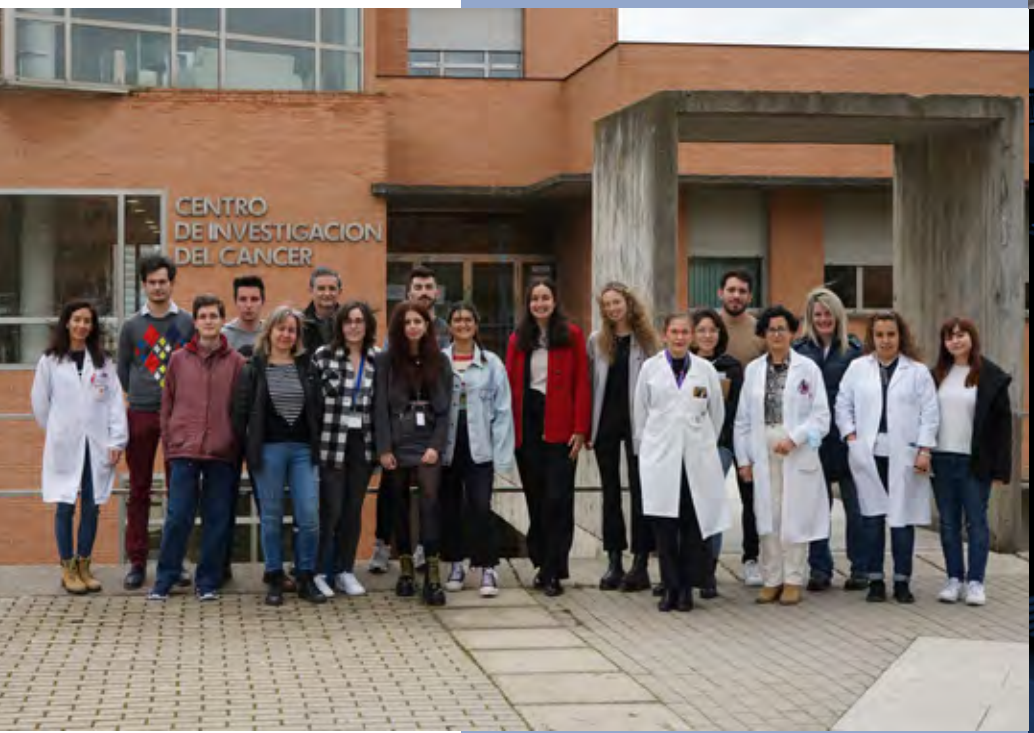

RESEARCH TEAM

POSTDOCTORAL
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Jesica Pérez García

PREDOCTORAL
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Carlos Gutierrez Cerrajero
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Paula García Vallés
Diego Iglesias Corral
Paloma Martín-Bejarano Soto
David Díez Castro
Nuria Arroyo Garrapucho

STUDENT
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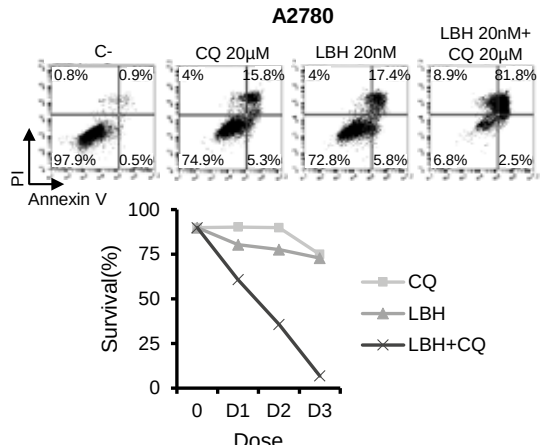
LABORATORY 14

FAMILIAL AND HEREDITARY CANCER. EARLY ONSET COLORECTAL CANCER

RESEARCH SUMMARY

The primary aim of our laboratory is the characterization of molecular abnormalities in patients with familiar cancer within the program of Genetic Counsel in Hereditary Cancer supported by the Junta de Castilla y León. Beyond this project, the laboratory is characterizing molecular abnormalities in women with familiar breast cancer (more than 3 family members with breast or ovarian cancer) that do not carry BRCA mutations using WES. We are also characterizing variants of unknown significance in BRCA1 and BRCA2 in two *"in vitro"* models that allow us to detect DNA repair abnormalities. Related to breast cancer we are studying the role of antiandrogen therapy in breast cancer tumour cell lines.

In colon cancer our aim is to characterize the molecular changes in tumour in patients under 50 years old. Actually we are part of a multidisciplinary group, involving different groups from different hospitals of the Country as well as other groups from Europe and EEUU. In this project we have characterized a short region in chromosome 16 that is mostly deleted in early onset colon cancer and we are studying the role of NOMO1 gene in this subgroup of tumours. Related to colon cancer and in collaboration with the Service of Gastroenterology of the University Hospital of Salamanca we are also studying the molecular changes either germ line or somatic in families with polyposis.



Dose		D1	D2	D3	D1	D2	D3	D1	D2	D3
CQ (µM)	-	10	15	20	-	-	-	10	15	20
LBH (nM)	-	-	-	-	10	15	20	10	15	20
Survival (%)	97.9	90.2	89.9	74.9	80.3	77.6	72.8	60.7	35.6	6.8
Fa	0.02	0.10	0.10	0.25	0.20	0.22	0.27	0.39	0.64	0.93
CI	-	-	-	-	-	-	-	0.46	0.26	0.08

Synergistic effect of the co-treatment with Panobinostat and chloroquine in OCCLs. Cells were exposed for 72 h to the indicated concentrations of LBH and CQ at a constant ratio and the percentage of apoptotic cells were assessed by flow cytometry (after cell staining with annexin V and propidium iodide). CI values less than 1 indicated a synergistic effect. These values were calculated using Compusyn Software. C-: negative control (untreated cells).

In ovarian cancer we are studying, in collaboration with the Department of Pharmaceutical Science of the University of Salamanca, the putative role of new microtubule inhibitors. We are also analysing novel combinations of compounds that could act in a synthetic lethal interaction pathway.

We have also generated novel cell lines derived from patients with squamous head and neck cancer and actually we are generating resistance to different drugs in an attempt to characterize the molecular basis of this resistance.

Our group is also involved in a study of liquid biopsy in Glioblastoma in collaboration with the Fundación Jiménez Díaz.

All these projects are carried in collaboration with the Department of Oncology of the University Hospital of Salamanca.

PUBLICATIONS

- **Establishment of a conditional Nomo1 mouse model by CRISPR/Cas9 technology.** *García-Tuñón I, Vuelta E, Lozano L, Herrero M, Méndez L, Palomero-Hernandez J, Pérez-Caro M, Pérez-García J, González-Sarmiento R, Sánchez-Martín M.* **Mol Biol Rep. 2020. 47:1381-1391. doi: 10.1007/s11033-019-05214-7.** PMID: 31833031 **IF: 2.316 / Q4**

- **Identification of a truncated ′ 1-chimaerin variant that inactivates nuclear Rac1.** *Casado-Medrano V, Barrio-Real L, Gutiérrez-Miranda L, González-Sarmiento R, Velasco EA, Kazanietz MG, Caloca MJ.* **J Biol Chem. 2020. 295: 1300-1314. doi: 10.1074/jbc.RA119.008688.** PMID: 31871052 **IF: 5.157 / Q2**

- **A mutation in p62 protein (p. R321C), associated to Paget's disease of bone, causes a blockade of autophagy and an activation of NF-kB pathway.** *Usategui-Martín R, Gestoso-Uzal N, Calero-Paniagua I, De Pereda JM, Del Pino-Montes J, González-Sarmiento R.* **Bone. 2020; 133: 115265. doi: 10.1016/j.bone.2020.115265.** PMID: 32036052 **IF: 4.398 / Q2**

- **Cutaneous Squamous Cell Carcinoma: From Biology to Therapy.** *Corchado-Cobos R, García-Sancha N, González-Sarmiento R, Pérez-Losada J, Cañueto J* **Int J Mol Sci. 2020; 21: E2956. doi: 10.3390/ijms21082956.** PMID: 32331425 **IF: 5.924 / Q1**

- **Association of Alk1 and Endoglin Polymorphisms with Cardiovascular Damage.** *Garzon-Martinez M, Perretta-Tejedor N, Garcia-Ortiz L, Gomez-Marcos MA, Gonzalez-Sarmiento R, Lopez-Hernandez FJ, Martinez-Salgado C.* **Sci Rep. 2020; 10: 9383. doi: 10.1038/s41598-020-66238-9.** PMID: 32523017 **IF: 4.380 / Q1**

- **VAV3 rs7528153 and VAV3-AS1 rs1185222 polymorphisms are associated with an increased risk of developing hypertension.** *Miramontes-González JP, Usategui-Martín R, Martín-Vallejo J, Ziegler M, de Isla LL, O Connor D, González-Sarmiento R.* **Eur J Intern Med. 2020; 80: 60-65. doi: 10.1016/j.ejim.2020.05.014.** PMID: 32540412 **IF: 4.624 / Q1**

- **Novel Dominant KCNQ2 Exon 7 Partial In-Frame Duplication in a Complex Epileptic and Neurodevelopmental Delay Syndrome.** *Lazo PA, García JL, Gómez-Puertas P, Marcos-Alcalde Í, Arjona C, Villarroel A, González-Sarmiento R,* **Fons C. Int J Mol Sci. 2020; 21: 4447. doi: 10.3390/ijms21124447.**PMID: 32585800 **IF: 5.924 / Q1**

- **Matrix Metalloproteinases in age-related macular degeneration (AMD).** *García-Onrubia L, Valentín-Bravo FJ, Coco-Martín R, González-Sarmiento R, Pastor JC, Usategui-Martín R, Pastor-Idoate S.* **Int J Mol Sci 2020. 21: 5934. doi: 10.3390/ijms21165934.** PMID: 32824762 **IF: 5.924 / Q1**

- **VAV2 signaling promotes regenerative proliferation in both cutaneous and head and neck squamous cell carcinoma.** *Lorenzo-Martín LF, Fernández-Parejo N, Menacho-Márquez M, Rodríguez-Fdez S, Robles-Valero J, Zumalave S, Fabbiano S, Pascual G, García-Pedrero JM, Abad A, García-Macías MC, González N, Lorenzano-Menna P, Pavón MA, González-Sarmiento R, Segrelles C, Paramio JM, Tubío JMC, Rodrigo JP, Benitah SA, Cuadrado M, Bustelo XR.* **Nat Commun. 2020; 11: 4788. doi: 10.1038/s41467-020-18524-3.** PMID: 32963234 **IF: 14.919 / D1**

- **Oncogenic driver mutations predict outcome in a cohort of head and neck squamous cell carcinoma (HNSCC) patients within a clinical trial.** *Fernández-Mateos J, Pérez-García J, Seijas-Tamayo R, Mesía R, Rubió-Casadevall J, García-Girón C, Iglesias L, Carral Maseda A, Adansa Klain JC, Taberna M, Vazquez S, Gómez MA, Del Barco E, Ocana A, González-Sarmiento R*, Cruz-Hernández JJ.* **Sci Rep. 2020; 10: 16634. doi: 10.1038/s41598-020-72927-2.** PMID: 33024167 **IF: 4.308 / Q1**

- **Copy neutral loss of heterozygosity (cnLOH) patterns in synchronous colorectal cancer.** *Tapial S, García JL, Corchete L, Holowatyj AN, Pérez J, Rueda D, Urioste M, González-Sarmiento R, Perea J.* **Eur J Hum Genet. 2021; 29: 709-713. doi: 10.1038/s41431-020-00774-w.** PMID: 33268847 **IF: 4.246 / Q2**

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- **Microtubule Destabilizing Sulfonamides as an Alternative to Taxane-Based Chemotherapy.** *González M, Ovejero-Sánchez M, Vicente-Blázquez A, Álvarez R, Herrero AB, Medarde M, González-Sarmiento R*, Peláez R.* **Int J Mol Sci. 2021; 22: 1907. doi: 10.3390/ijms22041907.** PMID: 33673002 **IF: 5.924 / Q1**

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GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Estudio clínico y molecular de poliposis de colon sin mutación en genes asociados a cáncer hereditario	Rogelio González Sarmiento	Mutua Madrileña Foundation	2020-2022	90,000.00 €
Caracterización de nuevos biomarcadores moleculares y su papel en la patogénesis de cáncer colorectal de comienzo precoz (EOCRC) (PI20/01589)	Rogelio González Sarmiento	Carlos III Health Institute (ISCIII)	2021-2023	221,430.00 €
Manipulación de la estabilidad genómica como estrategia de letalidad sintética en oncología (CSI264P20)	Pedro Lazo-Zbikowski	Regional Government of Castilla and León	2020-2023	172,000.00 €
Firma molecular en biopsia líquida para respuesta a radioterapia y recaída temprana en cáncer de próstata	Juan Jesús Cruz Hernández / Rogelio González Sarmiento	Ministry of Science and Innovation / State Research Agency (RETOS-Colaboración Program)	2020-2023	1,108,098.75 €

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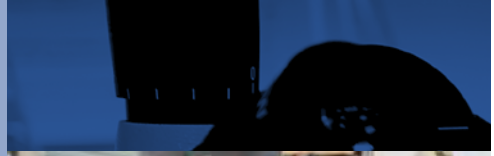

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LABORATORY 15

BREAST AND OVARIAN CANCER

RESEARCH SUMMARY

Substantial part of the work carried out along the last couple of years focused on the study of resistance to anti-HER2 therapies in breast cancer. HER2 is a transmembrane tyrosine kinase which appears overexpressed in 20% of patients with breast cancer. Because of that, strategies aimed at targeting that kinase have been developed and have reached the oncology clinic. Using resistant cells generated in our laboratory, we have identified potential therapeutic vulnerabilities that could be used to reverse resistance to anti-HER2 therapies. Bioinformatic studies made it possible to identify a dysregulation of death pathways and more specifically the cell death induced by TRAIL. We showed that this dysregulation was due to an increase in the amount of DR4 and DR5 cell receptors for TRAIL in resistant cells, at the same time that there was a lower amount of other inhibitory proteins (FLIP) of the signal transduction system. On the other hand, in models of resistance to trastuzumab, we have defined that these models have greater resistance to tyrosine kinase inhibitory (TKIs) drugs such as lapatinib or neratinib. The mechanism responsible for such cross-resistance appears to have its origin in a decreased sensitivity to the pro-apoptotic effect of TKIs in cells resistant to trastuzumab. A third work that has defined a new vulnerability in HER2 positive mammary tumors resistant to various conventional therapies is related to the use of an antibody-drug conjugate (ADC) against HER3, termed EV20/MMAF. EV20/MMAF was constructed using as a backbone the EV20 antibody that interacts with the extracellular region of HER3, to which the anti-microtubule agent monomethylauristatin (MMAF) was bound. We found that HER3 expression was common in cellular models of HER2 overexpression. EV20/MMAF displayed potent antitumor activity against HER2+ breast cancer cells, including cells exhibiting primary or secondary resistance to anti-HER2 drugs. Furthermore, mice with human HER2+ tumor cell xenografts that were primarily or secondarily resistant to various anti-HER2 therapies and that were treated with EV20/MMAF, responded with complete regression of their tumors with no relapses observed in periods of up to one year of follow-up. These results are very promising and have prompted us to further study EV20/MMAF to optimize its use in the treatment of HER2+ tumors, a topic that is part of our current interests. Furthermore, the strong antitumor activity of EV20/MMAF has stimulated us to try to develop a phase I trial whose viability we are currently studying.

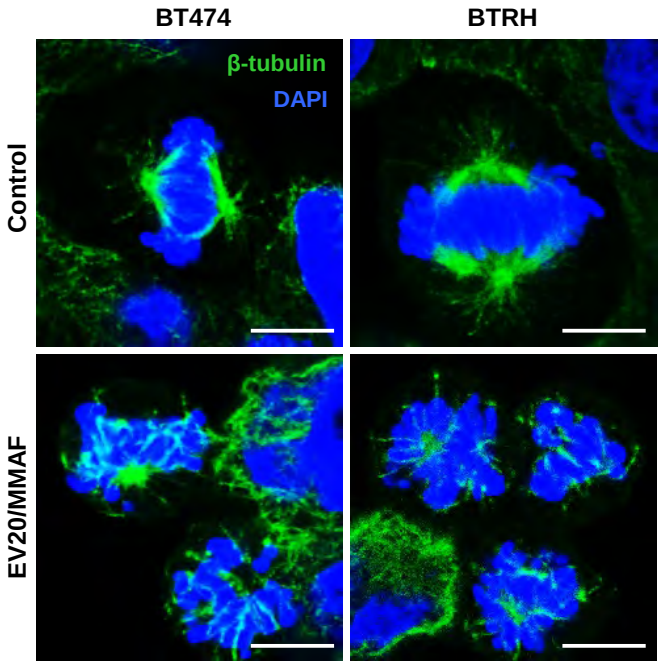
Another research interest of the laboratory focused on the identification and characterization of novel HER receptor signaling intermediates. A few years ago, we observed that a 60 kDa protein exhibited cross-reactivity with an antibody directed against phospho-S313 of P-Rex1. Phosphorylation of that 60 kDa protein was stimulated after activation of the those receptors. The identity of that protein was revealed by separation on 2D gels and Western blotting, followed by proteomic analysis. This protein turned out to be PDCD4, a highly unstable protein tumor suppressor, which has been attributed a negative regulatory role in the progression of cells along the cell cycle. In fact, the activation of the HER receptors was observed to cause a rapid degradation of PDCD4, dependent on the activity of the proteasome. We have identified the PDCD4 phosphorylation site after the activation of HER receptors, and which is recognized by the antibody (anti p-S313 from P-Rex1) which is serine 67. Furthermore, we have analyzed the importance of this phosphorylation in protein degradation through studies with phosphomimetic mutants, as well as the importance of PDCD4 in breast cancer with gain and loss of function experiments. In those studies we have observed that the reduction of PDCD4 caused cell cycle arrest, although these cells have a greater capacity for migration / invasion.

OVERARCHING FUTURE OBJECTIVE:

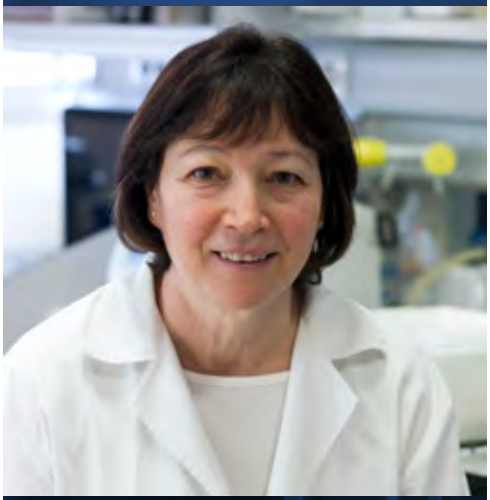
Despite the impressive clinical benefit from HER2-targeted therapies, in advanced stages, especially in the metastatic setting, HER2+ tumors remain incurable. Due to this, it is necessary to develop new therapeutic strategies to treat patients with HER2+ tumors. That is our general goal.

SPECIFIC OBJECTIVES:

We intend to focus on the study of two ADCs: T-DM1 and EV20/MMAF. Using various models of resistance to T-DM1 we will try to (A) Identify new mechanisms of resistance to T-DM1. In the case of EV20/MMAF, and due to its intense antitumor activity against HER2+ tumors, particularly those that become refractory to anti-HER2 therapies, we consider important to (B) Increase our knowledge on EV20/MMAF to optimize its use against HER2+ tumors.



Action of the ADC EV20/MMAF on mitotic spindle formation. BT474 and BTRH cells were treated, fixed, and stained for β-tubulin (green) and DAPI (blue). Treatment with EV20/MMAF provoked the appearance of abnormal mitotic spindles. That abnormality is followed by cell death caused by the ADC. Bar: 7.5 µm



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THE MEK5/ERK5 PATHWAY IN CANCER

The MEK5/ERK5 signal transduction pathway belongs to the Mitogen-activated Protein Kinase (MAPK) family. MAPKs routes control multiple essential biological processes, such as cell proliferation, differentiation or regulation of apoptotic cell death, among others.

In the last years, we and others have indicated that the MEK5/ERK5 route is deregulated in several types of cancer. Those studies reported that such route is involved in sustaining proliferative signals in tumoral cells, resistance to cell death, invasion and metastasis, as well as induction of angiogenesis; all of them distinctive features of the tumoral phenotype.

Recently, using a mouse model that we genetically engineered to express a constitutively active form of MEK5, we showed that the sole activation of this pathway caused the onset of lung adenocarcinomas that resembled human features. Moreover, analysis of human lung adenocarcinoma samples showed constitutive activation and increased expression of MEK5 and its downstream target kinase ERK5 when compared to healthy tissue. In addition, high levels of MEK5/ERK5 associated with worse prognosis in lung adenocarcinoma patients. These findings moved us to study the prognostic relevance and potential therapeutic value of its targeting in lung cancer over the last two years. Using genetic (RNAi and CRISPR/Cas9) and pharmacological (kinase inhibitors of MEK5 and ERK5) tools, we demonstrated that targeting the MEK5/ERK5 route is therapeutically effective both in vitro and in vivo. We show that inhibition of MEK5 and ERK5 reduce tumour growth and synergizes with drugs currently used in the lung cancer clinic.

The relevance of our studies lies in the identification of a new signalling route, therapeutically accessible, which participates in lung cancer pathophysiology and whose inhibition could be useful in the treatment of that disease. Because of the novelty and relevance of these findings, our group is currently focused on

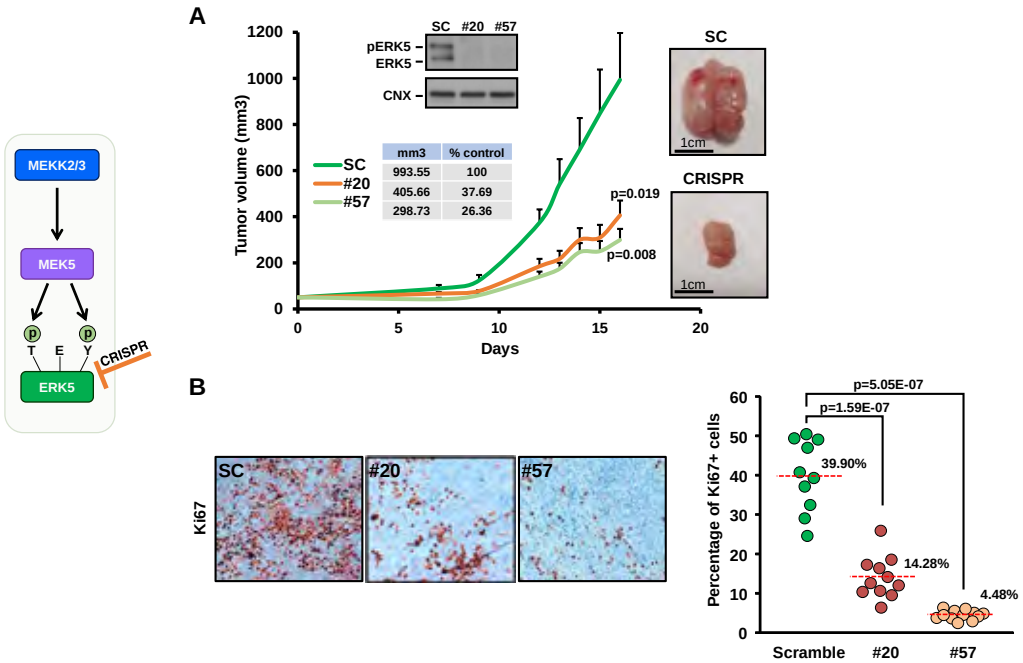
(i) developing specific and potent inhibitors targeting MEK5 and ERK5 in order to offer novel therapeutic opportunities to fight lung cancer and potentially other tumors in which this pathway plays a pathophysiological role.

(ii) identification of genes or genesets to biomark tumors sensitive to MEK5/ERK5 inhibition with the aim of selecting patients who may benefit from targeted therapies against MEK5 or ERK5.

In addition, we are actively working on the role of MEK5/ERK5

(iii) in resistance to anti MEK therapies in cancer.

(iv) in the response of tumors to immune checkpoint inhibitors.



ERK5 knockout: effect on tumor growth of lung cancer cells. (**A**) Tumor growth evolution of mice xenoinjerted with H460 SC (scramble) cells or ERK5 CRISPR cells (#20 and #57 clones). Data in the inset table indicates the volume percentage of ERK5 CRISPR tumors when compared to scramble tumors. (**B**) Ki67 immunostaining was quantified from 10 to 12 different pictures of each condition (SC and ERK5 CRISPR clones) using a Leica LAS V3.7 software. Left panels show representative pictures of each condition. Right panel represents the percentage of Ki67 positive cells from total. The average percentage value (red line) and p-value for each ERK5 CRISPR clone are indicated.

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- **Genomic Mapping Identifies Mutations in RYR2 and AHNAK as Associated with Favorable Outcome in Basal-Like Breast Tumors Expressing PD1/PD-L1.** *Cimas FJ, Manzano A, Baliu-Piqué M, García-Gil E, Pérez-Segura P, Nagy Á, Pandiella A, Győrffy B, Ocana A.* **Cancers (Basel). 2020 Aug 11;12(8):2243. doi: 10.3390/cancers12082243.** PMID: 32796628. **IF: 6.639 / Q1**

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- **Medicinal Plants as Sources of Active Molecules Against COVID-19.** *Benarba B, Pandiella A.* **Front Pharmacol. 2020 Aug 7;11:1189. doi: 10.3389/fphar.2020.01189. eCollection 2020.** PMID: 32848790. **IF: 5.811 / Q1**

- **An Overview of Antibody Conjugated Polymeric Nanoparticles for Breast Cancer Therapy.** *Juan A, Cimas FJ, Bravo I, Pandiella A, Ocaña A, Alonso-Moreno C.* **Pharmaceutics. 2020 Aug 25;12(9):802. doi: 10.3390/pharmaceutics12090802.** PMID: 32854255. **IF: 6.321 / Q1**

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- **Checkpoint Kinase 1 Pharmacological Inhibition Synergizes with DNA-Damaging Agents and Overcomes Platinum Resistance in Basal-Like Breast Cancer.** *Nieto-Jimenez C, Alcaraz-Sanabria A, Martinez-Canales S, Corrales-Sanchez V, Montero JC, Burgos M, Nuncia-Cantarero M, Pandiella A, Galan-Moya EM, Ocaña A.* **Int J Mol Sci. 2020 Nov 27;21(23):9034. doi: 10.3390/ijms21239034.** PMID: 33261142. **IF: 5.924 / Q1**

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- **In silico transcriptomic mapping of integrins and immune activation in Basal-like and HER2+ breast cancer.** *Rojas K, Baliu-Piqué M, Manzano A, Saiz-Ladera C, García-Barberán V, Cimas FJ, Pérez-Segura P, Pandiella A, Győrffy B, Ocana A.* **Cell Oncol (Dordr). 2021 Jun;44(3):569-580. doi: 10.1007/s13402-020-00583-9.** PMID: 33469836. **IF: 6.730 / Q1**

- **Mapping of Genomic Vulnerabilities in the Post-Translational Ubiquitination, SUMOylation and Neddylation Machinery in Breast Cancer.** *Fuentes-Antrás J, Alcaraz-Sanabria AL, Morafraile EC, Noblejas-López MDM, Galán-Moya EM, Baliu-Pique M, López-Cade I, García-Barberán V, Pérez-Segura P, Manzano A, Pandiella A, Győrffy B, Ocaña A.* **Cancers (Basel). 2021 Feb 17;13(4):833. doi: 10.3390/cancers13040833.** PMID: 33671201. **IF: 6.639 / Q1**

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- **Transcriptomic Profiles of CD47 in Breast Tumors Predict Outcome and Are Associated with Immune Activation.** *Noblejas-López MDM, Baliu-Piqué M, Nieto-Jiménez C, Cimas FJ, Morafraile EC, Pandiella A, Corbi ÁL, Győrffy B, Ocaña A.* **Int J Mol Sci. 2021 Apr 7;22(8):3836. doi: 10.3390/ijms22083836.** PMID: 33917174. **IF: 5.924 / Q1.**

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- **Preclinical and Clinical Characterization of Fibroblast-derived Neuregulin-1 on Trastuzumab and Pertuzumab Activity in HER2-positive Breast Cancer.** *Guardia C, Bianchini G, Arpí-LLucià O, Menendez S, Casadevall D, Galbardi B, Dugo M, Servitja S, Montero JC, Soria-Jiménez L, Sabbaghi M, Peña R, Madoz-Gúrpide J, Lloveras B, Lluch A, Eroles P, Arribas J, Pandiella A, Gianni L, Rojo F, Rovira A, Albanell J.* **Clin Cancer Res. 2021 Sep 15;27(18):5096-5108. doi: 10.1158/1078-0432.CCR-20-2915.** PMID: 34385295. **IF: 12.531 / D1**

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- **Clinical, genetic and pharmacological data support targeting the MEK5/ERK5**

module in lung cancer. *Sánchez-Fdez A, Re-Louhau MF, Rodríguez-Núñez P, Ludeña D, Matilla-Almazán S, Pandiella A, Esparís-Ogando A.* **NPJ Precis Oncol. 2021 Aug 17;5(1):78. doi: 10.1038/s41698-021-00218-8.** PMID: 34404896. **IF: 8.254 / D1**

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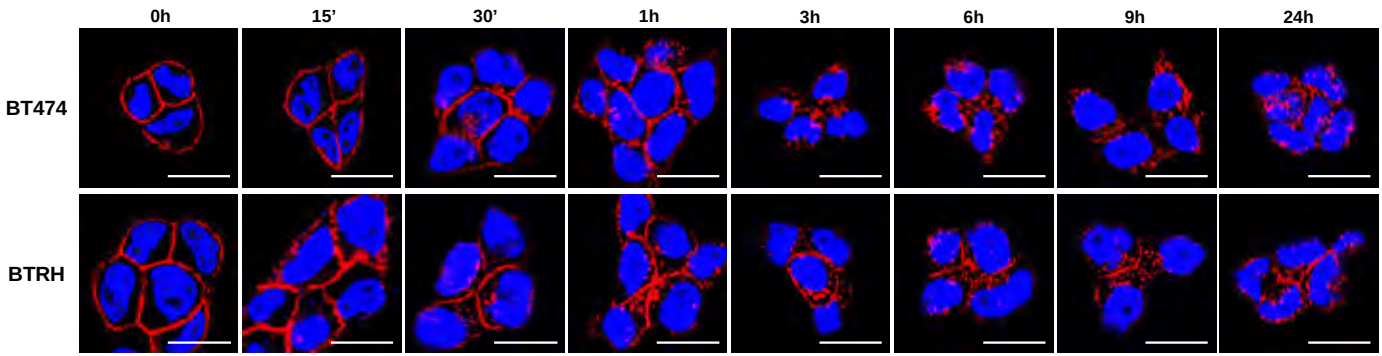
- **Modelling hypersensitivity to trastuzumab defines biomarkers of response in HER2 positive breast cancer.** *Díaz-Gil L, Brasó-Maristany F, Locatelli C, Centa A, Győrffy B, Ocaña A, Prat A, Pandiella A.* **J Exp Clin Cancer Res. 2021 Oct 7;40(1):313. doi: 10.1186/s13046-021-02098-z.** PMID: 34620206. **IF: 11.161 / Q1**

- **JKST6, a novel multikinase modulator of the BCR-ABL1/STAT5 signaling pathway that potentiates direct BCR-ABL1 inhibition and overcomes imatinib resistance in chronic myelogenous leukemia.** *Aranda-Tavío H, Recio C, Martín-Acosta P, Guerra-Rodríguez M, Brito-Casillas Y, Blanco R, Junco V, León J, Montero JC, Gandullo-Sánchez L, McNaughton-Smith G, Zapata JM, Pandiella A, Amesty A, Estévez-Braun A, Fernández-Pérez L, Guerra B.* **Biomed Pharmacother. 2021 Oct 19;144:112330. doi: 10.1016/j.biopha.2021.112330.** PMID: 34673425. **IF: 6.529 / D1**

- **Transcriptomic Correlates of Immunologic Activation in Head and Neck and Cervical Cancer.** *Saiz-Ladera C, Baliu-Piqué M, Cimas FJ, Manzano A, García-Barberán V, Camarero SC, Hinojal GF, Pandiella A, Győrffy B, Stewart D, Cruz-Hernández JJ, Pérez-Segura P, Ocana A.* **Front Oncol. 2021 Oct 6;11:714550. doi: 10.3389/fonc.2021.714550. eCollection 2021.** PMID: 3469249. **IF: 6.244 / Q2**

- **ERK5 inhibition elicits cellular senescence in melanoma via the cyclin-dependent kinase inhibitor p21.** *Tubita A, Lombardi Z, Tusa I, Lazzeretti A, Sgrignani G, Papini D, Menconi A, Gagliardi S, Lulli M, Dello Sbarba P, Esparís-Ogando A, Pandiella A, Stecca B, Rovida E.* **Cancer Res. 2021 Nov 19: canres.0993.2021. doi: 10.1158/0008-5472.CAN-21-0993.** PMID: 34799355 **IF: 12.701 / D1**



Internalization of the anti-HER3 antibody drug conjugate EV20/MMAF in cells sensitive to trastuzumab (BT474) or resistant to that drug (BTRH). The cells were incubated with EV20/MMAF for the indicated times. EV20/MMAF is marked in red and nuclei in blue. The dotted pattern corresponds to internalized EV20/MMAF that reached the endolysosomal pathway. Scale bar, 20 µm.

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Señalización por receptores ERBB/HER en cáncer. (BFU2015-71371-R)	Atanasio Pandiella Alonso	Spanish Ministry of Economy and Competitiveness	2016-2020	369,050.00 €
Consorcio CIBER. Programa de cáncer de mama (CB16/12/00317)	Atanasio Pandiella Alonso	Carlos III Health Institute	2016-2021	266,450.00 €
Terapia de precisión en cáncer de mama: resistencia a terapias anti-HER2 e inmunoterapia basada en identificación de neoantígenos	Atanasio Pandiella Alonso & Alberto Ocaña Fernández	CRIS against cancer Foundation	2018-2021	150,000.00 €
Anticuerpos conjugados contra proteínas de membrana e inmunoterapia en cáncer de ovario	Atanasio Pandiella Alonso & Alberto Ocaña Fernández	CRIS against cancer Foundation	2018-2021	210,000.00 €
La ruta de señalización MEK5/ERK5 en cáncer	Azucena Esparís Ogando	Carlos III Health Institute	2020-2022	129,470.00 €
Terapia de tumores HER2 positivos. (CSI146P20)	Atanasio Pandiella Alonso	Regional Government of Castilla y Leon	2020-2023	264,000.00 €
Identificación de nuevas dianas terapéuticas, preparación y eficacia antitumoral de ADCs en TNBC y cáncer de ovario	Juan Carlos Montero González	Carlos III Health Institute	2019-2022	113,320.00 €

OTHER ACTIVITIES & RELEVANT FACTS

Participation in international committees:

- Chairman of the Basic Cancer Research Evaluation Panel. Lund University (Sweden). Topic: Health, cancer area. RQ2020 Evaluation process of Lund University. (2020)
- Member of the Proposal Evaluation Panel, Young Investigator return Program. Associazione Italiana per la Ricerca sul Cancro (AIRC), Italy. Topic: Health, cancer area (2020-2021)
- Member of the Proposal Evaluation Panel, TRANSCAN-2 Program: European Union. Topic: Health, cancer area. Participation in the Evaluation Committee in three different annual calls (2017, 2019, 2020) and follow-up meetings in 2017, 2018 and 2019.
- Chairman of the Proposal Evaluation Panel, TRANSCAN-3 Program. European Union. Topic: Health, cancer area (2021)

R&D management activities:

- Deputy Director of the Institute of Molecular and Cellular Biology of Cancer (IBMCC-CIC). Internal management of activities. (2007-present)
- Director of the Translational Oncopharmacology Laboratory. Institute of Molecular and Cellular Biology of Cancer (IBMCC-CIC). Internal management of activities. (2005-present)
- CIBERONC group leader. Coordination of group activities (2017-present)
- IBSAL group leader. Coordination of group activities. (2016-present)
- Member of the Animal Facility Commission, University of Salamanca. Internal management of activities. (2018-present)
- Member of the Doctorate Program Commission, University of Salamanca. Internal management of activities. (2017-present)

Diversity in research policy:

- Our laboratory is strongly committed to stimulate equality and diversity in science. We have hosted students, pre and postdoctoral fellows, coming from several countries in the world, with different ethnical, culturas, religious and gender characteristics. We strongly foster and value the training of scientists from these countries and will keep the doors of our lab open to them.

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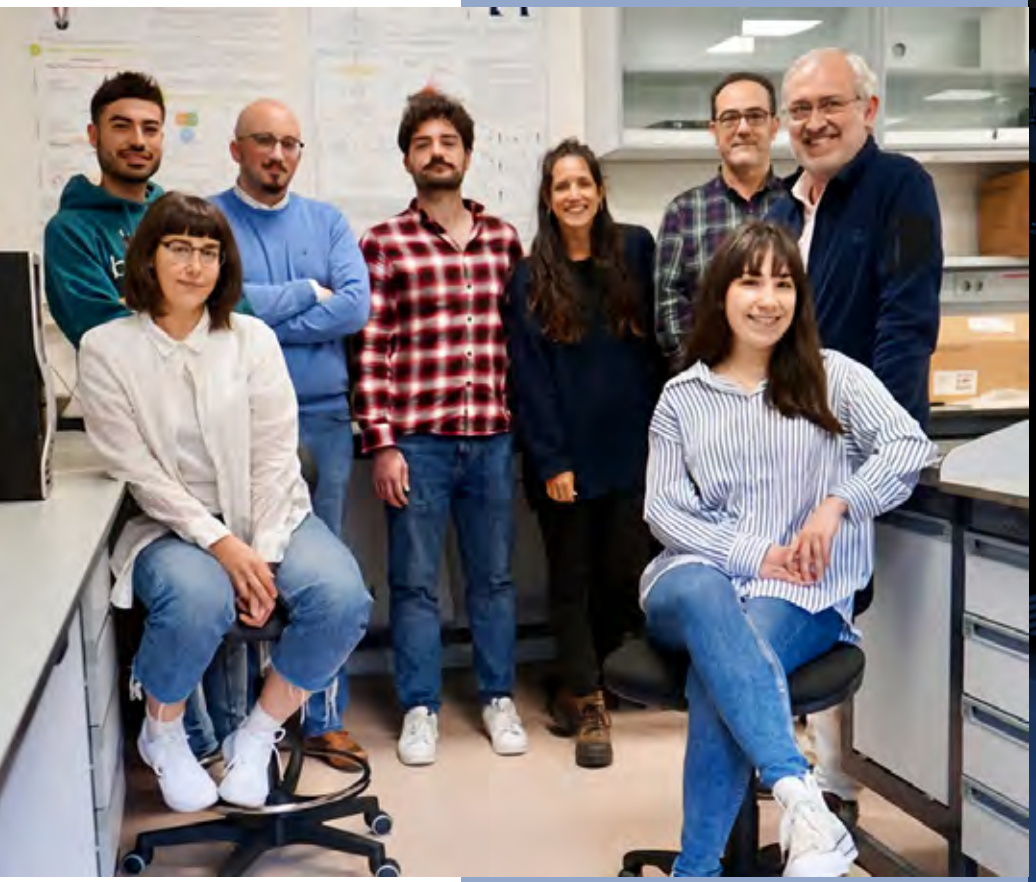

RESEARCH TEAM

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VISITING RESEARCH
Soraya Moradi Bachiller

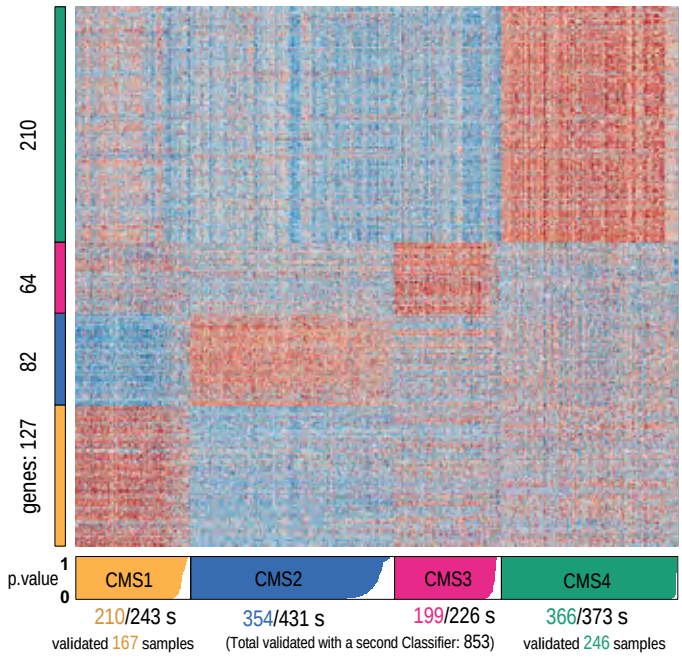
LABORATORY 19

BIOINFORMATICS AND FUNCTIONAL GENOMICS

RESEARCH SUMMARY

Research framed within the field of Bioinformatics, Computational Biology and Functional Genomics applied to the biomedical areas of Cancer, Oncology and Neurodegenerative diseases:

- Functional Genomics and Bioinformatics: Development of methods and strategies for the analysis of genomic data derived from different large-scale technologies (such as RNA-seq, DNA-seq, etc) to determine expression of genes, miRNAs and ncRNAs; or to identify gene splicing, copy-number alterations, changes in the methylation pattern, etc. Data mining, integration and analysis of genomic-transcriptomic profiles to achieve robust assignment of signal values and identify gene signatures associated to specific biological or pathological stages. All this work is focused on cancer samples from patients to identify disease subtypes, disease evolution and treatment responses (always in close collaboration with medical groups).
- Big Data, Machine Learning and Computational Omics: Application of methods of big data mining and artificial intelligence (such as Machine and Deep Learning, Reverse Engineering, Non-linear Dimensionality Reduction, etc) to omics data for: (i) the discovery



Cohort of 1273 CRC patients classified in CMSs.

of biomolecular signatures associated to specific pathological states; (ii) to build prognosis predictors derived from survival analysis; (iii) to build treatment response predictors; (iv) to identify resistance features. At present our studies are focused mainly on cancer, but also on neurodegenerative disorders (based in our participation in several EU projects). As indicated above, most of the work is done on samples derived from patients and in close collaboration with medical-clinical groups.

- Proteomics, Interactomics and Network Biology: Development of a biomolecular database of experimentally determined protein-protein interactions (PPIs) including strategies for quality control and validation. Use of this PPIs-DB to build comprehensive human interactome networks and derive cancer-related networks. Integration of genome-wide co-expression data and proteomic interaction data to build multiplex human biomolecular networks. Identification of regulatory circuits associated to these networks to identify causal genes (gene drivers) in specific disease subtypes or pathological states. Construction of bipartite interaction networks between drugs and proteins using pharmacogenomic data. Analysis of these networks for drug-target predictions.

PUBLICATIONS

- **Transcriptomic analysis of patients with immune thrombocytopenia treated with eltrombopag.** *Hernández-Sánchez JM, Bastida JM, Alonso-López D, Benito R, González-Porras JR, De Las Rivas J, Hernández Rivas JM, Rodríguez-Vicente AE.* **Platelets. 2020 Nov 16;31(8):993-1000. doi: 10.1080/09537104.2019.1702156.** PMID: 31838946. **IF: 3.862 / Q2**

- **Computational approaches in cancer multidrug resistance research: Identification of potential biomarkers, drug targets and drug-target interactions.** *Tolios A, De Las Rivas J, Hovig E, Trouillas P, Scorilas A, Mohr T.* **Drug Resist Updat. 2020 Jan;48:100662. doi: 10.1016/j.drup.2019.100662.** PMID: 31927437. **IF 18.500 / D1**

- **Transcriptomic landscape, gene signatures and regulatory profile of aging in the human brain.** *González-Velasco O, Papy-García D, Le Douaron G, Sánchez-Santos JM, De Las Rivas J.* **Biochim Biophys Acta Gene Regul Mech. 2020 Jun;1863(6):194491. doi: 10.1016/j.bbagrm.2020.194491.** PMID: 32006715. **IF: 4.490 / Q1**

- **Deciphering Master Gene Regulators and Associated Networks of Human Mesenchymal Stromal Cells.** *Sánchez-Luis E, Joaquín-García A, Campos-Laborie FJ, Sánchez-Guijo F, Rivas JL.* **Biomolecules. 2020 Apr 5;10(4):557. doi: 10.3390/biom10040557.** PMID: 32260546. **IF: 4.879 / Q2**

- **A reference map of the human binary protein interactome.** *Luck K, Kim DK, Lambourne L, Spirohn K, Begg BE, Bian W, Brignall R, Cafarelli T, Campos-Laborie FJ, Charloteaux B, Choi D, Coté AG, Daley M, Deimling S, Desbuleux A, Dricot A, Gebbia M, Hardy MF, Kishore N, Knapp JJ, Kovács IA, Lemmens I, Mee MW, Mellor JC, Pollis C, Pons C, Richardson AD, Schlabach S, Teeking B, Yadav A, Babor M, Balcha D, Basha O, Bowman-Colin C, Chin SF, Choi SG, Colabella C, Coppin G, D'Amata C, De Ridder D, De Rouck S, Duran-Frigola M, Ennajdaoui H, Goebels F, Goehring L, Gopal A, Haddad G, Hatchi E, Helmy M, Jacob Y, Kassa Y, Landini S, Li R, van Lieshout N, MacWilliams A, Markey D, Paulson JN, Rangarajan S, Rasla J, Rayhan A, Rolland T, San-Miguel A, Shen Y, Sheykhkarimli D, Sheynkman GM, Simonovsky E, Taşan M, Tejeda A, Tropepe V, Twizere JC, Wang Y, Weatheritt RJ, Weile J, Xia Y, Yang X, Yeger-Lotem E, Zhong Q, Aloy P, Bader GD, De Las Rivas J, Gaudet S, Hao T, Rak J, Tavernier J, Hill DE, Vidal M, Roth FP, Calderwood MA.* **Nature. 2020 Apr;580(7803):402-408. doi: 10.1038/s41586-020-2188-x.** PMID: 32296183. **IF: 49.962 / D1**

- **Mining Drug-Target Associations in Cancer: Analysis of Gene Expression and Drug Activity Correlations.** *Arroyo MM, Berral-González A, Bueno-Fortes S, Alonso-López D, Rivas JL.* **Biomolecules. 2020 Apr 25;10(5):667. doi: 10.3390/biom10050667.** PMID: 32344870. **IF: 4.879 / Q2**

- **Exomes of Ductal Luminal Breast Cancer Patients from Southwest Colombia: Gene Mutational Profile and Related Expression Alterations.** *Cortes-Urrea C, Bueno-Gutiérrez F, Solarte M, Guevara-Burbano M, Tobar-Tosse F, Vélez-Varela PE, Bonilla JC, Barreto G, Velasco-Medina J, Moreno PA, Rivas JL.* **Biomolecules. 2020 Apr 30;10(5):698. doi: 10.3390/biom10050698.** PMID: 32365829. **IF: 4.879 / Q2**

- **Cancer immunotherapy resistance based on immune checkpoints inhibitors: Targets, biomarkers, and remedies.** *Pérez-Ruiz E, Melero I, Kopecka J, Sarmento-Ribeiro AB, García-Aranda M, De Las Rivas J.* **Drug Resist Updat.**

2020 Dec;53:100718. doi: 10.1016/j.drup.2020.100718. PMID: 32736034. **IF:18.500 / D1**

- **An intact gut microbiome protects genetically predisposed mice against leukemia.** *Vicente-Dueñas C, Janssen S, Oldenburg M, Auer F, González-Herrero I, Casado-García A, Isidro-Hernández M, Raboso-Gallego J, Westhoff P, Pandyra AA, Hein D, Gössling KL, Alonso-López D, De Las Rivas J, Bhatia S, García-Criado FJ, García-Cenador MB, Weber APM, Köhrer K, Hauer J, Fischer U, Sánchez-García I, Borkhardt A.* **Blood. 2020 Oct 29;136(18):2003-2017. doi: 10.1182/blood.2019004381.** PMID: 32911536. **IF: 23.629 / D1**

- **Stromal SNAI2 Is Required for ERBB2 Breast Cancer Progression.** *Blanco-Gómez A, Hontecillas-Prieto L, Corchado-Cobos R, García-Sancha N, Salvador N, Castellanos-Martín A, Sáez-Freire MDM, Mendiburu-Eliçabe M, Alonso-López D, De Las Rivas J, Lorente M, García-Casas A, Del Carmen S, Abad-Hernández MDM, Cruz-Hernández JJ, Rodríguez-Sánchez CA, Claros-Ampuero J, García-Cenador B, García-Criado J, Orimo A, Gridley T, Pérez-Losada J, Castillo-Lluva S.* **Cancer Res. 2020 Dec 1;80(23):5216-5230. doi: 10.1158/0008-5472.CAN-20-0278.** PMID: 33023950. **IF: 12.701 / D1**

- **Conditional expression of HGAL leads to the development of diffuse large B-cell lymphoma in mice.** *Raboso-Gallego J, Casado-García A, Jiang X, Isidro-Hernández M, Gentles AJ, Zhao S, Natkunam Y, Blanco O, Domínguez V, Pintado B, Alonso-López D, De Las Rivas J, Vicente-Dueñas C, Lossos IS, Sanchez-Garcia I.* **Blood. 2021 Apr 1;137(13):1741-1753. doi: 10.1182/blood.2020004996.** PMID: 33024996 **IF: 23.629 / D1**

- **Inhibition of inflammatory signaling in Pax5 mutant cells mitigates B-cell leukemogenesis.** *Isidro-Hernández M, Mayado A, Casado-García A, Martínez-Cano J, Palmi C, Fazio G, Orfao A, Ribera J, Ribera JM, Zamora L, Raboso-Gallego J, Blanco O, Alonso-López D, De Las Rivas J, Jiménez R, García Criado FJ, García Cenador MB, Ramírez-Orellana M, Cazzaniga G, Cobaleda C, Vicente-Dueñas C, Sánchez-García I.* **Sci Rep. 2020 Nov 5;10(1):19189. doi: 10.1038/s41598-020-76206-y.** PMID: 33154497. **IF: 4.379 / Q1**

- **Systematic comparison and assessment of RNA-seq procedures for gene expression quantitative analysis.** *Corchete LA, Rojas EA, Alonso-López D, De Las Rivas J, Gutiérrez NC, Burguillo FJ.* **Sci Rep. 2020 Nov 12;10(1):19737. doi: 10.1038/s41598-020-76881-x.** PMID: 33184454. **IF: 4.379 / Q1**

- **Joining European Scientific Forces to Face Pandemics.** *Vasconcelos MH, Alcaro S, Arechavala-Gomeza V, Baumbach J, Borges F, Brevini TAL, Rivas JL, Devaux Y, Hozak P, Keinänen-Toivola MM, Lattanzi G, Mohr T, Murovska M, Prusty BK, Quinlan RA, Pérez-Sala D, Scheibenbogen C, Schmidt HHHW, Silveira I, Tieri P, Tolios A, Riganti C.* **Trends Microbiol. 2021 Feb;29(2):92-97. doi: 10.1016/j.tim.2020.10.008.** PMID: 33288385. **IF: 17.079 / D1**

- **Stroma-Mediated Resistance to S63845 and Venetoclax through MCL-1 and BCL-2 Expression Changes Induced by miR-193b-3p and miR-21-5p Dysregulation in Multiple Myeloma.** *Algarín EM, Quwaider D, Campos-Laborie FJ, Díaz-Tejedor A, Mogollón P, Vuelta E, Martín-Sánchez M, San-Segundo L, González-Méndez L, Gutiérrez NC, García-Sanz R, Paíno T, De Las Rivas J, Ocio EM, Garayoa M.* **Cells. 2021 Mar 4;10(3):559. doi: 10.3390/cells10030559.** PMID: 33806619. **IF: 6.600 / Q2**

- **Cancer-associated fibroblast-derived gene signatures determine prognosis in colon cancer patients.** *Herrera M, Berral-González A, López-Cade I, Galindo-Pumariño C, Bueno-Fortes S, Martín-Merino M, Carrato A, Ocaña A, De La Pinta C, López-Alfonso A, Peña C, García-Barberán V, De Las Rivas J.* **Mol Cancer. 2021 Apr 29;20(1):73. doi: 10.1186/s12943-021-01367-x.** PMID: 33926453. **IF: 27.401 / D1**

- **Cancer drug resistance induced by EMT: novel therapeutic strategies.** *De Las Rivas J, Brozovic A, Izraely S, Casas-Pais A, Witz IP, Figueroa A.* **Arch Toxicol. 2021 Jul;95(7):2279-2297. doi: 10.1007/s00204-021-03063-7.** PMID: 34003341. **IF: 5.153 / Q1**

- **40 Years of RAS-A Historic Overview.** *Fernández-Medarde A, De Las Rivas J, Santos E.* **Genes (Basel). 2021 May 1;12(5):681. doi: 10.3390/genes12050681.** PMID: 34062774. **IF: 4.096 / Q2**

- **Ten simple rules for organizing a bioinformatics training course in low- and middle-income countries.** *Moore B, Carvajal-López P, Chauke PA, Cristancho M, Dominguez Del Angel V, Fernandez-Valverde SL, Ghouila A, Gopalasingam P, Guerfali FZ, Matimba A, Morgan SL, Oliveira G, Ras V, Reyes A, De Las Rivas J, Mulder N.* **PLoS Comput Biol. 2021 Aug 19;17(8):e1009218. doi: 10.1371/journal.pcbi.1009218.** PMID: 34411091. **IF: 4.475 / Q1**

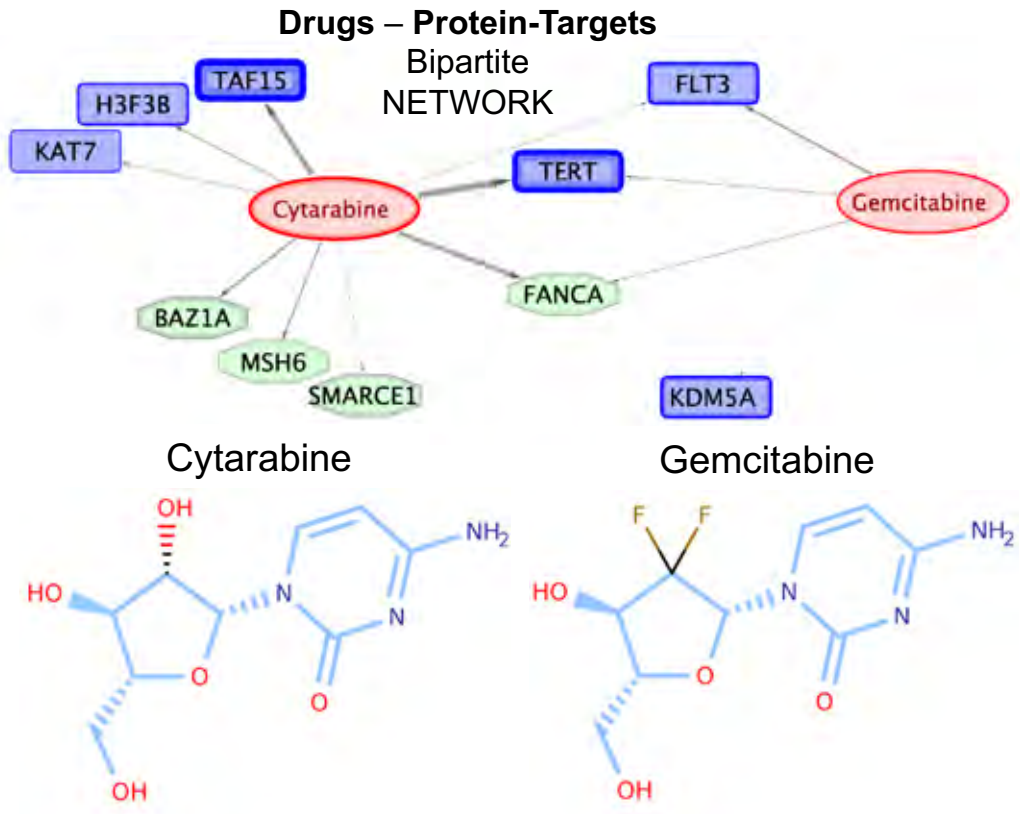
- **Resistance to Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia-From Molecular Mechanisms to Clinical Relevance.** *Alves R, Gonçalves AC, Rutella S, Almeida AM, De Las Rivas J, Trougakos IP, Sarmento Ribeiro AB.* **Cancers (Basel). 2021 Sep 26;13(19):4820. doi: 10.3390/cancers13194820.** PMID: 34638304. **IF: 6.639 / Q1**

- **Hypoxia as a driver of resistance to immunotherapy.** *Kopecka J, Salaroglio IC, Perez-Ruiz E, Sarmento-Ribeiro AB, Saponara S, De Las Rivas J, Riganti C.* **Drug Resist Updat. 2021 Dec;59:100787. doi: 10.1016/j.drup.2021.100787.** PMID: 34840068. **IF: 18.500 / D1**

OTHER PUBLICATIONS & BOOK CHAPTERS

- **Omics Technologies and Precision Medicine.** *De Las Rivas, Javier; Rojas, Ana M.; Montoliu, Lluis; Mora, Leticia; Pazos, Florencio.* **Volume 3 "Genome and Epigenetics" (2020) pag. 28-49 (Chapter 2) http://dx.doi.org/10.20350/digitalCSIC/12650. Consejo Superior de Investigaciones Científicas (España). CSIC Scientific Challenges: Towards 2030. Topic Coordinators: Lluis Montoliu José & Alvaro Rada Iglesias ISBN: 978-84-00-10739-0**

- **Brain & Spinal Cord Damage & Rehabilitation.** *Planas, Anna M; Moreno, Juan C.; Álvarez-Dolado, Manuel; Casas-Tinto, S.; Corbí, Angel L.; De Las Rivas, Javier; Delgado, Manuel; Fuentes-García, Manuel; González-Rey, Elena; Iglesias, Teresa; Llebaria, Amadeu; López-Atalaya, José P.; Mittelbrunn, M.; Rocón, Eduardo; Serrano, Teresa; Villa, Rosa; Yúfera, Alberto; Duarte, Esther; Gil-Agudo, Ángel.* **Volume 5 "Brain, Mind and Behaviour" (2020). Pag. 106-123 (Chapter 8) http://dx.doi.org/10.20350/digitalCSIC/12652 Consejo Superior de Investigaciones Científicas (España). CSIC Scientific Challenges: Towards 2030. Topic Coordinators: Eloisa Herrera & José Antonio Esteban. ISBN: 978-84-00-10746-8**



PATENTS

PATENT REFERENCE	TITLE	INVENTORS	PRIORITY DATE
EP21383041	In vitro method for the identification of human Mesenchymal Stem/Stromal Cells	Javier De Las Rivas, Sandra Muntion, Elena Sánchez-Luis, Fermín Sánchez-Guijo	17 /11/2021

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
3-O-sulfated heparan sulfate translocation in altered membrane biology: A new strategy for early population screening and halting Alzheimer's neurodegeneration -ArrestAD (Project Ref. 737390)	Javier De Las Rivas	European Union	2017-2022	452,375.00 €
Plataforma de Bioinformática: Bioinformatics and Functional Genomics in Cancer (PT17/0009/0008)	Javier De Las Rivas	Carlos III Health Institute	2018-2021	31,899.00 €
Onco-proteogenómica personalizada aplicada a hemopatías malignas e inmunomodulación: desarrollo y uso de métodos bioinformáticos para búsqueda de marcadores, predictores de riesgo y dianas en pacientes y donantes (PI18/00591)	Javier De Las Rivas	Carlos III Health Institute	2019-2022	99,220.00 €
Infraestructura de datos para Medicina Personalizada IMPaCT-Data (IMP/00019)	Javier De Las Rivas (CoIP)	Carlos III Health Institute	2021-2023	112,250.00 €
Red Iberoamericana de Inteligencia Artificial para Big BioData (RIABIO) (Red 521RT0118)	Javier De Las Rivas (CoCoordinador)	CYTED Program (Ibero-American program for Science & Technology for Development)	2021-2024	100,000.00 €

OTHER ACTIVITIES & RELEVANT FACTS

- President of the Sociedad Iberoamericana de Bioinformática / Iberoamerican Society for Bioinformatics (SOIBIO), from Oct.2016 (second mandate 2019-21). www.soibio.org
- Member & Vice-Chair of European COST ACTION CA17104: STRATAGEN, New diagnostic and therapeutic tools against multidrug resistant tumors (4 years Action). From September.2018 - September.2022.
  https://www.cost.eu/actions/CA17104/
- Member of European COST ACTION CA17118: TRANSCOLONCAN, Identifying biomarkers through translational research for prevention & stratification of Colorectal Cancer (4 years Action). From October.2018 - October.2022. https://www.cost.eu/actions/CA17118/
- Member of the Executive Board of the Global Organization for Bioinformatics Learning, Education & Training (GOBLET) (Member of GOBLET from 2012, and Member of the Executive Board from 2019). www.mygoblet.org
- Member & Co-coodinator of the Red Iberoamericana de Inteligencia Artificial para Big BioData (RIABIO) (Ref. 521RT0118) supported by CYTED (Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo, Redes Temáticas de investigación y desarrollo I+D). 4 years: 2021 - 2024.
  http://www.cyted.org/?q=es/detalle_proyecto&un=1021; www.cyted.org.

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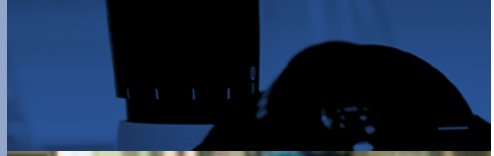

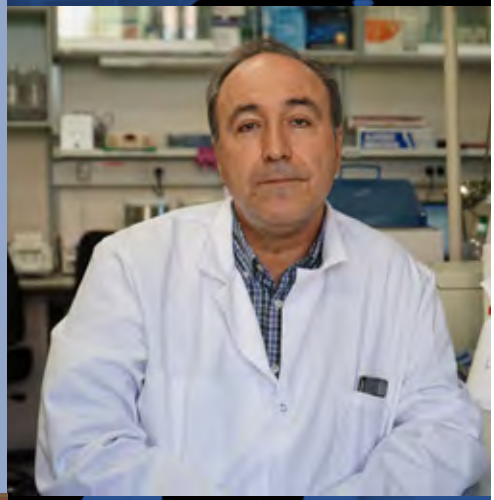

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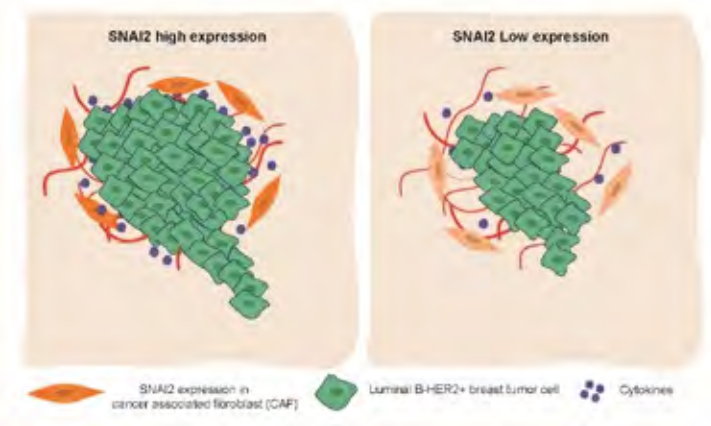
LABORATORY 20

MOLECULAR AND GENETIC DETERMINANTS OF CANCER SUSCEPTIBILITY, EVOLUTION AND TREATMENT RESPONSE

RESEARCH SUMMARY

Identification of genetic determinants of breast cancer susceptibility and evolution

There is a broad variation in cancer susceptibility and evolution, including response to treatment among patients, even those with the same tumor type. This variation is explained because cancer is a complex disease influenced by multiple genes of low penetrance and expressiveness that influence the function of the driver genes and modify cancer evolution (modifier genes). Also, cancer as a complex trait results from other intermediate phenotypes involved in its development and evolution. The interactions between intermediate phenotypes generate a network of phenotypes located at different levels: systemic, organs, tissues, cells, and intracellular. The interaction between phenotypes forms a chaotic system that can be studied from a System Biology perspective. All those intermediate phenotypes are regulated by multiple modifier genes that explain the polygenic nature of cancer processes that follow a quantitative inheritance model. When attempting to identify these susceptibility polygenes to a complex disease, such as cancer, the genes identified only account for 30% or less of the phenotypic variability due to Genetics (heritability); this phenomenon is known as "missing heritability." We postulated that some of the missing heritability would be defined by polygenes associated with intermediate phenotypes that cannot be detected at the level of the complex trait



Graphical abstract. SNAI2 overexpression in the stroma and not in the epithelium is associated with a poor prognosis in luminal B-HER2+ breast cancer patients (Blanco-Gómez A. *et al*., Cancer Res. 2020).

Considering this, we generated cohorts of mice by backcrossing with different susceptibility to breast cancer treated with anthracyclines and taxanes. We identify

the DNA variants (DSVs) associated with the complex phenotype considered cancer susceptibility evolution and treatment response through intermediate phenotypes. With this approach, we identified new genetic markers of susceptibility to cardiotoxicity due to anthracyclines in breast cancer patients (submitted article); and the response to breast cancer treatment by anthracyclines and taxanes (work in preparation). Prevention of breast cancer

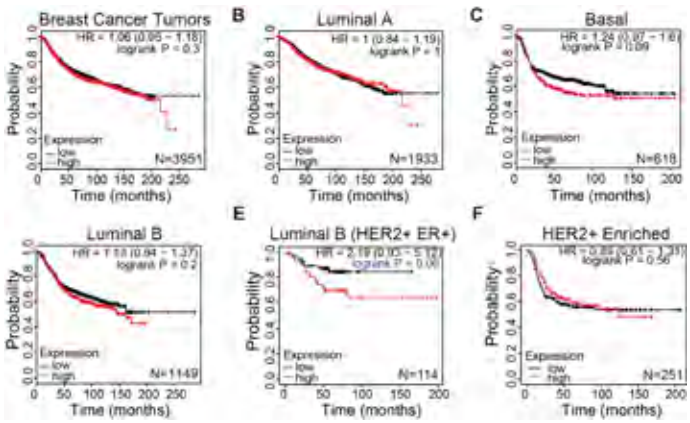
Strategies for breast cancer chemoprevention

Also, the environment has been essential to modeling the development of the different intermediate phenotypes that control complex traits and their interaction throughout the species evolution. Therefore the high prevalence of breast cancer in humans should be seen from an Evolutionary Medicine perspective. As Theodosius Dobzhansky alleged, "Nothing in Biology makes sense except in the light of evolution." In the past, pregnancy generally occurred early and repeated; only in the Western World in the last 50-70 years pregnancy often takes place late and unique. Together with an increased life expectancy, this fact has led to an increase in the incidence of breast cancer.

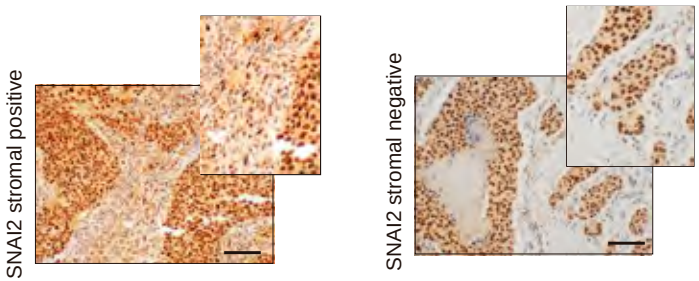
We pretend to use associations between complex phenotypes to try to generate new prevention strategies against breast cancer. Previously, we observed that Snai2 deficiency produces a postlactational involution defect and increases tumor susceptibility (Castillo-Lluva et al., Oncogene 2015). Also, we have shown that Snai2 deficiency in stroma results in lower aggressiveness of ERBB2+ breast cancer in mice and patients (Blanco-Gómez et al., Cancer Research 2020). We pretend to design breast cancer prevention strategies by modifying post-lactational drug involution. Current prevention strategies have significant side effects and cannot be applied to most of the population; new approaches are needed for fewer side effects of reducing the incidence of breast cancer.

Squamous Cell Carcinoma studies

Our laboratory is also interested in studying the prognosis heterogeneity of cutaneous squamous cell carcinoma and novel therapeutic opportunities in this tumor. Currently, this is an independent line of work carried out by Dr. Cañueto. Dr. Cañueto awarded his PhD in our laboratory in 2016, is a Medical Doctor in the Department of Dermatology at the University Hospital of Salamanca, and Associate professor at the University of Salamanca. Currently, he forms part of our laboratory as a visiting senior researcher.



Association of tumor *Snai2* overexpression with evolution in different subtypes of breast cancer. Survival curves (Kaplan-Meier) were obtained from the Kaplan-Meier plotter database. (**A**) Survival of patients with breast cancer in the whole cohort regardless of tumor subtype. (**B**) Survival of patients with the Luminal A subtype of tumors. (**C**) Patients with basal tumors. (**D**) Patients with luminal B tumors. (**E**) Patients with luminal B HER2+/ER+ tumors. (**F**) Patients with HER2+ enriched ER- tumors. The statistical significance of the Kaplan-Meier curves (A-F panels) was evaluated using the Log-Rank test, according to the public database website, Kaplan-Meier plotter (Blanco-Gómez A. *et al*., Cancer Res. 2020)..

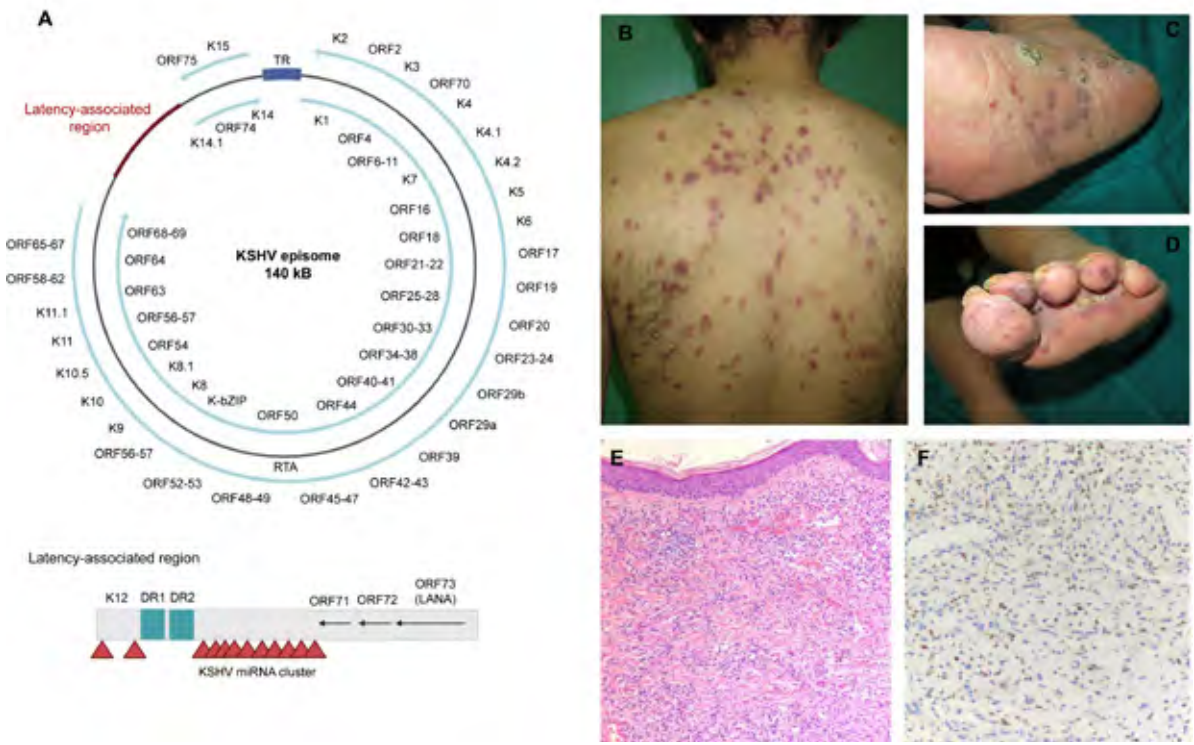


Breast tumors with SNAI2 expression in breast cancer stroma. (A) Breast tumors with SNAI2 expression in the stroma and the epithelium assessed by immunohistochemistry, (**B**) or only in the epithelium of the tumor (Blanco-Gómez A. *et al*., Cancer Res. 2020).

CSCC is the second most common tumor in humans after basal cell carcinoma (BCC). Its incidence is increasing but is underestimated because it is excluded from the Surveillance, Epidemiology, and End Results (SEER) Program and other national cancer registries. Although it is usually quickly resolved with surgery, it can progress locally, metastasize,

and cause death in a subset of patients. There are an estimated 15,000 deaths per year from CSCC in the United States, surpassing the number of melanoma deaths (www.skincancer.org). The increase in life expectancy will mean an increase in the health impact of the CSCC (in 2050, 15.3% of the population will be over 80 years, almost three times more than in 2011 [http://envejecimientoenred. es]).

Defining the prognosis of high-risk (HR) CSCC remains a challenge. Based on the limitations identified in the current AJCC8 staging system, our group has identified prognostic subgroups of HRCSCC and proposed alternatives to the current AJCC8 system. However, when comparing it with other alternative systems, we have seen that the prognostic precision of alternative staging systems is not suitable for HRCSCC, making improvements essential. Therefore, improving these staging systems is essential to improving clinical practice. The recognition of new prognostic factors in CSCC is a priority, as it would allow better identification of patients with the highest risk of relapse and improve current staging systems. Therefore, to discriminate the groups at higher risk, we examined the usefulness of some already known prognostic factors in greater depth. Thus, we better defined perineural invasion (PNI) and its relationship with the prognosis of the disease and identified groups of tumors with PNI that would benefit from postoperative radiotherapy, which would not be helpful in all CSCCs presenting this trait. Also, we explored the impact of the growth rate. There are other clinic-pathological variables whose prognostic relevance has yet to be adequately defined and on which we are focusing.



Human herpesvirus 8 and Kaposi's sarcoma: (**A**) Scheme of HHV8. (**B–D**) The clinical aspect of Kaposi's sarcoma, consistent with erythematous nodules located in the trunk of an HIV+ male (**B**) and in the foot of an elderly woman (**C**,**D**). (**E**) The H&E aspect. (**F**) The positive stain for HHV8. All the photographs were generated and provided by the authors (Becerril *et al*., Int J Mol Sci, 2021).

The study of the tumor microenvironment, consisting of the stroma and associated inflammatory infiltrate, has become increasingly important. Beyond clinical and histopathologic features, a more translational approach has let us recognize the prognostic impact of specific miRNAs, the overexpression of EGFR and D2-40. Currently, we are trying to more precisely stratify HR-CSCC based on genomic, RNAseq, and multi-omic approaches.

Until just over two years ago, there had been very few advances in the pharmacological treatment of CSCC. In 2018 and 2020, the FDA approved cemiplimab and pembrolizumab to treat locally advanced and metastatic CSCCs. However, around half of the patients do not respond to anti-PD1 drugs, and there are no approved alternatives for the treatment of advanced forms of CSCC. Therefore, identifying patients who will respond to these new therapies and potential new therapeutic targets is a priority, as highlighted in a recent review. These studies are another research priority of our group.

PUBLICATIONS

- **Stromal SNAI2 Is Required for ERBB2 Breast Cancer Progression.** *Blanco-Gómez A, Hontecillas-Prieto L, Corchado-Cobos R, García-Sancha N, Salvador N, Castellanos-Martín A, Sáez-Freire MDM, Mendiburu-Eliçabe M, Alonso-López D, De Las Rivas J, Lorente M, García-Casas A, Del Carmen S, Abad-Hernández MDM, Cruz-Hernández JJ, Rodríguez-Sánchez CA, Claros-Ampuero J, García-Cenador B, García-Criado J, Orimo A, Gridley T, Pérez-Losada J(*), Castillo-Lluva S(*).* **Cancer Res. 2020 Dec 1;80(23):5216-5230. doi: 10.1158/0008-5472.CAN-20-0278.** PMID: 33023950 **IF: 12.701 / D1**

- **Overcoming Resistance to Immunotherapy in Advanced Cutaneous Squamous Cell Carcinoma.** *García-Sancha N, Corchado-Cobos R, Bellido-Hernández L, Román-Curto C, Cardeñoso-Álvarez E, Pérez-Losada J, Orfao A, Cañueto J.* **Cancers (Basel). 2021 Oct 13;13(20):5134. doi: 10.3390/cancers13205134.** PMID: 34680282 **IF: 6.639 / Q1**.

- **Viruses and Skin Cancer.** *Becerril S, Corchado-Cobos R, García-Sancha N, Revelles L, Revilla D, Ugalde T, Román-Curto C, Pérez-Losada J, Cañueto J.* **Int J Mol Sci. 2021 May 20;22(10):5399. doi: 10.3390/ijms22105399.** PMID: 34065594. **IF: 5.923 / Q1**.

- **Cutaneous Squamous Cell Carcinoma: From Biology to Therapy.** *Corchado-Cobos R, García-Sancha N, González-Sarmiento R, Pérez-Losada J, Cañueto J.* **Int J Mol Sci. 2020 Apr 22;21(8):2956. doi: 10.3390/ijms21082956.** PMID: 32331425. **IF: 5.923 / Q1**.

- **Patterns of incidental perineural invasion and prognosis in cutaneous squamous cell carcinoma: A multicenter, retrospective cohort study.** *Conde-Ferreirós A, Corchete LA, Jaka A, Santos-Briz Á, Fuente MJ, Posada R, Pons L, Podlipnik S, Pujol RM, Román-Curto C, Toll A, Cañueto J.* **J Am Acad Dermatol. 2021 Jun;84(6):1708-1712. doi: 10.1016/j.jaad.2020.08.017.** PMID: 32781186. **IF: 11.527 / D1**

- **Performance of Salamanca refinement of the T3-AJCC8 versus the Brigham and Women's Hospital and Tübingen alternative staging systems for high-risk cutaneous squamous cell carcinoma.** *Puebla-Tornero L, Corchete-Sánchez LA, Conde-Ferreirós A, García-Sancha N, Corchado-Cobos R, Román-Curto C, Cañueto J.* **J Am Acad Dermatol. 2021 Apr;84(4):938-945. doi: 10.1016/j.jaad.2020.12.020.** PMID: 33333151. **IF: 11.527 / D1**

- **Definition of prognostic subgroups in the T3 stage of the eighth edition of the American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: Tentative T3 stage subclassification.** *Conde-Ferreirós A, Corchete LA, Puebla-Tornero L, Corchado-Cobos R, García-Sancha N, Román-Curto C, Cañueto J.* **J Am Acad Dermatol. 2021 Nov;85(5):1168-1177. doi: 10.1016/j.jaad.2020.03.088.** PMID: 32278798. **IF: 11.527 / D1**

- **Hyperspectral imaging and robust statistics in non-melanoma skin cancer analysis.** *Courtenay LA, González-Aguilera D, Lagüela S, Del Pozo S, Ruiz-Mendez C, Barbero-García I, Román-Curto C, Cañueto J, Santos-Durán C, Cardeñoso-Álvarez ME, Roncero-Riesco M, Hernandez-Lopez D, Guerrero-Sevilla D, Rodríguez-Gonzalvez P.* **Biomed Opt Express. 2021 Jul 20;12(8):5107-5127. doi: 10.1364/BOE.428143.** PMID: 34513245. **IF: 3.732 / Q1**

- **Clinical and histopathological evaluation of 50 acantholytic cutaneous squamous cell carcinomas: Analysis outcome in a retrospective case-control study.** *Conde-Ferreirós A, Moyano-Bueno D, Santos-Briz Á, Revelles-Peñas L, Revilla-Nebreda D, Becerril-Andrés S, Román-Curto C, Cañueto J.* **J Cutan Pathol. 2021 Aug 7. doi: 10.1111/cup.14116.** PMID: 34363705. **IF: 1.587 / Q4**

OTHER PUBLICATIONS & BOOK CHAPTERS

- **Evolution of Health and Diseases.** *Jesús Blázquez, Jordi Gómez, Elena Gómez-Díaz, Jesús Pérez-Losada, and Francisco Sobrino. Coordinators: Santiago F. Elena and Iñaki Comas.* **Book Section: "D. Origins and (co)Evolution and Diversity of Life" Topic coordinators: Paola Bovolenta, Miguel Manzanares and Javier Buceta CSIC Topic: "Origin and Evolution of Life and Synthetic Biology" (2020). Editor: Consejo Superior de Investigaciones Científicas (CSIC). URI:** http://hdl.handle.net/10261/221138 **DOI:** http://dx.doi.org/10.20350/digitalCSIC/12649. **Libro Blanco CSIC 2, regarding "Las temáticas y desafíos para el próximo decenio**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Estrategias farmacológicas de prevención del cáncer de mama mediante modificación de la involución postlactancia (SAF2017-88854-R)	Jesús Pérez Losada	Spanish Ministry of Economy and Competitiveness	2018-2020	159,400.00 €
Nuevas aproximaciones terapéuticas para la prevención de la leucemia aguda infantil (CSI234P18)	Isidro Sánchez García (UIC17) (Collaborator: Jesús Pérez Losada)	Regional Government of Castilla y Leon	2018-2021	120,000.00 €
Nueva aproximación a la definición del pronóstico del carcinoma epidermoide cutáneo: identificación y validación de nuevos marcadores (PI18/00587)	Javier Cañueto Álvarez	Carlos III Health Institute	2019-2021	99,220.00 €
La pandemia causada por el virus Sars-Cov-2 y su implicación en la génesis de la leucemia infantil. (CSI144P20)	Isidro Sánchez García (UIC17) (Collaborator: Jesús Pérez Losada)	Regional Government of Castilla y Leon	2020-2023	172,000.00€
Evaluation of breast cancer prevention using somatostatin analogs (2020AEP111)	Jesús Pérez Losada	Spanish Ministry of Economy and Competitiveness	2021	12,500.00 €
Development and Validation of a Gene Expression Assay to Predict the Risk of Recurrence Disease in Cutaneous Squamous Cell Carcinoma	Javier Cañueto Álvarez	Castle Biosciences	2021	100,324.00 €
Caracterización del microambiente tumoral y del perfil inmunológico global en el carcinoma epidermoide cutáneo de alto riesgo (GRS2129/A/20)	Javier Cañueto Álvarez	Regional Health Management	2021	15,800.00 €
Breast cancer prevention by enhancing postlactational involution with cabergoline (PDC2021-121735-I00)	Jesús Pérez Losada	Spanish Ministry of Science and Innovation / European Union (Next Generation EU)	2021-2023	133,400.00 €
Evaluation of breast cancer prevention using somatostatin analogs (PID2020-118527RB-I00)	Jesús Pérez Losada	Spanish Ministry of Economy and Competitiveness	2021-2024	205,700.00 €
Prognostic stratification of high-risk cutaneous squamous cell carcinoma through a multi-omic approach. Identification of novel targeted therapies. (PI21/01207)	Javier Cañueto Álvarez	Carlos III Health Institute	2021-2024	145,200.00 €
Characterization of the global immunological profile and identification of biomarker signatures of response and toxicity in cutaneous squamous cell carcinoma under treatment with cemiplimab through next-generation flow cytometry. (SGZ-2020-13098)	Javier Cañueto Álvarez	Sanofi-Genzyme	2021-2024	199,670.56 €

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LABORATORY 7B

RECEPTOR INHIBITORS AND CDK4 INHIBITORS

(from September 2021)

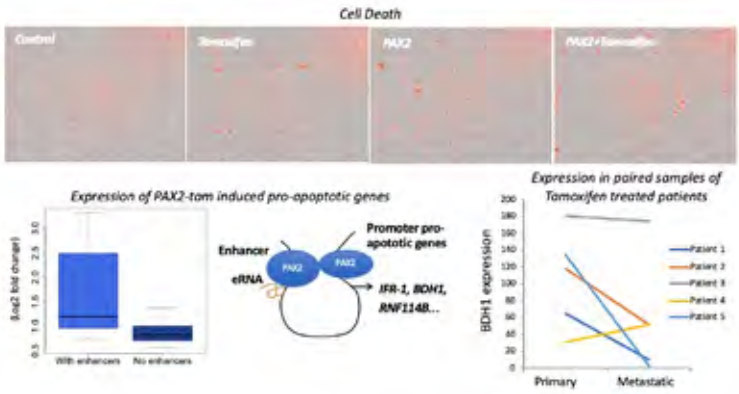
RESEARCH SUMMARY

1. The Group investigates the mechanisms of resistance to breast cancer treatments. Breast cancer is the most common cancer in women of developed countries, and at least two thirds of breast tumors are positive for the expression of Estrogen Receptor alpha (ER). ER is a transcription factor that binds to estrogen and activates transcription in mammary cells. ER drives proliferation of this breast cancer type and current treatments pursuit targeting its activity. Tamoxifen and Aromatase Inhibitors (AI) are the most used anti-estrogen drugs for adjuvant therapy in breast cancer patients, but patients frequently fail to respond to those treatments. To the present date, several works have described distinct factors that influence the function of ER and ultimately dictate the efficacy of the anti-estrogen therapies. The presence of these cooperative factors raises a new level of complexity for ER transcriptional regulation and endocrine response. Our group investigates the mechanisms of hormone-resistance. In particular, our research project is structured in two comprehensive and often overlapping areas. How anti-ER drugs performs: One area entails chemical systems approaches to: (1) functionally understand how anti-ER drugs perform their repressive effects and (2) identify novel mechanism by which hormone-resistant cells overcome ER inhibition. The second area involves the validation of the findings by means of using both in vivo and *in vitro* models.
2. Recently, the group has published a work (Wang et al, Oncogene 2020: IF: 9,8) where we have stablished a new interplay between interferon signaling and the anti ER drug tamoxifen. Briefly, our work has revealed that the transcription factor PAX2 and tamoxifen have an additive effect and both induce coding genes and enhancer RNAs (eRNAs). The enrichment of eRNAs is associated with the highest expression of genes that positivity regulate apoptotic processes. In luminal tumors, the expression of a subset of these proapoptotic genes predicts good outcome and their expression are significantly reduced in tumors of patients with relapse to tamoxifen treatment. Mechanistically, PAX2 and tamoxifen coexert an antitumoral effect by maintaining high levels of transcription of tumor suppressors that promote cell death. The apoptotic effect is mediated in large part by the gene interferon regulatory factor 1. Altogether, we conclude that PAX2 contributes to better clinical outcome in tamoxifen treated ER-positive breast cancer patients by repressing estrogen signaling and inducing cell death related pathways.

3. In relation to the interplay of different transcription factors and response to breast cancer treatments, we have also identified that post-translational modifications of the transcription factor FOXA1 play an important role in the response to treatment in breast cancer. Now, we have identified that HER2/3 activation in hormone-resistant tumors hinders FOXA1 acetylation and facilitates FOXA1 binding at non-ER interacting regions enriched towards poor prognosis genes. Moreover, FOXA1 deacetylation confers insensitivity to anti-ER drugs inhibitory effect in ER positive cells. These results elucidate how post-translational modifications of FOXA1 control transcription independently of ER in hormone-resistant tumors with enhanced HER2/3 signaling (Gilfillan et al, NAR in revision, IF:16,9). In addition to acetylation, we have also identified that FOXA1 can be phosphorylated by the kinase CDK4/6 (Wang, Palomeque et al, manuscript in preparation). Our study has revealed that CDK4/6-CyclinD1 kinase complex negatively regulates FOXA1 to prevent HER2 activation and apoptosis evasion in HER2+/ER+ breast cancers. Mechanistically, CDK4 phosphorylate and negatively regulates the activity of FOXA1 on specific genomic locations. Importantly, those genes that are specifically affected by CDK regulation of FOXA1 are involved in cell proliferation and escape from apoptosis. This is particularly relevant since CDK inhibitors are currently being put forward as a treatment of choice for advanced breast cancer disease. However, resistance to these treatments is starting to emerge. Here we show that a potential mechanism by which breast cancer cells can evade cell death in response CDK inhibitors involves the reprogramming of FOXA1 binding to chromatin.

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Programa Ramon y Cajal. (RYC-2017-22715)	Toni Hurtado	Spanish Ministry of Economy and Competitiveness	2019-2024	308,600.00 €
RESCUER-Resistance Under Combinatorial Treatment in ER+ and ER- Breast Cancer. (402156 RESCUER)	Toni Hurtado (Leader Work package 11)	European Union	2020-2025	465,000.00 €



Tamoxifen is the most prescribed selective estrogen receptor (ER) modulator in patients with ER-positive breast cancers. Tamoxifen requires the transcription factor paired box 2 protein (PAX2) to repress the transcription of ERBB2/HER2. Now, we identified that PAX2 inhibits cell growth of ER+/HER2- tumor cells in a dose-dependent manner. Moreover, we have identified that cell growth inhibition can be achieved by expressing moderate levels of PAX2 in combination with tamoxifen treatment. Global run-on sequencing of cells overexpressing PAX2, when coupled with PAX2 ChIP-seq, identified common targets regulated by both PAX2 and tamoxifen. The data revealed that PAX2 can inhibit estrogen-induced gene transcription and this effect is enhanced by tamoxifen, suggesting that they converge on repression of the same targets. Moreover, PAX2 and tamoxifen have an additive effect and both induce coding genes and enhancer RNAs (eRNAs). PAX2-tamoxifen upregulated genes are also enriched with PAX2 eRNAs. The enrichment of eRNAs is associated with the highest expression of genes that positivity regulate apoptotic processes. In luminal tumors, the expression of a subset of these proapoptotic genes predicts good outcome and their expression are significantly reduced in tumors of patients with relapse to tamoxifen treatment. Mechanistically, PAX2 and tamoxifen coexert an antitumoral effect by maintaining high levels of transcription of tumor suppressors that promote cell death. The apoptotic effect is mediated in large part by the gene interferon regulatory factor 1. Altogether, we conclude that PAX2 contributes to better clinical outcome in tamoxifen treated ER-positive breast cancer patients by repressing estrogen signaling and inducing cell death related pathways.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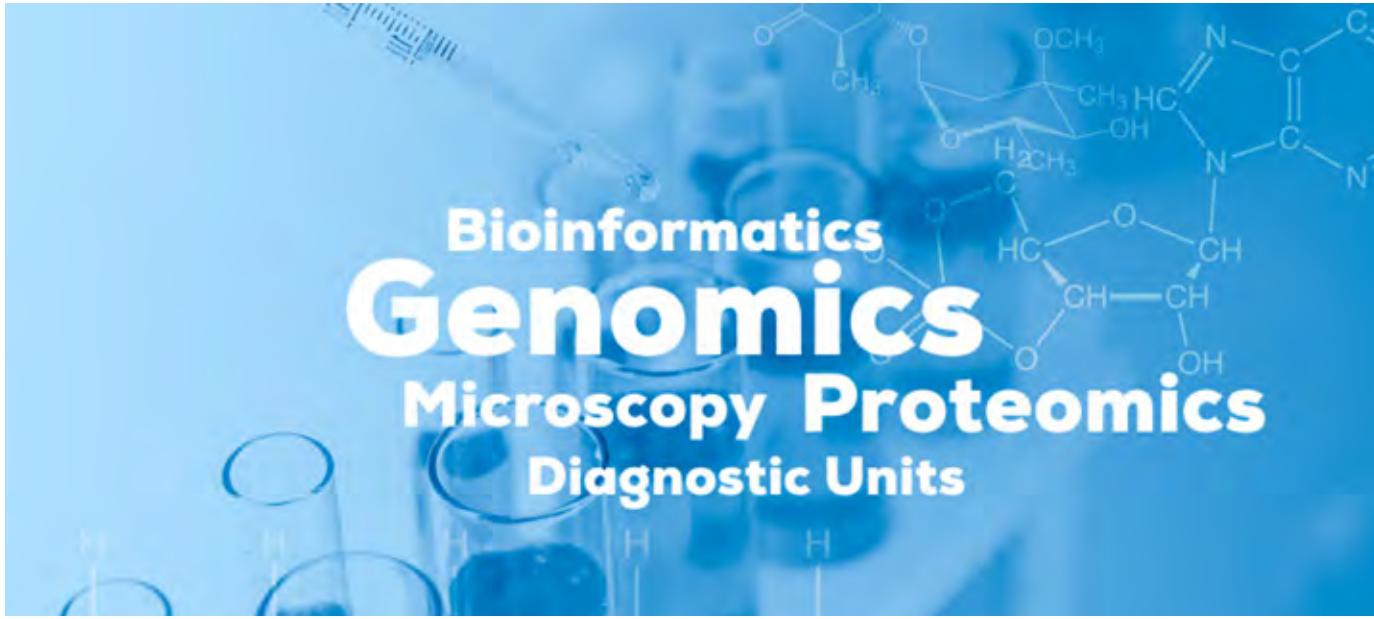
5

CORE FACILITIES & SERVICES


Bioinformatics
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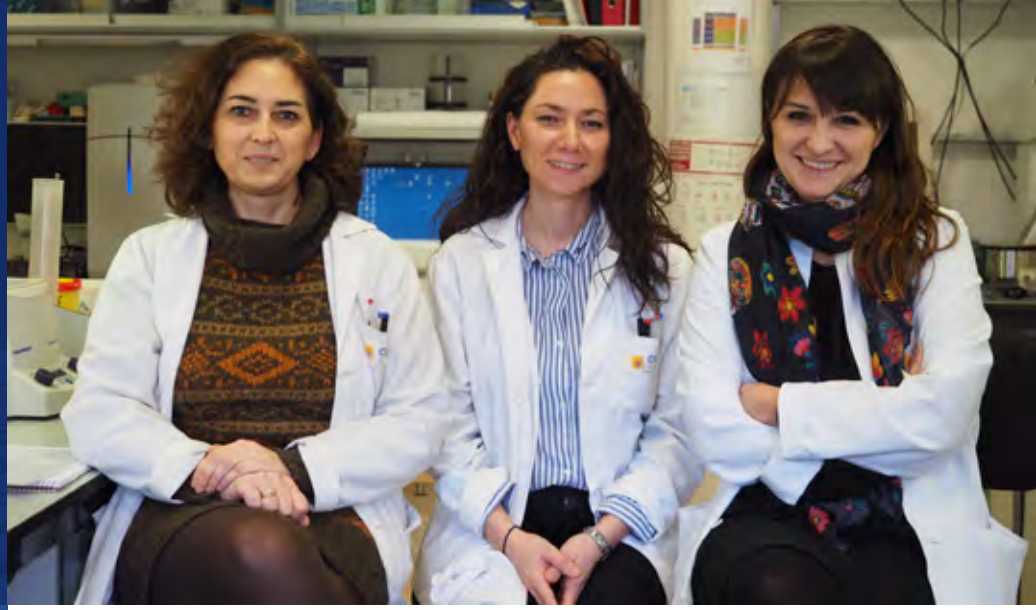

5.1.

GENOMICS

DESCRIPTION

This CIC facility provides full services for: (a) Genome-wide expression profiling and genotyping using Affymetrix technology. (b) Printing and processing of home-made chips not available commercially. (c) DNA Sequencing. (d) Genomics-related techniques (e.g., quantitative RT-PCR).

The philosophy of this Unit is to provide full services to both internal and external customers. By full services we understand carrying out the whole analytic process: starting with the experimental sample provided by the customer (total RNA, genomic DNA), the Facility's personnel carries out all the required analytical and quality control steps as well as the standard bioinformatics analysis of the data obtained. Further analyses (e.g., functional annotation) will be done using the services of the Bioinformatics Unit.

The facility work and protocols are ISO9001:2015 certified. The occupational health and safety management system of the facility are also ISO 45001:2018 certified.

SERVICES

- DNA Sequencing using the ABI-3130xl sequencer (Applied Biosystems). This system is able to do both genotyping and SNPs analysis.
- Genomics studies using Affymetrix technology in different species. The main array services included in this category are:
  - Gene Chip Human Genome U133 Plus 2.0
  - Gene Chip Mouse Genome 430 2.0
  - Gene Chip Rat Genome 230 2.0 array
  - Gene Chip Arabidopsis ATH1 Genome array
  - Gene Chip Drosophila Genome 2.0 array
  - Gene Chip Yeast Genome 2.0 array
  - Prime View Human Genome
- Analysis of expression profiles using the Gene ST System of Affymetrix in different organisms. The main arrays used are:
  - Gene Chip Human Gene 1.0 and 2.0 ST array
  - Gene Chip Mouse Gene 1.0 and 2.0ST array
  - Gene Chip Rat Gene 1.0 and 2.0 ST array
  - Clariom S human/mouse arrays
- Analysis of expression profiles and splicing alternative using the Exon ST System of Affymetrix. The main arrays used are:
  - Gene Chip Human Exon 1.0 and 2.0 ST array
  - Gene Chip Mouse Exon 1.0 and 2.0 ST array
  - Gene Chip Rat Exon 1.0 and 2.0 ST array
  - HTA Array
  - MTA Array
  - Clariom D human/mouse arrays
- Identification of regulatory promoter sites using immunoprecipitation (ChIP on chip) and other techniques that involve complete genome analyses. The main arrays used are:
  - Gene Chip S. pombe Tiling 1.0 FR array
  - Gene Chip S. cerevisiae Tiling 1.0 FR array
  - Gene Chip Human Tiling 1.0 R array
- SNP and copy number analyses. The main arrays used are:
  - Gene Chip Human Mapping 250K NspI/StyI arrays
  - Genome-Wide Human SNP array 6.0
  - CytoScan 750K array
  - CytoScan HD array
  - OncoScan CNV array
- Analysis of miRNAs and biosynthestic precursors using the Gene Chip miRNA 2.0, 3.0 and 4.0 arrays
- Printing and processing home-made chips: We provide services to prepare home-made microarrays using the MGII Arrayer (Biorobotics). The samples are provided by the user (oligonucleotides, cDNAs, DNA cloned in BACs, antibodies, purified proteins or cellular lysates). Once generated, the microarrays are hybridized using the automatized system hs4800pro (Tecan) and scanned using the GenePix4000 system (Axon).

EQUIPMENT

- 16-capillary ABI Prism 3130xl (Applied Biosystems) for DNA sequencing
- Agilent 2100 Bioanalyzer for quality control of RNA samples
- Affymetrix equipment, composed of the GeneChip Hybridization Oven 640, the GeneChip Fluidics Station 450, and the Gene Array Scanner 3000 7G
- Biorobot 3000 (Qiagen) and Arrayer (Biorobotics) for homemade array manufacturing
- HS4800Pro Hybridization station (Tecan) for hybridization of home-made microarrays
- GenePix 4000B (Axon) for scanning of data from both home-made and commercial (double colored) chips

TRAINING

- Teaching of the class "DNA Microarrays" (2h) within the subject "Structure and Function of Genomes" and within the framework of the Master's program "Cellular and Molecular Biology" of USAL.

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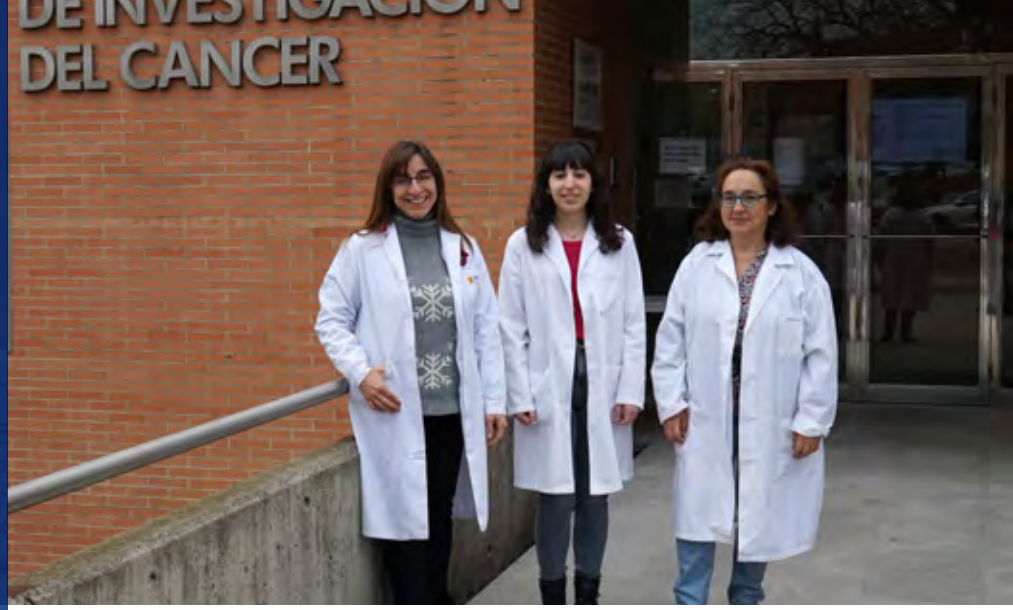
Rosa M. Dégano Blázquez
Nahia Hernández Quitián



5.2.

PROTEOMICS

DESCRIPTION

This CIC Facility offers advanced proteomics services to support research with optimized cost. To maintain a high level of quality in our services we have developed standard operating procedures (SOPS) and carry out quality controls of our equipment (we are certified with the ISO 9001 Quality Certification). The Occupational Health and Safety Management System of the Facility has been also certified using the OHSAS18001 system.

The Facility provides consultancy service for many biological research goals involving mass spectrometry or protein arrays and adapts its services to meet projects´ requirements and objectives.

To keep up with the state of art of the rapidly evolving mass spectrometry based proteomics field, services are modified according to the latest methods and technologies, and new services are implemented through input and request from our users.

The Facility is part of the Technological Platform for Biomolecular and Bioinformatics resources (PRB3) by the Carlos III Health Institute, (https://prb3.org).

SERVICES

- PROTEIN AND PEPTIDE SEPARATION
  - Electrophoresis. SDS-PAGE gels of different sizes are elaborated: 10x8 cms (minigel); 16x14 cms; 18,5x20 cms; 26x22 cms and stained with mass spectrometric compatible stains.
  - Bidimensional Electrophoresis. Before protein separation in SDS-PAGE gels, we perform a first protein separation by isoelectrophocusing using one of the following strip lengths 7, 13, 18 o 24 cms.
  - OFFGEL isoelectrofocusing fractionation.Proteins or peptides are fractionated in 12 or 24 cm stripes according to their pI by Agilent OFFGEL 3100. HPLC fractionation, we fractionate peptides or proteins using and analytic HPLC 1100 from Agilent
  - Microfractionation by SPE.We use SPE filters to fractionate, desalt and concentrate peptide samples.
- PROTEIN IDENTIFICATION by LC MS/MS.

  Peptides derived from trypsin or other protease sample digestion are separated by a chromatographic gradient in a nano-UPLC system before its analysis by the mass spectrometer attached. The gradient length is chosen to meet the depth of analysis required by the different sample complexities.
- RELATIVE PROTEIN QUANTITATION BY LC-MS/MS
  - Label Free–LC-MS/MS. Protein relative quantitation is performed by comparing peptide chromatographic profiles obtained by LC-MS/MS analysis of the different samples.
  - Relative quantitation by SILAC. SILAC is a precise quantitation technique based on the labeling with different isotopic amino-acids all the proteins of eachsample. The incorporation in all the proteins of each sample of an amino-acid isotope with different m/z, allows mixing, process and analyzing together the samples to compare.
- PROTEIN POSTRANSLATIONAL MODIFICATION CHARACTERYZATION BY LC MS/MS.

  We analyse posttranslationalmodifications in simple and complex protein samples. Usually protein postranslation analysis in complex samples needs previous modified peptide enrichment.
- PROTEIN MICROARRAYS

  Design and development of protein microarrays in multiple formats (planar, beads,...) with predefined or customized content (high,medium, low density). We are able to provide complete analysis pipeline according to samples and/ or project requirements. Among, a library >10000 Human recombinant proteins(full length sequence validated) available to provide customized content or IVTT protein expression.

EQUIPMENT

- SEPARATION EQUIPMENT
  - Ettan IPGPHOR (Amersham,, GE Healthcare) and Ettan Dalt-6 Electrophoresis system (Amersham), Hoefer miniVE electrophoresis (Amersham), Hoefer SE 600 Ruby (Amersham):for electrophoresis 2D and vertical gel electrophoresis.
  - HPLC 1100 (Agilent): liquid chromatography separation equipment.
  - 3100 OFFGEL (Agilent): for in solution peptide or protein separation based on isoelectric point.
- LC-MS/MS EQUIPMENT
  - NanoAcquity (Waters)-LTQ Orbitrap velos ETD (Thermo): NanoAcquity nanoUPLC chromatography system coupled to an LTQ velos Orbitrap with ETD mass spectrometer.
  - NanoElute(Bruker)-TIMSTOFpro(Bruker):NanoElute nanoUPLC chromatography system coupled to TIMS TOF pro ionmobility massspectrometer analyzer.
- PROTEIN MICROARRAYS
  - Ultra-MarathonMicroarray Printer (Arrayjet)
  - Scanner Sensovation
  - Array Processor M2
  - Luminex MagPix Instrument.

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5.3.

MICROSCOPY

DESCRIPTION

The CIC-IBMCC Microscopy and Cytometry Unit offers microscopy and cytometry service to the CIC-IBMCC and also external users. The unit offers state-of-the-art equipment and a complete range of services including basic maintenance and cleaning of the equipment, technical support, training and image analysis advice.

SERVICES

- Flow cytometry: BDFACS-Aria-III and AccuriC6 systems. Multicolor sorting and immunophenotypic analysis. The flow citometry based sorting system has shown an important increase in demand as one of the services we provide. This system allows the enrichment of cell populations, as well as the expansion of hozygous colonies starting from a single cell.
- Our unit carries out regular quality checks to ensure optimal system performance.
- We also provide users guidance and tech-suppoprt, along scientific advising to reach the full potential of every experiment.
- Confocal imaging: Fixed samples, time-lapse, Z-Series, quantitative co-localization, FRAP and FRET experiments.
- Super-resolution microscopy (STED, PALM/STORM).

- FLIM
- TIRF microscopy.
- Widefield live cell imaging: live cell Thunder® imager and Nikon Eclipse TE2000 microscopes, CO2-and temperature-controlled. Image processing and deconvolution of images available upon request.
- Conventional widefield microscopy for fixed samples (upright) and for tissue culture (inverted).
- Monthly revisions of the microscopes, including phase adjustment, Kohler adjustment, objective cleaning and weekly revisions.
- Training and advising regarding image capture and analysis software and hardware (Metamorph, Leica LAS AF, LSM Image Browser, ImageJ, Openlab, etc.).
- Creating, updating and maintaining the webpage Unit, including updates of technical specifications or new equipment incorporated by the Center. Quality assessment. Certifications: ISO-9001 and OHSAS-18001.

EQUIPMENT

The Microscopy Unit of the Cancer Research Center offers a complete range of cytometry and microscopy applications. The main equipment consists of:

- Flow cytometer and sorter BD FACS-AriaIII. Co-funded by CSIC-MINECO and FEDER. It supports up to 6 excitation lasers combined with 20 detectors. Cell damage is minimized by a temperature controlled system.
- Cell analyzer cytometer BD Accuri-C6®. Co-funded by CSIC-MINECO and FEDER. Accuri-C6® is a simple and easy platform that offers an optimum configuration which detects four fluorochromes simultaneously.
- Laser Scan Confocal Microscopy Leica SP5. Funded by FEDER, Ministerio de Sanidad y Consumo and Instituto de Salud Carlos III. It has four lasers with seven excitation lines, which in combination with the spectral detection technology, allows any fluorochrome to be detected in the visible range. Due to its confocal module, it is highly demanded to obtain high resolution images of cell cultures or tissues.
- Live Cell Microscopy Delta-Vision. FEDER and CSIC funding. It is mainly used for in vivo time-lapse experiments. The microscopy's main advantages are the ultra-precise stage; the lighting system which combines a xenon lamp with an excitation filters wheel. Deconvolution module contributes to a more complex image processing.
- Inverted microscope Nikon TE2000 for in vivo analysis combined with Metamorph (it will be updated to NIS-elements software and a new workstation in 2022).
- Laser Scan Confocal/STED microscope Leica SP8. Co-funded by FEDER, Ministerio de Economía, Industria y Competitividad and Universidad de Salamanca. Equipped with a powerful white laser allowing the precise excitation of fluorophores. In combination with the spectral detection technology, it allows any fluorochrome to be detected in the visible range. In addition, it can perform depletion (STED)-based super-resolution in the green, red and far red channels, up to 50 nanometers, as well as lifetime-based STED imaging. The equipment is complemented with Huygens Deconvolution and lightning Software that provide a significant increase in the contrast and resolution.
- 9 fluorescence microscopes, 11 inverted microscopes for cell culture, 1 microscope for cytogenetic and 1 microscope for histological analysis.

In 2020-2021 the Microcopy Unit has upgraded existing modules:

- The Leica SP5 confocal microscope has been upgraded with a hybrid detector improving the signal detection and a 100x objective.
- The Leica SP8 confocal microscope has been upgraded to optimize the Hyvolution and Lightning environment applications. A new 775nm depletion laser and a 405nm laser have been installed as well as the Falcon® module for STED-FLIM imaging.

The unit has also incorporated two new modules that extend the range of microscopy applications that the unit offers to the researchers (Funded by FEDER/Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación).

- A new Thunder® microscope for transmitted light and fluorescence with opto-digital technology that uses a new computational clearing method to generate high resolution (0.05um) and high contrast images.
- A Thunder® system with inverted microscope for in vivo microscopy equipped with a TIRF and photo-manipulation modules for FRAT, FRET, photo-conversion and uncaging experiments and high intensity lasers for single molecule localization experiments PALM/STORM.

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5.4.

BIOINFORMATICS

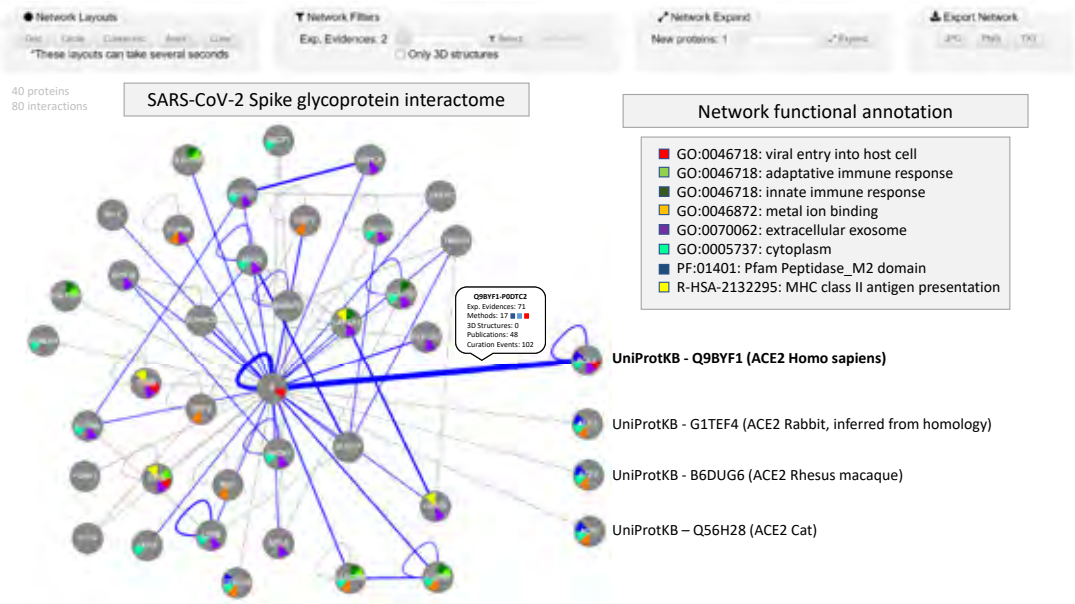
DESCRIPTION

The Bioinformatics Unit works in the CiC-IBMCC with the help and support of the Bioinformatics and Functional Genomics Research Group, to provide technical and scientific service on bioinformatic and computational data analyses to scientists and research groups from the CiC, the University of Salamanca or from outside. From 2019 the Bioinformatics Unit is also integrated in the CSIC as a service Unit providing Bioinformatic and Computational Biology data analysis also within the INB (Instituto Nacional de Bioinformática) - ELIXIR Spain supported by CSIC. The Unit has major expertise in the analysis of omic data (such as transcriptomic, genomic, proteomic, interactomic, etc.) derived from the study of complex biological systems that generally apply to cancer research.

The Bioinformatics Unit was launched to provide services in June 2008 and, since then, more than 5000 samples coming from different labs and including a broad spectrum of experimental platforms (high throughput sequencing, custom panels, microarrays, etc.) have been analyzed.

SERVICES

- Multivariate analyses and comparison of biological states using omic data. Analysis to search and identify genes (or other biomolecular entities such as miRNAs, ncRNAs, proteins, etc.) that show statistically significant changes using robust techniques of differential contrast of two states (Normal versus Altered) or between different classes.
- Biomarker profiling and pharmacogenomic studies. Integrated analysis of omic data across multiple states, conditions or individuals for the identification of biological feature profiles (biomarkers), such as those derived from genome-wide expression studies. Search and analysis on drug-to-target data.
- Functional enrichment analysis. Annotation and assignment of biological functions based on enrichment studies and clustering analyses. These types of analysis vary widely according to the objectives of each study and generally provide complex results that also require the Unit's help in interpretation.
- Bioinformatics tools and big data management. The unit facilitates the use of various bioinformatics software tools and the access to scientific data repositories:
  - Tools and databases provided to the scientific community by other research institutions, for example: TCGA, NCI-GDC Data Portal, NCBI-GEO, NCBI-SRA, Bioconductor, etc
  - Open Access Software developed within the CiC-IBMCC: GeneTerm-Linker, FGNet, APID Interactomes, DECO, GEDA, etc.
- Custom analysis and data integration. The unit also offers customized analyses for data from non-standard platforms as well as new analysis of datasets that have been studied previously and the integration with other accessible series.
- Advice and assistance. Frequently the unit also provides support and assistance to the scientists and researchers of the CIC-IBMCC and the University Campus who ask for help in Bioinformatics.



Visualization and functional annotation of SARS-CoV-2 Spike glycoprotein interactome in APID Interactomes web application (http://apid.dep.usal.es)

5.5. DIAGNOSTIC UNITS

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5.5.1.

CYTOMETRY

DESCRIPTION

The Cytometry Service (SGC) is a common research platform of open use to all members of the Institute (Cancer Research Center) as well as to other external research and clinical groups. It is aimed at supporting research and education in cytometry. The most relevant activities include cell analysis and sorting for research purposes with more than 50 different techniques being currently set up and available in the area of immunophenotyping, cell cycle analysis, apoptosis, drug resistance and screening, quantification of phosphorylated proteins and their associated intracellular signalling pathways, among others. In addition, it provides tests to support the diagnosis of cancer acting as a common platform for the immunophenotypic diagnosis of leukemias and lymphomas for the Spanish RTICC from the Instituto de Salud Carlos III. In there are several ongoing technologically oriented research projects. Finally, the SGC has an important role in education in Cytometry with more than 90 researches from all over the world being trained during the last year, and more than 1350 in the last 15 years.

Since 2018 University of Salamanca offers an official title in flow Cytometry named "Diploma of Flow Cytometry specialization in diagnostic and monitoring of malignant hemopathies and primary immunodeficiencies"

ISO Certifications: The SGC is certified with the ISO-9001:2000, applied to "Molecular, Genetic and immunophenotypic studies to support the diagnosis and monitoring of haematological malignancies, using flow cytometry, FISH and molecular biology" since the 3rd of August 2007.

The Flow Cytometry Service, since 2018 have one assay (Euroflow based NGF method for minimal residual disease in multiple myeloma) accredited by ISO-15189

SERVICES

- Screening of monoclonal gammapathy
- Screening of lymphocytosis or suspect of mature T-cell lymphoid neoplasms in peripheral blood, cerebrospinal fluid, bone marrow, lymph node or other tissue
- Immunophenotypic characterization of Mature B-cell lymphoid neoplasms y Waldenstrom's macroglobulinemia
- Screening of clonality of mature alfa-beta T-and gammadelta T cells lymphoid neoplasms by flow cytometry
- Immunophenotypic characterization of mature T and NKcell neoplasm
- Screening of acute leukemias
- Immunophenotypic characterization of myeloid acute leukemias and myelodysplastic syndromes
- Screening and immunophenotypic characterization of B-precursor lymphoblastic leukaemia and T-cell lineage acute lymphoblastic leukaemia
- Immunophenotypic characterization of chronic myeloid leukaemia
- Detection of minimal residual diseases in acute and chronic leukaemias studied at diagnosis in our service
- Detection of minimal residual diseases in acute and chronic leukaemias and acute myeloid leukaemias
- Screening of mastocytosis
- Immunophenotypic screening of histiocytosis and Reed Stenberg cells
- Screening of primary immunodeficiency and paroxysmal nocturnal hemoglobinuriaparallel, at the SGC
- Immunophenotypic characterization of the platelets
- Detection of antiplatelet autoantibodies in platelets and plasma
- Quantitation of CD34+ cells
- Control of leucodepletion
- Antigenic quantitation
- Spherocytosis
- DNA quantitation in mature and immature B cell, plasma cells and epithelial cells
- Evaluation of Zap70
- Evaluation of viability by DRAQ5 or Dye Cycle
- DNA quantitation with phenotype and DRAQ5 or Dye Cycle in myeloid leukemia or myelodisplastic syndromes
- Evaluation of each individual antigen
- Study of the presence of one, two or three genetic abnormalities by in situ hybridization
- Study of the presence of prognostic genetic abnormalities in B-cell chronic lymphocytic leukemia
- Evaluation of each individual genetic abnormality by in situ hybridization
- Sample purification for molecular biology techniques
- Evaluation of CKIT mutations by molecular biology
- Humara PCR test for one cell population
- Sorting of cell populations
- Acquisition and analysis at the flow cytometer
- Immunobead protein assays

EQUIPMENT

- Cytometer Analyzer FACScanto II (BDB) for analysis in 8 fluorescence
- 2 Cytometer Analyzer FACScalibur I (BDB) for analysis in 4 fluorescence
- 1 Cytometer LSR-Fortessa X20 (BDB) for analysis in 13 fluorescence
- Termocyclers
- Fluorescence microscopies
- Other equipment: centrifuges, refrigerators, freezers, bathrooms...

5.5. DIAGNOSTIC UNITS

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Sandra Pujante
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5.5.2.

CYTOGENETICS

DESCRIPTION

The Molecular Cytogenetic Service (MCU) is a facility devoted to the karyotypic analysis, fluorescence «in situ» hybridization, comparative genomic hybridization, microarrays and next generation sequencing of cancer patients. More than 100 hospitals in Spain, and occasionally others from the EU, have used the MCU services. The Unit collaborates with the most relevant groups in the treatment of the hematological malignancies such as Pethema, GEL-TAMO, GEM or GETH providing technical support and characterization of the genetic abnormalities in the patients included in clinical trials. In addition, the MCU is involved in several international projects related such as oncNGS with aim at developing an integrated solution for predictive, prognostic and diagnostic analysis in liquid biopsies of solid tumours (including appropriate haematological indications) based on Next Generation sequencing (NGS) technology; HARMONY, which through the use of Big Data will help improve the care of patients with hematologic malignancies; SYNTHERAPY, which aim is to develop a machine learning-based model to predict personalized

treatment and to identify novel therapeutic strategies based on synthetic lethality approach for relapsed or refractory acute leukemia patients by using multilayer analysis of omics data, including RNASeq, Copy Number Alterations by SNP array and DNA targeted NGS)

SERVICES

- Bone Marrow Cytogenetic: leukemia, lymphoma and myeloma.
- Peripheral blood cytogenetic: leukemia, lymphoma and myeloma.
- Lymph node and spleen cytogenetics: lymphoma.
- Solid tumour cytogenetics.
- Centromeric «in situ» hybridization: FISH performed with centromeric probes to analyse numerical abnormalities.
- Painting «in situ» hybridization: FISH performed with libraries of DNA to analyse structural abnormalities.
- Loci specific «in situ» hybridizations: FISH performed with probes to analyse either losses or gains of genetic material or fusion genes.
- Genomic microarrays highest resolution gene-level. Genotyping, methylation, transcriptomics and pharmacogenomics assays.
- High quality and Formalin Fixed Paraffin Embedded (FFPE) samples.
- Next generation sequencing to analyses genetic alterations by flexible and scalable methodology for target regions, genes, individual exons or hot spots. Available disease-focused panels (custom and commercial), fusion gene panels and RNA seq.
- High-Depth next-generation sequencing for somatic variant detection.
- Germline variant detection by next-generation sequencing in key genes involved in severe congenital coagulation bleeding disorders.
- DNA/RNA shearing service for NGS.
- Ultra–sensitive droplet digital PCR for detecting low prevalence somatic mutations.
- Absolute quantification of gene expression and alternatively spliced transcripts with digital PCR.
- DNA and Protein Liquid Biopsy.

EQUIPMENT

- Full authomatised system for karyotyping and FISH (Cytovision) with 3 analysis stations.
- Full authomatised system for karyotyping and FISH (Metasystems) including a karyotype finder with 3 analysis stations.
- Microbeads-based system for cellular isolation (Miltenyi).
- Microscopes of light and fluorescence.
- Veriti 96W Thermal Cycler.
- Pyrosequencer (Pyromark Q24, Qiagen).
- Affymetrix GeneChip® Instrument System: Hybridization Oven 646/Fluidics Station 450 and GeneChip® Scanner 3000 7G.
- Droplet Digital PCR QX200 system (Bio–Rad Laboratories, Hercules, CA, USA).
- Bioanalyzer for fragment analysis: 4200 Tapestation system (Agilent technologies Santa Clara, CA).
- Covaris M220 Focused Ultrasonicator (Covaris, Woburn, MA, USA).
- Next-generation sequencing facilities. MiSeq sequencer (Illumina), Agilent Magnis NGS Library Prep Systemr
- Automated capillary nano-immunoassay–Simple Western assay "WES™ ProteinSimple"

5.5. DIAGNOSTIC UNITS

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Sandra Lucas
Leticia Gallo
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5.5.3.

MOLECULAR BIOLOGY

DESCRIPTION

The Molecular Biology Unit (MBU) is a facility with the aim of providing molecular analysis for cancer patients, with special focus on patients with haematological malignancies (leukaemia, lymphoma, and myeloma). In addition, the MBU carries out HLA typing for histocompatibility studies in receptors candidates to allogeneic stem-cell transplantation, as well as chimerism monitorization in those who finally undergo it, molecular studies in coagulopathies, and HLA typing for disease association.

The MBU is the reference center for Castilla y León Hospitals. Furthermore, more than 50 hospitals in Spain, multicentric clinical trials, and some occasional foreign institutions, have used the MBU services.

The Unit actively collaborates with the most relevant Spanish groups in both research and in the treatment of the haematological malignancies such as SEHH, PETHEMA, GELTAMO, GEM, GELLC,

GETH, or GBMH by characterizing molecular abnormalities and carrying out studies on molecular monitoring of drug efficacy (Minimal Residual Disease -MRDStudies) for patients included in clinical trials. In addition, the

MBU has participated in several international projects focused on methodological standardization (Biomed I, Biomed II, Europe Against Cancer and Eurochimerism projects), and it is involved in several international projects related to clonality assessment (EuroClonality), next generation sequencing (EuroClonality-NGS Consortium), and TP53 sequencing (European Research Initiative in CLL- ERIC TP53 Network, and RED53 from the Spanish group for the study of CLL, GELLC).

SERVICES

- Screening and quantification of chromosomal translocations (qualitative and real-time quantitative PCR, RT-PCR) for diagnosis and MRD monitoring in haematological malignancies.
- Gene expression: RT-PCR for diagnosis, prognosis and MRD detection.
- B-cell and T-cell clonality for diagnosis or MRD detection in fresh cells (bone marrow, peripheral blood, lymph node, spleen, etc...) and/or formalin-fixed paraffin-embedded.
- Analysis of somatic mutations: diagnosis, prognostic value, screening of potential MRD markers and/or identification of therapeutic targets (Sanger sequencing, allelic-specific PCR, etc.).
- Next generation sequencing: Analysis of genetic alterations using commercial kits (i.e. AML panel) and custom panels for diagnosis and prognostic value.
- Digital PCR for low allele frequency mutation detection.
- Liquid biopsy. Analysis of circulating tumour DNA in lymphoproliferative disorders.
- Fragment analysis and Sanger sequencing.
- Genetic polymorphisms (single nucleotide polymorphisms [SNP], short tandem repeats [STR]) analysis: SNP array, SNP assays. Identification of patients with different drug sensibility, susceptibility to second neoplasia, etc.
- Hematopoietic chimerism analysis and cell-lines characterization with STR polymorphisms.
- Low- and high-resolution HLA typing: donor typing, disease association.

EQUIPMENT

- Real-time quantitative (4): One7900HT, two StepOnePlus (Applied Biosystems) and one LightCycler (Roche Diagnostics)
- Next generation sequencing systems: MiSeq and MiniSeq (Illumina; CA)
- Digital PCR system: QX200 Droplet Digital PCR system (Bio- Rad Laboratories, Hercules, California, USA)
- Bioanalyzer for fragment analysis: 4200 Tapestation system (Agilent technologies Santa Clara, CA)
- Automatic sequencer (1): ABI3500 XL (16-capillary, Applied Biosystems)
- Fluoroanalyzer (2): Luminex XYP (Luminex Corp.) and FluoVista (Inno-train)
- Thermocyclers (11): seven Veriti 96-Well Thermal Cycler and one GeneAmp PCR System 9700 (Applied Biosystems), and three Biometra (T1, T3, and T Professional Thermocycler)
- Automatic nucleic acid extractor (2): one Maxwell16 and one Maxwell RSC (Promega)

5.5. DIAGNOSTIC UNITS

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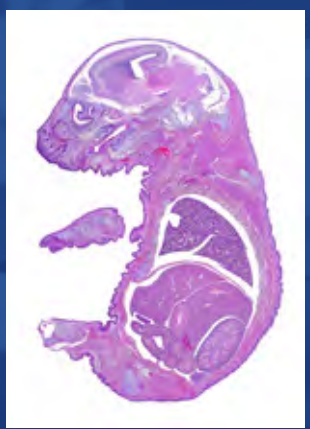
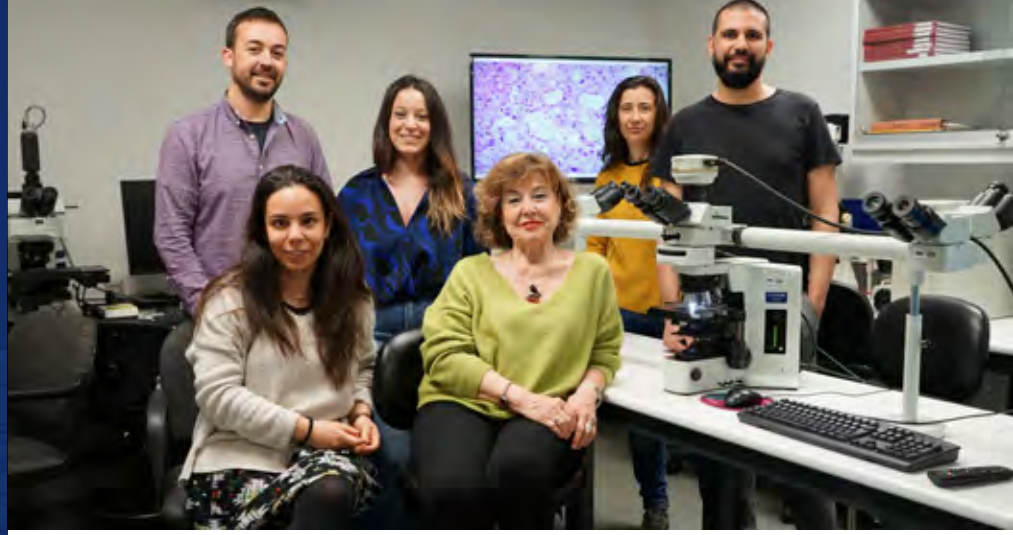




5.5.4.

COMPARATIVE MOLECULAR PATHOLOGY

DESCRIPTION

PMC has two different functions of interest for the entire University Community.

1) The Compared Molecular Pathology Unit analyzes samples of transgenic, human and plant animal and offers a complete and variable range, designed and adapted to each request, of histological, immunohistochemical and molecular analysis techniques.

The PMC unit is certified in Quality by ISO9001:2015.

SERVICES

Tissue processing and routine stain (each paraffin block). Our service processes animal models provided by other CSIC researchers to produce hematoxylin-eosin stained sections. Animal tissues are prepared for inclusion and paraffin embedding, and then cut and

stained. Approximately 6.100 samples are processed per year, from 550 job applications.

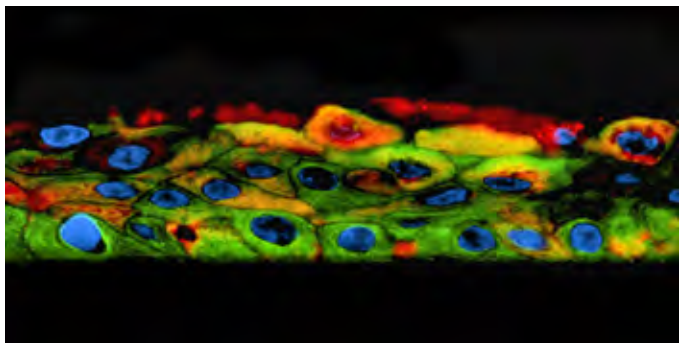
- Paraffin embedding. Previously fixed tissue is embedded in paraffin.
- Sectioning/staining. Tissue previously embedded in paraffin is sectioned and stained.
- Immunohistochemistry (each stain). The process includes setting up an assay for a particular antibody, as well as the performance of an actual immunohistochemical stain. We have 145 antibodies for murine tissues ready, available to different researchers from both the CIC and the rest of the Campus Units.
- Tissue microarray. 1-mm Tissue Cores from 100-200 human or animal tumors are arrayed into a paraffin block. This allows the simultaneous study of a series of cases with minimal interobserver biopsies.
- Diagnostic samples processed in the Service by the Responsible Pathologist, when they are required by the researchers.
- Microscopy Service offered:
  - Multihead Optical Microscope.
  - One automated scanning microscope and image analysis system, ARIOL.
  - Virtual Microscope DOT SLIDE, to scan and processed samples.
  - Microscope laser microdissection: essential for molecular characterization of individual cells of complex solid tissues to identify differences that show respect to other cell lines to identify new molecular targets that reveal the altered cellular pathways and study the origin of the equipment disease and possible treatment.
- The Service Comparative Molecular Pathology imparts teaching to:
  - Students in practice, as a Senior Technician of Pathological Anatomy of the Institute "IES Ramon y Cajal" of Valladolid, of School Aloya of Vigo, and Institute "CIFP Río Ebro" of Miranda de Ebro (Burgos).
  - Master students in biobanks.
  - Collaborates with the Communication Service of the Center for Cancer Research in the program of guided tours to the CIC, to different groups such as schools, universities, businesses, associations and Town Hall.
- The Compared Molecular Pathology unit is a research support service and is associated with the NUCLEUS Service of the University of Salamanca. CMP offers its services to all the Researchers of the Cancer Research Center, where it is located, and to all the Centers of the University of Salamanca (IBFG, Departmental, INCyL, Hospital Clínico Universitario...) and to other Spanish centers.

2) This Unit is also a Coordinating Node of the Biobank in Network of Oncological Diseases of Castilla y León (BEOCyL). The Compared Molecular Pathology Unit coordinates all requests for tissue samples from the seven Biobanks that make up the Network and from researchers.

- Tissue request from a cancer cooperative biobank network. Requests from researchers are evaluated by the external committees of the biobank, and served, if ethical and scientific standards are accomplished, and enough tissue is banked in the network.
- Tissue banking (each individual case aliquot). In each of the hospitals affiliated to the Biobank Network, cases are collected, interesting tissue areas are selected, prepared and stored. In addition, this process includes getting all basic clinical information linked to the sample, which is stored in a central database. Collection can take place only when a written informed consent has been taken from the patient after detailed information has been provided to him/her.

The tissue of the biobank is given, if there are enough samples, if the Project meets the appropriate ethical and scientific requirements.

More information: http://www.cicancer.org/en/compared-molecular-pathology-service-and-main-beocyl-node



5.5. DIAGNOSTIC UNITS

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HEREDITARY CANCER & GENETIC COUNSELING UNIT
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Miguel de Unamuno s/n
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UNIT COORDINATORS
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PERSONNEL
Eva María Sánchez Tapia
Jésica Pérez García
Teresa Martín Gómez
Rosario Vidal Tocino
Raquel Seijas Tamayo

5.5.5.

HEREDITARY CANCER & GENETIC COUNSELING

DESCRIPTION

Cancer is a very heterogeneous disease caused by different factors. Those factors can be environmental and genetic and both are responsible for its etiopathogeny. It is estimated that between 5% and 10% of all tumors are hereditary. In those cases, the genetic alterations which determine the appearance of a series of cancer types can be transmitted from parents to their off spring together with a high possibility that the carriers of this particular mutation can therefore develop a tumor. This implies the necessity to carry

out a genetic check-up of the entire family who then will be informed not only about the probability of a neoplasm appearance and transmitting the cancer predisposition to the descendants, but also about the prognosis, early detection strategies and proper treatment.

Therefore, the study of hereditary cancer is currently one of the most developing areas within oncology. The possibility of detecting people with high risk of suffering from cancer is going to help us progress in two directions. On the one hand, the possibility of reducing the risk of suffering from certain neoplasmic types or at least of detecting them early, and on the other hand, the possibility of having a better knowledge of the disease that will help transfer this information onto other types of tumors.

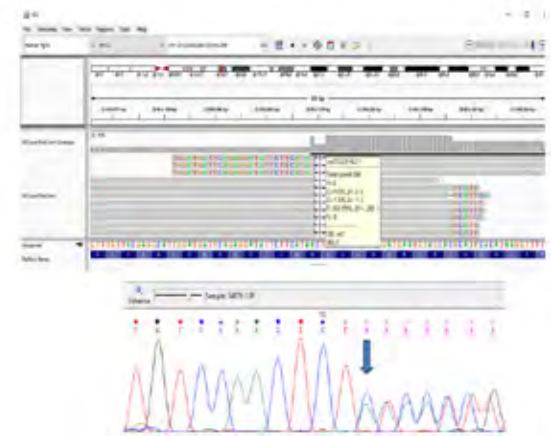
The thorough knowledge of the genetic factors related to cancer will be helpful in estimating more precisely the risk of developing it by each individual. It will also help establish precautionary measures which will be personalized and therefore efficient. Talking about the hereditary cancer is closely connected to genetic counseling. Except for clearly investigatory situations, anything that can be even remotely related to the hereditary cancer should be inscribed into the proper genetic counseling. This will imply a series of communication phases with the person and/ or relatives who are going to require an expert specialized in the concrete area.

The main objective of the Laboratory of Hereditary Cancer of CIC-IBMCC (Institute of Molecular and Cellular Biology of Cancer) is to pay attention, prevent from and investigate the hereditary and family cancer. It can be fulfilled through counseling, evaluation, and study of the family with an increased genetic susceptibility to cancer. For this reason the Laboratory collaborates with the Genetic Counseling Unit of Hereditary Cancer that is part of the Clinical Oncology Department at the University Hospital of Salamanca. Both the Genetic Counseling Unit and the Laboratory of Hereditary Cancer are supported by the "Consejería de Sanidad" of the"Junta de Castilla y León". Among their shared objectives are (i) to carry out an early diagnosis among people with a medical record that could suggest hereditary transmission. In those cases there can be no existing clinical indication of suffering from cancer but they can show high probability of developing one at any time in their lives or be carriers of a certain genetic mutation currently known to be involved in the development of hereditary tumors, (ii) chooses families at a considerable risk of suffering from hereditary cancer by means of defining the genetic mutations implicated in each case and (iii) finally, offers genetic counseling to the affected individuals.

The Laboratory collaborates closely also with professionals from other hospitals in order to assist and monitor patients by means of offering their service to hospitals and professionals in any part of Spain. In the laboratories of the Cancer Genetic Units of CIC-IBMCC genetic and cytogenetic studies are being carried out.

The work procedures of the Laboratory of Hereditary Cancer of CIC-IBMCC in coordination with the Genetic Counseling Unit of the Clinical Oncology Department include: 1) Evaluation of a personal and family record of cancer, 2) Evaluation of the risk and choosing the most appropriate genetic study taking characteristics of the family into account and 3) Collecting biological samples necessary to carry out one or more different genetic studies. The Genetic Counseling Unit of the Clinical Oncology Department offers Genetic counseling, planning a family research depending on the results obtained from the genetic testing and recommendations of how to reduce the risk, and in case of already existing one, recommending the clinical monitoring of patients.

Even though the programs that currently have the highest level of development, at the Laboratory of Hereditary Cancer are mainly focused to the detection of the mutations of the hereditary breast and ovarian familial cancer and colorectal cancer, the laboratory analyze any syndrome of a hereditary cancer should undergo genetic study.



6

SUPPORT UNITS

Personnel
Gerardo Arévalo Vicente

SUPPORT UNITS

FICUS MANAGER

The manager, with the broadest of powers of the Board, develops:

- The management and implementation of the agreements and guidelines adopted by the Board of the FICUS.
- The management of existing services in the FICUS and as many management functions are accurate to the best achievement of the aims of FICUS.
- Oversee the accounting of FICUS and formulate draft reports; budgets and annual accounts.
- Directing the human resources policy of staff employed by the FICUS.
- Formal monitor compliance with fiscal and tax obligations of FICUS.
- Advise the Board on economic or tax legal issues that may affect the Foundation
- Acts of complete implementation of the agreements of the Board as may be ordered by the member of the Board in each case be responsible for the implementation of the same.
- Formulate proposals to the Board deemed appropriate for the smooth running of the Foundation

Personnel
Nuria Morán Aguirre

SUPPORT UNITS

SECRETARY

- Administrative and logistic assistance to the personnel and visitors (travels, meetings, events, bookings...).
- Processing of internship programs for students in the center.
- Preparation of annual and semi-annual reports of activities of the center.
- Implementation and control of the Annual Training Plan for FICUS employees
- Processing (Customs, Project Authorizations, Bioethics Certificates ...)
- Assistance to the FICUS and IBMCC management team.

The unit has the ISO 45001:2018 Certification

Personnel
Juan Pablo Clavero Herrero

SUPPORT UNITS

IBMCC-CSIC MANAGER

The IBMCC-CSIC manager performs the operation of the services related to the competencies of the CSIC within the institute (staff and budget) as:

- Economics and financial management
- Personnel management
- Management accounting
- Advice on the preparation and justification for projects
- Elaboration of the IBMCC Budget

Personnel
Maria Angeles Mazas Juanes

SUPPORT UNITS

IBMCC-CSIC PAYMASTER

- Conservation, management and justification of the IBMCC funds
- Registration of economic operations
- Making payments.
- Verification of proof of expenditure.
- Identification of the recipients with the corresponding documentation.
- Custody of funds and collection of interest that may arise
- Practice accounting and bank reconciliations.
- Facilitate the Statements of Treasury Situation.
- Render supporting accounts of the funds transferred from fixed cash advances.
- Preservation and custody of all the documentation related to the supporting accounts of the expense.

Personnel

Antonio Mata Domínguez
Cristina Santos Gallego
Álvaro Menéndez Sánchez
Margarita Villamor Carba
Miguel Ángel Moreno Valle
Mª Manuela Calvo González

ADMINISTRATION

The Administration Unit in coordination with other institutions is responsible for the operation of the services to FICUS, such as:

• Budgetary and financial management: (i) annual budget institutional and financial management operations, (ii) budget and justification of competitive grants, (iii) management of contracts and agreements with public and private institutions and (iv)administration of revenues derived from direct services delivered by our technical scientific units.

• Human resources: (i) recruitment of scientific, technical, and administrative personnel and (ii) payroll and social security obligations management for staff employed by each of the institutions.

• Administrative management: (i) presentation of national and international scientific and the corresponding economic justification dossiers to the granting agencies, (ii) administrative coordination with the USAL, CSIC, FICUS and other institutions and (iii) administrative work related to Ph.D. and Master program of the Institute.

Personnel
Almudena Timón Sánchez

SUPPORT UNITS

COMMUNICATION & MARKETING

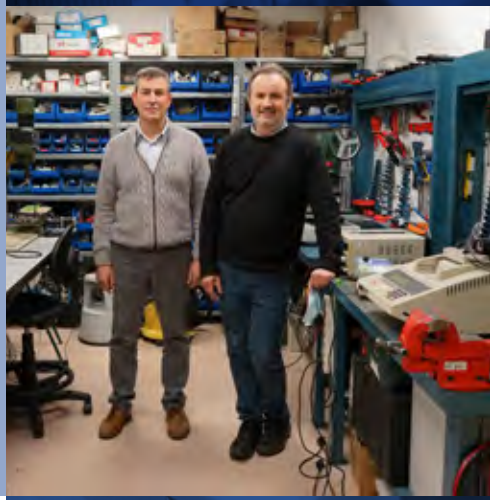
The essential target of the Communication and Marketing Unit of the Cancer Research Center is to improve the scientific culture in society through scientific dissemination and social marketing development.

The Communication and Marketing unit of the CIC holds four main services:

- Management of the scientific culture unit (belonging UCC+i Network) of the Cancer Research Center (2016-2021).
- Social marketing to achieve behavioral goals for a social benefit: enhancing cancer research. Some projects have improved the scientific culture in order to interact with the general public, young people and media. Communication activities have been developing to reinforce the positioning of CIC.
- Corporate public communications that includes: media relations, press releases, press conferences, social networking services, media monitoring and evaluation.
- Internal communications

SERVICES:

- Promotion of scientific culture through educational projects.
- Attention to the guided tours request to visit of schools, university students and society in general.
- Attention to the media.
- Attention to the consults and managements of the donations to the CIC through its foundation (FICUS).
- Elaboration of press releases and organization of press conferences.
- Follow up of news published in newspapers and journals.
- CIC Scientific seminars series.
- Internal support to the meetings organized by scientists at the center.
- Management of training and commercial activities requested by entities outside the center.



Personnel

Celso Collazo López
Carlos M. de los Dolores Redondo

SUPPORT UNITS

EQUIPMENT & BUILDING MAINTENANCE

The Equipment & Building Maintenance unit has the following functions:

- Modification, reparation and maintenance programs of laboratory equipment and building facilities.
- Oversees and management maintenance contracts and externals for repairs by outside contractors and supplies for laboratory equipment and building facilities.
- Helps research laboratories and core services units in verification and internal calibration of laboratory equipment for Quality Management System and/or purchases, replacement or any technical problem.
- Registration into the management software for equipment inventory, instruction manuals and work orders.

Although not considered as a service for external users, sporadically the unit gives support to other centers on the university campus. The unit has the ISO ISO 45001:2018 Certification.

SERVICES

- Installation and initial setup of new equipment
- Modification and repairs of simple lab equipment.
- Complex repair of laboratory equipment using some specific maintenance tools or equipment.
- Programmed routine maintenance, corrective and preventive building facilities (fancoil filters, oil vacuum replacement, CO2 cell culture incubators, spectrophotometer etc.) and steam checkout
- Verification/calibration of balances, pipettes, dry heat incubators, refrigerators, thermoblocks, etc.
- Request of an intervention, overseeing of the work of outside contractors and management of repairs made by external companies

Personnel
María José Campo Beneitez

SUPPORT UNITS

QUALITY CONTROL & RISK PREVENTION

The Quality & Risk Unit Labor is responsible for:

- Management of ISO 9001 and ISO 45001 standard, elaboration of general quality procedures applicable to all Units and review of standard operation protocols. Quality control, assurance and improvement in the center
- Control of occupational and environmental safety and health in the institute and elaboration of customized procedures for labor risks prevention and safety instructions according current regulations on safety and health
- Training and education of newly incorporated personnel on occupational safety and emergency procedures and all personnel with regards to Environmental Safety and Health programs
- Organization of annual drills, annual revision and update of Emergency Plans and health monitoring and checkups and communication between centralized Risk Prevention Services of center and the USAL
- Record keeping and management of occupational accidents/incidents

SERVICES

- Follow-up control of the units and laboratories certified to check for the compliance of rules under the ISO 45001 and ISO 9001 requirements
- Preparation, follow-up and modification of quality procedures and occupational risks prevention
- Internal and external quality and prevention audits. Yearly health monitoring and preparation of paperwork, data filling, and elaboration of annual report to be reviewed by the Direction.
- Training of new personnel joining the center and emergency drill preparation and execution
- Coordination of business activities in preventive matters

Personnel

María Sonia Pérez Díez
Mª Eugenia Fdez. de la Torre

SUPPORT UNITS

CENTRAL WAREHOUSE & RADIOLOGICAL PROTECTION

Facility intended to acquisition cell culture material, reagents, antibodies, office supplies and research material, for the institute in general and the different research projects carried out.

SERVICES

- Negotiation of supplier purchase agreements.
- Purchase supplier orders.
- Stocks maintenance of material, culture media, reagents, etc. in the warehouse
- Making claims of damaged or wrong orders.
- Find alternatives like any product in case of stock out.
- Advises and informs about prices, offers and availability of products requested by users.
- Acquisition of radioisotopes, non-encapsulated sources, and radioactive measuring equipment.
- Radioactive waste management.
- Permanent control of the radioactive material existing in the radioactive facility.
- Elaboration of standards that lead to the development of personnel work with the lowest possible risk: radiological protection manual, devices verification/calibration procedures, operations logbook, CSN reports, etc.

Personnel

Ana Brufau Redondo
Mª del Rosario García Rubia
Vanessa Centeno Talayero

SUPPORT UNITS

GLASSWARE AND MEDIA STERILIZATION

DESCRIPTION

The Washing and Sterilization unit performs its services for the research and service units of the institute in the following áreas:

- Ordering and storage of research materials.
- Decontamination, cleaning of labware and sterilization of material.
- Preparation of different media and solutions usually requiered in the laboratories of our center, and some media and solutions not available and specifically requested as needed.
- Biological and hazardous waste management.

The unit has the ISO Certification: ISO 45001:2018 since 2007 and it having successfully passed the successive external audits required.

SERVICES

1. Cleaning and sterilization of material needed in laboratories.

   Each day the dirty material gets cleaned in special washing machines and then gets prepped to be sterilized by autoclave, or heater.

2. Stocking of research materials. The unit will renovate research material from time to time, as well as aquire more units depending of the needs of use in laboratories

3. Media preparation.

   Every day new media gets prepared so there is always stock available to researchers.Most of them get sterilized before they are used. Special requests for media not ready available are also attended every day.

4. Competent cell preparation.

   The unit prepares competent DH5α bacteria for use in the laboratories.

5. Sterilization of biological waste.

   Every culture room has specially designed disposal units that get picked up every day, and processed so no contaminants remain after the sterilization process, and they can be discarded safely.

6. Management of dangerous waste biohazard disposal.

   The manager of the unit is responsible to ensure the correct pick-up of hazardous waste by the competent authorities, to ensure that the CIC complies with current laws regarding dangerous materials.

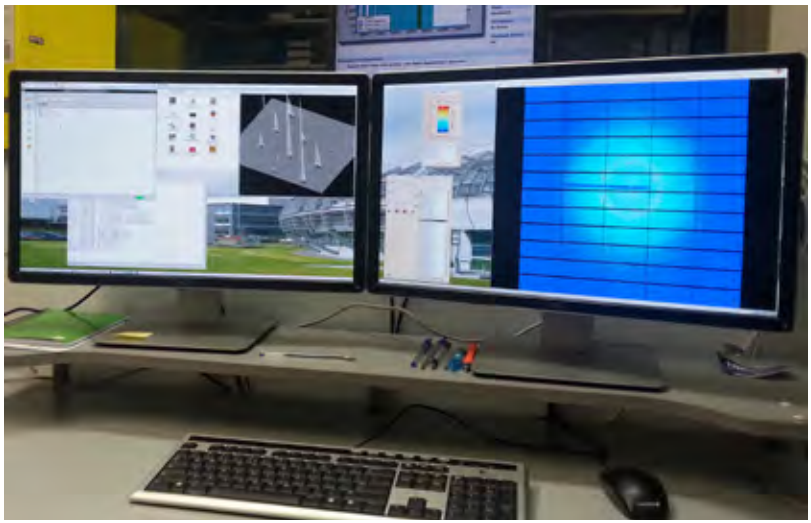
Personnel

Sonia Pedraza Flores
Pablo González Delgado

INFORMATION TECHNOLOGIES SERVICE (IT)

The Computer Service is responsible for the development, maintenance, management, and control information technology resources and communications as well as providing technical support to users, works to provide the following services:

- Guidance, negotiation, and follow-up on the purchase of corporation hardware.
- Management of network users, e-mail accounts and distribution lists.
- Installation, maintenance and repair of end-user computer equipment, software and hardware.
- Incident management, technical support, user help and assistance.
- Development and maintenance of the data network infrastructure, wireless network, and audiovisual media.
- Installation, configuration and maintenance of local servers (file server, domain controllers, web server, etc.).
- Network data and database administration department.
- Application Development.(Analysis, design, implementation and maintenance of custom software)



7
SCIENTIFIC ACTIVITIES

LIST OF JOURNALS

This list reflects the 183 scientific journals in which the investigators of the CIC-IBMCC have published original articles during 2020-2021. The publications with an impact factor over 10 points are highlighted.

JOURNAL	Nº PAPERS	IF (JCR 2020)	QUARTILE (JCR 2020)
Acta Pharmaceutica Sinica B	**1**	**11.614**	**D1**
Advances in Therapy	1	3.847	Q2
American Journal of Case Reports	1	NI	NI
American Journal of Dermatopathology	1	1.533	Q4
American Journal of Hematology	**7**	**10.047**	**D1**
American Journal of Human Genetics	**1**	**11.025**	**D1**
American Journal of Transplantation	1	8.086	D1
Annals of Allergy Asthma & Immunology	1	6.347	Q1
Annals of Clinical and Translational Neurology	1	4.511	Q2
Annals of Hematology	7	3,673	Q2
Annals of Oncology	**1**	**32.976**	**D1**
Annual Review of Cell and Developmental Biology	**1**	**13.827**	**D1**
Antioxidants	1	6.313	D1
Archives of pathology & laboratory medicine	1	5.534	Q1
Archives of Toxicology	1	5.153	Q1
Autophagy	**1**	**16.016**	**D1**
Biochimica et Biophysica Acta-Gene Regulatory Mechanisms	1	4.490	Q1
Biochimica et Biophysica Acta-Reviews on Cancer	**1**	**10.680**	**D1**
Biology of Blood and Marrow Transplantation	3	5.742	Q1
Biology	2	5.079	Q1
Biomedical Optics Express	1	3.732	Q1
Biomedicine & Pharmacotherapy	1	6.530	D1
Biomedicines	2	6.081	Q1
Biomolecules	5	4.879	Q2
Blood	**15**	**23.629**	**D1**

JOURNAL	Nº PAPERS	IF (JCR 2020)	QUARTILE (JCR 2020)
Blood Advances	8	6.799	Q1
Blood Cancer Discovery	1	NI	NI
Blood Cancer Journal	**14**	**11.037**	**D1**
Blood Cells Molecules and Diseases	1	3.039	Q3
Blood Reviews	1	8.250	Q1
BMC Cancer	2	4.430	Q2
BMJ Open	1	2.692	Q2
Bone	1	4.398	Q2
Bone Marrow Transplantation	11	5.483	Q1
Brain Communications	1	NI	NI
Brain Pathology	1	6.508	D1
Breast Cancer Research	1	6.488	Q1
British Journal of Biomedical Science	1	3.829	Q1
British Journal of Clinical Pharmacology	1	4.340	Q2
British Journal of Haematology	23	6.998	Q1
British Journal of Surgery	1	6.939	D1
Cancer	1	6.860	Q1
Cancer Genetics	1	2.523	Q3
Cancer Letters	3	8.679	D1
Cancer Medicine	4	4.452	Q2
Cancer Research	**2**	**12.701**	**D1**
Cancers	35	6.639	Q1
Cell Death and Disease	1	8.469	Q1
Cells	9	6.600	Q2
Cellular and Molecular Life Sciences	1	9.261	D1
Cellular Oncology	2	6.730	D1
Clinical & Translational Oncology	1	3.405	Q3
Clinical and Translational Medicine	**1**	**11.492**	**D1**
Clinical Cancer Research	**3**	**12.531**	**D1**
Clinical Lymphoma Myeloma & Leukemia	8	3.231	Q3
Clinical Medicine	1	2.659	Q2
Clinical Transplantation	1	2.863	Q2

JOURNAL	Nº PAPERS	IF (JCR 2020)	QUARTILE (JCR 2020)
CRISPR Journal	1	6.071	Q1
CTS-Clinical and Translational Science	1	4.689	Q2
Current Biology	**1**	**10.834**	**D1**
Cytometry Part B-Clinical Cytometry	4	3.058	Q2
Cytotherapy	1	5.414	Q1
Diagnostics	4	3.706	Q2
Drug Resistance Updates	**3**	**18.500**	**D1**
EBioMedicine	1	8.143	Q1
EMBO Journal	**1**	**11.598**	**D1**
EMBO Molecular Medicine	**1**	**12.137**	**D1**
ERJ Open Research	1	NI	NI
ESMO Open	2	6.540	Q1
European Journal of Cancer	1	9.162	Q1
European Journal of Haematology	3	2.997	Q3
European Journal of Human Genetics	1	4.246	Q2
European Journal of Internal Medicine	1	4.624	Q1
EXCLI Journal	1	4.068	Q2
Experimental and Therapeutic Medicine	1	2.447	Q3
Expert Opinion on Investigational Drugs	1	6.206	Q1
Farmacia Hospitalaria	1	NI	NI
FEBS Journal	2	5.542	Q1
Frontiers in Cell and Developmental Biology	5	6.684	Q1
Frontiers in Cellular and Infection Microbiology	1	5.293	Q1
Frontiers in Cellular Neuroscience	1	5.505	Q1
Frontiers in Immunology	8	7.561	Q1
Frontiers in Medicine	2	5.093	Q1
Frontiers in Oncology	4	6.244	Q2
Frontiers in Pharmacology	1	5.811	Q1
Future Oncology	1	3.404	Q3
Genes	3	4.096	Q2
Haematologica	12	9.941	D1
Head Neck	1	NI	NI

JOURNAL	Nº PAPERS	IF (JCR 2020)	QUARTILE (JCR 2020)
Hemasphere	5	NI	NI
Hematological Oncology	1	5.271	Q2
Hepatoma Research	1	NI	NI
HLA	1	4.513	Q1
Human Genomics	1	4.639	Q2
Human Immunology	1	2.850	Q3
Infection and Immunity	1	3.441	Q3
International Angiology	1	2.789	Q3
International Journal of Cancer	3	7.396	Q1
International Journal of Cardiovascular Imaging	1	2.357	Q3
International Journal of Molecular Sciences	16	5.924	Q1
JAMA Oncology	**1**	**31.777**	**D1**
Journal for ImmunoTherapy of Cancer	**1**	**13.751**	**D1**
Journal of Allergy and Clinical Immunology	**2**	**10.793**	**D1**
Journal of Allergy and Clinical Immunology-In Practice	2	8.861	D1
Journal of Biological Chemistry	1	5.157	Q2
Journal of Blood Medicine	1	NI	NI
Journal of Cancer Research and Clinical Oncology	1	4.553	Q2
Journal of Cardiovascular Surgery	1	1.888	Q3
Journal of Cell Science	2	5.285	Q2
Journal of Cellular And Molecular Medicine	3	5.310	Q2
Journal of Clinical Apheresis	1	2.821	Q3
Journal of Clinical Medicine	2	4.242	Q1
Journal of Clinical Oncology	**7**	**44.544**	**D1**
Journal of Clinical Pharmacology	1	3.129	Q3
Journal of Cutaneous Pathology	1	1.587	Q4
Journal of Enzyme Inhibition And Medicinal Chemistry	1	5.051	Q1
Journal of Experimental & Clinical Cancer Research	**4**	**11.161**	**Q1**
Journal of Hematology & Oncology	**3**	**17.388**	**D1**
Journal of Molecular Diagnostics	4	5.568	Q1
Journal of Pediatric Genetics	1	NI	NI
Journal of Personalized Medicine	2	4.945	Q1

JOURNAL	Nº PAPERS	IF (JCR 2020)	QUARTILE (JCR 2020)
Journal of Surgical Case Reports	1	NI	NI
Journal of the American Academy of Dermatology	**3**	**11.527**	**D1**
Journal of Thrombosis and Haemostasis	1	5.824	Q1
Journal of Translational Medicine	1	5,531	Q2
Lancet	**4**	**79.323**	**D1**
Lancet Haematology	**4**	**18.959**	**D1**
Lancet Oncology	**3**	**41.316**	**D1**
Leukemia	**19**	**11.528**	**D1**
Leukemia & Lymphoma	6	3.280	Q3
Leukemia Research	2	3.156	Q3
Materials	1	3.623	Q1
Medicina Clinica	2	1.725	Q3
Molecular & Cellular Oncology	1	NI	NI
Molecular Biology of the Cell	1	4.138	Q3
Molecular Biology Reports	1	2.316	Q4
Molecular Cancer	**2**	**27.401**	**D1**
Molecular Cytogenetics	1	2.009	Q4
Molecular Diagnosis & Therapy	1	4.074	Q2
Molecular Oncology	1	6.603	Q1
Molecular Therapy-Methods & Clinical Development	1	6.698	Q1
Molecules	1	4.412	Q2
Nanomaterials	2	5.076	Q1
Nature	**2**	**49.962**	**D1**
Nature Cancer	1	NI	NI
Nature Communications	**6**	**14.919**	**D1**
Nature Reviews Immunology	**1**	**53.106**	**D1**
Neoplasia	1	5.715	Q2
Neurology-Genetics	1	3.485	Q2
New England Journal of Medicine	**1**	**91.523**	**D1**
npj Precision Oncology	1	8.254	Q1
Nutrients	1	5.719	Q1
Oncogene	2	9.867	D1

JOURNAL	Nº PAPERS	IF (JCR 2020)	QUARTILE (JCR 2020)
Oncology and Therapy	1	NI	NI
Pharmaceutics	1	6.321	Q1
Pharmacogenomics Journal	1	3.550	Q2
Platelets	3	3.862	Q2
PLoS Computational Biology	1	4.475	Q1
PLoS One	3	3.240	Q2
Revista Espanola de Anestesiologia y Reanimacion	1	NI	NI
Revista Espanola de Medicina Nuclear e Imagen Molecular	1	1.359	Q4
Revista Española de Cardiologia	2	4.753	Q2
RNA Biology	2	4.652	Q2
Sao Paulo Medical Journal	1	1.044	Q4
Science Advances	**1**	**14.143**	**D1**
Science Signaling	1	8.218	Q1
Scientific Reports	9	4.380	Q1
Seminars In Cancer Biology	**1**	**15.707**	**D1**
Signal Transduction and Targeted Therapy	**2**	**18.187**	**D1**
Stem Cell Research & Therapy	1	6.832	Q1
Stem Cells	2	6.277	Q1
Stem Cells Translational Medicine	1	6.940	Q1
The European Journal of Case Reports in Internal Medicine	1	NI	NI
Theranostics	**1**	**11.556**	**D1**
Thrombosis and Haemostasis	1	5.723	Q1
Transfusion and Apheresis Science	1	1.764	Q4
Transplantation and Cellular Therapy	2	NI	NI
Trends in Cancer	**1**	**14.226**	**D1**
Trends in Immunology	**1**	**16.687**	**D1**
Trends in Microbiology	**1**	**17.079**	**D1**
Trials	2	2.279	Q4
Value in Health	1	5.728	D1
Virchows Archiv	1	4.064	Q2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CLINICAL CYTOMETRY
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haematologica
nature methods
REDES 14
Inmunología
Oncologist
Lab Times

NATIONAL AND INTERNATIONAL COLLABORATIONS

NATIONAL COLLABORATIONS

CENTER	CITY	RESEARCHERS
Asociación Española de Mastocitosis	Toledo	Muñoz-González JI / Álvarez-Twose I
Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER) / Universidad Pablo de Olavide	Sevilla	José C. Reyes / Rául Durán
Centro de Biología Molecular "Severo Ochoa" (CBMSO)	Madrid	Iñigo Marcos-Alcalde / Felipe X. Pimentel / César Cobaleda
Centro de Biología Molecular Severo Ochoa (CSIC – UAM) / CIBERER	Madrid	José M. Cuezva / Paulino Gómez-Puertas
Centro de Investigación Cooperativa en Biociencias (CIC-Biogune)	Bilbao	Arkaitz Carracedo
Centro de Investigaciones Biológicas (CIB)-Margarita Salas	Madrid	Aurora Gómez / Rodrigo Bermejo
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid	Jesús M. Paramio / José Carlos Segovia
Centro de Regulación Genómica (CRG)	Barcelona	Eva M. Novoa
Centro Nacional de Investigaciones Cardiovasculares (CNIC)	Madrid	Francisco Sanchez-Madrid
Centro Nacional de Investigaciones Oncológicas (CNIO)	Madrid	Tomás Didomenico / Marcos Malumbres
Centro Nacional de Supercomputación (BSC) / Instituto Nacional de Bioinformática (INB)	Barcelona	Alfonso Valencia
Clínica Universitaria de Navarra / Centro de Investigaciones Médicas Aplicadas (CIMA) / Universidad de Navarra	Pamplona	Bruno Paiva / Jesús SanMiguel / Juan Jose LaHuerta / Felipe Prósper / Silvestre Vicent Cambra
Hospital Clinic	Barcelona	Elías Campo / Armando López-Guillermo / Eva Giné / Silvia Beá / Aleix Prat / Fara Brasó
Hospital Clínico San Carlos,	Madrid	Alberto Ocaña Fernández
Hospital Gregorio Marañón	Madrid	Miguel Martín
Hospital La Fe de Valencia	Valencia	Pilar Sepúlveda / Pau Montesinos
Hospital Nacional de Paraplejicos	Toledo	Diego Clemente
Hospital Ramón y Cajal	Madrid	Pilar Garrido
Hospital Universitario Central de Asturias / Universidad de Oviedo	Oviedo	Juan P. Tapia

CENTER	CITY	RESEARCHERS
Hospital Universitario Niño Jesús	Madrid	Manuel Ramírez Orellana
Hospital Vall d'Hebrón	Barcelona	Francesc Bosch / Pau Abrisqueta / Marta Crespo
Hospital Virgen de la Arrixaca	Murcia	José María Moraleda
Hospital Virgen del Rocío	Sevilla	José Antonio Pérez Simón
Institut de Recerca Sant Joan de Déu (IRSJD) / CIBERER / Instituto de Salud Carlos III	Barcelona	Carmen Fons
Institut Universitari d'Investigació en Atenció Primària (IDIAP Jordi Gol)	Barcelona	Mercè Marzo Castillejo
Institute Catalán de Oncología (ICO) / IDIBELL	Barcelona	Ernest Nadal / Alberto Villanueva
Instituto de Biofísica (CSIC) / Universidad del País Vasco	Lejona (Bizkaia)	Álvaro Villarroel
Instituto de Biología y Genética Molecular	Valladolid	Andrés Alonso / Yolanda Bayón
Instituto de Investigación Biomédica (IRB)	Barcelona	Salvador Aznar-Benitah
Instituto de Investigación Biomédica A Coruña (INIBIC)	A Coruña	Angélica Figueroa
Instituto de Investigación contra la Leucemia Josep Carreras	Barcelona	Manel Esteller / Sonia Guil / Esteban Ballestar
Instituto de Investigaciones Biomédicas "Alberto Sols"	Madrid	Jorge Martín Pérez
Instituto de Salud Carlos III (ISCIII)/ UFIEC / CIBERONC	Madrid	José María Rojas Cabañeros
Instituto Hospital del Mar de Investigaciones Médicas (IMIM)	Barcelona	Joaquín Arribas López / Joan Albanell Mestres
Instituto para el Estudio de la Biología de la Reproducción Humana (INEBIR)	Sevilla	Ana T. Marcos-Rodriguez
Instituto Pediátrico de Enfermedades Raras (IPER) / Hospital Sant Joan de Déu	Barcelona	Cesar Arjona
Laboratorio de Investigación de Oncología Médica / Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS)	Madrid	Cristina Peña Maroto
QGenomics	Barcelona	María Segura / Luis Armengol
Universidad Complutense	Madrid	Sonia Castillo Lluva
Universidad de Cantabria / IBTTEC (CSIC)	Santander	Piero Crespo
Universidad de Cantabria-IDIVAL / CIBERNED	Santander	Miguel Lafarga
Universidad de Castilla La Mancha	Ciudad Real	Carlos Alonso Moreno
Universidad de Extremadura	Badajoz	Pedro Fernández-Salguero
Universidad de Santiago de Compostela / CIMUS	Santiago of Compostela	Rubén Nogueiras / Carlos Diéguez / Miguel López / José Tubío
Universidad Europea del Atlántico	Santander	José M. Navarro-Pando
Vall d'Hebron Institut de Recerca (VHIR) / Hospital Universitari Vall d'Hebron / Universidad Autónoma de Barcelona	Barcelona	Marcella Salzano

INTERNATIONAL COLLABORATIONS

CENTER	COUNTRY	RESEARCHERS
Amsterdam University Medical Center	Netherlands	Connie Jimenez / Frank Rolfs / Sander Piersma
Barts Cancer Institute	United Kingdom	Jude Fitzgibbon / Jessica Okosun / Yong-Jie Lu
Cancer Research Center of Toulouse (CRCT)	France	Stéphanie Cabantous
Cardiff University	United KIngdom	Tomasz Jurkowski
Center for Cancer Systems Biology (CCSB) / Dana-Farber Cancer Institute / Harvard Medical School (DFCI-HMS)	USA	Marc Vidal
Center for Molecular Medicine/ Maine Medical Center Research Institute, Scarborough (ME)	USA	Thomas Gridley
Center for Novel Therapeutics - University of California, San Diego	United States	Thomas J Kipps / Laura Z Rassenti
Center for Structural Biology-Vrije Universiteit Brussel	Belgium	Jan Steyaert / Els Pardon
Centre de Recherche des Corderliers	France	Santos A Susin
Dana-Farber Cancer Institute	USA	Constantine S Mitsiades
Darmouth College	USA	Henry Higgs
EuroFlow Consortium LUNC University	The Netherlands	van Dongen JJM / van der Velden VHJ
University Hospital of Friedrich-Alexander-University Erlangen, Nürnberg	Germany	Regine Schneider-Stock
Institute de Biologie	France	Katja Wassmann
Institute for Computational Biomedicine / Heidelberg University / Heidelberg University Hospital	Germany	Julio Saez-Rodríguez
Institute of Psychopharmacology / Central Institute of Mental Health / Medical Faculty Mannheim / University of Heidelberg	Germany	Rainer Spanagel
Juntendo University	Japan	Akira Orimo
Khalifa University	UAE	Abdulrahim Abdulrahman Sajini
Københavns Universitet / Center for Protein Research, Copenhagen	Denmark	Guillermo Montoya
La Pitié-Salpêtrière Hospital – APHP / Sorbonne Université	France	Boris Keren
Lawrence Berkeley National Laboratory (LBNL) / University of California. Berkeley (CA)	USA	Jian Hua Mao
Molecular Biotechnology Center (MBC) / University of Torino	Italy	Chiara Ambrogio
Netherlands Cancer Institute-NKI	The Netherlands	Arnoud Sonnenberg
National Institutes of Health (NIH)	USA	Jim Sellers
Ohio State University	USA	Sarah Heissler
Oslo University Hospital	Norway	Júrgen Geisler / Vessela Kristensen / Therese Sorlie
Princess Margaret Hospital, Toronto	Canada	Eitan Amir
Queen Mary Hospital-The University of Hong Kong	Hong Kong	Yao Q / Chim CS
Queens University of Belfast	United Kingdom	David González / Peter Stewart
Rowan University School of Osteopathic Medicine, Stratford	USA	Dimitri G Pestov

CENTER	COUNTRY	RESEARCHERS
Sanford Research, South Dakota.	USA	Pilar de la Puente
Sorbonne Université - Université Pierre et Marie Curie / Institut du Cerveau et de la Moelle épinière (INSERM)	France	Fanny Mochel
St. Jude Children's Research Hospital	USA	Kim E. Nichols
The Firc Institute of Molecular Oncology (IFOM), Milano	Italy	Giorgio Scita
The Medical University of Vienna/ The European Competence Network of Mastocytosis (ECNM)	Austria	Peter Valent / Ulrich Jaguer
TiMaScan Research Group	The Netherlands	van den Bossche WBL/ Vincent AJPE/ Teodosio C
ULB-Cancer Research Center	Belgium	Denis Lafontaine
Ulm University	Germany	Daniel Mertens
Umea University	Sweden	Francesca Aguilo / Sun Nyu Wang
University Heinrich Heine, Düsseldorf	Germany	Arndt Borkhardt
Universidade Federal de São Paulo (EPM-UNIFESP)	Brasil	de Faria-Moss M /Yamamoto M
Università degli Studi di Milano-Bicocca (UNIMIB)	Italy	Giovanni Cazzaniga
Università di Chieti	Italy	Gianluca Sala
Università di Firenze	Italy	Elisabetta Rovida
Università di Siena	Italy	Emanuele Giurisato
Université Paris-Est Créteil Val-de-Marne (UPEC)	France	Dulce Papy-Garcia
University of Antioquía	Colombia	Juan Carlos Gallego-Gómez
University of Bayreuth	Germany	Olaf Stemmann
University of Budapest	Hungary	Balazs Györffy
University of Cambridge	United Kingdom	Jason Carroll
University of Cincinnati	USA	José Cancelas
University of Delaware	USA	Aditya Dutta
University of Florence.	Italy	Elisabetta Rovida
University of Kent	United Kingdom	Benjamin T Goult
University of Lisbon (ULISBOA)	Portugal	Margarida Gama-Carvalho, Francisco Rodrigues Pinto
University of Miami Health System	USA	Izidore Lossos
University of Newcastle	United Kingdom	Owen Davies
University of Oklahona	USA	Dean S. Dawson
University of Porto	Portugal	Sandra Macedo-Ribeiro
University of Quilmes, Buenos Aires	Argentina	Pablo Lorenzano-Menna
University of Torino (UNITO)	Italy	Simone Ferrero / Chiara Riganti
University of Utrecht	The Netherlands	Dirk de Rooij / Richard Scheltema
Washington University School of Medicine, Saint Louis	USA	Sabine Dietmann
Weizmann Institute of Science, Rehovot	Israel	Emmanuel Levy / Daniel Osterle
William Harvey Research Institute	United Kingdom	Ezra Aksoy / Jesmond Dalli

ONCOLOGY BIOMEDICAL RESEARCH NETWORKING CENTER (CIBERONC)

CIBER (Biomedical Research Networking Centers; https://www.ciberisciii.es/en) are stable, co-operative research structures that, in the form of public research consortia with recognized legal status, were created under an initiative by the Instituto de Salud Carlos III.

The aim of the CIBER, is to further excellence research in Biomedicine and Health Sciences done in the National Health System and in the Science and Technology System. To this end efforts and interdisciplinary and multi-institutional research are combined with a preferential dedication of financial resources around knowledge networks formed by centers and research groups reporting to different administrations and public and private institutions

At the present time, the CIBER has a staff of 804 persons and around 6.000 attached researchers integrated in over 420 research groups working in separate locations, associated with 99 institutions in the consortium (hospitals, universities and public research institutions, with a broad geographical distribution, which are collaborating for research excellence in the different fields, among which is cancer research and belonging to administrations and public and private sector institutions of Spain's different regional "Autonomous Communities".

The proven improvement of the scientific quality and the maturation of the cooperative activity in cancer of the Spanish scientific community that took place within the RTICC in its successive editions since 2003 constituted an essential factor for the decision of the Management of the Institute of Health Carlos III (ISCIII) in the sense of changing, from 2017, the structure of cooperative research in cancer in Spain (previously in RTICC format) to a structure of organization and more stable format within the organizational chart of the ISCIII as it is a new area of Cancer (named CIBERONC; https://www.ciberonc.es/en) of the CIBER of ISCIII.

In actual fact, the work done by the RTICC over its thirteen years' operation under the management of Dr. Eugenio Santos has made setting up the CIBERONC far easier. Based on this prior experience, and taking advantage of all the organizational advantages of belonging to a CIBER, we now have a chance to head more quickly towards achieving our basic aim: improving the reality of the cancer patient. Therefore, the main aim of the CIBERONC is to promote excellence in oncology research in Spain, as well as to incorporate new findings to clinical practice.

In order to achieve this aim, CIBERONC has 50 research groups located in the main centers all over Spain. These groups have adopted a structure of 6 scientific programs, 5 focusing on the major challenges in prevention, diagnosis and treatment of the most prevalent neoplastic typologies. The sixth works on better understanding how malignant cells work as a way to use their weaknesses in the development of new precision therapies. The CIBERONC also has a transversal training and mobility program which will contribute to generating excellence among our present and future researchers.

In order to ensure the integration of the results of our research in patients' treatment, there is a balance between basic and clinical researchers in all CIBERONC structures. The central objectives of each program are furthermore

intended to improve the diagnosis and treatment of cancer patients.

Last, but not least, our center wishes to narrow the gap between scientific knowledge and society. We will therefore clearly explain the benefits of our research to the general public by means of different endeavors.

In order to ensure the integration of the results of our research in patients' treatment, there is a balance between basic and clinical researchers in all CIBERONC structures.

CIBERONC has thus adopted a structure with the following specific aims:

- To carry out joint programs for research, development and innovation in the cancer area.
- To contribute to solving the problems faced by healthcare in the field of oncology.
- To promote the participation of research groups in national and international research activities, especially the ones included in European R+D+I Framework Programs.
- To promote the transfer of results of research processes to society and in particular to the production sector.
- To promote the dissemination of its activities and the training of researchers in the cancer field.

Undoubtedly, 2020 and 2021 has been years marked by the pandemic. The serious global health crisis has had very important repercussions in all areas, including, as could not be otherwise, that of research.

Throughout 2020-2021, CIBERONC has focused on fostering interaction between groups from different disciplines and areas and promoting interaction between basic and clinical groups. As a result of this interaction, CIBERONC has a significant representation in the recently granted national platform for genomic medicine (IMPaCT).

This panel has been created as an additional body for structural and scientific advice in our area and has endorsed the internal call for strategic projects for 2021, aimed at aligning groups in the area in view of the next Horizon Europe Mission on Cancer.

CIBERONC has continued to foster the training of our youngest researchers, allocating a large part of the training program budget to research initiation contracts for young graduates and graduates.

Five groups of the CIC-IBMCC, led by Dr. Eugenio Santos (CB16/12/00352), Xosé R. Bustelo (Coordinator of the Tumour Progression Mechanisms program; CB16/12/00351), Alberto Orfao (CB16/12/00400), Ramón García-Sanz (CB16/12/00351) and Atanasio Pandiella Alonso (CB16/12/00317) are involved in several programs of the CIBERONC.

GROUPS OF CIC-IBMCC RECOGNIZED AS "UNIDAD DE INVESTIGACIÓN CONSOLIDADA" (UIC) BY CASTILLA-LEÓN AUTONOMOUS GOVERNMENT

Nº	PI	RESEARCHERS
002	**Xosé Ramón García Bustelo**	Mercedes Dosil Castro / Javier Robles Valero / Myriam Cuadrado López
009	**Atanasio Pandiella Alonso**	María Azucena Esparís Ogando / Juan Carlos Montero González / María Elena Díaz Rodríguez / Alberto Ocaña Fernández
017	**Isidro Sánchez García**	Rafael Jiménez Fernández / Francisco Javier García Criado / Jesús Pérez Losada / Carolina Vicente Dueñas
066	**Alberto Martín Pendás**	Elena Llano Cuadra / Manuel Sánchez Martín / José Luis Barbero Esteban
076	**Eugenio Santos de Dios**	Javier De Las Rivas Sanz / Alberto Fernández Medarde / José María Rojas Cabañeros / Fernando Calvo Baltanás
106	**Mª del Carmen Guerrero Arroyo**	José Ramón González Porras / Francisco Santiago Lozano Sánchez / Francisco Martín Herrero / José María de Pereda Vega / Jose María Bastida Bermejo / Almudena Porras Gallo
110	**Norma Carmen Gutiérrez Gutiérrez**	María Victoria Mateos Manteca / Mercedes Garayoa Berrueta / Noemí Puig Morón / María Teresa Paíno Gómez / Luis Antonio Corchete Sánchez
116	**Fermín Sánchez-Guijo Martín**	Silvia Preciado Pérez / María Díez Campelo / Lika Osugui / Sandra Muntión Olave / Juan Francisco Blanco Blanco / Eva María Villarón Ríos
143	**Jesús María Hernández Rivas**	Juan Luis García Hernández / Ana Eugenia Rodríguez Vicente / M. Rocío Benito Sánchez / Ignacio García-Tuñón Llanio / María Abaigar Alvarado / María Hernández Sánchez / María Teresa González Martínez / Mónica del Rey González
151	**José Alberto Orfao de Matos Correia e Vale**	Julia Mª Almeida Parra / Manuel Fuentes García / Mª Dolores Tabernero Redondo / Andrés Celestino García Montero / Martín Pérez Andrés
155	**Marcos González Díaz**	Ramón García Sanz / Cristina Jiménez Sánchez / María del Carmen Chillón Santos / María Eugenia Alonso Sarasquete / María Belén Vidriales Vicente / Verónica González de la Calle
252	**Andrés Avelino Bueno Núñez**	Felipe Xosé Pimentel Muiños / María Sacristán Martín / Rodrigo Bermejo Moreno
258	**Pedro Alfonso Lazo-Zbikowski Taracena**	Juan Jesús Cruz Hernández /Rogelio González Sarmiento / Sandra Blanco Benavente
265	**María Dolores Caballero Barrigón**	Alejandro Martín García-Sancho / Pilar Tamayo Alonso / Miguel Alcoceba Sánchez / Lucía López Corral / María García Álvarez

GROUPS OF CIC-IBMCC RECOGNIZED AS "GRUPOS DE INVESTIGACIÓN RECONOCIDA" (GIR) BY THE SALAMANCA UNIVERSITY (USAL)

NAME	PI	RESEARCHERS	COLLABORATIONS	RESEARCH LINES
Inestabilidad Genética y Autofagia	Bueno Núñez, Andrés Avelino	Sacristán Martín, María / Pimentel Muiños Felipe / Bermejo Moreno, Rodrigo		- Identificación y estudio del significado biológico de los mecanismos que revierten la tolerancia al daño en el DNA - Estudio de la fosforilación de proteínas en respuesta a daño en el DNA - Mecanismos de estabilización de horquillas de replicación - El papel de la autofagia en la prevención de patologías inflamatorias graves
Linfomas y Trasplantes	Caballero Barrigón, Dolores	Martín García-Sancho, Alejandro / Alcoceba Sánchez, Miguel / Tamayo Alonso, Mª Pilar / López Corral, Lucía		- Promoción y desarrollo de ensayos clínicos controlados en LNH para la investigación de nuevos fármacos - Mejorar los procedimientos del trasplante autólogo y alogénico, la eficacia y tolerancia de los regímenes de acondicionamiento pretrasplante, así como la prevención y manejo de la enfermedad injerto contra huésped - Identificación de biomarcadores clínicos y genéticos que permitan identificar subgrupos de LNH con diferente evolución clínico/ pronóstica - Identificación de biomarcadores clínicos y genéticos asociados a complicaciones del trasplante: EICH, infecciones, miroangiopatía trombótica, etc. - Monitorización de la respuesta terapéutica de los síndromes linfoproliferativos e impacto de la misma en la supervivencia mediante la prueba metabólica PET/TC, así como citometría de flujo y biología molecular

NAME	PI	RESEARCHERS	COLLABORATIONS	RESEARCH LINES
Señalización, División y Crecimiento Celular	Dosil Castro, Mercedes	Llano Cuadra, Elena/ Robles Valero, Javier	Martín Pendás, Alberto / García Bustelo, Xosé Ramón / Vicente Manzanares, Miguel	- Papeles de moléculas de señalización celular en procesos tumorales y en otras enfermedades de alta incidencia - Formación de ribosomas y regulación del crecimiento celular - Análisis funcional de genes implicados en segregación cromosómica y su implicación en enfermedades humanas: cáncer, envejecimiento e infertilidad
CANCIRMED	García Criado, Francisco J.	González Sarmiento, Rogelio / Jiménez Fernández, Rafael / Cruz Hernández, Juan Jesús / Holgado Madruga, Marina	Vicente Dueñas, Carolina / Pérez Losada, Jesús / Sánchez J. García, Isidro / Lazo-Zbikowski Taracena, Pedro A / Juárez Vela, Raúl	- Programa de oncología traslacional: Biología de células madre tumorales y su aplicabilidad clínica
Biología Molecular y Celular en Hemopatías	González Díaz, Marcos	García Sanz, Ramón / Vidriales Vicente, Mª Belén	Chillón Santos, Mª del Carmen / Alonso Sarasquete, Mª Eugenia / Jiménez Sánchez, Cristina	- Alteraciones genéticas/moleculares de la célula tumoral de las hemopatías malignas - Factores pronósticos clínico-biológicos y fenotípicos/moleculares de las hemopatías malignas - Monitorización terapéutica mediante técnicas Fenotípicas y de Biología molecular (estudio de enfermedad mínima residual -EMR) - Polimorfismos genéticos en hemopatías malignas - Biología del Trasplante de precursores hematopoyéticos: Mecanismos de la Enfermedad Injerto Contra Huésped y Enfermedad Injerto Contra Leucemia
Mecanismos de Señalización en Enfermedades Cardiovasculares y otras Patologías: De la Investigación Básica a la Clínica	Guerrero Arroyo, Carmen	Lozano Sánchez, Francisco Santiago / González Porras, José Ramón / Martín Herrero, Francisco / Hernández Cano, Luis / Fernández Infante, Cristina / Rodríguez Blázquez, Antonio / Morán Vaquero, Alba / Herranz Varea, Óscar	Porras Gallo, Almudena / Pereda Vega, José María de / Bastida Bermejo, Jose Mª	- Modelos animales para el estudio de la ruta de señalización C3G-Rap1 en plaquetas - Implicación del C3G plaquetario en isquemia cardiaca y angiogénesis utilizando modelos murinos - Implicación de C3G en la patología cardiovascular humana - Papel de la ruta C3G-Rap1 en la diferenciación megacariocítica - Mecanismos de regulación intramolecular de PCa3pGel de C3G en la regulación de los procesos de migración/invasión y en las metástasis. Implicación de C3G en la transición epitelio-mesénquima - Fenotipo y Genotipo plaquetario

NAME	PI	RESEARCHERS	COLLABORATIONS	RESEARCH LINES
Genética Molecular en Oncohematología	Hernández Rivas, Jesús Mª	García Hernández, Juan Luis / Robledo Montero, Cristina / Rodríguez Vicente, Ana E. / Benito Sánchez, M. Rocío / del Rey González, Mónica / García-Tuñón Llanio, Ignacio	Lumbreras González, Eva / Hernández Sánchez, María / Montaño Brioso, Adrián / Janusz, Kamila / Quijada Álamo, Miguel / Martín Izquierdo, Marta / Hernández Sánchez, Jesús María / Abáigar Alvarado, María / Alonso Pérez, Verónica / Ordóñez García, José Luis / Marín Quilez, Ana	- Determinación de marcadores moleculares con interés diagnóstico y pronóstico en las hemopatías malignas y en los tumores sólidos - Identificación de mecanismos genéticos relacionados con la patogénesis de las hemopatías - Incorporación de las nuevas metodologías de análisis genético masivo (microarrays y secuenciación) al estudio de las neoplasias humanas
Citómica	Orfao de Matos, José Alberto	Almeida Parra, Julia / García Montero, Andrés Celestino / Fuentes García, Manuel / Tabernero Redondo, Mª Dolores / Sayagués Manzano, José Mª / Corrales Hernández, Juan J / Pérez Andrés, Martín /Reis da Silva Augusto, Paulo		- Identificación de patrones de expresión protéica aberrantes en tumores hematológicos (leucemias y linfomas) y relación con su origen genético, así como su aplicación para mejorar el diagnóstico y clasificación de estas neoplasias, como marcadores de seguimiento de enfermedad residual tras tratamiento y para la identificación de posibles dianas terapéuticas
GTPASAS y Cáncer: Señalización mediada por RAS	Santos de Dios, Eugenio	Rivas Sanz, Javier de las / Fernández Medarde, Alberto / Gómez Rodríguez, Carmela / Jimeno García, David / Fuentes Mateos, Rocío / Castellano Sánchez, Esther	Calvo Baltanás, Fernando / M García Navas, Rósula	

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ACADEMIC & TRAINING ACTIVITIES

POSTGRADUATE PROGRAM: MASTER'S DEGREE IN "BIOLOGY AND CLINIC OF CANCER"

Training constitutes a strong pilar of the CIC-IBMCC. The Master´s Degree in *"Biology and Clinic of Cancer"* is a distinctly postgraduate program focused on specialized training on basic, translational and clinical or bioinformatics research in cancer. It prepares students with an interest in Cancer Biology and without prior experimental experience in the fields of molecular and cell biology for inclusion in cancer-related PhD programs. Thus, the title is related to the Degrees in Biology, Biotechnology, Biomedicine, Biochemistry, Medicine and Pharmacy, which could be called powers of the biomedical area.

The rationale for this Master Program is determined by the need to integrate modern studies of cancer at the molecular level with the body of knowledge of this pathology clinically. The progress generated in this field of study ranges from basic research (biochemical and molecular biology fields) to clinical research areas related to diagnosis, prognosis and experimental treatment. In this sense, the training consists of proposing an interdisciplinary approach to graduate with academic interest and /or applied in the medical, pharmaceutical, biological, biotechnological or bioinformatics fields. The integration of molecular and clinical contents in the same program gives an extremely unique character and training key for future researchers in this field.

The Master *"Biology and Clinic of Cancer"* aims also to transfer to future doctors the experience and knowledge generated about the different diseases that collectively we call cancer as well as introduce the culture of cutting-edge research that will cure or turn into chronic these diseases in the future.

The Master´s Academic Program is taught by professors and researchers specialized in each of the subjects, most of them belonging to the CIC-IBMCC but also by visiting researchers, experts on specific topics, invited for that purpose.

An essential and outstanding feature of the Program is its high practical profile. Thus, out of a total of 60 ECTS, 30 correspond to experimental practices: students become part of a research group from the beginning of the course and carry out a research project, under the direct supervision of a tutor, that leads to the final Master Thesis. The CIC makes available to the students all facilities and technological units.

Moreover, one additional activity of the Master is the active participation of the students in the Scientific Seminar Program prepared annually by the CIC. Students have the opportunity to meet prestigious researchers invited by the Center as well as to know the research projects carried out by the different laboratories at the CIC.

Interestingly, the Program participates in two international initiatives aimed at developing active networks in the cancer research field, boosting the quality and competitiveness of students: 1) Master in Cancer Biology, Coimbra Life Science Group Master Programs. A joint Program of 11 European Universities, in which students can develop their practical training (or part of it) in one of the 11 Universities. 2) Master in Lifelong well-being and Healthy Ageing. A multidisciplinary master's degree from 7 European Universities within the framework of "European Campus of City Universities".

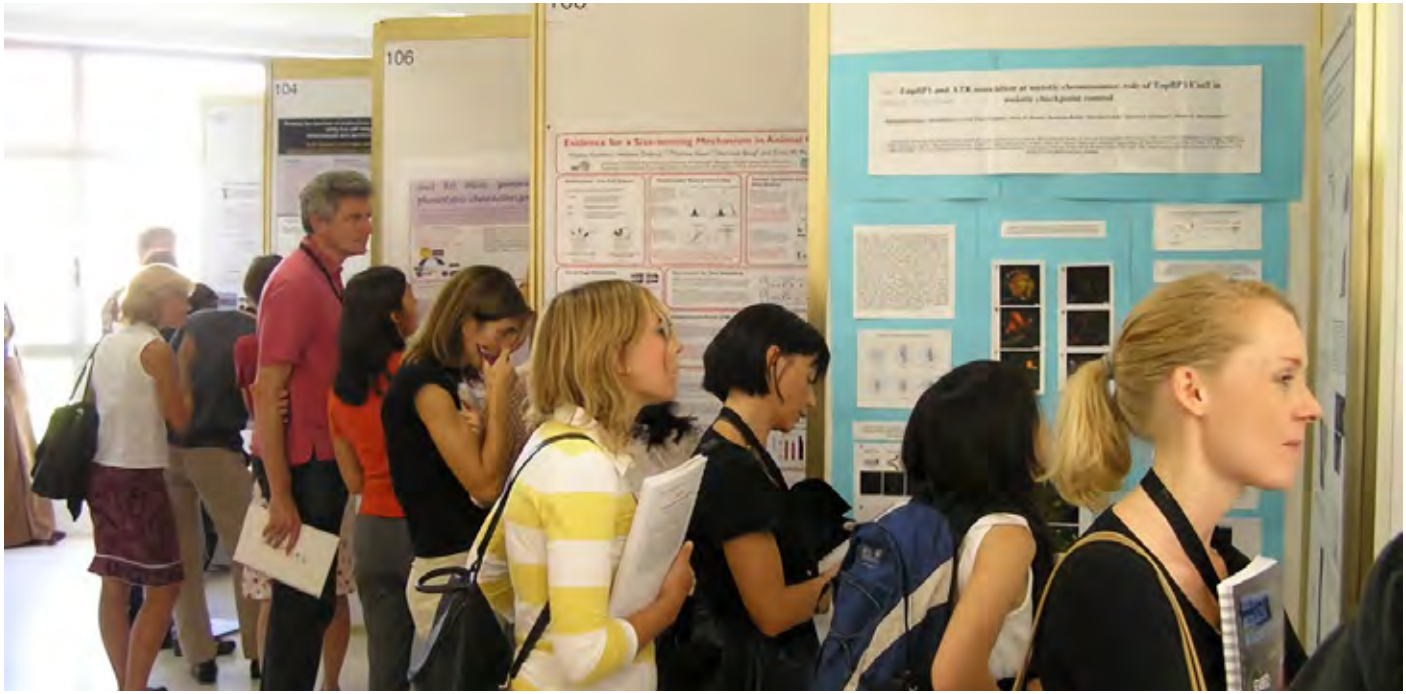
In summary, the aim of this Master´s Program is to provide students with the most complete research training in the field of cancer research.

STUDENTS MASTER PROGRAM

2019/2020	2020/2021	2021/2022
Vanessa Acebes Fernández	Cristina Arévalo Alameda	Natalia Alonso Moreda
Marta Alcón Pérez	Nuria Arroyo Garrapucho	Miguel Bastos Boente
Silvia Alemán Arteaga	Marta Bernal Ribes	Bárbara Castellanos García
Ana Macrina Añazco Guenkova	Aurora Campos Díaz	Lorea Chaparro González
Blanca Ayuso Íñigo	Sonia Carretero Domínguez	Maritza Cruz Hernández
David Bastante Rodríguez	Enrique de la Rosa Morón	Ana Dávila Hidalgo
Víctor Coca Ruiz	Lorena Díaz Ajenjo	Ana Garcia Gimeno
Alejandro Crespo Carazo	Marina Garrido Casado	Guillermo González Salso
Celia Gálvez Merchán	Marta González Rodríguez	Iván Hernández Navas
Ángela Patricia Hernández García	Mariem Lachaal	David Hughes Herrera
Óscar Herranz Varea	Ángela Patricia Hernández García	Iván Maldonado Marcos
Diego Iglesias Corral	Lucía Méndez García	Belén Martínez Castedo
Alejandro Jiménez Navas	Oscar Monteagudo Garcia	Pablo Rodríguez Ramos
Mauro Lorenzo Mohamed	Andrea Olarte San Juan	Juan Manuel Ruiz Robles
Marcos Manrique Crespo	Manuel Jesús Pérez Baena	Antonio Sanz Solas
Paloma Martín Bejarano Soto	Alberto Rodríguez Sánchez	José Manuel Serrano Lozano
María Matorra Miguel	Inés Solano Sánchez Cabezudo	David Tena Chaves
Verónica Salgado Pacheco		Nerea Hongfen Vidaña Bedera
Sandra Santos Mínguez		
Tatiana Ugalde Catarinella		

MASTER THESES

MASTER STUDENT	DIRECTOR	*TITLE MASTER THESES*	DATE
María Almeida Sánchez	Andrés C. García Montero	*Utilidad clínica del análisis genético en mastocitosis sistémicas*	08/07/2020
Ana Macrina Añazco Guenkova	Sandra Blanco Benavente	*Functional role of METTL1 RNA methylase in senescence-associated secretory phenotype induction*	20/07/2020
Blanca Ayuso Íñigo	Miguel Pericacho	*Efecto de la sobreexpresión de endoglina sobre el microambiente tumoral*	20/07/2020
Víctor Coca Ruiz	Miguel Vicente-Manzanares	*Bases moleculares de la metástasis: posibles roles de la miosina II no muscular en la diseminación de células tumorales*	20/07/2020



MASTER STUDENT	DIRECTOR	*TITLE MASTER THESES*	DATE
Óscar Herranz Varea	Carmen Guerrero Arroyo	*Participación de C3G en el tráfico vesicular y en la formación de Invadopodios en células de Glioblastoma. Revisado*	20/07/2020
Marta Alcón Pérez	Esther Castellano Sánchez	*Caracterización de la señalización dependiente de RAS en la comunicación entre la célula tumoral y el macrófago*	21/07/2020
Paloma Martín Bejarano Soto	Rogelio González-Sarmiento / Ana Belén Herrero	*Desarrollo de un ensayo funcional para determinar el potencial patogénico de variantes de significado incierto en BRCA1*	21/07/2020
María Matorra Miguel	Jesús M. Hernández Rivas / Mª Rocío Benito Sánchez / Adrián Montaño Brioso	*Study of the genetic profile of B-other all patients using an NGS custom panel to improve their stratification, prognosis and treatment selection*	21/07/2020
Diego Iglesias Corral	Rogelio González-Sarmiento / Ana Belén Herrero	*Estudio del efecto sinérgico de Cloroquina y Panobinostat en líneas celulares de cáncer de colon*	22/07/2020
Mauro Lorenzo Mohamed	Teresa Paíno Gómez	*Estudio del efecto antitumoral e inmunomodulador de Claritomicina y su contaminación con IMIDs y Dexametasona en mieloma múltiple*	22/07/2020
Tatiana Ugalde Catarinella	Jesús Pérez Losada	*Evaluación de comportamiento tumoral tras la administración de agonistas Dopaminérgicos como estrategia de quimioprevención frente al cáncer de mama en modelos murinos*	22/07/2020
Alejandro Crespo Carazo	Mercedes Garayoa Berrueta	*Papel de las vesículas extracelulares en la resistencia al anticuerpo monoclonal anti-CD38 Isatuximab*	23/07/2020
Alejandro Jiménez Navas	Jesús Pérez Losada	*Estudio de la evolución de los subtipos de cáncer de mama triple negativo y ERBB2/NEU-positivo tras la quimioprofilaxis y tratamiento con agonistas de la Somatostatina*	23/07/2020
Marcos Manrique Crespo	Andrés Avelino Bueno Núñez	*Control de la ubiquitinación de PCNA en la maduración de los fragmentos de Okazaki*	23/07/2020
Verónica Salgado Pacheco	Fermín Sánchez-Guijo / Sandra Muntión Olave	*Estudio del perfil de ARNm de células mesenquimales procedentes de médula ósea de pacientes con síndromes mielodisplásicos que cursan con sobrecarga férrica y de las posibles implicaciones del estrés oxidativo en la patología mieloide*	23/07/2020
Vanessa Acebes Fernández	Manuel Fuentes García	*Diseño y desarrollo de la caracterización del Inmunopeptidoma en líneas celulares hematooncológicas y su correlación Neoantigénica*	24/07/2020
Celia Gálvez Merchán	Sergio Moreno / Livia Pérez Hidalgo	*Estudio del papel de la CDK no esencial PEF1 de Schizosaccharomyces pombe en la transición G1/S en condiciones de escasez de nitrógeno*	24/07/2020
Sandra Santos Mínguez	Jesús M. Hernández Rivas / Mª Rocío Benito Sánchez	*Caracterización de la microbiota intestinal humana mediante NGS y su relación con el riesgo cardiovascular*	24/07/2020
Silvia Alemán Arteaga	Isidro Sánchez García / Carolina Vicente Dueñas	*Efecto inmunomodulador de Ruxolitinib para prevenir la leucemia linfoblástica aguda*	11/09/2020

MASTER STUDENT	DIRECTOR	*TITLE MASTER THESES*	DATE
David Bastante Rodríguez	Xosé R. Bustelo / Myriam Cuadrado López	*Vías de señalización de las RHO GTpasas como diana para el tratamiento del cáncer. Caracterización de nuevos compuestos dirigidos contra la proteína VAV3*	11/09/2020
Armando Mena Durán	Fermín Sánchez-Guijo Martín	*Aplicaciones clínicas de exosomas derivados de células mesenquimales en la enfermedad injerto contra receptor*	15/10/2020
Gianfilippo Nifosi	Fermín Sánchez-Guijo Martín	*Uso de células madre mesenquimales en la prevención y el tratamiento de la osteonecrosis de mandíbula*	15/10/2020
Roberta Palmitessa (University of Trieste)	Alberto Martín Pendás / Elena Llano Cuadra	*Functional analysis of mammalian gametogenesis*	01/03/2021
Aurora Campos Díaz	Pedro Lazo-Zbikowski Taracena	*Implicación de las variantes patogénicas de VRK1 en neurodegeneración*	21/06/2021
Sonia Carretero Domínguez	Rogelio González-Sarmiento	*Caracterización de nuevas líneas celulares de carcinoma escamoso de cabeza y cuello*	21/06/2021
Enrique de la Rosa Morón	Javier De Las Rivas	*Robust assignment of human CD markers of haematological cell types based on single-cell data*	21/06/2021

MASTER STUDENT	DIRECTOR	*TITLE MASTER THESES*	DATE
Lorena Díaz Ajenjo	María Sacristán Martín / Andrés Avelino Bueno Núñez	*Estudio de la interacción funcional entre la ubiquitin proteasa UBP10 y la nucleasa DNA2*	21/06/2021
Nuria Arroyo Garrapucho	Rogelio González-Sarmiento	*Androgen receptor independent pathways in the response to enzalutamide in breast cancer cell lines*	22/06/2021
Marta González Rodríguez	Miguel Vicente-Manzanares	*Control de la polaridad migratoria antero-posterior por el filamento intermedio Vimentina*	22/06/2021
Mariem Lachaal	Mercedes Garayoa Berrueta	*Role of exosomes from multiple myeloma cell lines in resistance to the immunomodulatory agent Pomalidomide*	22/06/2021
Lucía Méndez García	Miguel Pericacho	*Efecto de la sobreexpresión de endoglina en el microambiente tumoral/ Effect of endoglin overexpression in the tumor microenvironment*	23/06/2021
Andrea Olarte San Juan	Alberto Fernández-Medarde / Eugenio Santos	*Disruption of SOS1 and SOS2 triggers alterations in adipose tissue*	23/06/2021
Manuel Jesús Pérez Baena	Jesús Pérez Losada	*Papel de GAB1 en la respuesta a la Doxorrubicina en el cáncer de mama*	23/06/2021
Marta Bernal Ribes	Julia Almeida Parra	*Monitorización estrecha de la respuesta inmune en pacientes con infección por el virus SARS-CoV-2*	25/06/2021
Alberto Rodríguez Sánchez	Jesús M. Hernández Rivas	*Mutaciones en ZMYM3: impacto clínico y biológico en la Leucemia Linfática Crónica*	25/06/2021
Inés Solano Sánchez Cabezudo	Miguel Pericacho / Alicia Rodríguez Barbero	*El tratamiento de los gliomas con TAT-Cx43266-283 altera la angiogénesis tumoral*	25/06/2021
Cristina Arévalo Alameda	Esther Castellano Sánchez	*La señalización RAS-PI3K en fibroblastos asociados a cáncer (CAFs) regula la proliferación de la célula tumoral a través de la remodelación de la matriz extracelular (ECM)*	26/07/2021
Marina Garrido Casado	Miguel Vicente-Manzanares	*Novel insights into the regulatory functions of NMii related kinases: CITK and ZIPK in the spotlight*	26/07/2021
Ángela Patricia Hernández García	Manuel Fuentes García	*Diseccionando la respuesta humoral en la infección por SARS-CoV-2 / Dissecting humoral response in SARS-CoV-2 infection*	26/07/2021
Oscar Monteagudo Garcia	Sandra Blanco Benavente	*Identification of critical 6-methyladenosine regulators as malignant prognosis factors in prostate adenocarcinoma*	26/07/2021
Manuel Jacob Fuentes Matos	María Sacristán Martín	*Estudio de la implicación de la fosfatasa Cdc14A en la regulación del citoesqueleto*	10/09/2021

POSTGRADUATE PROGRAM: PhD PROGRAM IN "BIOSCIENCE: BIOLOGY AND CLINIC OF CANCER AND TRANSLATIONAL MEDICINE"

The PhD program entitled *"Bioscience: Biology and Clinic of Cancer and Translational Medicine"* is academically sponsored by the Department of Microbiology and Genetics (Faculty of Biology) and the Department of Medicine (Medical School) at the University of Salamanca and involves the adaptation to the Education European Space of the PhD programs.

The program aims at training high qualified and fully autonomous professionals for future work in academia, health care and industry. It is based on an interdisciplinary approach to the study of cancer. Thus, two offered initial courses are focused on topics related to cellular and molecular biology of cancer, as well as to the basic knowledge for diagnosis, prognosis and cancer treatment. In addition, genetic, development, and clinical pathology of various human solid or hematologic tumors are analyzed. These subjects integrate "molecular" and "clinical" approaches with an emphasis on the molecular links with the disease.

Continuous training activities offered to postgraduate students include: 1) participation in the Scientific Seminar Program prepared annually by the CIC, where students meet prestigious researchers in the oncology field invited by the Center and know the research projects carried out by the different laboratories at the CIC; 2) work meetings for research project monitoring and analysis of results; 3) assistance to national or international conferences, and 4) mobility: short stays in foreign research groups related with their projects.

Students at the CIC-IBMCC PhD program are supervised by leading scientists, have full access to state-of-the-art facilities and undergo annual evaluations and personalized mentoring. The CIC-IBMCC is very dynamic and highly multidisciplinary with research areas ranging from molecules to patients, which constitutes and excellent appeal for motivated and knowledgeable young scientists. This Postgraduate training Program is indeed focused on graduates with academic interest and/or applied in the medical, pharmaceutical, biological, biotechnological or bioinformatics fields.

Together with the Master´s Degree *"Biology and Clinic of Cancer"*, these Programs provide students an excellent training in the oncology field, ranging from the most recent knowledge generated in both basic research and areas of clinical research related with the diagnosis, prognosis and experimental treatments.

ACHIEVEMENTS:

- The mentioned PhD program generates an average of 17 new PhDs annually.
- Around 62% of the graduates come from outside national and international Universities.

STUDENTS PhD PROGRAM

2019/2020	2020/2021	2021/2022
Abel Jesús Martel Martel	Abel Jesús Martel Martel	Abel Jesús Martel Martel
Adrián Ricardo Montaño Brioso	Adrián Sánchez Fernández	Alba Morán Vaquero
Adrián Sánchez Fernández	Alba Morán Vaquero	Alba Pérez Pons
Alba Morán Vaquero	Alba Pérez Pons	Alba Torres Valle
Alba Pérez Pons	Alba Torres Valle	Alberto Rodríguez Sánchez
Alba Torres Valle	Alberto Berral González	Alberto Ruíz Gómez
Alberto Berral González	Alberto Conde Ferreiros	Alejandro Alvarado Lorenzo
Alberto Conde Ferreiros	Alberto Ruíz Gómez	Alejandro Hernández Delgado
Alberto Rocha De Lossada	Alejandro Hernández Delgado	Alejandro Jiménez Navas
Alberto Ruíz Gómez	Alejandro Jiménez Navas	Alicia Landeira Viñuela
Alejandro Hernández Delgado	Alejandro Medina Herrera	Alvaro Fernández Cabrera
Alejandro Medina Herrera	Alejandro Olivares Hernández	Ana Casado García
Alejandro Olivares Hernández	Alex Viñolas Cuadros	Ana Macrina Añazco Guenkova
Alex Viñolas Cuadros	Alicia Landeira Viñuela	Ana Maria Mateos Diaz
Alfredo Barrio Rodriguez	Alvaro Fernández Cabrera	Ana Marín Quílez
Alicia Landeira Viñuela	Ana Casado García	Andrea Cristina Alvarado Rodas
Alvaro Casado Blanco	Ana Elisa Rodríguez Gude	Andrea Díaz Tejedor
Alvaro Fernández Cabrera	Ana Macrina Añazco Guenkova	Andrea Olarte San Juan
Álvaro Veiga Vaz	Ana María Marín Cassinello	Angie Alejandra Díaz Baquero
Ana Africa Martin Lopez	Ana Maria Mateos Diaz	Antonio Rodríguez Blázquez
Ana Casado García	Ana Marín Quílez	Aurora Campos Díaz
Ana Elisa Rodríguez Gude	Anda Magdalena Ciocea	Aysan Mahmoudi Asl
Ana María Marín Cassinello	Andre Barbosa Ventura	Berta Bote Bonaechea
Ana Maria Mateos Diaz	Andrea Díaz Tejedor	Blanca Fuentes Herrero
Ana María Orive Ramos	Andrea Noya Mourullo	Borja Miguel López
Ana María Vaquero Campos	Angie Alejandra Díaz Baquero	Carlos Gutiérrez Cerrajero
Ana Marín Quílez	Antía Briones de Miguel	Cecilia Higueruela Minguez
Ana Rico Sorli	Antonio Rodríguez Blázquez	Clara Llorente González
Anda Magdalena Ciocea	Aysan Mahmoudi Asl	Claudia Pérez Carretero
Andre Barbosa Ventura	Beatriz Barrios Collado	Cristina Fernández Infante
Andrea Díaz Tejedor	Belén Cigarral García	Cristina Lourdes Arévalo Alameda

2019/2020	2020/2021	2021/2022
Angie Alejandra Díaz Baquero	Blanca Fuentes Herrero	Daniel Salete Granado
Antonio Rodríguez Blázquez	Borja Miguel López	David Díez Castro
Aurora Gómez Vecino	Carlos Gutiérrez Cerrajero	Diego Iglesias Corral
Beatriz Maria Rivas Lopez	Carlos Llanes Alvarez	Elena Benito Clap
Belén Cigarral García	Clara Llorente González	Elena Navarro Carrasco
Berta Bote Bonaechea	Clara Sánchez Pablo	Elena Sánchez Luis
Bianca Paz Renau Mínguez	Claudia Pérez Carretero	Elena Vuelta Ramos
Blanca Fuentes Herrero	Cristian Morillo Losada	Eliana María Taveras Domínguez
Borja Miguel López	Cristina Cigarral Garcia	Elizabeta de los Ángeles Rojas Ricardo
Carlos Fabián Castaño Romero	Cristina de Ramón Sánchez	Enrique de la Rosa Morón
Carlos Gutiérrez Cerrajero	Cristina Fernández Infante	Ester Parra Vidales
Carlos Llanes Alvarez	Cristina Juliá Alvarez	Eva Monte Serrano
Catalina Gil Restrepo	Daniela Pinto Damasceno	Fernando Sánchez Sáez
Cátia Daniela Quintas Faria	David Gonzalez Calle	Francisco Humberto Mayorga Alvarado
Clara Llorente González	Diego Iglesias Corral	Francisco Javier Morán Plata
Clara Sánchez Pablo	Eduardo Sobejano Fuertes	Gemma Santacana Font
Claudia Pérez Carretero	Elena de Dios Rodriguez	Gerardo Javier Martí Chillón
Cristian Morillo Losada	Elena Diaz Pelaez	Gloria Asensio Juarez
Cristina Carbonell Muñoz	Elena Navarro Carrasco	Guillermo Oliva Ariza
Cristina Cigarral Garcia	Elena Sánchez Luis	Ignacio Jesús Cardona Benavides
Cristina De Ramón Sánchez	Elena Vuelta Ramos	Inés Romero Pérez
Cristina Egido Turrión	Eliana María Taveras Domínguez	Irene Ballesteros González
Cristina Fernández Infante	Elísabet González del Portillo	Isabel de Rojas de Pablo
Cristina Juliá Alvarez	Elizabeta de los Ángeles Rojas Ricardo	Jairo Eduardo Niño Ramirez
Daniela Pinto Damasceno	Enrique Stern Rodríguez	Javier Ignacio de la Iglesia Larrad
David Gonzalez Calle	Ester Parra Vidales	Javier Raboso Gallego
Diana Esther Castilla Perera	Eva Maria Bravo Barba	Javier Zamarreño Lozano
Eduardo Sobejano Fuertes	Eva Monte Serrano	José Antonio Sánchez Martín
Elena De Dios Rodriguez	Felipe Gómez Caminero López	Josephine Alessandra Sánchez Modesto
Elena Diaz Pelaez	Felix Lopez Cadenas	Judith López Luis
Elena Martín González	Fernando Sánchez Sáez	Lorena Díaz Ajenjo
Elena Navarro Carrasco	Francisco Javier Garcia Garcia	Lucía Fernández Nevado
Elena Sánchez Luis	Francisco Javier Morán Plata	Luis Hernández Cano
Elena Terraza Silvestre	Gerardo Javier Martí Chillón	Mª Concepción Piñero Pérez
Elena Vuelta Ramos	Gloria Asensio Juarez	Manuel Jesús Pérez Baena
Eliana María Taveras Domínguez	Guillermo Oliva Ariza	María Carmen Martín Gómez
Elizabeta De Los Ángeles Rojas Ricardo	Ignacio Jesús Cardona Benavides	Maria Cristina Hidalgo Calleja
Esperanza Macarena Algarín Pachón	Inés Marcos Romero	María del Pilar Andres Olivera
Estanislao Arana Fernández De Moya	Inés Romero Pérez	María García Duque

2019/2020	2020/2021	2021/2022
Ester Parra Vidales	Irene Esparcia Arnedo	María González-Tablas Pimenta
Eva García Piney	Isabel de Rojas de Pablo	María Jesús Canal Boyero
Eva Monte Serrano	Javier Raboso Gallego	María Millán Salanova
Felix Lopez Cadenas	Javier Zamarreño Lozano	María Ovejero Sánchez
Fernando Sánchez Sáez	Jesús Manuel Sampedro Gómez	Marina Garrido Casado
Francisco Javier Garcia Garcia	Jose Javier Garrido Sanchez	Marta Alcón Pérez
Francisco Javier Morán Plata	José Luis Revuelta Herrero	Marta González Rodríguez
Gerardo Javier Martí Chillón	Judith López Luis	Marta Huelamo Moruno
Guillermo Oliva Ariza	Julio Davila Valls	Marta Isidro Hernández
Ignacio Jesús Cardona Benavides	Laura Clavaín Mateo	Mauricio Molinari Ulate
Inés Romero Pérez	Laura Díaz Gil	Mauro Lorenzo Mohamed
Inmaculada Serramito Gómez	Lucía Fernández Nevado	Mercedes Garzón Martínez
Irene Andrés Ramos	Lucia Gandullo Sanchez	Miriam Rodrigo Caro
Irene Esparcia Arnedo	Lucía Rodríguez de Santos	Mónica Redondo Puente
Isabel Valriberas Herrero	Luis Hernández Cano	Natalia Fernández Parejo
Itzel Rivera Santos	Manuel Domínguez Gómez	Natalia García Sancha
Javier Ignacio Muñoz González	María Amparo Mateos Diego	Nerea Gestoso Uzal
Javier Raboso Gallego	María Asunción Juanes Bellido	Néstor Segurado Tostón
Javier Zamarreño Lozano	Maria Auxiliadora Brenes Fernandez	Noelia Dasilva Freire
Jendri Manuel Perez Perozo	Maria Cristina Hidalgo Calleja	Nuria Arroyo Garrapucho
Jesús Manuel Sampedro Gómez	María del Pilar Leoz Allegretti	Oihane Pérez Escurza
José Andrés Lorenzo Martín	María Dolores Calabria Gallego	Oscar González López
Jose Javier Garrido Sanchez	María Elena Tundidor Sanz	Óscar Herranz Varea
José Luis Revuelta Herrero	María Elisa Acosta de LA Vega	Óscar Monteagudo García
Josepa Sebastia Morant	María González-Tablas Pimenta	Pablo Berrocal Navarro
Juan Alejandro Cascon Hernandez	María Jesús Canal Boyero	Pablo José Antúnez Muiños
Juan Carlos Caballero Berrocal	María Millán Salanova	Pablo Juanes Velasco
Juan Carlos Fiorini Talavera	María Ovejero Sánchez	Pablo Pérez Sánchez
Judith López Luis	María Paulina Pérez Yuste	Paloma Martín-Bejarano Soto
Julie Milena Galvis Jiménez	Maria Teresa Gonzalez Sanchez	Patricia Morejón García
Julio Davila Valls	Marta Alcón Pérez	Paula García Vallés
Laura Clavaín Mateo	Marta Fonseca Santos	Rachid Taouil Hammouti
Laura Díaz Gil	Marta Gómez Iglesias	Raquel Garcia Vilchez
Laura Gómez Hernández	Marta Gómez Sánchez	Raquel Sainz Urruela
Lorena Carrascal Laso	Marta Isidro Hernández	Raquel Villamuera del Sordo
Lucía Fernández Nevado	Marta López Serna	Roberto Corchado Cobos
Lucia Gandullo Sanchez	Marta Martín Izquierdo	Sergio de Hita Román
Luis Figuero Pérez	Marta Ortiz Aneiros	Sergio López Tejero
Luís Gómez-Lechón Quirós	Mauricio Molinari Ulate	Sheila Almaraz Postigo

2019/2020	2020/2021	2021/2022
Luis Hernández Cano	Mauro Lorenzo Mohamed	Silvia Alemán Arteaga
Luzalba Del Carmen Sanoja Flores	Mercedes Garzón Martínez	Sofía María Toribio Castelló
M.De La Paz Vaquero Herrero	Miguel Quijada Álamo	Sofía Matilla Vicente Almazán
Mª Concepción Piñero Pérez	Miriam López Parra	Sonia Carretero Domínguez
Manuel Domínguez Gómez	Natalia Fernández Parejo	Sonia Gómez Gaspar
Marco Lopez Zubizarreta	Natalia García Sancha	Sonia Miguel Criado
María Ángeles Fidalgo Fernández	Nerea Gestoso Uzal	Tamara Jiménez Solas
Maria Auxiliadora Brenes Fernandez	Noemí Muñoz García	Valentina Ramírez Maldonado
María Carmela Rodríguez Martín	Oihane Pérez Escurza	Vega Riesco Cuadrado
Maria Cristina Hidalgo Calleja	Olga Compán Fernández	Víctor Manuel Pérez Rosa
Maria Del Carmen Martín Gómez	Olga Durán Bobín	Yazmine Bejarano Condezo
María Del Pilar Leoz Allegretti		
María Dolores Calabria Gallego		
María Elena Tundidor Sanz		
María Elisa Acosta De La Vega		
María García Duque		
María González-Tablas Pimenta		
María Isabel Garavís Vicente		
María Jesús Baldeón Conde		
María Jesús Canal Boyero		
María Millán Salanova		
María Ovejero Sánchez		
María Paulina Pérez Yuste		
Maria Teresa Gonzalez Sanchez		
Mariana Sánchez Magdaleno		
Marta Gómez Iglesias		
Marta Gómez Sánchez		
Marta Isidro Hernández		
Marta López Serna		
Marta Martín Izquierdo		
Marta Ortiz Aneiros		
Mauricio Molinari Ulate		
Miguel Quijada Álamo		
Miriam López Parra		
Natalia Eugenia Espinosa Lara		
Natalia Felipe Medina		
Natalia Fernández Parejo		
Natalia García Sancha		
Nerea Gestoso Uzal		

2019/2020	2020/2021
Noemí Muñoz García	Oscar González López
Olga Durán Bobín	Oscar Gonzalez Velasco
Oscar González López	Óscar Herranz Varea
Oscar Gonzalez Velasco	Pablo Juanes Velasco
Pablo Juanes Velasco	Pablo Luengo Mondéjar
Pablo Luengo Mondéjar	Paloma Martín-Bejarano Soto
Pablo Segovia Alonso	Pamela Vázquez Cárdenas
Pamela Vázquez Cárdenas	Patricia Morejón García
Patricia Morejón García	Paula García Vallés
Paula García Vallés	Pedro Mogollón Arroyo
Pedro Mogollón Arroyo	Rachid Taouil Hammouti
Rachid Taouil Hammouti	Rafael Hipola Muñoz
Rafael Hipola Muñoz	Raquel Garcia Vilchez
Rafael Roberto Rodríguez Calzada	Raquel Jiménez Gómez
Ramón Rodríguez Borrego	Raquel Sainz Urruela
Raquel Garcia Vilchez	Raquel Villamuera del Sordo
Raquel Jiménez Gómez	Raúl García González
Raquel Sainz Urruela	Rebeca Lozano Mejorada
Raquel Villamuera Del Sordo	Roberto Corchado Cobos
Raúl García González	Rocío Fuentes Mateos
Rebeca Lozano Mejorada	Rocío Taboada Taboada
Roberto Corchado Cobos	Rosario María Carmona Flores
Rocío Fuentes Mateos	Ruben Fernandez Caloto
Rocío Taboada Taboada	Rubén García Castro
Ruben Fernandez Caloto	Ruth García García
Sara Marcos Asensio	Sara Marcos Asensio
Sofía María Toribio Castelló	Silvia Alemán Arteaga
Sofía Matilla Vicente Almazán	Sofía María Toribio Castelló
Soledad Medina Valdivieso	Sofía Matilla Vicente Almazán
Sonia Gómez Gaspar	Sonia Gómez Gaspar
Sonia Miguel Criado	Sonia Miguel Criado
Sonia Peña Balbuena	Sonia Peña Balbuena
Tamara Jiménez Solas	Tamara Jiménez Solas
Tomas Fernando Benito Gonzalez	Tomas Fernando Benito Gonzalez
Valentina Ramírez Maldonado	Valentina Ramírez Maldonado
Víctor Eduardo Vallejo García	Víctor Eduardo Vallejo García
Victor Manuel Pérez Rosa	Víctor Manuel Pérez Rosa
Yazmine Bejarano Condezo	Yazmine Bejarano Condezo
Yolanda Maria Guillen Perez	Yolanda Maria Guillen Perez

DOCTORAL THESES

PhD STUDENT	DIRECTOR	*TITLE*	DATE
Aurora Gómez Vecino	Jesús Pérez Losada / Pedro Luis Sánchez Fernández / Marina Holgado Madruga	*New strategies to identify susceptibility to cardiotoxicity by antthracyclines and proteasome inhibitors*	27/03/2020
Luzalba del Carmen Sanoja Flores	José Alberto Orfao de Matos / Mª Victoria Mateos Manteca / Martín Pérez y Andrés	*Desarrollo y validación de un nuevo método de citometría de flujo de nueva generación para la detección sensible y estandarizada de células plasmáticas tumorales en médula ósea y sangre periférica de pacientes con neoplasias de células plasmáticas: Utilidad clínica*	21/07/2020
Esperanza Macarena Algarín Pachón	Mercedes Garayoa Berrueta / Enrique Mª Ocio San Miguel / Javier De Las Rivas Sanz / Marcos González Díaz (tutor)	*Preclinical evaluation of BH3-Mimetics Targetingmcl-1 (S63845) and BCL-2 (Venetoclax) in multiple myeloma*	22/07/2020
Roberia Mendonça de Pontes	Alberto Orfao de Matos	*Perfil de regeneração de células B e doença residual minima na medula óssea de pacientes com mieloma multiplo em tratamento*	30/10/2020
Álvaro Casado Blanco	Rogelio González Sarmiento / Emiliano Hernández Galilea	*Análisis epidemiológico, tomográfico y genético del engrosamiento retiniano en pacientes con diabetes mellitus tipo 1*	20/11/2020
Juan Carlos Caballero Berrocal	María Díez Campelo / Jesús Mª Hernández Rivas / Mª Consuelo del Cañizo Fernández-Roldán (tutora)	*Impacto de las mutaciones somáticas en pacientes con síndromes mielodisplásicos sometidos a distintas modalidades de tratamiento*	25/11/2020
Dalia Salim Quwaider	Norma Carmen Gutiérrez Gutiérrez / Ana Belén Herrero Hernández / Marcos González Díaz (tutor)	*New insights into plasma cell differentiation and unfolded protein response in multiple myeloma: role of DEPTOR and IRE1*	25/11/2020

PhD STUDENT	DIRECTOR	*TITLE*	DATE
Adrián Montaño Brioso	Jesús Mª Hernández Rivas / Mª del Rocío Benito Sánchez / Teresa González Martínez (tutora)	*Molecular Characterization of B-Acute Lymphoblastic leukemia: Genomic and functional analysis of acute Lymphoblastic leukemia and an in vitro model of targeted genetic modification*	26/11/2020
Álvaro Veiga Vaz	Fermín Sánchez-Guijo Martín / Eva Mª Villarón Rios / Rogelio González Sarmiento (tutor)	*Células Stem mesenquimales en el trasplante alogénico de progenitores hematopoyéticos. Análisis de la experiencia clínica de la unidad de producción celular del Complejo Asistencial Universitario de Salamanca*	26/11/2020
Mª Ángeles Fidalgo Fernández	Jesús Mª Hernández Rivas / José Ramón González Porras / José MªBastida Bermejo (tutor)	*Características clínicas y biológicas del tromboembolismo pulmonar no provocado. Estudio de mutaciones somáticas relacionadas con la hematopoyesis clonal de significado indeterminado*	27/11/2020
Natalia Felipe Medina	Alberto Martín Pendás / Elena Llano Cuadra	*Análisis funcional de los genes Usp26 y Hsf2bp como responsables de infertilidad humana*	27/11/2020
Javier Ignacio Muñoz González	Andrés Celestino García Montero / José Alberto Orfao de Matos Correia e Vale	*Utilidad diagnóstica y pronostica de las alteraciones genéticas en mastocitosis sistémica*	27/11/2020
Julie Milena Galvis Jiménez	Jesús Pérez Losada / Marina Holgado Madruga / Adrian Blanco Gómez	*Identificación de determinantes genéticos y moleculares asociados a los miRNAS en la variabilidad de la evolución y respuesta al tratamiento del cáncer de mama*	27/11/2020
Ana Rico Sorli	Fermín Sánchez-Guijo Martín / Sandra Muntión Olave / Silvia Preciado Pérez	*Estudio de la capacidad terapéutica de las vesículas extracelulares procedentes de células estromales mesenquimales de la médula ósea sobre la cardiotoxicidad inducida por doxorubicina*	30/11/2020
Elisabet González del Portillo	Rogelio González Sarmiento / Luis Alberto Pérez Romasanta	*Evaluación del efecto sinérgico entre radioterapia y moduladores de la autofagia*	15/04/2021
Giselle Castillo Villa	Rogelio González Sarmiento / María Sánchez Ledesma	*Estudio de genes de autofagia y la susceptibilidad a tuberculosis en españoles*	21/04/2021
Óscar González Velasco	Javier de las Rivas Sanz /José Manuel Sánchez Santos	*Bioinformatic analysis and deep learning on large- scale human transcriptomic data: studies on aging, Alzheimer's neurodegeneration and cancer*	02/06/2021
Raquel Jiménez Gómez	Juan Jesús Cruz Hernández / Mª Isabel Rihuete Galve / Eduardo José Fernández Rodríguez	*Adaptación y validación al español de la escala everyday cognition battery de evaluación de cognición cotidiana en adultos 05res*	24/06/2021

PhD STUDENT	DIRECTOR	*TITLE*	DATE
Pamela Vázquez Cárdenas	Rogelio González Sarmiento / Juan Luis García / Francisco Veiga	*Caracterización clínico-molecular del receptor de andrógenos y sus isoformas en pacientes con cáncer de próstata metastásico de NOVO*	16/07/2021
Laura Clavaín Mateo	Xosé R. García Bustelo / María Isabel Fernández Pisonero / Mercedes Dosil Castro (tutora)	*Functional characterization of RRAS2 mutations and role of RRAS2Q72L in ovarian cancer*	16/07/2021
Adrián Sánchez Fernández	Azucena Esparís Ogando	*The MEK5/ERK5 pathway in lung and ovarian cancer*	19/07/2021
Raúl García González	Pedro Lazo-Zwikowski Taracena	*Regulación de la acetiltransferasa TIP60/KAT5 por la quinasa VRK1 en la respuesta al daño génico*	20/07/2021
Alejandro Medina Herrera	Ramón García Sanz /Mª Eugenia Alonso Sarasquete /Cristina Jiménez Sánchez	*Caracterización molecular del reordenamiento de la cadena pesada de inmunoglobulinas en mieloma múltiple: Utilidad como marcador de enfermedad mínima residual*	21/07/2021
Miguel Quijada Álamo	Jesús María Hernández Rivas / María del Rocío Benito Sánchez / Ana Eugenia Rodríguez Vicente	*Unraveling the Biological Determinants of the Origin, Clonal Evolution and Therapeutic Vulnerabilities of del(11q) Chronic Lymphocytic Leukemia through Genome-Editing Approaches*	22/07/2021
Laura Díaz Gil	Atanasio Pandiella Alonso	*Hipersensibilidad y resistencia a trastuzumab en cáncer de mama HER2+: Identificación de nuevos biomarcadores*	23/07/2021
Marta Martín Izquierdo	Jesús María Hernández Rivas / M. del Rocío Benito Sánchez / María Abáigar Alvarado	*Molecular Mechanisms and Clonal Evolution underlying the Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia: Genomic characterization by Next Generation Sequencing*	06/10/2021
Pedro Mogollón Arroyo	Enrique María Ocio San Miguel / Mercedes Garayoa Berrueta Mª Teresa Paíno Gómez / Marcos González Díaz (tutor)	*Evaluación preclínica de mecanismos de resistencia a fármacos inmunomoduladores en mieloma múltiple*	29/10/2021
Rubén Fernández Caloto	Xosé R. García Bustelo / Mercedes Dosil Castro (tutora)	*Systematic analysis of RHO GTPases pathway alterations in cancer*	12/11/2021
Noemí Muñoz García	Julia Mª Almeida Parra	*Diagnóstico de clonalidad de los síndromes linfoproliferativos crónicos de células T Y NK T Y NK*	24/11/2021
Yolanda Guillén Pérez	Azucena Esparís Ogando	*Relación entre la vía de transducción de señales ERK5 y la vía glutaminolítica en cáncer*	25/11/2021
Lucía Gandullo Sánchez	Atanasio Pandiella Alonso	*Cáncer de mama HER2+: mecanismos de resistencia a tratamientos dirigidos y nuevas dianas terapéuticas*	26/11/2021
Rocío Fuentes Mateos	Eugenio Santos / Alberto Fernández Medarde	*Role of HRas and NRas in murine lung development and neonatal survival*	03/12/2021

SCIENTIFIC SEMINAR PROGRAM

DATE	TITLE	SPEAKER	AFFILIATION
09/01/2020	Somatic structural variation and cancer	*José Manuel C. Tubio*	CIMUS - University of Santiago de Compostela. [Santiago de Compostela]
16/01/2020	Deciphering the role of 7-guanine tRNA methylation in Prostate Cancer progression	*Raquel García Vílchez*	CIC-IBMCC (CSIC-USAL) Lab 5
23/01/2020	Which are the rules dictating the responsiveness between genes and enhancers?	*Álvaro Rada Iglesias*	Institute of Biomedicine & Biotechnology of Cantabria (IBBTEC), [Santander]
29/01/2020	Tumor genomes shed light into somatic mutational processes and cancer vulnerabilities	*Nuria López-Bigas*	Institute for Research in Biomedicine (IRB), [Barcelona]
30/01/2020	Rho GTPase signaling in skin tumor formation	*Cord Brakebusch*	BRIC - University of Copenhagen [Copenhagen, Denmark]
06/02/2020	Targeting RAS-PI3K signaling to re-educate the stroma of RAS mutant lung cancer	*Cristina Cuesta Apausa*	CIC-IBMCC (CSIC-USAL) Lab 5
07/02/2020	Carrera científica en Investigación Traslacional	*Rafael Bañares*	Universidad Complutense de Madrid / Hospital General Universitario Gregorio Marañón, [Madrid]
13/02/2020	Mechanisms and consequences of large nuclear deformation: from microchannels to mammary tumors	*Matthieu Piel*	Institut Curie de París [Paris, France]
27/02/2020	Oesophageal mechanic switch dictates developmental transition towards homeostasis	*María Pilar Alcolea*	University of Cambridge [Cambridge, UK]
05/03/2020	Understanding the transcriptome to treat KRAS-driven tumors: how far can we get?	*Silve Vicent Cambra*	Center for Applied Medical Research (CIMA), [Pamplona]
09/07/2020	Tyrosine Phosphorylation of the Myosin Regulatory Light Chain Controls Non-muscle Myosin II Assembly and Function in Migrating Cells	*Miguel Vicente Manzanares*	CIC-IBMCC (CSIC-USAL) Lab 6
16/07/2020	Identification of Differentially Expressed Genes and Network Analysis in the search of potential molecular signatures associated with breast cancer	*Marina Mendiburu-Eliçabe Garganta*	CIC-IBMCC (CSIC-USAL) Lab 7
15/10/2020	A missense in HSF2BP causing Primary Ovarian Insufficiency affects meiotic recombination by its novel interactor C19ORF57/BRME1.	*Natalia Felipe Medina*	CIC-IBMCC (CSIC-USAL) Lab 9
12/11/2020	CAR-T cells for the treatment of cancer: current challenges and opportunities	*Sonia Guedan*	Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), [Barcelona]
19/11/2020	Using cryo-electron microscopy to study molecular mechanisms in cancer	*Óscar Llorca*	Spanish National Cancer Research Centre (CNIO), [Madrid]


CANCER RESEARCH CENTER (CIC- IBMCC)
SCIENTIFIC SEMINAR SERIES
SALAMANCA 2019/2020
2019
SEPTEMBER/19
Pablo José Fernández Marcos
OCTOBER/19
James Turner
David Santamaría
Aitor Hierro
NOVEMBER/19
Roger Gomis
Guillaume Jacquemet
DECEMBER/19
Silvestre Vicent Cambra
Doreen Dean
2020
JANUARY/20
José M. Tobío
Álvaro Rada Iglesias
Coré Brakebusch
FEBRUARY/20
María Pilar Alcolea
MARCH/20
Óscar Llorca
APRIL/20
Verena Ruprecht
Sonia Gordon
MAY/20
Dana L.J. Lafontaine
Ignacio Molero Serneja
Patricia Sancho
JUNE/20
Alain Prat
CSIC
CANCER RESEARCH CENTER (CIC- IBMCC)
SCIENTIFIC SEMINAR SERIES
SALAMANCA 2021/22
2021
OCTOBER/21
Trevor Graham
María Pilar Sánchez-Belda
NOVEMBER/21
Roberto Chiarle
Chiara Ambrogio
Claire Hivroz
DECEMBER/21
Melina Schuh
Michael L. Dustin
Antonio Giráldez
2022
JANUARY/22
Renée Beekman
FEBRUARY/22
Diruna Alonso Curbelo
Angélica Figueroa Conde-Valvís
MARCH/22
Pablo Alcón
Claudia Voena
María Muñoz Cofferet
APRIL/22
Victoria Sanz-Moreno
MAY/22
Eduard Batlle
Helena F. Florindo
Alejo Efeyan
JUNE/22
Francisco Vega Moreno
Miguel Ángel del Pozo
Luis Enjuanes
Alejo Rodríguez-Fraticelli
CIC
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DATE	TITLE	SPEAKER	AFFILIATION
24/11/2020	Diagnostic use and prognostic impact of genetic variants in systemic mastocytosis	*Javier Ignacio Muñoz González*	CIC-IBMCC (CSIC-USAL) Lab 11
10/12/2020	Metabolic determinants of stemness in Pancreatic Ductal Adenocarcinoma	*Patricia Sancho*	Instituto de Investigación Sanitaria Aragón/ Centro de Investigación Biomédica de Aragón (CIBA), [Zaragoza]
14/01/2021	Sensing from the inside: how the nucleus controls adaptive cell responses to shape deformations	*Verena Ruprecht*	Centre for Genomic Regulation (CRG), [Barcelona]
21/01/2021	Twists and turns in the development of CD137 (4-1BB)-based immunotherapy	*Ignacio Melero Bermejo*	Clínica Universidad de Navarra / Centro de Investigación Médica Aplicada (CIMA), [Pamplona]
04/02/2021	Combination Therapies to Potentiate the Impact of KRAS-G12C Inhibitors	*Miriam Molina Arcas*	Oncogene Biology Laboratory, Francis Crick Institute, [London, UK]
11/02/2021	Commensal gut microbiota protects genetically predisposed mice against acute lymphoblastic leukaemia	*Carolina Vicente-Dueñas*	CIC-IBMCC (CSIC-USAL) Lab 13
18/02/2021	Genetic tuning of actin remodelling at the plasma membrane	*Klemens Rottner*	Division of Molecular Cell Biology of Zoological Institute/Technische Universität Braunschweig, [Braunschweig, Germany]
25/02/2021	Synergistic effect of Chloroquine and Panobinostat in ovarian cancer through induction of DNA damage and inhibition of DNA repair	*María Ovejero Sánchez*	CIC-IBMCC (CSIC-USAL) Lab 14
04/03/2021	Challenges in breast cancer treatment: understanding the actions and effectiveness of anti-ER drugs	*Antoni Hurtado*	Universidad de Barcelona, [Barcelona]
11/03/2021	Targeting anti-apoptotic proteins in multiple myeloma	*Mercedes Garayoa*	CIC-IBMCC (CSIC-USAL) Lab 12
18/03/2021	Machine learning in cardiovascular research: integrating molecular and phenotypical information in large cohort studies	*Fátima Sánchez Cabo*	Centro Nacional de Investigaciones Cardiovasculares (CNIC), [Madrid]
25/03/2021	HER-3 targeting with an antibody-drug conjugate	*Lucía Gandullo*	CIC-IBMCC (CSIC-USAL) Lab 15
08/04/2021	Role of C3G in megakaryopoiesis, hypoxia-induced angiogenesis and melanoma metastasis	*Luis Hernández*	CIC-IBMCC (CSIC-USAL) Lab 17
15/04/2021	Decoding the epitranscriptome at single molecule resolution	*Eva Novoa*	Centre for Genomic Regulation (CRG), [Barcelona]
22/04/2021	Deep learning and bioinformatics on human large-scale transcriptomic data: studies of neurodegeneration and cancer	*Óscar González-Velasco*	CIC-IBMCC (CSIC-USAL) Lab 19
29/04/2021	tRNA biology in health and disease: from expanding proteome diversity to promising biomarkers in medicine	*Adrián Gabriel Torres*	Institut de Recerca Biomèdica (IRB), [Barcelona]
06/05/2021	Critical requirement of SOS1 RAS-GEF function for mitochondrial dynamics, metabolism and redox homeostasis	*Rósula García Navas*	CIC-IBMCC (CSIC-USAL) Lab 1
13/05/2021	Mechanisms of KRAS signaling in lung cancer development	*Matthias Drosten*	Spanish National Cancer Research Centre (CNIO), [Madrid]
27/05/2021	Receptor nanoclustering modulates chemokine responses	*Mario Mellado Alonso*	Centro Nacional de Biotecnología (CNB), [Madrid]

DATE	TITLE	SPEAKER	AFFILIATION
03/06/2021	VRK1-mediated regulation of Tip60/KAT5 acetyltransferase during DDR	*Raúl García*	CIC-IBMCC (CSIC-USAL) Lab 4
10/06/2021	Novel mechanisms controlling KRAS oncogenic output: impact on tumour fitness and cancer vulnerabilities	*David Santamaria*	University of Bordeaux, [Bordeaux, France]
17/06/2021	Role of cytosine-5 methylation of ribosomal RNA in cell cycle control	*Judith López Luis*	CIC-IBMCC (CSIC-USAL) Lab 5
24/06/2021	Control of Actin Polymerization in Cells Through Activation and Inhibition of the Arp2/3 Complex	*Roberto Dominguez*	Department of Physiology, University of Pennsylvania/Perelman School of Medicine [Philadelphia, USA]
01/07/2021	Role of RRAS2 as an oncogenic driver	*Laura Clavaín*	CIC-IBMCC (CSIC-USAL) Lab 2
07/10/2021	Targeting RAS-PI3K signaling to re-educate the stroma of RAS mutant lung cancers	*Esther Castellano*	CIC-IBMCC (CSIC-USAL) Lab 5
14/10/2021	Evolutionary dynamics of human cancers	*Trevor Graham*	Barts Cancer Institute Queen Mary University of London [London, UK]
21/10/2021	Insights into the biological determinants of clonal evolution and therapeutic vulnerabilities of del(11q) chronic lymphocytic leukemia	*Miguel Quijada Álamo*	CIC-IBMCC (CSIC-USAL) Lab 12
28/10/2021	Arginine methylation and ubiquitylation crosstalk controls DNA end resection and homologous recombination repair	*María Pilar Sánchez-Bailón*	Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch [Berlin, Germany]
04/11/2021	Tumor-specific pathways of therapy resistance in ALK-rearranged lymphoma	*Roberto Chiarle*	Harvard Medical School [Boston, USA]
11/11/2021	Insights into KRAS biology to identify novel therapeutic strategies for cancer	*Chiara Ambrogio*	Molecular Biotechnology Center (MBC) / University of Torino [Torino, Italy]
18/11/2021	High-risk cutaneous squamous cell carcinoma: our contributions to the current understanding and research priorities	*Javier Cañueto Álvarez*	Hospital Universitario de Salamanca, IBSAL- CIC-IBMCC (CSIC-USAL) Lab 7
25/11/2021	Intracellular traffic of LAT and its role in T cell activation	*Claire Hivroz*	Institut Curie, [Paris, France]
02/12/2021	Illuminating the beginning of life	*Melina Schuh*	Max Planck Institute for Biophysical Chemistry [Göttingen Germany]
09/12/2021	Protein bombs and liquid adhesions in immune cell mediated killing in cancer and infection	*Michael Dustin*	University of Oxford [Oxford, UK]
16/12/2021	Mechanisms of gene regulation after fertilization: from transcription to decay	*Antonio Giráldez*	Yale University School of Medicine [New Haven,USA]

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SCIENCE OUTREACH

SCIENCE OUTREACH

THE MOST RELEVANT ACTIVITIES 2020-2021

During 2020 and 2021, the institutional communication is combined with activities of attention to different targets, such as patient and family associations, the organization of training events. The Scientific Culture and Innovation unit of the Cancer Research Center (included in the UCC+i Network of the Spanish Foundation for Science and Technology (FECYT)) brings together all the communication activities of the CIC.

The most relevant activities are:

PRESS RELEASES

09/01/2020 A new method makes it possible to discover how tumor cells produce ribosomes to grow faster.

http://www.cicancer.org/es/actualidad/197/un-nuevo-metodo-permite-descubrir-como-las-celulas-tumorales-producen-ribosomas-para-crecer-mas-rapidamente

17/01/2020 Improving understanding of the maintenance of the acute lymphoblastic leukaemia phenotype.

http://www.cicancer.org/es/actualidad/198/mejora-de-la-comprension-del-mantenimiento-del-fenotipo-de-la-leucemia-aguda-linfoblastica

22/01/2020 Xosé R. Bustelo elected member of the Royal Galician Academy of Sciences.

http://www.cicancer.org/es/actualidad/199/el-doctor-xose-r-bustelo-elegido-miembro-de-la-real-academia-gallega-de-ciencias

28/01/2020 Núria López-Bigas awarded the IX National Prize for Cancer Research 'Doctores Diz Pintado'.

https://saladeprensa.usal.es/node/122328

31/01/2020 Presentation Cunina, a pioneering project for the prevention of acute lymphoblastic leukaemia.

http://www.cicancer.org/es/actualidad/200/isidro-sanchez-garcia-investigador-del-centro-de-investigacion-del-cancer-de-salamanca-cic-ibmccclave-en-el-proyecto-cunina-pionero-para-la-prevencion

14/02/2020 Key genes identified in the aging human brain.

http://www.cicancer.org/es/actualidad/202/identificados-genes-clave-en-el-envejecimiento-del-cerebro-humano

28/02/2020 Awarded Accelerator project to the Cancer Research Center (CIC-IBMCC) for the study of monoclonal B-cell lymphocytosis

http://www.cicancer.org/es/actualidad/203/concedido-proyecto-accelerator-al-centro-de-investigacion-del-cancer-cic-ibmcc-para-el-estudio-de-la-linfocitosis-monoclonal-de-celulas-b

20/03/2020 Review of the biological and functional role of fragments derived from small non-coding RNAs.

http://www.cicancer.org/es/actualidad/204/revision-del-papel-biologico-y-funcional-de-fragmentos-derivados-de-pequenos-arn-no-codificantes

02/04/2020 Described the specific contribution of the C3G gene to the haemostatic function of platelets.

http://www.cicancer.org/es/actualidad/206/descrita-la-contribucion-especifica-del-gen-c3g-a-la-funcion-hemostatica-de-las-plaquetas

08/04/2020 Published the global map of communications between human proteins

http://www.cicancer.org/es/actualidad/208/publicado-el-mapa-global-de-las-comunicaciones-entre-las-proteinas-humanas-el-interactoma-humano

08/04/2020 Identified a new inhibitory control of the SEPARASE protein through the SGO2 protein

http://www.cicancer.org/es/actualidad/207/identificado-un-nuevo-control-inhibitorio-de-la-proteina-separasa-a-traves-de-la-proteina-sgo2

30/04/2020 Development of a hopeful therapy against one of the most aggressive breast cancers.

http://www.cicancer.org/es/actualidad/209/desarrollo-de-una-esperanzadora-terapia-contra-uno-de-los-canceres-de-mama-mas-agresivos

08/05/2020 New project to identify risk factors for severe infection and those infected by SARS-CoV-2

http://www.cicancer.org/es/actualidad/210/nuevo-proyecto-para-identificar-factores-de-riesgo-de-infeccion-grave-e-infectados-por-sars-cov-2

13/05/2020 New regulatory mechanisms of a molecule with key functions in the immune system and tumours identified

http://www.cicancer.org/es/actualidad/211/identificados-nuevos-mecanismos-reguladores-de-una-molecula-con-funciones-clave-en-el-sistema-inmunitario-y-tumores

04/06/2020 "Use the force": a new mechanism that determines cell migration and specialization through texture control.

http://www.cicancer.org/science-society/cic-news/utiliza-la-fuerza-un-nuevo-mecanismo-que-determina-la-migracion-y-especializacion-celular-a-traves-del-control-de-la-textura

16/06/2020 New genetically modified mouse models are developed to validate a new pharmacological target in cancer

http://www.cicancer.org/science-society/cic-news/desarrollan-nuevos-modelos-de-raton-modificados-geneticamente-para-validar-una-nueva-diana-farmacologica-en-cancer

01/07/2020 Awarded new research project on treatment and diagnosis of Covid-19

http://www.cicancer.org/science-society/cic-news/concedido-nuevo-proyecto-de-investigacion-sobre-tratamiento-y-diagnostico-de-la-covid-19

01/09/2020 Awarded new research project to delve into the genetic alterations present in lymphomas

http://www.cicancer.org/science-society/cic-news/otorgado-nuevo-proyecto-de-investigacion-para-profundizar-en-las-alteraciones-geneticas-presentes-en-linfomas

03/09/2020 Identified the mechanism by which two mutations cause infertility

http://www.cicancer.org/science-society/cic-news/identificado-el-mecanismo-por-el-cual-dos-mutaciones-provocan-infertilidad

14/09/2020 A study shows that the intestinal microbiome protects against genetic predisposition to leukaemia

http://www.cicancer.org/science-society/cic-news/un-estudio-muestra-que-el-microbioma-intestinal-protege-frente-a-la-predisposicion-genetica-a-la-leucemia

22/09/2020 A study identifies key molecules for the development and evolution of malignant properties of head and neck cancers

http://www.cicancer.org/science-society/cic-news/un-estudio-identifica-moleculas-clave-para-el-desarrollo-y-evolucion-de-propiedades-malignas-de-los-canceres-de-cabeza-y-cuello

29/09/2020 They identify the genetic cause of a type of female infertility

http://www.cicancer.org/science-society/cic-news/identifican-la-causa-genetica-de-un-tipo-de-infertilidad-femenina

02/10/2020 New retrospective research project on archival samples of rhabdoid meningiomas

http://www.cicancer.org/science-society/cic-news/nuevo-proyecto-de-investigacion-retrospectiva-sobre-muestras-de-archivo-de-meningiomas-rabdoides

05/10/2020 Dissemination of the call for the X National Award for Cancer Research "DOCTORES DIZ PINTADO"

http://www.cicancer.org/science-society/cic-news/bases-x-premio-nacional-de-investigacion-en-cancer-doctores-diz-pintado

13/10/2020 Described the involvement of HGAL in the development of diffuse large B-cell lymphomas

http://www.cicancer.org/science-society/cic-news/descrita-la-implicacion-de-hgal-en-el-desarrollo-de-linfomas-difusos-de-celulas-b-grandes

26/10/2020 Published first Human Proteome map endorsed by the Human Proteome Organization

http://www.cicancer.org/science-society/cic-news/publicado-primer-mapa-de-proteoma-humano-respaldado-por-la-organizacion-del-proteoma-humano-hupo

30/10/2020 Javier Ignacio Muñoz González awarded with the First New Talent Award

http://www.cicancer.org/science-society/cic-news/javier-ignacio-munoz-gonzalez-recibe-i-premio-al-talento-novel

12/11/2020 Essential mechanism discovered to maintain the development of B-cell acute lymphoblastic leukaemia

http://www.cicancer.org/science-society/cic-news/descubierto-mecanismo-esencial-para-mantener-el-desarrollo-de-leucemia-linfoblastica-aguda-de-celulas-b

18/11/2020 Identified a new biological pathway that determines the amount of muscle we can develop

http://www.cicancer.org/science-society/cic-news/identificada-una-nueva-ruta-biologica-que-determina-la-cantidad-de-musculo-que-podemos-desarrollar

03/02/2021 World cancer day.

https://www.cicancer.org/science-society/cic-news/el-4-de-febrero-conmemoramos-el-dia-mundial-del-cancer

09/02/2021 Researchers at the Cancer Research Center develop a new prognostic classification for mastocytosis.

https://www.cicancer.org/science-society/cic-news/investigadores-del-centro-de-investigacion-del-cancer-desarrollan-nueva-clasificacion-pronostica-de-la-mastocitosis

11/02/2021 RNA chemistry may hold the key to new cancer treatments.

https://www.cicancer.org/science-society/cic-news/la-quimica-del-arn-puede-ser-la-clave-en-nuevos-tratamientos-del-cancer

12/02/2021 Researchers from the Cancer Research Center (CIC-IBMCC and the Severo Ochoa Molecular Biology Center delve into the origins of childhood leukaemia.

https://www.cicancer.org/science-society/cic-news/estrechando-el-cerco-a-la-leucemia-infantil

07/04/2021 Novel dynamic changes identified in B cell metabolism during their differentiation.

https://www.cicancer.org/science-society/cic-news/identificados-nuevos-cambios-dinamicos-en-el-metabolismo-de-celulas-b-durante-su-diferenciacion

16/04/2021 The combined use of a new drug improves the efficiency of some breast cancer treatments.

https://www.cicancer.org/science-society/cic-news/el-uso-combinado-de-un-nuevo-farmaco-mejora-la-eficiencia-de-algunos-tratamientos-de-cancer-de-mama

03/05/2021 Seven researchers from the Cancer Research Center of Salamanca among the 2% of the most influential in the world. Another CIC-IBMCC researcher has also been included in the Forbes list of the 100 most recognized names in the medical care, research and teaching scene in Spain.

https://www.cicancer.org/science-society/cic-news/6-investigadores-del-centro-de-investigacion-del-cancer-de-salamanca-entre-el-2-de-los-mas-influyentes-del-mundo

07/05/2021 VI edition of the Vicente del Bosque Alumni Tournament sports competitions have been in favour of the Cancer Research Center.

https://www.cicancer.org/science-society/cic-news/agradecimiento-a-alumni-de-la-universidad-de-salamanca

11/05/2021 Demonstrated the crucial role of Sos1-Sos2 proteins in a population of epidermal stem cells.

https://www.cicancer.org/science-society/cic-news/demostrado-el-papel-crucial-de-las-proteinas-sos1-sos2-en-una-poblacion-de-celulas-madre-epidermicas

02/05/2021 Alberto Orfao will be part of the committee on myeloid neoplasms of the World Health Organization.

https://www.cicancer.org/science-society/cic-news/alberto-orfao-formara-parte-del-comite-de-neoplasias-mieloides-de-la-organizacion-mundial-de-la-salud

03/06/2021 Presentation of the 10th Doctors Diz Pintado National Cancer Research Award.

https://www.cicancer.org/science-society/cic-news/entrega-del-x-premio-nacional-de-investigacion-de-cancer-doctores-diz-pintado

02/05/2021 Participation in Divulga AECC, aimed at researchers to help them disseminate their research results. Divulgación | Asociación Española Contra el Cáncer (aecc.es)

16/06/2021 SNAI2 gene overexpression in the stroma is associated with poor prognosis in HER2-positive luminal B breast cancer

https://www.cicancer.org/science-society/cic-news/la-sobreexpresion-del-gen-snai2-en-el-estroma-se-asocia-con-un-mal-pronostico-en-el-cancer-de-mama-luminal-b-her2-positivo

30/06/2021 New function of SOS proteins discovered in mitochondrial dynamics and metabolism

https://www.cicancer.org/science-society/cic-news/descubierta-nueva-funcion-de-las-proteinas-sos-en-la-dinamica-y-metabolismo-mitocondrial

19/07/2021 New project awarded for preclinical study aimed at blocking RAS-mediated signalling

https://www.cicancer.org/science-society/cic-news/concedido-nuevo-proyecto-para-estudio-preclinico-dirigido-a-bloquear-la-senalizacion-mediada-por-ras

01/07/2021 Cancer; basic science joins forces against the enemy within. Drafting and dissemination of the CSIC investiga 2 magazine.

https://digital.csic.es/handle/10261/245271

09/09/2021 Delivery of the IX Ramiro Carregal Award for Oncology.

https://www.cicancer.org/science-society/cic-news/entrega-del-ix-premio-ramiro-carregal-de-oncologia

10/09/2021 Demonstrated the therapeutic capacity of CRISPR in mice with chronic myeloid leukaemia

https://www.cicancer.org/science-society/cic-news/demostrada-la-capacidad-terapeutica-de-crispr-en-ratones-con-leucemia-mieloide-cronica

17/09/2021 The Cancer Research Center lays the foundations for the development of early diagnosis of leukaemia.

https://www.cicancer.org/science-society/cic-news/el-centro-de-investigacion-del-cancer-pone-las-bases-para-el-desarrollo-del-diagnostico-precoz-de-leucemia-mediante-un-estudio-observacional-de-la-poblacion

23/09/2021 The Cancer Research Center participates in the coordination of the new "Conexión-Cáncer", a network that will bring together all cancer research at the CSIC.

https://www.cicancer.org/science-society/cic-news/el-centro-de-investigacion-del-cancer-participa-en-la-coordinacion-de-la-nueva-conexion-cancer-una-red-que-aglutinara-toda-la-investigacion-en-cancer-del-csic

24/09/2021 Researchers from the Cancer Research Center explain why they do research, on World Cancer Research Day

https://www.cicancer.org/science-society/cic-news/dia-mundial-de-la-investigacion-del-cancer

01/10/2021 New way of attacking lung adenocarcinoma defined that could improve current treatments

https://www.cicancer.org/science-society/cic-news/definida-nueva-forma-de-atacar-al-adenocarcinoma-de-pulmon-que-podria-mejorar-los-tratamientos-actuales

06/10/2021 Announced the XI National Cancer Research Award "Doctors Diz Pintado"

https://www.cicancer.org/science-society/cic-news/xi-premio-nacional-de-investigacion-en-cancer-doctores-diz-pintado

14/10/2021 Renewal of the agreement with "CRIS against cancer" for three more years

https://www.cicancer.org/science-society/cic-news/convocatoria-de-rueda-de-prensa

19/10/2021 Word breast cancer day.

https://www.cicancer.org/science-society/cic-news/dia-mundial-del-cancer-de-mama

08/11/2021 New variable defined to evaluate prognosis of chronic lymphocytic leukaemia

https://www.cicancer.org/science-society/cic-news/definida-nueva-variable-para-evaluar-pronostico-de-leucemia-linfatica-cronica

15/12/2021 Detected two new compounds that inhibit the Ras gene and show less toxicity

https://www.cicancer.org/science-society/cic-news/detectados-dos-nuevos-compuestos-que-inhiben-al-gen-ras-y-muestran-menos-toxicidad

20/12/2021 José Tubío awarded with the XI National Cancer Research Award "Doctors Diz Pintado"

https://www.cicancer.org/science-society/cic-news/jose-tubio-galardonado-con-el-xi-premio-nacional-de-investigacion-en-cancer-doctores-diz-pintado

SCIENTIFIC CULTURE & FUNDRAISING

28/10/2020 Presentation to the media of the exhibition Con-Ciencia-Con-Arte

http://www.cicancer.org/science-society/cic-news/rueda-de-prensa_28-octubre

The inauguration of the Con-Ciencia-Con-Arte exhibition, which featured a speech by the director of the Pamplona Planetarium, Javier Armentia. The exhibition was open to the public (respecting Covid security measures) from October 30 to November 29 in the Experimental Art Space 2 of the Hospedería Fonseca.

Link to catalogue: http://www.cicancer.org/media/1504/ciencia-arte-catalogo_web.pdf

08/02/2021 Celebration of the World Day of Women and Girls in Science. Two activities have been organized in collaboration with ASEICA and the University of Salamanca. Get to know them https://www.cicancer.org/science-society/cic-news/ Get to know them and Women who change the USAL. https://www.cicancer.org/science-society/cic-news/la-mujer-y- the-girl-in-science

21/05/ 2021 - 25/05/2021 Introductory workshop on Ethics and Legislation in Animal Experimentation. The director of communication and marketing of the CIC was part of the teaching staff of this teaching innovation project at the University of Salamanca (ID2019/092)

https://www.usal.es/files/biiusal_20210416.pdf

28/06/2021-02/07/2021 First edition of the USAL Scientific Campus.

Development and delivery of the workshop "The invisible world of bacteria" by staff from the Cancer Research Center.

The workshop was part of the summer camp organized by the University of Salamanca. The final works were exhibited at the University of Salamanca from November 19 to January 16, 2022.

https://culturacientifica.usal.es/campamento-2021/

08/10/2021-07/11/2021 Exhibition Con-Ciencia-Con-Arte. The Energy Museum (Ponferrada) has hosted the exhibition Con-Ciencia-Con-Arte developed by the Cancer Research Center.

https://www.cicancer.org/science-society/cic-news/con-ciencia-con-arte-en-la-fabrica-de-luz-museo-de-la-energia

01/07/2021 Participation in Documentary "Conversas". The director of Communication of the Cancer Research Center is interviewed in the documentary "Conversas" of the University of Salamanca, which is a documentary about perceptions and expectations about science, financed by the FECYT. https://www.ocausal.es/investigacion/proyectos/conversas/resultados/

13/09/2021 Participation in the welcome fair of the University of Salamanca.

https://bienvenida.usal.es/

06/11/2021-25/11/2021 The CIC supports Movember Charro. Reading of the manifesto in the City Council of Salamanca and participation in media attention. https://www.cicancer.org/science-society/cic-news/movember

08/11/2021-10/11/2021 Science Week: Talk on ethical aspects related to research with animal models. The presentations were complemented with guided tours of the OMG animal facility and the comparative molecular pathology service of the Cancer Research Center. https://www.cicancer.org/science-society/cic-news/semana-de-la-ciencia

24/09/2021 The European Researchers´ Night

September 2021. A video was made to explain the objectives of the project directed by Prof. Orfao and in which several research groups from the center participate, ECRIN_M3. Early Cancer Research Initiative Network on MBL.

http://nocheinvestigadorescyl.org/rincon-europeo
https://youtu.be/XbgLQmICmX8

12/02/2021 Mock press conference on scientific progress for journalism students from the Pontifical University of Salamanca.

GUIDED VISITS

From January to March 13, 2020, 360 students have been assisted through guided visits to the Cancer Research Center, prior to which an introductory talk on biomedical research is given. Visits have been cancelled during 2020-2021 due to the pandemic.

TRAINING FOR RESEARCHERS

Preparation of the Communication and Marketing Unit of the CIC of a webinar for the Scientific Foundation of the AECC for the dissemination training program called Divulga AECC. The webinar "A speaker for science" was published on May 14 (https://www.aecc.es/es/investigacion/divulgaaecc#09)

INSTITUTIONAL VISITS

On 6th October 2020, a meeting and institutional visit was held by the Government delegate in Castilla y León, Mr. José Javier Izquierdo Roncero.

On 11th November 2021: The Institutional Delegation of the CSIC in Castilla y León and the British Embassy in Madrid visited the Cancer Research Center to explore collaboration opportunities.

COMMUNICATIONS SUPPORT FOR FUNDRAISING

During 2020 and 2021, FICUS has received 255,973.45 euros in donations.

Profiles of the Cancer Research Center in Networks:

The Cancer Research Center has a Twitter, Facebook and LinkedIn account.

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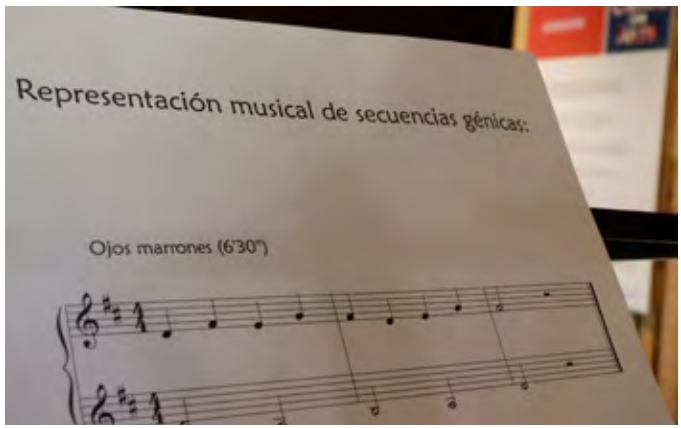

PROGRAMA DE FORTALECIMIENTO DE ESTRUCTURAS DE INVESTIGACIÓN DE CASTILLA Y LEÓN "ESCALERA DE EXCELENCIA" COFINANCIADO POR EL P.O. FEDER DE CASTILLA Y LEÓN 14-20 (Ref. CLC-2017-01)

El objetivo temático de este tipo de actuaciones es promover el desarrollo tecnológico, la innovación y una investigación de calidad (OT.1)

CIC
Centro de Investigación del Cáncer

SCIENTIFIC REPORT

2020 | 2021

VNiVERSiDAD D SALAMANCA
CAMPUS DE EXCELENCIA INTERNACIONAL

CSIC
Consejo Superior de Investigaciones Científicas

HR EXCELLENCE IN RESEARCH

NOS IMPULSA Junta de Castilla y León

Europa impulsa nuestro crecimiento

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