CiC

Centro de Investigación del Cáncer

SCIENTIFIC REPORT

2016 | 2017

iBMCC

Instituto de Biología Molecular y Celular del Cáncer (USAL - CSIC)

CSIC

Consejo Superior de Investigaciones Científicas

Universidad de Salamanca

Campus de Excelencia Internacional

Usal 800 años 1218 - 2018

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Instituto de Biología Molecular y Celular del Cáncer (USAL - CSIC)

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SCIENTIFIC REPORT

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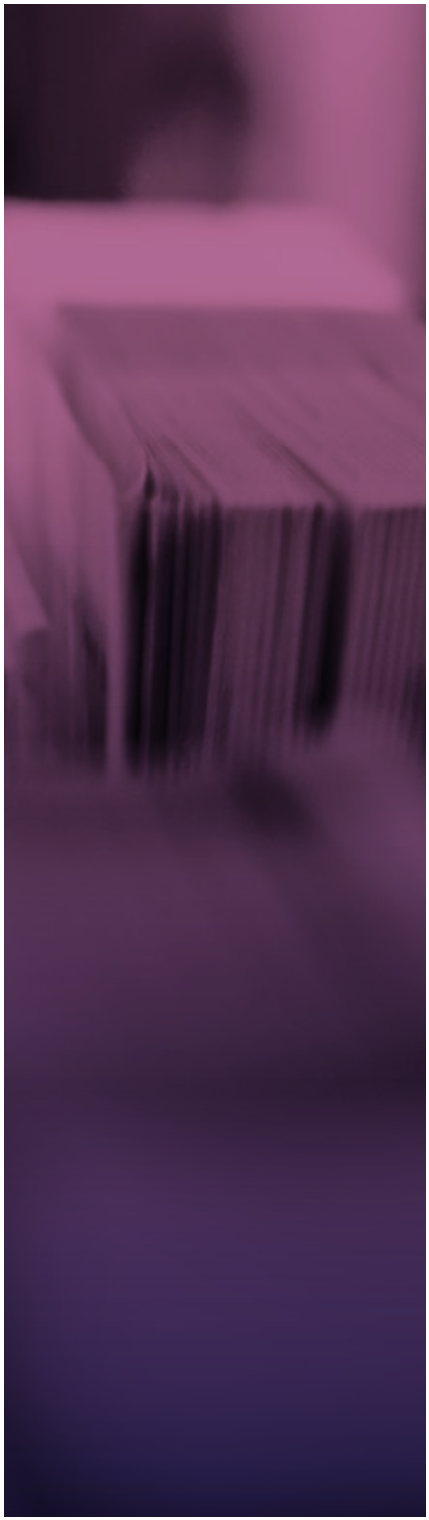
INDEX




CENTRO
DE INVESTIGA
DEL CANCER

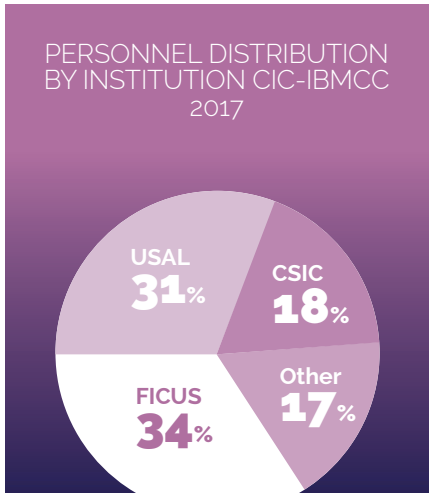
1
FOREWORD

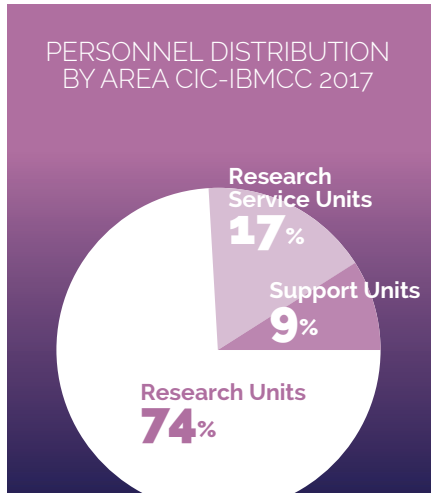
FOREWORD

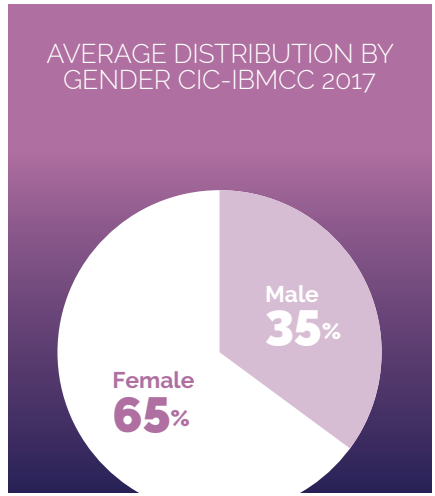
This biannual report describing the scientific activities of the Centro de Investigación del Cáncer - Instituto de Biología Molecular y Celular del Cáncer (CIC-IBMCC, CSIC-USAL) through the years 2016 and 2017, marks the 18th anniversary of our center and is being released within the year of celebration of the 800th anniversary of our host institution, the University of Salamanca (USAL).

As of December 2017, the CIC-IBMCC was composed by 16 independent **Research Units** led by senior PIs, 7 Research Units led by junior PIs, 9 **Socio-sanitary Service Units** and 8 **Technical Support Units.** The present report contains in-depth descriptions of the composition and function of each of our Research and Support Units during 2016 and 2017.

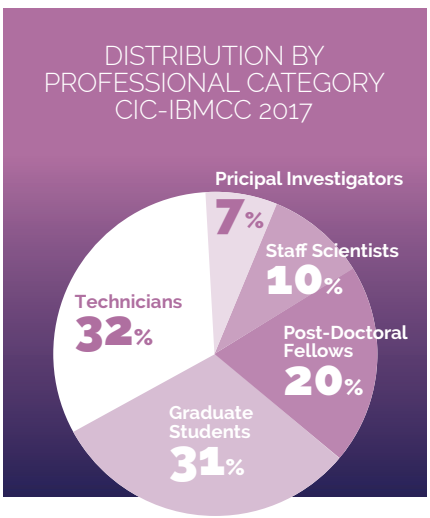
I am happy to mention that, in contrast to our loss of scientific staff during previous years (2012-2015), the CIC-IBMCC was able to incorporate **new, independent researchers** to its roster during this period, as Dr **Miguel Ángel Vicente-Manzanares** (2016) and Dr **Sandra Blanco** (2017) won competitive calls for permanent positions with us as CSIC Tenured Scientist (Científico Titular). Dr Vicente-Manzanares´group, focusing on Tumor Biophysics is already housed in Lab 6 of our building since 2017, and the incorporation of Dr Blanco´s group is expected to be complete by the summer of 2018. On behalf of everyone in our Center, I send our very warm welcome to these new senior researchers and wish them the best of personal and professional success during their tenure with us at the CIC-IBMCC.

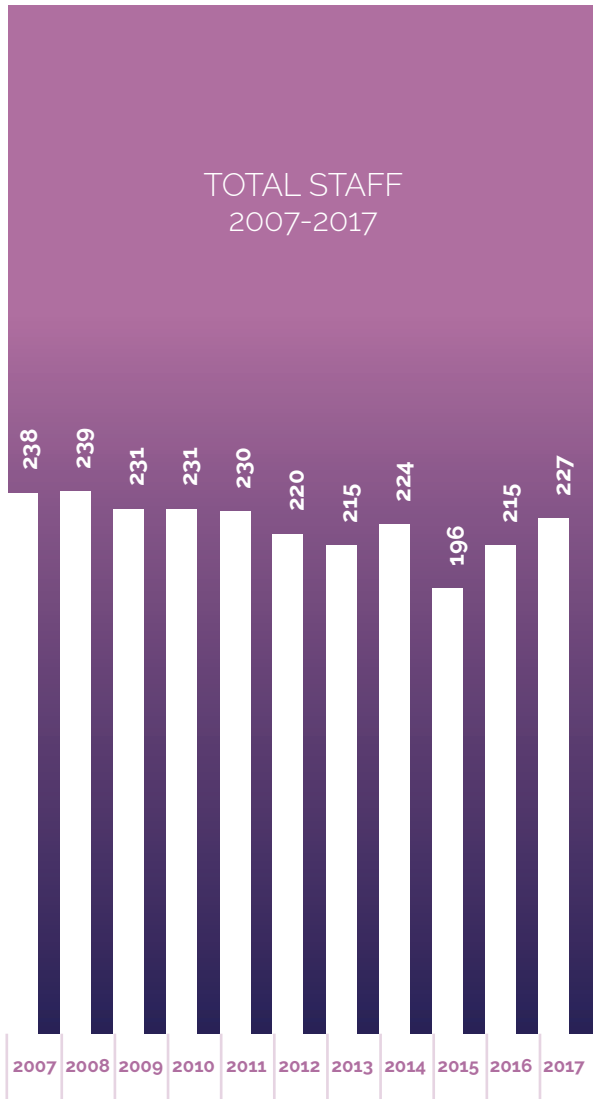






A our Center is jointly sponsored (**Instituto Mixto**) by the University of Salamanca (USAL) and the Spanish Research Council (**CSIC**), about 49% of our staff were formally affiliated with either USAL or CSIC during this period. On the other hand, 34% of our scientific staff was supported by contracts underwritten by our supporting **FICUS** Foundation (Fundación de Investigación del Cáncer de la Universidad de Salamanca), whose Board of Trustees includes representatives from USAL, CSIC, Carlos III National Health Institute (ISCIII) and the regional Ministries of Health and Education of the Castile and Leon Government. Finally, a small percentage (17%) of the personnel of our institute were supported by funds from other external institutions dependent from ISCIII such as CIBERONC or Ibsal. Of notice is the predominant female component (63%) of our scientific staff during this period.





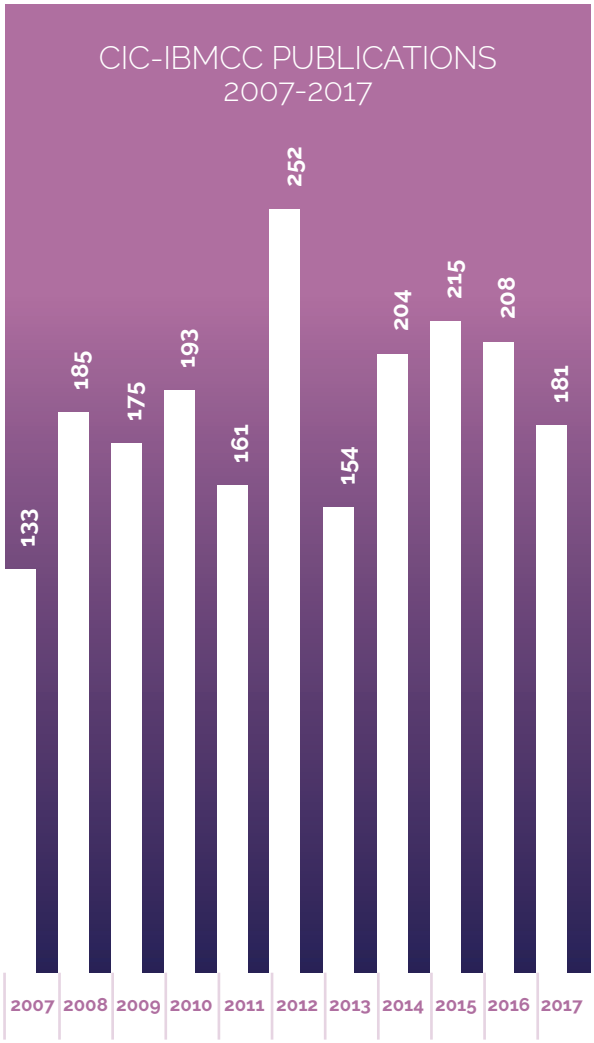
Within the 2016-2017 period, the CIC-IBMCC researchers published a total of **389 original articles** dealing with various aspects of basic, translational or clinical cancer research. Our publications appeared in **151** different, indexed journals involving a total Impact Index of 2.381. Most of these articles (**63%**) were published in scientific journals ranked within the **first quartile (Q1)** of its area and the **average impact factor per paper was 6.12.** Among them, we may call attention to the **57 papers published with an IF> 10.** The detailed list of these publications can be found in the corresponding sections of this report for each individual Research or Service group.

The competitiveness of the PIs from CIC-IBMCC to attract research funds can also be gauged from **the more than 52 competitive research projects** granted by different outside institutions within this 2 year period. Approximately **31%** of these projects were granted by **national agencies** (FIS, Plan National, etc) and **10% by international institutions** (H2020 European Program IMI, NIH, International Myeloma Foundation USA and Fraunhofer Institut für Toxikologie und Experimentelle Medizin); 25% derived from regional or autonomous calls for project funds, and the rest came from projects granted by non-profit institutions, foundations or agreements and contracts signed with pharmaceutical or biotechnology companies. In total, the research groups of the CIC-IBMCC managed to obtain more **than 5,3 M€ during this period.**

When it comes to technology transfer, the CIC-IBMCC scientists kept generating intellectual property during this period and registered **3 different patents** which are currently at different stages of development in the corresponding patent offices.

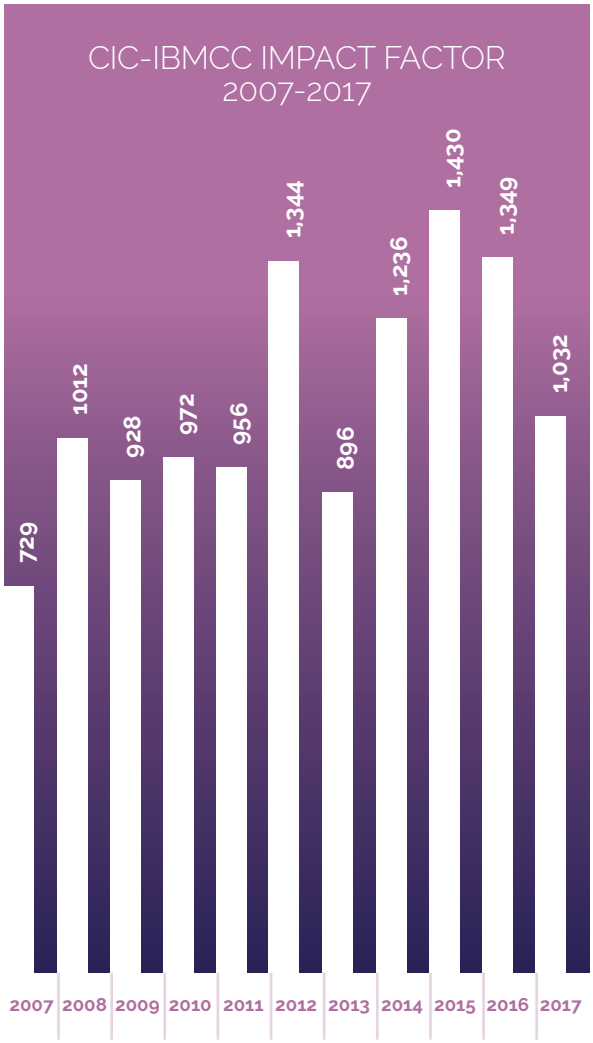
The CIC-IBMCC scientists have also developed significant **networking and scientific collaborations** with outside scientists or institutions during this period. Special mention should be made to the contribution of several individual CIC groups to various **European research consortia,** or the integration of 5 different groups of our Center in **cooperative cancer research structures** sponsored by Carlos III National Health Institute (ISCIII) including **RTICC** (until 2017) or **CIBERONC** (currently active).

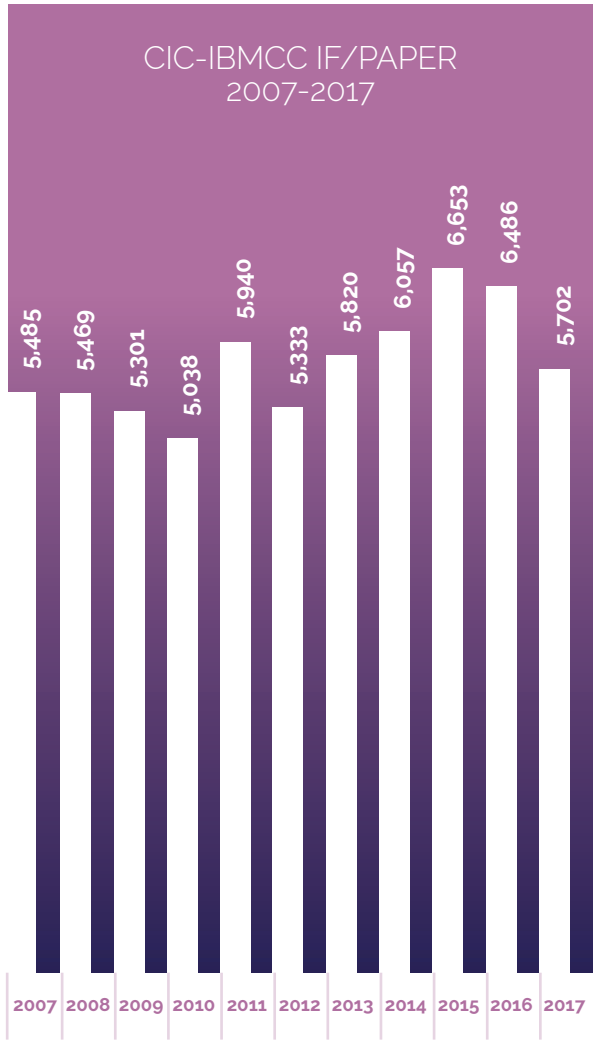
At the end of 2017, and after a thorough **external evaluation,** the CIC-IBMCC renewed its accreditation by the Quality Assurance Agency for Higher Education in Castile and Leon (ACSUCYL) as an **Academic Research Institute.** In this evaluation our center received an scoring of Excellent (93,51 points over 100) that exceeded by almost 3 points the previous qualification obtained in of 2011. We may also mention the recognition of our center as a **Research Unit of Excellence of USAL,** which involves additional financing (175.000€) for the period 2017-2018 within the framework of the Strategic Plan for Research and Transfer Knowledge of USAL. It is also worth mentioning that, during this period, 12 research groups led by PIs from the



CIC-IBMCC renovated their accreditation as **«Consolidated Research Units (UIC)»** in Castile and Leon on the basis of their excellence and scientific record during recent years, and 6 groups were also accredited as **«Grupos de Investigación Reconocida (GIR)»** in USAL.

The scientific work carried out by CIC-IBMCC members has also been recognized with several awards during 2016-2017. We may highlight here the award to **Dr. Juan Jesús Cruz** of the «2016 Premio Castilla y León de Investigación Científica y Técnica e Innovación»; the International Award for Research in Leukaemia-Lady Tata Memorial Trust 2016-2017 to **Dr. Carolina Vicente-Dueñas,** ; the recognition of **Dr. Xosé R. Bustelo** with a Distinguished Speaker's Lecture at the Sylvester Comprehensive





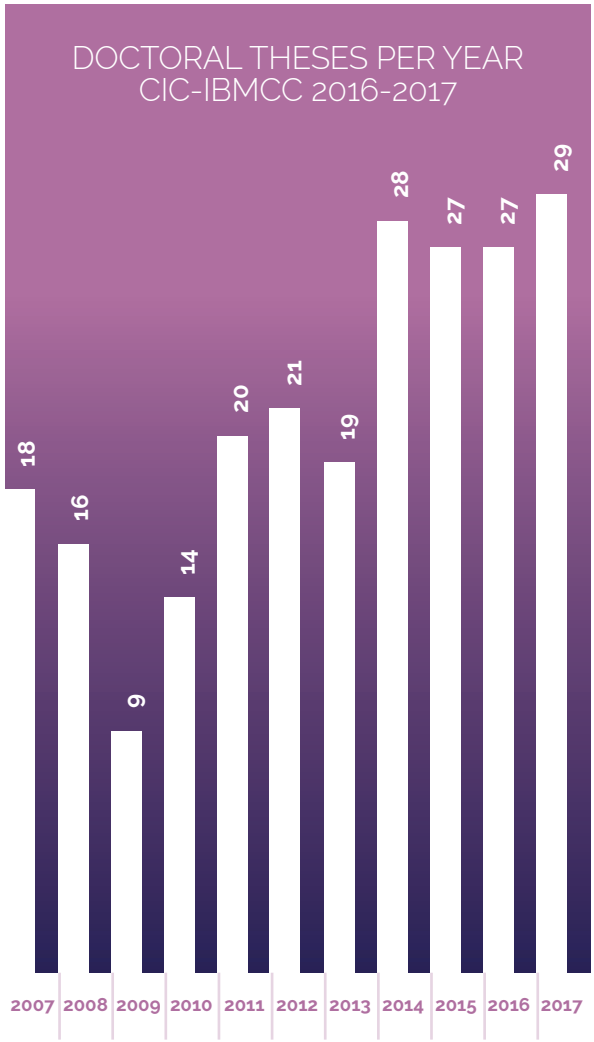
Cancer Center of Miami University; the María de Maeztu award for Scientific Excellence from Salamanca University to **Dr. Andrés Avelino Bueno** or the Award «Innovador 2017» from the «El Mundo of Castilla y León» newspaper to **Dr. Alberto Martín Pendás.**

Communicating with the outside cancer scientific community at large and implementing outreach activities directed to patients, society and the general public were also important goals for an integral, comprehensive cancer research center like ours during this period. To that end, the CIC-IBMCC continued to sponsor during this period the **«Doctores Diz Pintado Award»** aimed at recognizing each year the excellence of the most outstanding Spanish cancer researcher younger than 45. The awardees in 2016 and 2017 were, respectively, **Dr. Salvador Aznar-Benitah** (IRB, Barcelona) and **Dr. Arkaitz Carracedo** (CIC bioGUNE, Bizkaia), two of the most relevant and recognized young cancer scientists at the current Spanish and international cancer scene.

As an Academic Research Institute belonging to the USAL academic community, the CIC-IBMCC continued during this period a variety of teaching activities at the graduate and postgraduate level on different cancer areas. Our academic activities included a **Master program on «Biology and Clinic of Cancer»** aimed at the basic training of graduates interested in cancer and without prior experimental experience in the fields of molecular and cell biology. Our Master «Biology and Clinic of Cancer» has been rated by the national press (El Mundo newspaper) as one of the **five best Masters programs** taught by Spanish Universities, Companies or Institutions, in the field of Medical Specialties within the Health Area in 2017 (http://www.elmundo.es/especiales/mejores-masters/). A total of **41 students graduated** from this program during 2016-2017.

Our PhD program entitled «Bioscience: Biology and Clinic of Cancer and Translational Medicine» was approved in 2010 and is sponsored by the CIC-IBMCC in collaboration with the USAL departments of Microbiology& Genetics (School of Biology) and Medicine (School of Medicine). 245 students were enrolled during 2016-2017 in this program and a total **56 Doctoral Theses** (PhD) directed by CIC-IBMC scientists were presented and successfully defended during this period.

As complement to our training and dissemination program, the CIC-IBMCC has also continued during these two years our open **Cancer Seminar Series** program, which has involved the participation of **70 national and international speakers.** We also celebrated **9 specialized congresses/symposia/ courses** also organized by our institution that involved the participation of more than **50 different speakers** and the attendance of more than **1.000 participants.**



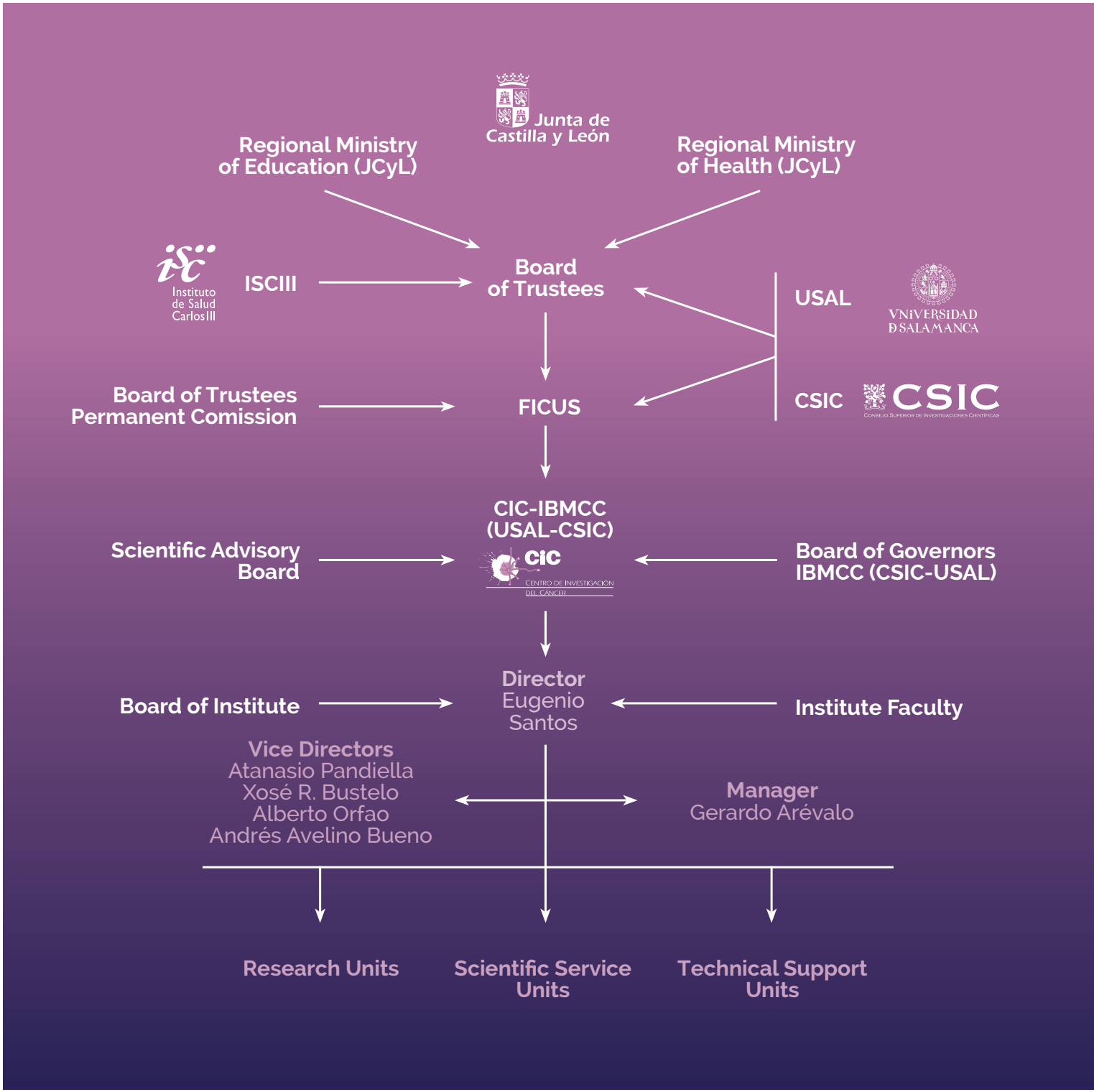
The main **challenge facing the CIC IBMCC** for the near future is maintaining and improving our past scientific productivity and competitiveness at the national and international levels. Using **SWOT** analysis terminology, a major **threat** to achieving that goal has always been the **chronic lack of stable budget support provided by our sponsor institutions to cover the costs of regular operations** (building maintenance, security, administration, etc) in our Center. In the current situation, it is fairly apparent that the CIC-IBMCC will need better institutional support to be able to progress and secure enough human and economic resources which would allow the recruitment of new young investigators and the development of new research lines that are needed to tackle the scientific challenges associated to an effective and efficient fight against cancer. This implies that we will need a more definite and stable show of **economic support from our sponsoring institutions (USAL, CSIC, ISCIII, JCyL)** in order to **compete under equal opportunity conditions** with our peers in other national and international in cancer research centers. Unfortunately our success with this request has been rather limited in years past.

In any case, I am convinced that the many, varied research achievements described in this biannual report constitute a significant contribution to the understanding of the molecular basis of cancer and to the rapid transfer of results from the laboratory to the clinical practice. I am also confident and hopeful that the research advances obtained during this period in our center will also help and encourage our investigators to pursue new and more ambitious goals in the upcoming years.

I want to conclude this foreword by expressing the most sincere **gratitude and recognition to the scientific, technical and support staff personnel** of our Center for their dedication and professionalism. Only their commitment and hard work has made it possible for the CIC-IBMCC to achieve its scientific goals and reputation at the national and international level during the last years. Thanks also to our **Scientific Advisory Board** and the outside **sponsors and anonymous donors** who helped our center during these years. I am convinced that the combined effort and contributions of all of us will allow the CIC-IBMCC to overcome its present difficulties and to continue producing high quality scientific research in the field of oncology for years to come.

Eugenio Santos
Director, CIC-IBMCC

2
ORGANIZATION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Gerardo Arévalo
Research Units
Scientific Service Units
Technical Support Units

ORGANIZATION
SUMMARY

The governing bodies of the CIC-IBMCC are: (i) the Governing Committee composed of two representatives of the CSIC, appointed by the President of CSIC and two representatives of the USAL appointed by the Rector of the Salamanca University, (ii) the Board of the Institute, consisting of the director, Vice-Director, 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 Board of the Institute, (iv) Vice-Director, also appointed by the Presidents of the CSIC and the Rector of the University of Salamanca to proposal director of the center, (v) the center manager, responsible for budget management, economic, and administrative personnel, (vi) the Institute Faculty, an advisory body composed of all staff scientist assigned to the institute and finally (vii) the External Advisory Committee also consultative body appointed by the Governing Committee, after hearing the Board of the Institute, consisting of the least five prestigious international scientists in the lines Institute research.

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, representatives of the Regional ministries of Education and Health of the Junta de Castilla y León and Health Institute Carlos III.

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Dr. Julio Rodríguez Villanueva

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

RESEARCH UNITS

BASIC RESEARCH

GTPases and cancer. Ras mediated signaling
Eugenio Santos

Identification of early oncogenic drivers, signaling modifiers, and metabolic programs involved in cancer development and progression
Xosé R. Bustelo

Kinases in oncology and neurodegeneration. Signaling by nuclear serine-threonine kinases
Pedro Alfonso Lazo-Zbikowski Taracena

Reversible processes in cell cycle control: Phosphorylation by CDK in mitosis and ubiquitylation of PCNA
Andrés Avelino Bueno Núñez

Tumor biophysics
Miguel Vicente Manzanares (from March 2017)

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

Chromosome segregation and human disease
Alberto Martín Pendás

Kinases in oncology. Signaling by receptor tyrosine kinases
Atanasio Pandiella Alonso

Structural biology of cell adhesion and signaling
Jose María de Pereda Vega

TRANSLATIONAL RESEARCH

Cell death and cancer therapy
Faustino Mollinedo García (until October 2016)

Immunology and cancer
José Alberto Orfao de Matos Correia e Vale

Stem cells, cancer stem cells and cancer biology
Isidro Sánchez García

Unconventional autophagy in health and disease
Felipe X. Pimentel-Muiños

Bioinformatics and functional genomics of cancer
Javier De las Rivas

CLINICAL RESEARCH

Oncohematology
Marcos González Díaz

Hereditary cáncer
Rogelio González Sarmiento

Clinical and molecular analysis of solid tumors
Juan Jesús Cruz Hernández

SCIENTIFIC SERVICE UNITS

Genomics. Scientific Coordinator
Xosé R. Bustelo

Proteomics. Scientific Coordinator
Xosé R. Bustelo

Traslational Oncopharmacology. Scientific Coordinator
Atanasio Pandiella Alonso

Bioinformatics. Scientific Coordinator
Javier De las Rivas

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José María de Pereda Vega

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Secretary
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Equipment & Building Maintenance
Quality Control & Risk Prevention
Information Technologies Service
Central Warehouse & Radiological Protection
Glassware Cleaning, Media / Solutions Preparation & Sterilization


3
RESEARCH
UNITS

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Postdoctoral
Fernando Calvo Baltanás
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Begoña Anta Rodríguez
Rósula García Navas

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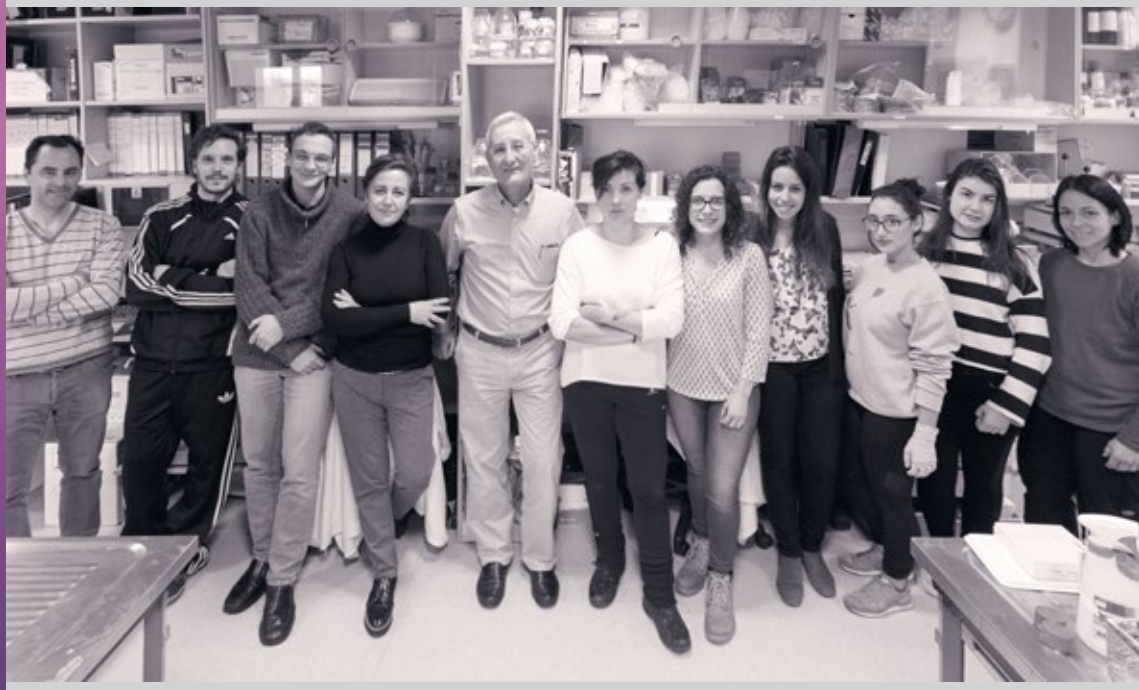
Mª Pilar Liceras Boillos
Rocío Fuentes Mateos

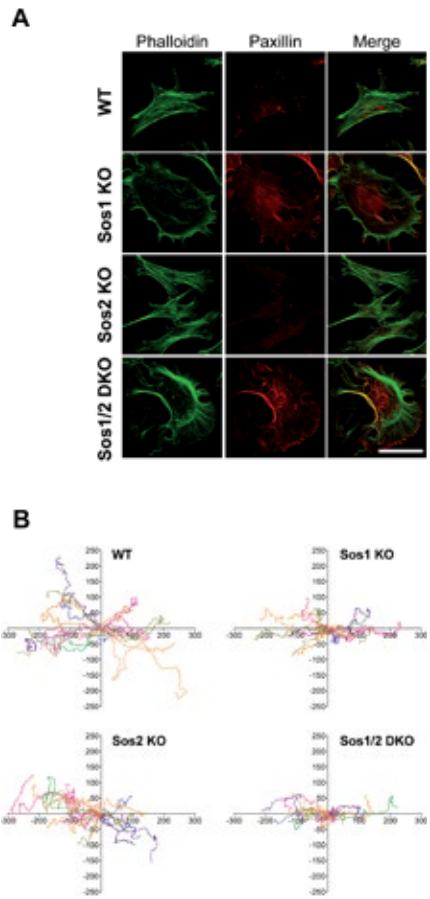
Technician
Nuria Calzada Nieto
María Santos Jiménez Rodríguez

Master Student
Marta López Yus



LABORATORY 1

GTPASES AND CANCER. RAS MEDIATED SIGNALING



Cytoskeletal (A) and migratory (B) alterations of primary MEFs devoid of SOS1 and/or SOS2.

During this period, our group focused its activities on analyzing the mechanisms of activation of RAS proteins by exchange factors (GEF) and ascertaining the functional specificity/redundancy of various RAS and RasGEF isoforms during physiological and/or tumoral processes. Our studies, centered on phenotypic and mechanistic characterization (at both the systemic and the cellular level) of various KO mouse models for RAS, SOS and GRF genes and isoforms participating in Ras Signaling Pathways, have been instrumental to identify potential biomarkers and/or therapy targets relevant for RAS-driven tumors.

Regarding the functional specificity of RAS family members, our group had previously shown that only KRAS is necessary and sufficient for embryonic development and reaching adult stage homeostasis, and had also documented the homo-oligomeric nature of RAS proteins. More recently, our studies have also demonstrated a critical involvement of NRAS in immune modulation/host defense and apoptosis; of KRAS in the control of cell cycle progression; of HRAS in the control of systemic vascular pressure; and RRAS2 in mammary gland development.

Our work analyzing RasGRF1 and RasGRF2 KO mice has also demonstrated the differential in vivo functionality of these RasGEFs. Our earlier work identified specific roles of RasGRF1 in pancreatic beta cells and in neurosensory and photoreception processes, and of RasGRF2 in T cell signaling and in alcohol addictive behavior. More recently, we have also uncovered a critical role of RasGRF2 in control of nuclear migration required for proper postnatal development and function of retinal cone photoreceptors as well as in regulation of stem cell density and onset of differentiation during adult neurogenesis in the brain.

We have also analyzed the functional role of the SOS1 and SOS2 RasGEF proteins using KO models in adult mice. In earlier work we showed that SOS1 is essential for mouse embryonic development whereas SOS2 is dispensable in adult mice. More recently, we have used a conditional, tamoxifen-inducible, SOS1-KO model generated in this laboratory to show that SOS1/2-DKO (double-knockout) animals die precipitously whereas individual, adult SOS1-KO and SOS2-KO mice are perfectly viable. These observations demonstrate functional redundancy between SOS1 and SOS2 for homeostasis and survival of the full organism and for development and maturation of T and B-lymphocytes. Furthermore, our functional analysis of the SOS1 and SOS2 alleles at the cellular level has uncovered a direct mechanistic link between SOS1 and control of intracellular and mitochondrial oxidative stress and has demonstrated functional prevalence of SOS1 over SOS2 with regards to cellular proliferation and viability. Finally, in collaboration with G. Scita's lab (IFOM, Milan) we have also recently demonstrated the critical mechanistic contribution of SOS1 to BCR-ABL-driven leukemogenesis.

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SENIOR RESEARCHER

ROLE FOR RAS GUANINE NUCLEOTIDE EXCHANGE FACTORS RASGRF1 AND RASGRF2 IN CENTRAL NERVOUS SYSTEM

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 for 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) Role of RasGRF1 in lens morphogenesis.
(VI) Analysis of RasGRF2 physiological role in olfaction.

MAIN LINES OF RESEARCH

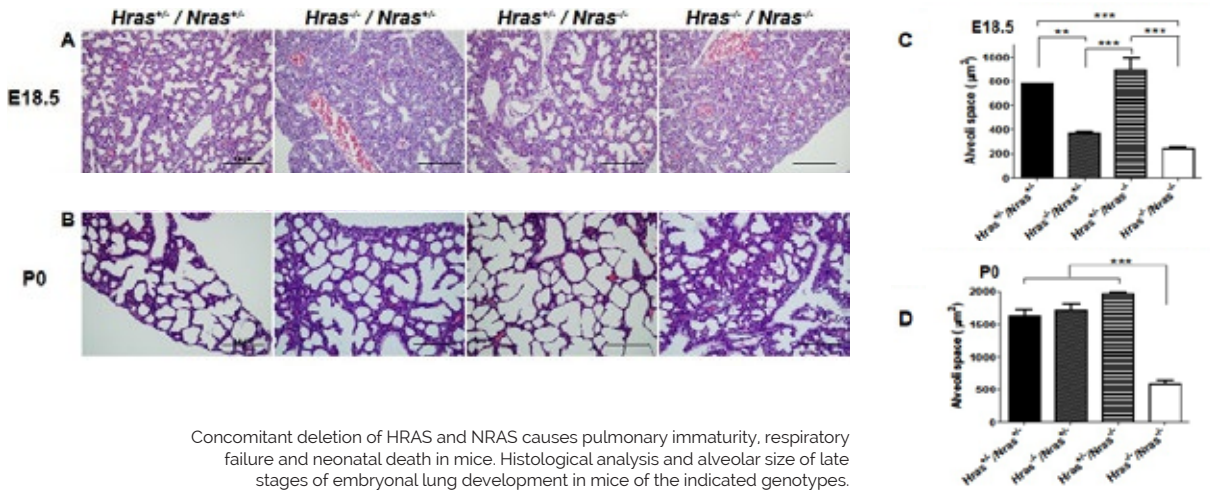
(1) Screening of Ras activation inhibitors (major).
(2) Analysis of RasGRF2 role in olfaction (minor).
(3) Study of RasGRF1 role in lens formation and myopia (minor).

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.

FUTURE GOALS

(a) Analysis of RasGRF1 and RasGRF2 in odor detection.
(b) Mechanisms underlying the changes in the lens of the RasGRF1 KO animals.
(c) «*In vitro*» and «*in vivo*» analysis of the Ras-GEF inhibitors and their toxicity.
(d) Preclinical studies using mice models of cancer with Ras-GEF inhibitors. Effect on tumor growth and metastasis formation.



Concomitant deletion of HRAS and NRAS causes pulmonary immaturity, respiratory failure and neonatal death in mice. Histological analysis and alveolar size of late stages of embryonal lung development in mice of the indicated genotypes.

PUBLICATIONS

1 **A translational systems biology approach in both animals and humans identifies a functionally related module of accumbal genes involved in the regulation of reward processing and binge drinking in males.** Stacey D, Lourdusamy A, Ruggeri B, Maroteaux M, Jia T, Cattrell A, Nymberg C, Banaschewski T, Bhattacharyya S, Band H, Barker G, Bokde A, Buchel C, Carvalho F, Conrod P, Desrivieres S, Easton A, Fauth-Buehler M, Fernández-Medarde A, Flor H, Frouin V, Gallinat J, Garavanh H, Heinz A, Ittermann B, Lathrop M, Lawrence C, Loth E, Mann K, Martinot JL, Nees F, Paus T, Pausova Z, Rietschel M, Rotter A, Santos E, Smolka M, Sommer W, Mameli M, Spanagel R, GiRaúlt JA, Mueller C, Schumann G. **IMAGEN consortium. J Psychiatry Neurosci. 2016 Apr;41(3):192-202.** PMID: 26679926 **IF: 5.165 / Q1**

2 **RASGRF2 controls nuclear migration in postnatal retinal cone photoreceptors.** Jimeno D, Gómez C, Calzada N, de la Villa P, Lillo C, Santos E. **J Cell Sci. 2016 Feb 15;129(4):729-42. doi: 10.1242/jcs.180919. Epub 2016 Jan 7.** PMID: 26743081 **IF: 4.706 / Q2**

3 **Sos1 disruption impairs cellular proliferation and viability through an increase in mitochondrial oxidative stress in primary MEFs.** Liceras-Boillos P, García-Navas R, Ginel-Picardo A, Anta B, Pérez-Andrés M, Lillo C, Gómez C, Jimeno D, Fernández-Medarde A, Baltanás FC, Santos E. **Oncogene. 2016 Dec 15;35(50):6389-6402. doi: 10.1038/onc.2016.169. Epub 2016 May 9.** PMID: 27157612 **IF: 7.932 / D1**

4 **A new functional role uncovered for RASGRF2 in control of nuclear migration in cone photoreceptors during postnatal retinal development.** Jimeno D, Santos E. **Small GTPases. 2017 Jan 2;8(1):26-30. doi: 10.1080/21541248.2016.1189989. Epub 2016 May 24.** PMID: 27221061 **IF: NI**

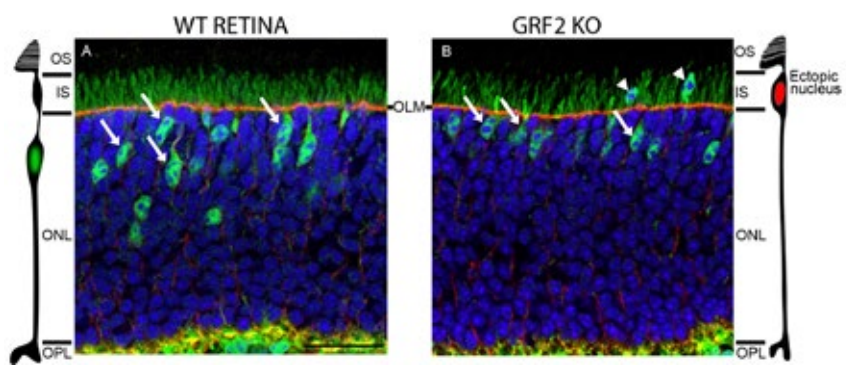
5 **PGA1-induced apoptosis involves specific activation of H-Ras and N-Ras in cellular endomembranes.** Anta B, Pérez-Rodríguez A, Castro J, García-Domínguez CA, Ibiza S, Martínez N, Durá LM, Hernández S, Gragera T, Peña-Jiménez D, Yunta M, Zarich N, Crespo P, Serrador JM, Santos E, Muñoz A, Oliva JL, Rojas-Cabañeros JM. **Cell Death Dis. 2016 Jul 28;7(7):e2311. doi: 10.1038/cddis.2016.219.** PMID: 27468687 **IF: 5.378 / Q1**

6 **Phosphorylation of SOS1 on tyrosine 1196 promotes its RAC GEF activity and contributes to BCR-ABL leukemogenesis.** Gerboth S, Frittoli E, Palamidessi A, Baltanas FC, Salek M, Rappsilber J, Giuliani C, Troglio F, Rolland Y, Pruneri G, Kreutmair S, Pallavicini I, Zobel M, Cinquanta M, Minucci S, Gomez C, Santos E, Illert AL, Scita G. **Leukemia. 2017 Aug 18. doi: 10.1038/leu.2017.267.** PMID: 28819285 **IF: 12.104 / D1**

7 **Ras-GRF2 regulates nestin-positive stem cell density and onset of differentiation during adult neurogenesis in the mouse dentate gyrus.** Gómez C, Jimeno D, Fernández-Medarde A, García-Navas R, Calzada N, Santos E. **Mol Cell Neurosci. 2017 Dec;85:127-147. doi: 10.1016/j.mcn.2017.09.006. Epub 2017 Sep 28.** PMID: 28966131 **IF: 3.084 / D1**

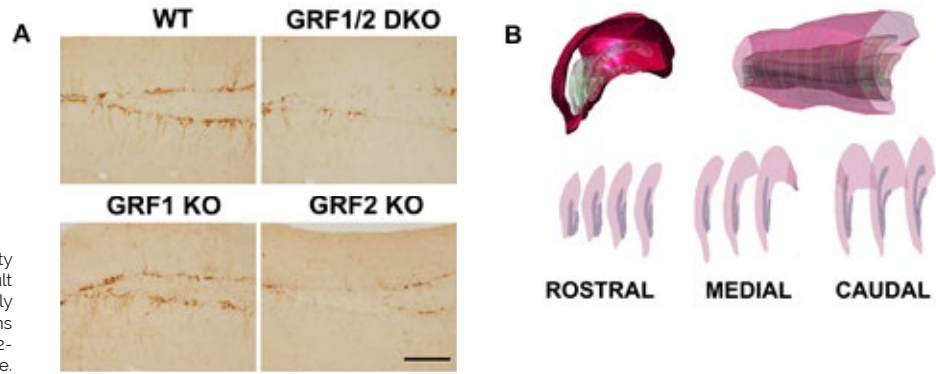
GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Red Temática de Investigación Cooperativa en Cáncer (RD12/0036/0001)	Eugenio Santos (national coordinator)	Instituto de Salud Carlos III	2013-2016	1,769,372.00 €
Activación de oncoproteínas Ras por GEFs de las familias Sos y Grf y su implicación en procesos fisiológicos y tumorales. Validación como biomarcadoresy/o dianas terapéuticas (PI13/02846)	Eugenio Santos	Instituto de Salud Carlos III	2014-2016	195,415.00 €
Subvención directa al Centro en Red de Medicina Regenerativa y Terapia Celular de Castilla y León.	Eugenio Santos	Consejería de Sanidad JCYL	2016	82,000.00 €
Subvención directa Consejería Sanidad a la Fundación de Investigación del Cáncer. Unidad de Consejo Genético.	Eugenio Santos	Consejería de Sanidad JCYL	2016	120,000.00 €
Subvención directa Consejería Sanidad a la Fundación de Investigación del Cáncer	Eugenio Santos	Consejería de Sanidad JCYL	2016	356,875.00 €
GTPASAS y cáncer: señalización mediada por RAS (Programa XIII (184118/463AC01)	Eugenio Santos	Universidad de Salamanca	2016	4,967.43 €
Análisis de la función del activador de las oncoproteínas Ras, RasGRF1 en la organogénesis del cristalino y el desarrollo de la miopía (FS/24-2015)	Alberto Fernández Medarde	Fundación Solórzano	2016	5,077.00 €



RasGRF2 controls nuclear migration in retinal cone photoreceptors. Abnormal presence of «ectopic» nuclei (tail-less arrows) in the photoreceptor segments (PS) of adult, GRF2-KO mouse retinas.

PROJECT	PI	GRANT	TIME	FUNDING
Identificación y validación de activadores RAS-GEF de las familias SOS y GRF como biomarcadores y dianas terapéuticas en procesos fisiológicos y tumorales mediante el uso de animales modelo y aproximaciones preclínicas (SA043U16)	Eugenio Santos	Consejería de Educación. Junta de Castilla y León	2016-2018	120,000.00 €
CIBERONC. Incorporación de nuevas áreas temáticas y nuevos grupos al consorcio CIBER, de la convocatoria 2016 de la Acción Estratégica en Salud 2013 – 2016. ÁREA TEMÁTICA DE CÁNCER (CB16/12/00352)	Eugenio Santos	Instituto de Salud Carlos III	2017	72,000.00 €
Caracterización y validación de las proteínas RAS y sus activadores GRF y SOS como drivers oncogénicos, biomarcadores y dianas terapéuticas en procesos tumorales y otras patologías (PI16/02137)	Eugenio Santos	Instituto de Salud Carlos III	2017-2019	147,015.00€



RasGRF2 regulates stem cell density and onset of differentiation during adult neurogenesis. Specific reduction of newly generated, Doublecortin-positive neurons (A) in the Dentate Gyrus (B) of RasGRF2-depleted mice.

OTHER ACTIVITIES & RELEVANT FACTS

- Board member, AECC Scientific Foundation (research project awards), Ferrer Foundation (Severo Ochoa Awards), Eugenio Rodríguez Pascual (research project awards)
- Overseeing Committee - Spanish Strategy Against Cancer (Spanish Health Ministry).
- Fellow, Royal Academy of Medicine Salamanca (RAMSA), European Academy of Cancer Sciences (EACS).

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Sonia Rodríguez Fernández

Technician
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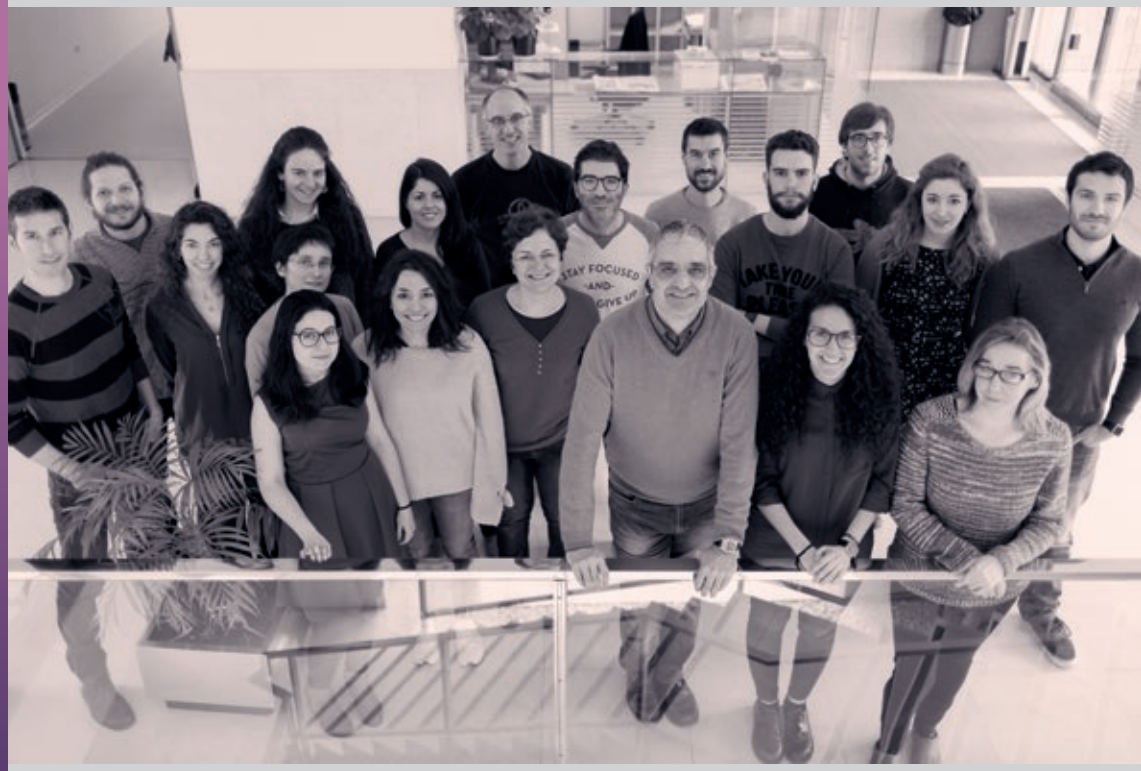
Maite Blázquez Ramos



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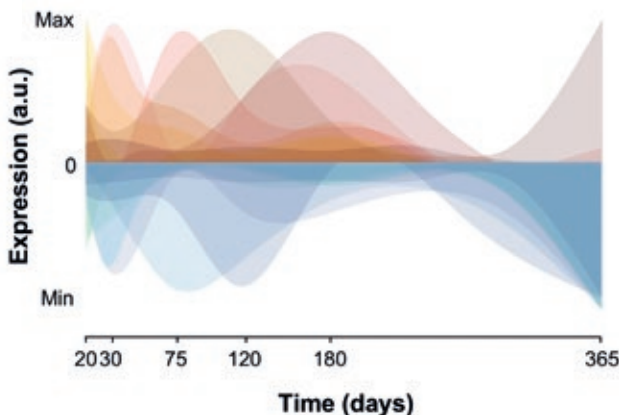
Luis González Moreno
Rodrigo Hernando Llorente
Regina Bou Puerto

Visiting researcher
Facundo Tonucci
Nazareno González

LABORATORY 2

IDENTIFICATION OF EARLY ONCOGENIC DRIVERS, SIGNALING MODIFIERS, AND METABOLIC PROGRAMS INVOLVED IN CANCER DEVELOPMENT AND PROGRESSION

Time-course expression patterns of dynamic genes in epidermal stem cells.



Our group aims at characterizing early signaling events and genetic lesions that are associated with cancer origin, progression, and therapeutic responsiveness. To achieve this end, we are focusing on the following experimental approaches:

(1) The development of in silico tools that will enable us to identify new oncogenic drivers, signaling modifiers, and metabolic programs that contribute to the formation, progression, and malignancy of a variety of tumors.
(2) The validation of the identified pro- and anti-tumorigenic hits using a variety of mouse models, cellular systems, and PDXs.
(3) The dissection of the signaling pathways and pathobiological programs regulated by those genes to identify new tumorigenic mechanisms, therapeutic targets, diagnostic signatures, and therapies.

Current molecular pathways of interest include those regulated by small GTPases of the RAS and RHO subfamilies, metabolic programs associated with primary tumorigenesis and metastasis, the cancer-specific alterations of ribosome biosynthetic pathways, and crosstalk between the foregoing pathways and tumor suppressor mechanisms.

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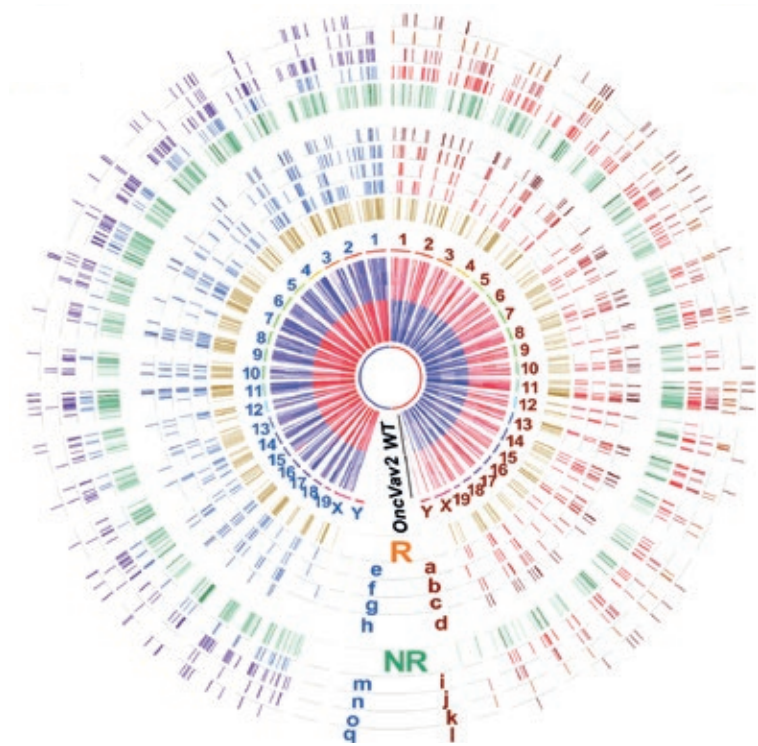
SENIOR RESEARCHER

RIBOSOME SYNTHESIS AND CELL GROWTH

Our group is interested on the characterization of the assembly and regulatory mechanisms that mediate the biosynthesis of ribosomes. In addition to its housekeeping roles, it is now known that alterations in this biological process can lead to human diseases. In this context, we have three main short-term goals:

(1) To study the factors that drive ribosome assembly in normal and transformed cells.
(2) To characterize how the ribosomal biosynthesis machinery crosstalk to other biological processes.
(3) To analyze the mechanism of action of drugs that target this biosynthetic route.

To this end, our lab uses a number of biochemical, proteomic, and genetic studies in human cells.



Circos plot of the differentially expressed genes in Vav2onc mouse skin. For each gene the chromosomal location (1-19,X,Y), functional annotation (a-q) and Vav2;Vav3 DKO reciprocity (R/NR) are depicted.

PUBLICATIONS

1 **Characterization of novel molecular mechanisms favoring Rac1 membrane translocation.** Castro-Castro A, Muriel O, Del Pozo MA, Bustelo XR. **PLoS One. 2016 11 (11): e0166715. doi: 10.1371/journal.pone.0166715.** PMID: 27835684. **IF: 3.057 / Q1**

2 **H-Ras and K-Ras oncoproteins induce different tumor spectra when driven by the same regulatory sequences.** Drosten M, Simón-Carrasco L, Hernández-Porras I, Lechuga CG, Blasco MT, Jacob HK, Fabbiano S, Potenza N, Bustelo XR, Guerra C, Barbacid M. **Cancer Res. 2017 77 (3):707-718. doi: 10.1158/0008-5472.CAN-16-2925.** PMID: 27872088. **IF: 8.556 / D1**

3 **Vav proteins are key regulators of Card9 signaling for innate antifungal immunity.** Roth S, Bergmann H, Jaeger M, Yeroslaviz A, Neumann K, Koenig PA, Prazeres da Costa C, Vanes L, Kumar V, Johnson M, Menacho-Márquez M, Habermann B, Tybulewicz VL, Netea M, Bustelo XR, Ruland J. **Cell Rep. 2016 17 (10):2572-2583. doi: 10.1016/j.celrep.2016.11.018.** PMID: 27926862. **IF: 7.870 / Q1**

4 **Activating mutations and translocations in the guanine exchange factor VAV1 in peripheral T-cell lymphomas.** Abate F, da Silva-Almeida AC, Zairis S, Robles-Valero J, Couronne L, Khiabanian H, Quinn SA, Kim MY, Laginestra MA, Kim C, Fiore D, Bhagat G, Piris MA, Campo E, Lossos IS, Bernard OA, Inghirami G, Pileri S, Bustelo XR, Rabadan R, Ferrando AA, Palomero T. **Proc Natl Acad Sci U S A. 2017 114 (4):764-769. doi: 10.1073/pnas.1608839114.** PMID: 28062691. **IF: 9.423 / Q1**

5 **Focal accumulation of preribosomes outside the nucleolus during metaphase-anaphase in budding yeast.** Moriggi G, Gaspar SG, Nieto B, Bustelo XR, Dosil M. **RNA. 2017. 23(9):1432-1443. doi: 10.1261/rna.061259.117.** PMID: 28588079. **IF: 4.065 / Q1**

6 **Plk1 regulates contraction of postmitotic smooth muscle cells and is required for vascular homeostasis.** de Cárcer G, Wachowicz P, Martínez-Martínez S, Oller J, Méndez-Barbero N, Escobar B, González-Loyola A, Takaki T, El Bakkali A, Cámara JA, Jiménez-Borreguero LJ, Bustelo XR, Cañamero M, Mulero F, de Los Ángeles Sevilla M, Montero MJ, Redondo JM, Malumbres M. **Nat Med. 2017. 23(8):964-974. doi: 10.1038/nm.4364.** PMID:28692064. **IF: 29.886 / D1**

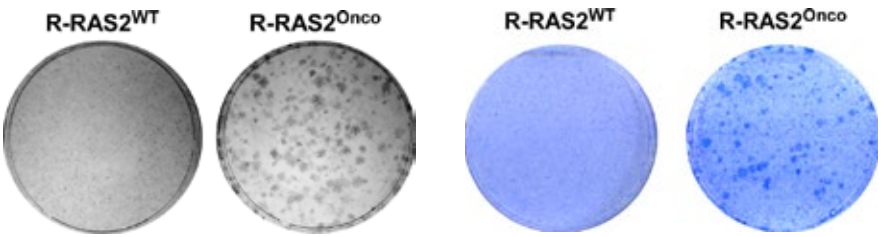
7 **Ribosome biogenesis and cancer: basic and translational challenges.** Bustelo XR, Dosil M. **Curr Opin Genet Dev. 2017 48:22-29. doi: 10.1016/j.gde.2017.10.003.** PMID: 29100209. **IF: 5.825 / Q1**

8 **Lung regeneration after toxic injury is improved in absence of dioxin receptor.** Morales-Hernández A, Nacarino-Palma A, Moreno-Marín N, Barrasa E, Paniagua-Quiñones B, Catalina-Fernández I, Álvarez-Barrientos A, Bustelo XR, Merino JM, Fernández-Salguero PM. **Stem Cell Res. 2017. 25: 61-71. doi: 10.1016/j.scr.2017.10.009.** PMID: 29107893. **IF: 3.963 / Q1**

9 **A paradoxical tumor-suppressor role for the Rac1 exchange factor Vav1 in T cell acute lymphoblastic leukemia.** Robles-Valero J, Lorenzo-Martín LF, Menacho-Márquez M, Fernández-Pisonero I, Abad A, Camós M, Toribio ML, Espinosa L, Bigas A, Bustelo XR. **Cancer Cell. 2017. 32 (5):608-623. doi: 10.1016/j.ccell.2017.10.004.** PMID: 29136506. **IF: 27.407 / D1**

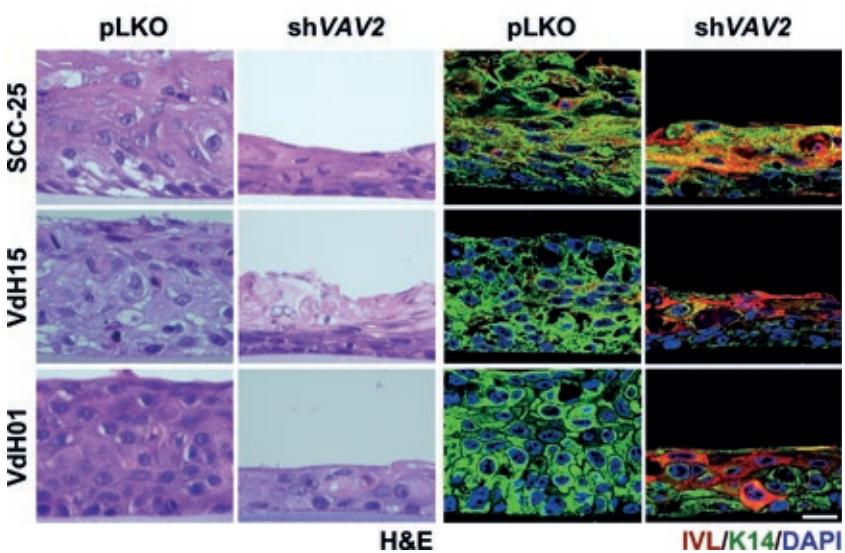
OTHER PUBLICATIONS & BOOK CHAPTERS

1 Bustelo, X.R. and Dosil, M. **(2017). The Vav family. In Encyclopedia of Signaling Molecules. 2nd Ed. S. Choi (Editor). Springer.** ISBN 978-1-4614-6438-9 (print), 978-1-4614-6438-9 (Online). **DOI: 10.1007/978-1-4614-6438-9_513-1**

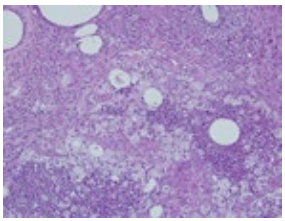
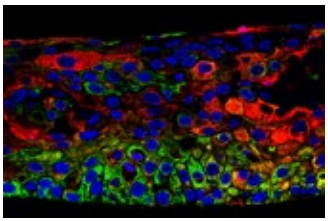
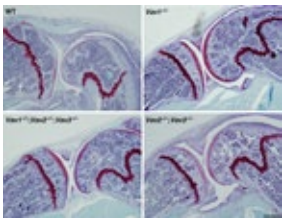


GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Spanish National Cooperative Network for Cancer Research (RTICC) (RD12/0036/0002)	Xosé R. Bustelo	Carlos III Health Institute	2013-2016	322,000.00 €
Vav proteins: catalytic role in skin tumorigenesis and tumor fate reprogramming (Ref. 14-1248)	Xosé R. Bustelo	Worldwide Cancer Research	2014-2017	232,000.00 €
Molecular mechanisms that integrate distinct steps of the ribosomal biosynthesis pathway (BFU2014-52729-P)	Mercedes Dosil	Ministerio de Economía y Competitividad	2015-2017	169,400.00 €
Pharmaco-mimetic analysis of the therapeutic role of Vav-dependent metabolic routes in breast cancer	Xosé R. Bustelo	Ramón Areces Foundation	2015-2018	128,000.00 €
Cell signaling, divisiona and growth (Program XIII (184075/463AC01)	Mercedes Dosil	University of Salamanca	2016	6,985.07 €
Vav family oncoproteins: regulatory layers, pathophysiological functions, and therapeutic potential (SAF2015-64556-R)	Xosé R. Bustelo	Spanish Ministry of Economy and Competitiveness	2016-2018	484,000.00 €
Genetic validation and therapeutic-translational applications of new oncogenic drivers (CSI049U16)	Xosé R. Bustelo	Ministry of Education, Regional Government of Castille and Leon	2016-2018	120,000.00 €
Function, diagnostic value and pharmacological inhibition of R-Ras2, a new oncogenic driver (GC16173472GARC)	Xosé R. Bustelo	Spanish Association against Cancer (AECC)	2016-2021	1,200,000.00 €
Center of Biomedical Research on Cancer (CIBERONC) (CB16/12/00351)	Xosé R. Bustelo	Carlos III Health Institute	2017	340,000.00 €



Sections from 3D cultures of control and VAV2 knockdown SCC cells, with the indicated stainings. Scale bar: 10 m

OTHER ACTIVITIES & RELEVANT FACTS

ACADEMIC ACTIVITIES

- Director Genomics and Proteomics Unit, Centro de Investigación del Cáncer/Cancer Research Center, Salamanca, Spain (2001-Present).
- Coordinator Molecular Mechanisms Program of the 3rd Spanish Cancer Cooperative Network (2013-2016).
- Member of the Executive Committee 3rd Spanish Cancer Cooperative Network (2013-2016).
- Vice-Director Centro de Investigación del Cáncer/Cancer Research Center, CSIC-University of Salamanca, Salamanca, Spain (2014-Present).
- Coordinator Mechanisms of Tumor Progression Program Centro de Investigación Biomédica en Red de Cáncer (CIBERONC) / Center for Biomedical Research in Oncology (2017-Present).
- Member of the Executive Committee (Comité de Dirección) CIBERONC (2017-Present).
- President Elect and Vice-President Spanish Association for Cancer Research / Asociación Española de Investigación sobre el Cáncer (ASEICA) (2017-Present).

EDITORIAL BOARDS

- Front. Immunol. (since 2010).
- Small GTPases (since 2011).
- Encyclopedia of Signaling Molecules (since 2012).
- Front. Cell Develop. Biol. (since 2015).
- Cell Comm. Adhes. (since 2017).
- Clin. Transl. Oncol. (since 2017).

SCIENTIFIC COMMITTEES

- External Scientific Committee. Santiago University Hospital Health Research Institute (Santiago of Compostela, Spain, 2008-Present).
- 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).
- External Recruiting Committee Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE), Univ. Buenos Aires-CONICET. Buenos Aires, Argentina (2017).
- Advisory Committee Axencia para a Avaliación da Calidade do Sistema Universitario de Galicia /Agency for the Control of the Quality of the Galician University System (2017).
- Scientific Committee I ASEICA Educational Symposium (2017).
- Kærtor Foundation Scientific Committee (2017-Present).

AD HOC MEMBERSHIP IN GRANT STUDY SECTIONS AND EVALUATION COMMITTEES

- Member, Biomedicine National Program Study Section (Spanish Ministry of Education and Science, Spain; 2017).
- Member, Biomedicine National JIN Program Study Section (Spanish Ministry of Economy and Competitiveness, Spain; 2016).
- Coordinator, Study Section for Axencia para a 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 and Networks (Galician autonomous government, Galicia, Spain, 2016).
- Advisory Board Member, Axencia para a 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 and Networks (Galician autonomous government, Galicia, Spain, 2017).
- Member, Study Section for Axencia para a 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 and Networks (Galician autonomous government, Galicia, Spain, 2017).

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Abel Jesús Martel Martel

Visiting researcher

Adrivanio Baranoski

LABORATORY 4

KINASES IN ONCOLOGY AND NEURODEGENERATION. SIGNALING BY NUCLEAR SERINE-THREONINE KINASES

Ser-Thr kinases regulate and transmit most of the intracellular signals. In the human kinome there is a unique and isolated family of Ser-Thr kinases known as VRK (vaccinia-related kinases), which is formed by three members, appeared very late in evolution and coordinates multiple functions in higher eukaryotes. These kinases affect multiple pathways regulating cell cycle, cell death and responses to many growth factors or cellular stress. Such as DNA damage. The group is focused on the study of the human VRK family signaling pathways and its implications in different phenotypes in relation with oncology in the context of chromatin remodeling and organization, DNA damage responses as well as their pathological implications in tumor biology and in neurological and neurodegenerative diseases. These kinases also regulate asymmetric division of stem cells and the dynamic remodeling of chromatin in different biological processes.

MAIN AIM

Identify and characterize the novel signaling pathways where human VRK proteins and determine the steps that form it and its functional interactions with other signaling pathways, particularly in the context of e biological processes associated to cell proliferation, DNA damage responses in the tumor phenotype cancer, and its participation in neurodegenerative syndromes such as Amyotrophic lateral sclerosis (ALS) and muscular dystrophies. We are also characterizing the human mutations associated to neurological diseases that are considered rare diseases, such as pontocerebelar hypoplasia in children.

SPECIFIC AIMS

1. Study how VRK proteins are regulated in response to specific stimulation including mitogenic growth factors or DNA damage. This regulation may be mediated by covalent modifications of the protein, or alternatively represent regulation of gene expression.
2. Identify upstream elements for each VRK protein, which are likely to be either a part of the pathway or a regulatory element, and associate them to specific functional responses.
3. Identify downstream elements of VRK proteins. These are likely to be intracellular substrates proteins of the kinases, but may also be interacting proteins. These interactions will be associated to functional responses and to cross-talk mechanisms with other signaling pathways.
4. Study the role of VRK proteins in the context of the cellular response to genetic damage either natural (oxidative stress, UV) or induced (tobacco, radiation, chemotherapy).
5. Characterize the role VRK1 in the regulation of alternative epigenetic modifications of histones, acetylation and methylation, which are mediated by four different enzymes whose coordination is unknown in the remodeling of chromatin.
6. Characterize and integrate VRK1 signaling pathways in the context chromatin remodeling and its association to DNA response pathways, neurodegenerative diseases and stem cells.
7. Characterize the mechanism by which human VRK1 mutations contribute to neurological diseases such as spinal muscular atrophy (SMA) or amyotrophic lateral sclerosis (ALS).

PUBLICATIONS

1 **Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition).** Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, Adachi H, Adams CM, ..., Layfield R, Lazo PA, Le Cam L, ..., Zhu XF, Zhu Y, Zhuang SM, Zhuang X, Ziparo E, Zois CE, Zoladek T, Zong WX, Zorzano A, Zughaier SM. **Autophagy. 2016;12(1):1-222. doi: 10.1080/15548627.2015.1100356.** PMID: 26799652. **IF: 9.108 / D1**

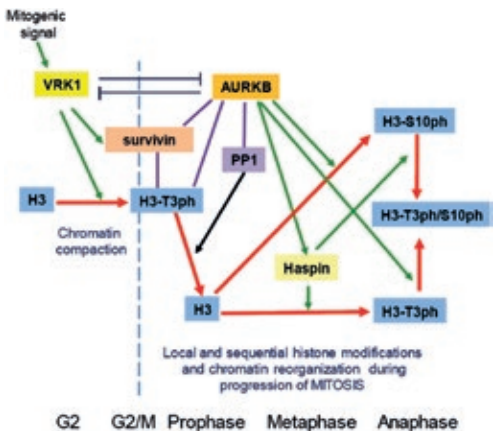
2 **VRK1 phosphorylates and protects NBS1 from ubiquitination and proteasomal degradation in response to DNA damage.** Monsalve DM, Campillo-Marcos I, Salzano M, Sanz-García M, Cantarero L, Lazo PA. **Biochim Biophys Acta. Mol. Cell. Res. 2016 Apr;1863(4):760-9. doi: 10.1016/j.bbamcr.2016.02.005. Epub 2016 Feb 9.** PMID: 26869104 **IF: 5.261 / Q1**

3 **Oncogenic Sox2 regulates and cooperates with VRK1 in cell cycle progression and differentiation.** Moura DS, Fernández IF, Marín-Royo G, López-Sánchez I, Martín-Doncel E, Vega FM, Lazo PA. **Sci Rep. 2016 Jun 23;6:28532. doi: 10.1038/srep28532.** PMID: 27334688 **IF: 5.228 / Q1**

4 **Gene amplification-associated overexpression of the RNA editing enzyme ADAR1 enhances human lung tumorigenesis.** Anadón C, Guil S, Simó-Riudalbas L, Moutinho C, Setien F, Martínez-Cardús A, Moran S, Villanueva A, Calaf M, Vidal A, Lazo PA, Zondervan I, Savola S, Kohno T, Yokota J, Ribas de Pouplana L, Esteller M. **Oncogene. 2016 Aug 18;35(33):4422. doi: 10.1038/onc.2016.27. Epub 2016 Jun 27.** PMID:27345394 **IF: 7.932 / D1**

5 **Is Centrosomal Protein 70, a Centrosomal Protein with New Roles in Breast Cancer Dissemination and Metastasis, a Facilitator of Epithelial-Mesenchymal Transition?** Lazo PA. **Am J Pathol. 2017 Mar;187(3):494-497. doi: 10.1016/j.ajpath.2016.12.008. Epub 2017 Jan 19.** PMID: 28109768. **IF: 4.026 / Q1**

6 **Reverting p53 activation after recovery of cellular stress to resume with cell cycle progression.** Lazo PA. **Cell Signal. 2017 May;33:49-58. doi: 10.1016/j.cellsig.2017.02.005. Epub 2017 Feb 9. Review.** PMID: 28189587. **IF: 4.191 / Q2**



Model of the sequential organization of VRK1 and AURKB in mitotic progression and phosphorylation of Histone H3. The red arrow indicates the fate of histone H3 and its phosphorylation as mitosis progresses. The lines indicate an interaction. Green arrows indicate an effect, either phosphorylation or gene expression in the case of survivin. PP1: Phosphatase 1.

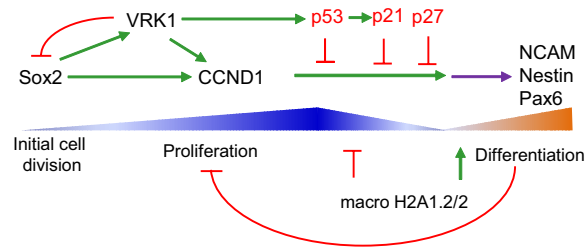


Diagram of the Sox2 and VRK1 roles in the regulation of cell proliferation and differentiation. As cells enter proliferate there is an increase in Sox2 levels that activate VRK1 and CCND1 gene expression. In this activation also participates VRK1. As cells enter the differentiation process there is an accumulation of cell cycle inhibitors, a reduction of Sox2 and VRK1 as well as an increase in terminally differentiation markers, such as NCAM, nestin and Pax6. In differentiated cells there is also a change in the pattern of macro histones and an accumulation of macro H2A1.1 and macro H2A2. The triangles represent the increase or decrease of different markers; for Sox2, VRK1 and CCND1 in blue, and for NCAM, Nestin and Pax6 in orange. Red lines indicate inhibition, and green lines indicate activation.

OTHER PUBLICATIONS & BOOK CHAPTERS

1 Cantarero, L., Moura, D.S., Salzano, M., Monsalve, D. M., Campillo-Marcos, I., Martin-Doncel, E., & Lazo, P.A. **(2017) «VRK1: vaccinia-related kinase 1» Encyclopedia of Signaling Molecules. Choi, S. (2nd ed.) Springer-Verlag. Chapter: 561-2. Pp:5955-5965.** ISBN 978-1-4614-6438-9. **DOI 10.1007/978-1-4614-6438-9_561-2.**

2 Monsalve, D. M., Blanco, S., Fernández, I.F., Vázquez-Cedeira, M., & Lazo, P. A. **(2017) «VRK2: vaccinia-related kinase 2» Encyclopedia of Signaling Molecules. Choi, S. (2nd Ed.). Springer-Verlag. Chapter 562-2. Pp: 5965-5973.** ISBN. 978-1-4614-6438-9. **DOI 10.1007/978-1-4614-6438-9_562-2.**

3 Moura, D.S., Cantarero, L., Martin-Doncel, E., Campillo-Marcos, I. & and Lazo, P.A. **(2017). «VRK3: vaccinia-related kinase 3» Encyclopedia of Signaling Molecules. Choi, S. 2nd (Ed.). Springer-Verlag. Chapter: 563-3. Pp: 5973-5976.** ISBN 978-1-4614-6438-9. **DOI 10.1007/978-1-4614-6438-9_563-2.**

4 Lazo, P.A. Yunta, M., Barcia, R. **(2017). «CD53» Encyclopedia of Signaling Molecules. Choi, S. (2nd Ed.). Springer-Verlag. Chapter: 566-1. Pp: 930-937.** ISBN 978-1-4614-6438-9. **DOI 10.1007/978-1-4614-6438-9_566-1.**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Señalización por la quinasa VRK1 humana y en la patogénesis del cáncer y la neurodegeneración (SAF2013-44810R)	Pedro A. Lazo-Zbikowski Taracena	Ministerio de Economía y Competitividad	2014-2016	338,800.00 €
Cancer Biology (Biología del Cáncer) (SAF2014-577DC-REDC)	Pedro A. Lazo-Zbikowski Taracena	Ministerio de Economía y Competitividad	2015-2016	45,000.00 €
Estudio del desarrollo de las leucemias linfoblásticas agudas infantiles con el fin de establecer nuevas bases terapéuticas y profilácticas (CSI001U16)	Pedro A. Lazo-Zbikowski Taracena	Consejería de Educación. Junta de Castilla y León	2016	40,000.00 €
Funciones de la quinasa VRK1 humana en la patogénesis del cáncer y enfermedades neurodegenerativas (SAF2016-75744-R)	Pedro A. Lazo-Zbikowski Taracena	Ministerio de Economía y Competitividad	2017-2019	314,600.00 €

OTHER ACTIVITIES & RELEVANT FACTS

- President of ASEICA (Spanish Society for Cancer Research).
- European Association for Cancer Research (EACR). Member of the Advisory Scientific Council.
- DAAD (Deutsche Akademischer Austauschdienst). Member Evaluation Board.
- AGAUR (Agència de Gestió d'Ajuts Universitaris i de Recerca). Member Evaluation Board.

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LABORATORY 5

REVERSIBLE PROCESSES IN CELL CYCLE CONTROL: PHOSPHORYLATION BY CDK IN MITOSIS AND UBIQUITYLATION OF PCNA

DNA damage is a major source of genome instability and cancer in living cells. To deal with DNA damage, living cells have evolved three pathways that are conserved among organisms: checkpoint response, DNA repair and tolerance to DNA damage. The checkpoint response pathway comprises a number of efficient surveillance mechanisms that sense all kinds of DNA damage. These mechanisms delay or arrest cell cycle progression and induce repair processes that ensure genome integrity. It is believed that the delay or arrest provides additional time for cells to repair the damage efficiently prior to resuming the cell division cycle. These surveillance mechanims are signal transduction cascades that, when activated, regulate repair responses including transcription of the DNA damage response genes, activation of DNA repair processes and recruitment of proteins to DNA damage sites to form in some cases foci at lesions. All major components of checkpoint pathways are remarkably well conserved in eukaryotes. Even though it has been recently demonstrated that phosphatases have important functions in the DNA damage response, the understanding of their role in these processes is still incomplete. We are currently undergoing the analysis of mammalian Cdc14B phosphatase in the control of the checkpoint response to DNA damage and/or its role in DNA repair.

During S-phase cells face damaged DNA or lesions that pose significant barriers to the progression of replication forks. It is thought that cells have evolved mechanisms of tolerance to DNA lesions that ensure the progression of normal DNA replication forks past the unrepaired damage. This tolerance to DNA damage is based on translesion synthesis (TLS) that is carried out either by specialized low-fidelity (error-prone) TLS DNA polymerases or by template switching, an error-free mechanism that involves sister-strand pairing within the replication fork. In the face of a DNA lesion, the ubiquitylation of the sliding clamp controls the choice of translesion synthesis in eukaryotes. While mono-ubiquitylation of PCNA at K164 enhances the affinity of error-prone TLS DNA polymerases, further K63-linked poly-ubiquitylation of mono-ubiquitylated K164-PCNA promotes template switching. This control mechanism is well characterized and widely conserved in eukaryotic organisms. On the contrary, the biological significance of the deubiquitylation of PCNA remains poorly/insufficiently understood. We have previously shown that Ubp10 is a major PCNA-DUB in Saccharomyces cerevisiae and that deubiquitylation of PCNA in fission yeast, Schizosaccharomyces pombe, is a complex process that requires several ubiquitin proteases with little or no functional redundancy among them. Having identified the ubiquitin proteases that revert in vivo PCNA ubiquitylation, we are currently dissecting the molecular basis of the down-regulation of DNA damage tolerance pathway and, also, testing whether or not these PCNA-DUBs form a safeguard mechanism ensuring that normal DNA replication progression is enforce during S-phase in both fission and budding yeast models.

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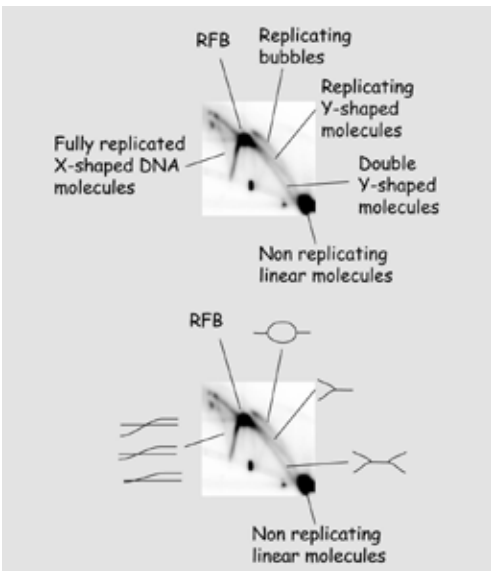
SENIOR RESEARCHER

PHOSPHORYLATION AND UBIQUITYLATION AS REVERSIBLE PROCESSES IN THE RESPONSE TO DNA DAMAGE

Proliferating-cell nuclear antigen (PCNA) is reversibly ubiquitylated during the cell cycle. In this post-translational modification underlies the mechanism of tolerance to DNA damage in eukaryotes. Although the evolutionary conserved mechanism of PCNA ubiquitylation is well understood, the deubiquitylation of ubPCNA remains poorly characterized. Our group is interested in understanding the role and, therefore, the biological significance of ubPCNA deubiquitylation in fission and budding yeast. Our working hypothesis is that Ubiquitin-specific proteases 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.

We have shown previously that fission yeast Cdc14-family phosphatase Flp1 is released from the nucleolus into the nucleus to regulate full activation of the checkpoint kinase Cds1/Chk2 in response to replication stress or MMS-mediated DNA damage. Metazoan Cdc14B also relocates from nucleoli into the nucleus after DNA damage. However, there is a long-standing controversy about the biological significance of this relocalization. We postulate that CDC14B has a role in the regulation of the checkpoint response to DNA damage in somatic mammalian cells. This hypothesis is compatible with the idea that Cdc14B phosphatase may be required for both checkpoint response and DNA repair. Our hypothesis predicts that deregulation of Cdc14B in somatic cells would alter the checkpoint response to different kinds of DNA damage.



Analysis of replication intermediates by two-dimensional gel electrophoresis

PUBLICATIONS

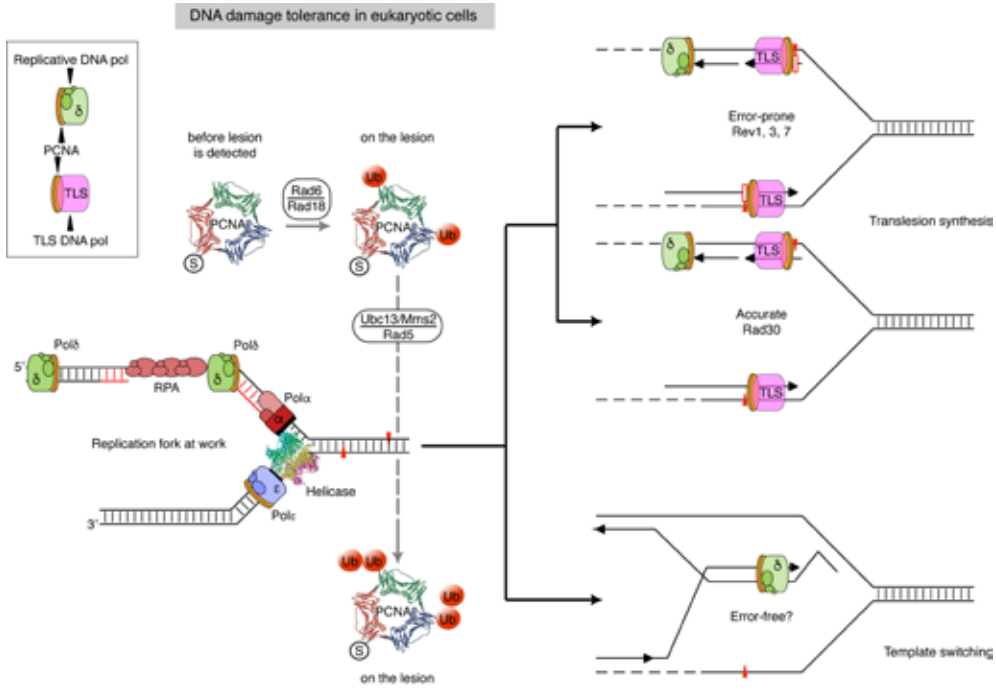
1 **Orderly progression through S-phase requires dynamic ubiquitylation and deubiquitylation of PCNA.** Álvarez V, Viñas L, Gallego-Sánchez A, Andrés S, Sacristán MP, Bueno A. **Sci Rep. 2016 May 6;6:25513. doi: 10.1038/srep25513.** PMID: 27151298 **IF: 5.228 / Q1**

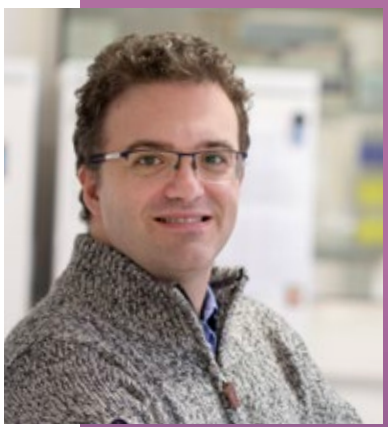
2 **The T300A Crohn's disease risk polymorphism impairs function of the WD40 domain of ATG16L1.** Boada-Romero E, Serramito-Gómez I, Sacristán MP, Boone DL, Xavier RJ, Pimentel-Muiños FX. **Nat Commun. 2016 Jun 8;7:11821. doi: 10.1038/ncomms11821.** PMID: 27273576 **IF: 11.329 / D1**

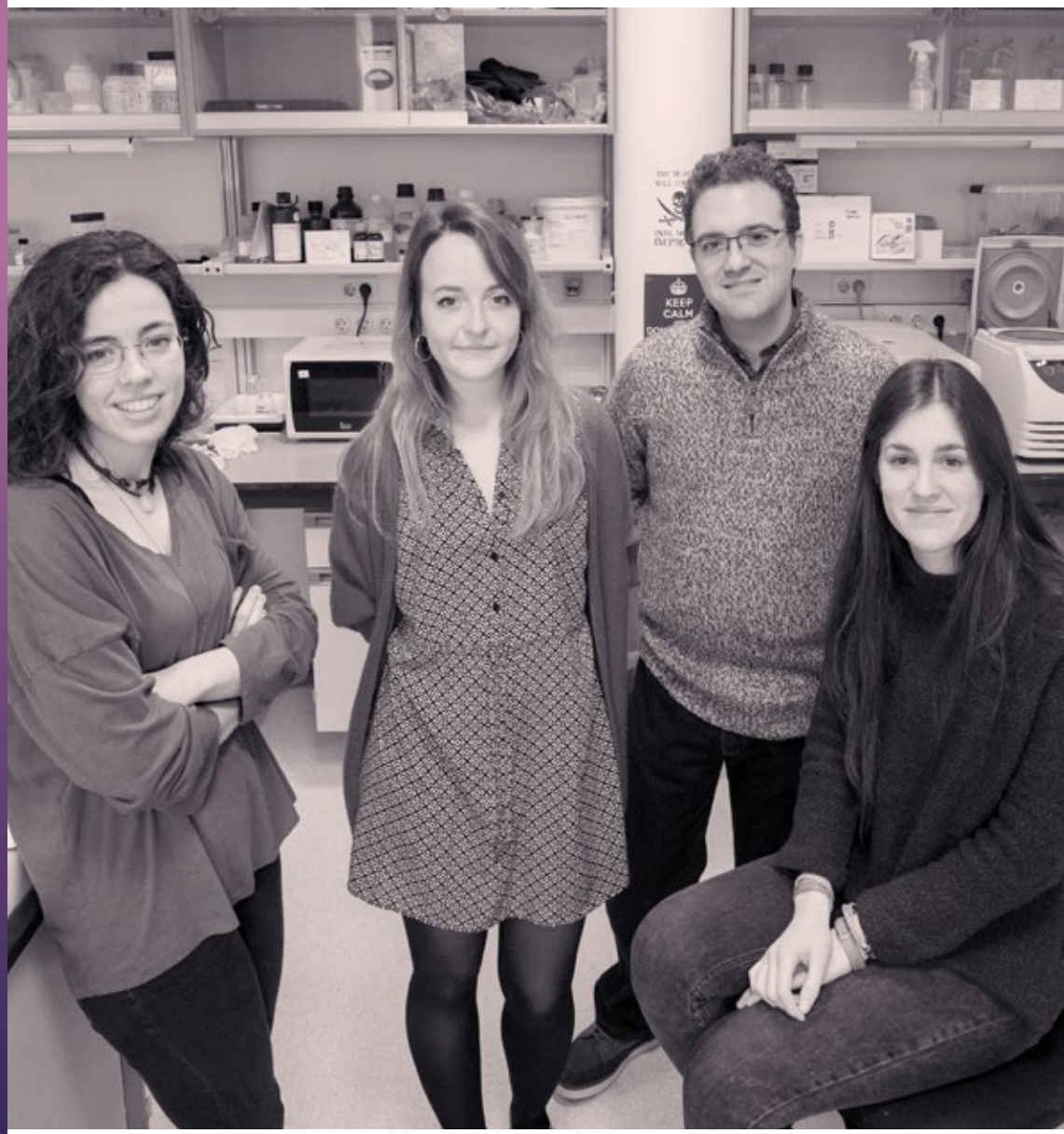
3 **The Multiple Roles of Ubiquitylation in Regulating Challenged DNA Replication.** Villa-Hernández S, Bueno A, Bermejo R. **Adv Exp Med Biol. 2017;1042:395-419. doi: 10.1007/978-981-10-6955-0_18.** PMID: 29357068 **IF: 1.953 / Q2**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Estudio de procesos reversibles en el control del ciclo celular: fosforilación por CDK en mitosis y ubiquitina de PCNA (BFU2012- 30787)	Andrés Avelino Bueno	Ministerio de Economía y Competitividad	2013-2016	196,560.00 €
Procesos reversibles en el control del ciclo celular: Ubiquitinación de PCNA y fosforilación de proteínas en respuesta a daño en el DNA (BFU2015-69709-P)	Andrés Avelino Bueno	Ministerio de Economía y Competitividad	2016-2018	142,296.00 €







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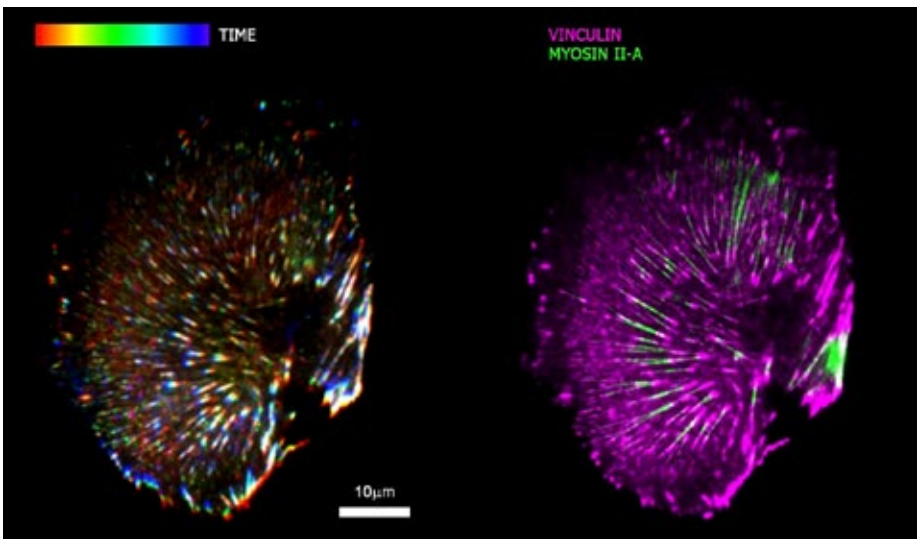
LABORATORY 6

TUMOR BIOPHYSICS

(FROM MARCH 2017)

Time-coded illustration (left) and spatial distribution of vinculin (in magenta) and non-muscle myosin II-A (in green) in a migrating mouse melanoma cell. *Credit: Clara Llorente-González.*



Our research aims at understanding the role of mechanics in metastasis, specifically the ability of individual metastatic cells to migrate and evade the immune response. We are characterizing the correlations between intracellular force generation, tissue mechanics, cell stemness and the ability of metastatic cells to migrate. Part of our research focuses on the identification of novel mechanisms of regulation of the function of molecular motors, which endow cells with increased migrating ability. By revealing novel mechanisms that control the detachment and migration of tumor cells from the primary tumor, we lay the foundation of the development of novel therapeutic approaches aimed at stopping tumor cell dissemination.

We are also investigating the relationship between tumor mechanics and immuno-suppression. We postulate that mechanical alterations during the development of the tumor niche compromise the ability of resident myeloid cells to perform their immune surveillance function by becoming unable to identify tumor cells and/or migrate to the lymph node. In this regard, we have revealed novel roles for classical molecular motors of the myosin superfamily in the activation of T cells and the establishment of transient contacts between myeloid tumor-resident immune cells and cancer cells.

These studies combine traditional approaches, including genetic screenings and biochemistry, with state-of-the-art imaging including different forms of quantitative microscopy, measurements of cell mechanics and in vivo models of tumor metastasis.

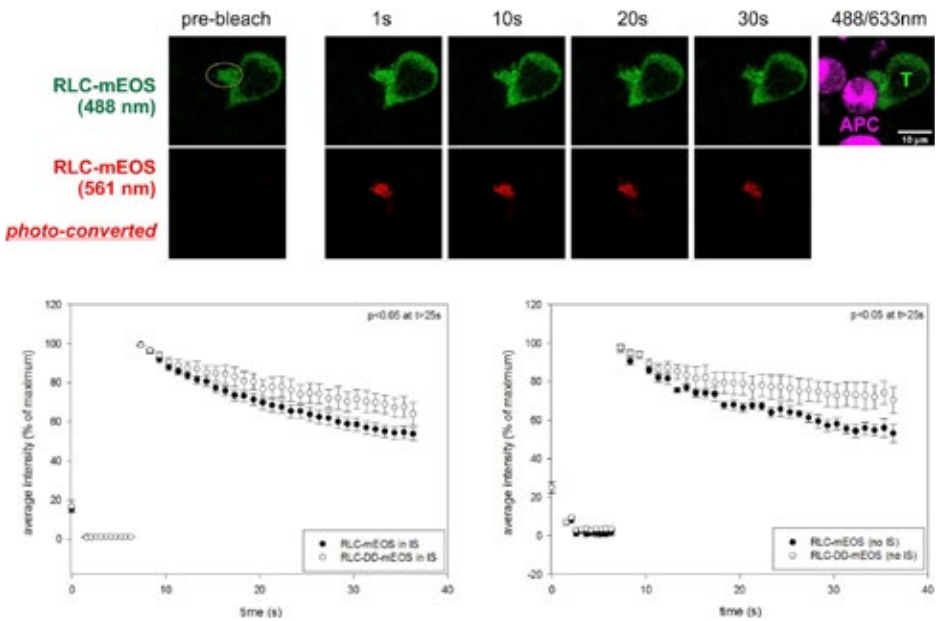
PUBLICATIONS

1 **Microfilament-coordinated adhesion dynamics drives single cell migration and shapes whole tissues.** Aguilar-Cuenca R, Llorente-Gonzalez C, Vicente C, Vicente-Manzanares M. **F1000Res. 2017 Feb 17;6:160. doi: 10.12688/f1000research.10356.1. eCollection 2017. Review.** PMID: 28299195 **IF: NI**

2 **Full L1-regularized Traction Force Microscopy over whole cells.** Suñé-Auñón A, Jorge-Peñas A, Aguilar-Cuenca R, Vicente-Manzanares M, Van Oosterwyck H, Muñoz-Barrutia A. **BMC Bioinformatics. 2017 Aug 10;18(1):365. doi: 10.1186/s12859-017-1771-0.** PMID: 28797233 **IF: 2.435 / Q1**

3 **Dasatinib reversibly disrupts endothelial vascular integrity by increasing non-muscle myosin II contractility in a ROCK-dependent manner.** Kreutzman A, Colom-Fernández B, Marcos Jiménez A, Ilander M, Cuesta-Mateos C, Pérez-García Y, Delgado Arévalo C, Brück O, Hakanen H, Saarela J, Ortega-Carrión A, de Rosendo A, Juanes-García A, Steegmann JL, Mustjoki S, Vicente-Manzanares M, Muñoz-Calleja C. **Clin Cancer Res. 2017 Aug 18. pii: clincanres.0667.2016. doi: 10.1158/1078-0432.CCR-16-0667.** PMID: 28821556 **IF: 8.738 / D1**

4 **Wavelet Imaging on Multiple Scales (WIMS) reveals focal adhesion distributions, dynamics and coupling between actomyosin bundle stability.** Toplak T, Palmieri B, Juanes-García A, Vicente-Manzanares M, Grant M, Wiseman. **PW.PLoS One. 2017 Oct 19;12(10):e0186058. doi: 10.1371/journal.pone.0186058. eCollection 2017.** PMID: 29049414 **IF: 3.057 / Q1**



Photoconversion of non-muscle myosin II at the immune synapse. T cells were transfected with mEOS-RLC, photoactivated at 405nm in the indicated region. Graphs indicate the decay of the signal over time as indicated in the X axis. Graphs represent the decay of photo-converted wild type myosin II (black circles) vs. an activated mutant in different regions of the cell. *Credit: María Millán-Salanova.*

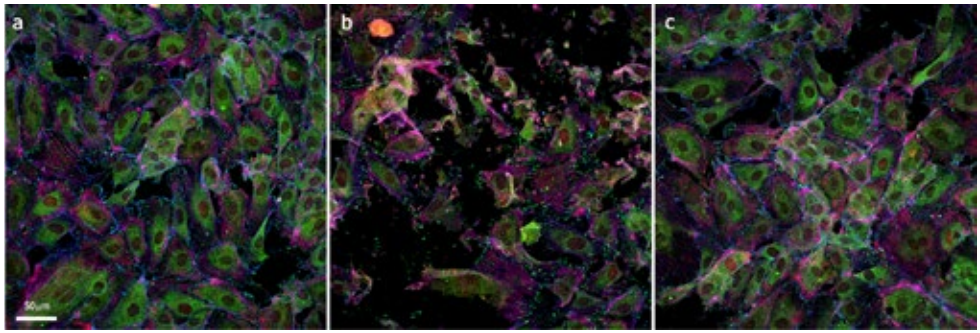
OTHER PUBLICATIONS & BOOK CHAPTERS

1 Juanes-García A, Llorente-Gonzalez C, Vicente-Manzanares M. **Non-muscle myosin II. In Encyclopedia of Signaling Molecules. Edited by Sandung Choi. Springer. 2017.** ISBN 978-1493967995. http://www.springer.com/gp/book/9783319671987

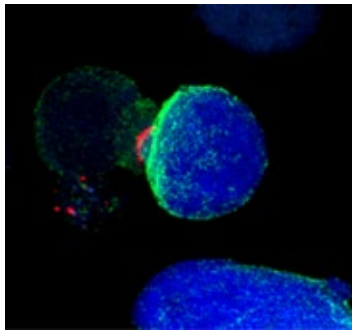
GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Mechanical determinants of cell migration and immune interaction	Miguel Vicente-Manzanares	Spanish Ministry of Economy and Competitiveness	2015-2017	217,800.00 €
Control de la heterogeneidad y evasión inmune tumoral por la mecánica tisular y la generación de fuerzas intracelulares	Miguel Vicente-Manzanares	Spanish Ministry of Economy and Competitiveness	2018-2020	205,700.00 €

Human umbilical cord endothelial cells (HUVECs) were treated for 60 min with DMSO (a), 100 nM dasatinib (b) or 100 nM dasatinib followed by 2h washout of the inhibitor (c). Cells were then fixed and stained for vinculin (green), pRLC (red) and F-actin (blue). Images are similar to those shown in Kreutzmann et al. Clin. Cancer Res. (2017).



Establishment of a cognate contact between a T cell (left) and an antigen-presenting cell (blue, right). In red, CD3, a canonical receptor involved in T cell activation; in green, part of the actin cytoskeleton of both cells. *Credit: María Millán-Salanova.*



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Visiting researcher
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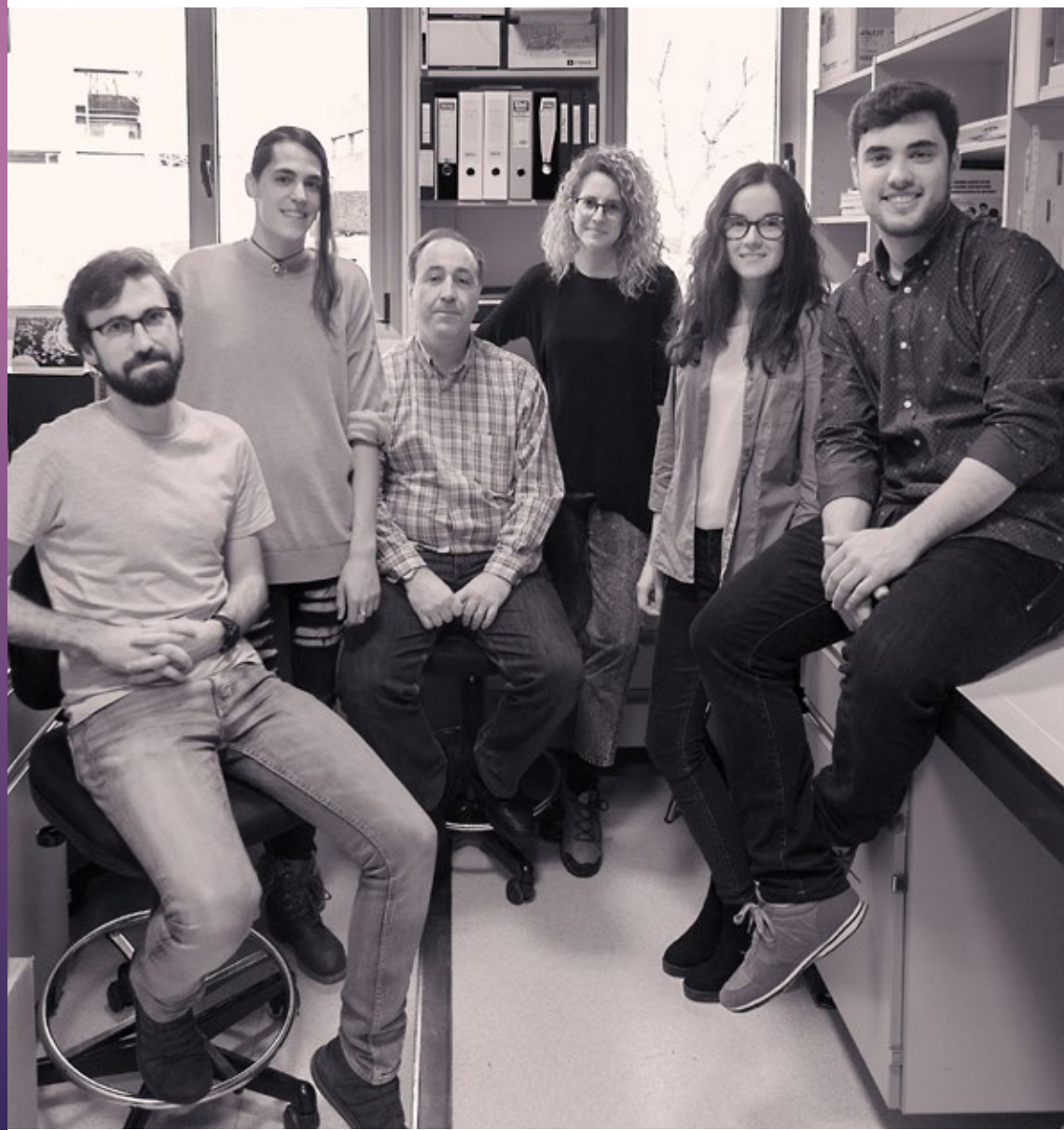
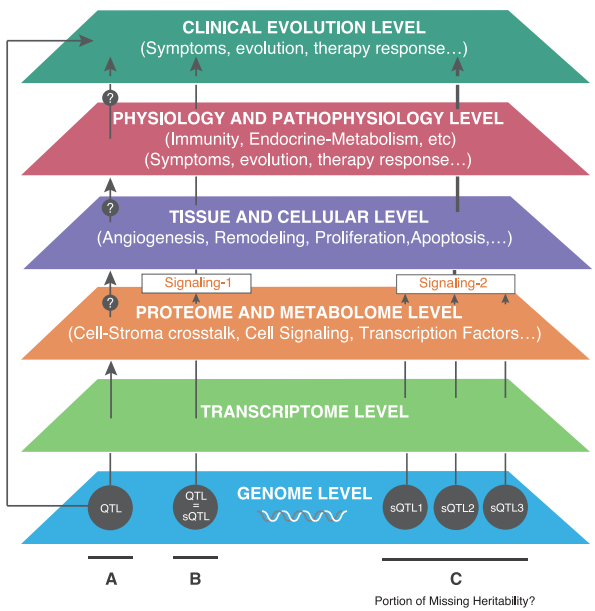
EL Habib Dakir



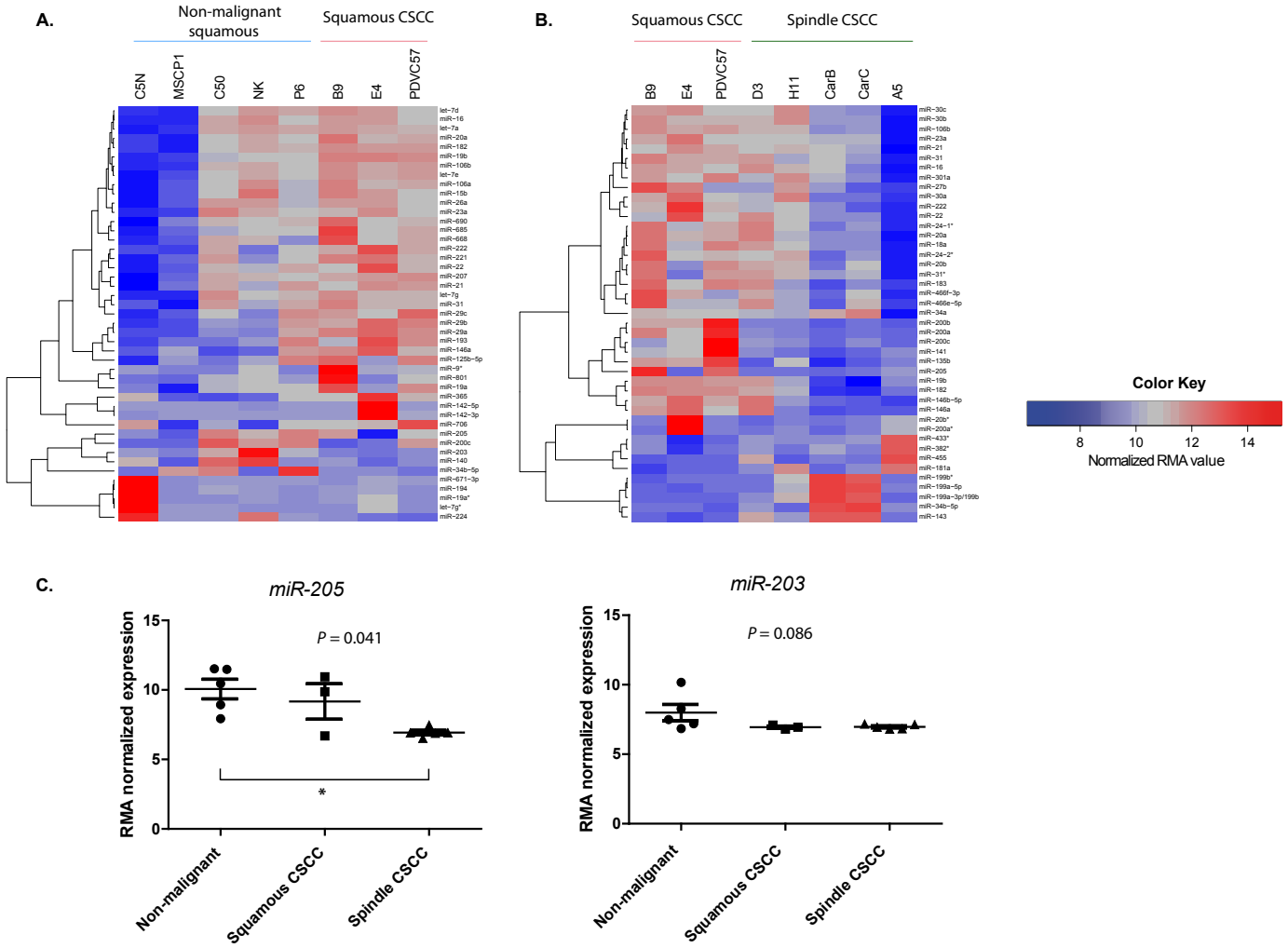
LABORATORY 7

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

The same type of tumor can have completely diverse outcomes in different patients and, alternatively, persons that have been exposed to the same carcinogenic insults during their lives can develop tumors or remain healthy for unknown reasons. Our group is interested in understanding the bases of these differences; therefore, the focus of our work is the identification of the genetic and molecular components that determine the different susceptibility, development, response to therapy and evolution of cancer, among different patients who seemingly have the same hystopathological disease. Cancer is a problem of public health of increasing importance; we need a better knowledge of the mechanisms that determine the susceptibility, development and evolution of the disease. These depend on the interaction of the genome with the environment. This interaction ►



The influence of a quantitative trait locus (QTL) or DNA sequence variant (DSV) over the susceptibility and/or variable presentation of a complex disease would be exerted by some intermediate phenotype located within any of the levels previously indicated (A). For example, it is possible that a QTL or DSV will exert its influence on a complex disease through a particular signaling pathway (B). It is feasible that another signaling pathway influences the variability of the complex disease in a very significant manner, but this signaling pathway in turn may be itself a complex phenotype influenced by multiple QTL. It is possible that these QTLs are, individually, powerful enough to affect a significant proportion of the variability of the signaling pathway. However, they would not induce a powerful enough variation in the signal to affect the main phenotype, and therefore be detected as genetic modifiers of the complex disease. These QTL influencing intermediate phenotypes, undetectable at the level of the main phenotype, would form part of the «missing heritability» (C).



Expression patterns of miRNAs in murine skin cancer cell lines with different grade of aggressiveness.
A) The heatmap shows the 45 miRNAs most differentially expressed between CSCC cell lines (PCVC57, B9, E4) and non-malignant skin cell lines, which included immortalized keratinocytes (C50, C5N, NK) and cells from benign papillomas (MSCP1, P6) generated by the DMBA/TPA protocol of carcinogenesis.
B) Heatmap showing the 43 miRNAs most differentially expressed between squamous CSCC cell lines (PCVC57, B9, E4) and the spindle group of CSCC cell lines (H11, A5, D3, CarB, CarC), that presented an EMT process. The lists of miRNAs from A and B heatmaps are shown in Supplementary Tables S3A and S3B, respectively. The A5 cell line was analysed from two different clones as an internal assay control and, as expected, both samples clustered together. In A and B, quantile normalization was performed using the Robust Microarray Analysis (RMA) algorithm, as indicated in the scale of the figure and in the material and methods section.
C) Expression of the *miR-205* (left) and the *miR-203* (right) in the different groups of skin cell lines. The P-value indicated was obtained by the Kruskal-Wallis test. The asterisk indicates in between which groups there is statistical significance after applying the Dunn´s multiple comparison test.

► determines the variability among patients in the predisposition and development of cancer, as well as in their response to treatment and evolution. The genetic component that contributes to this variability is constituted by the sum of actions of low-penetrance genes, whose allelic forms interact among them and with the environment to determine the clinical variability among individuals. These genes, named modifier genes, mainly present a pattern of quantitative heredity.

An essential question in cancer and complex diseases is why individuals with the same sickness have different clinical outcomes. Progress toward a more personalized medicine in cancer patients requires taking into account the underlying heterogeneity at different molecular levels. Recently, we presented a backcross mouse model in which there are complex interactions at different cellular and systemic levels that account for the heterogeneity of susceptibility to and evolution of ERBB2-positive breast cancers. Our model is based on our analyses of a cohort of mice that are characterized by heterogeneous susceptibility to ERBB2-positive breast cancers generated by a backcross. Our analysis revealed that there were similarities between ERBB2 tumors in humans and those of backcross mice at clinical, genomic, expression, and signaling levels. We also showed that mice that have tumors with intrinsically high levels of active AKT and ERK are more resistant to tumor metastasis. Our findings suggest that a site-specific phosphorylation at the serine 473 residue of AKT1 modifies the capacity for tumors to disseminate. We also presented two predictive models to explain the heterogeneous behavior of the disease in the mouse population when we consider simultaneously certain genetic markers, liver cell signaling and serum biomarkers that are identified before the onset of the disease.

Diseases of complex origin have a component of quantitative genetics that contributes to their susceptibility and phenotypic variability. However, after several studies, a major part of the genetic component of complex phenotypes has still not been found, a situation known as «missing heritability». Although there have been many hypotheses put forward to explain the reasons for the missing heritability, its definitive causes remain unknown. Complex diseases are caused by multiple intermediate phenotypes involved in their pathogenesis and, very often, each one of these intermediate phenotypes also has a component of quantitative inheritance. Recently, we proposed that at least part of the missing heritability could be explained by the genetic component of intermediate phenotypes that is not detectable at the level of the main complex trait. At the same time, the identification of the genetic component of intermediate phenotypes provides an opportunity to identify part of the missing heritability of complex diseases.

Our studies are mainly focus in breast cancer and Cutaneous squamous cell carcinoma (CSCC). CSCC is the second most widespread cancer in humans and its incidence is rising. These tumours can evolve as diseases of poor prognosis, and therefore it is important to identify new markers to better predict its clinical evolution. Recently, we have demonstrated that miR-205 is expressed in tumours with pathological features recognized as indicators of poor prognosis such as desmoplasia, perineural invasion and infiltrative growth pattern. miR-205 is mainly expressed in undifferentiated areas and in the invasion front, and was associated with both local recurrence and the development of general clinical events of poor evolution. miR-205 expression is an independent variable selected to predict events of poor clinical evolution using the multinomial logistic regression model. In contrast, miR-203 is mainly expressed in tumours exhibiting the characteristics associated with a good prognosis, is mainly present in well-differentiated zones, and rarely expressed in the invasion front. Therefore, the expression and associations of miR-205 and miR-203 were mostly mutually exclusive. Using a logistic biplot we identified three clusters of patients with differential prognosis based on miR-203 and miR-205 expression, and pathological tumour features. With this study we highlights the utility of miR-205 and miR-203 as prognostic markers in CSCC.

Our goal is to understand the variability in the tumour susceptibility, development and evolution in the global context of the physiology and pathophysiology of the organism, integrating factors both intrinsic and extrinsic to the tumour cell in the same scenario. To carry out our goal, we use common technologies of Molecular and Cellular Biology and Genetics, together with state-of the-art Genomics and Bioinformatics tools, applied to both in vitro and in vivo models (genetically modified mice) and human samples. All these technologies are applied in our group to study different tumour models. Our final goal is to obtain a better understanding of the molecular and cellular pathogenesis of cancer, and the differences among individuals in tumour susceptibility, development and evolution, which would finally result in the development of more individualized clinical applications for the benefit of patients.

PUBLICATIONS

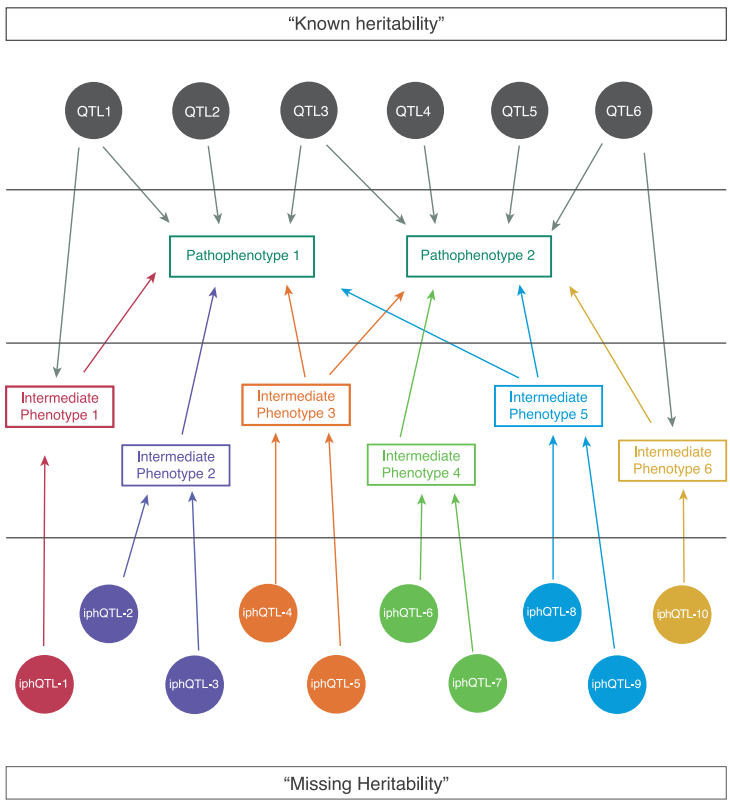
1 **Missing heritability of complex diseases: Enlightenment by genetic variants from intermediate phenotypes.** Blanco-Gómez A, Castillo-Lluva S, Del Mar Sáez-Freire M, Hontecillas-Prieto L, Mao JH, Castellanos-Martín A, Pérez-Losada J. **Bioessays. 2016 Jul;38(7):664-73. doi: 10.1002/bies.201600084. Epub 2016 May 31.** PMID: 27241833 **IF: 4.725 / Q1**

2 **Epidermal growth factor receptor expression is associated with poor outcome in cutaneous squamous cell carcinoma.** Cañueto J, Cardeñoso E, García JL, Santos-Briz Á, Castellanos-Martín A, Fernández-López E, Blanco Gómez A, Pérez-Losada J(*), Román-Curto C(*). **Br J Dermatol. 2017 May;176(5):1279-1287. doi: 10.1111/bjd.14936.** PMID: 27510450 **IF: 4.317 / D1**
(*) Equal contribution as senior authors.

3 **The expression of podoplanin is associated with poor outcome in cutaneous squamous cell carcinoma.** Cañueto J, Cardeñoso-Álvarez E, Cosano-Quero A, Santos-Briz Á, Fernández-López E, Pérez-Losada J(*), Román-Curto C(*). **J Cutan Pathol. 2017 Feb;44(2):144-151. doi: 10.1111/cup.12859.** PMID: 27859466 **IF: 1.409 / Q3**
(*) Equal contribution as senior authors.

4 **MicroRNA (miR)-203 and miR-205 expression patterns identify subgroups of prognosis in cutaneous squamous cell carcinoma.** Cañueto J, Cardeñoso-Álvarez E, García-Hernández JL, Galindo-Villardón P, Vicente-Galindo P, Vicente-Villardón JL, Alonso-López D, De Las Rivas J, Valero J, Moyano-Sanz E, Fernández-López E, Mao JH, Castellanos-Martín A, Román-Curto C, Pérez-Losada J. **Br J Dermatol. 2017 Jul;177(1):168-178. doi: 10.1111/bjd.15236. Epub 2017 May 8.** PMID: 27943259 **IF: 4.317 / D1**

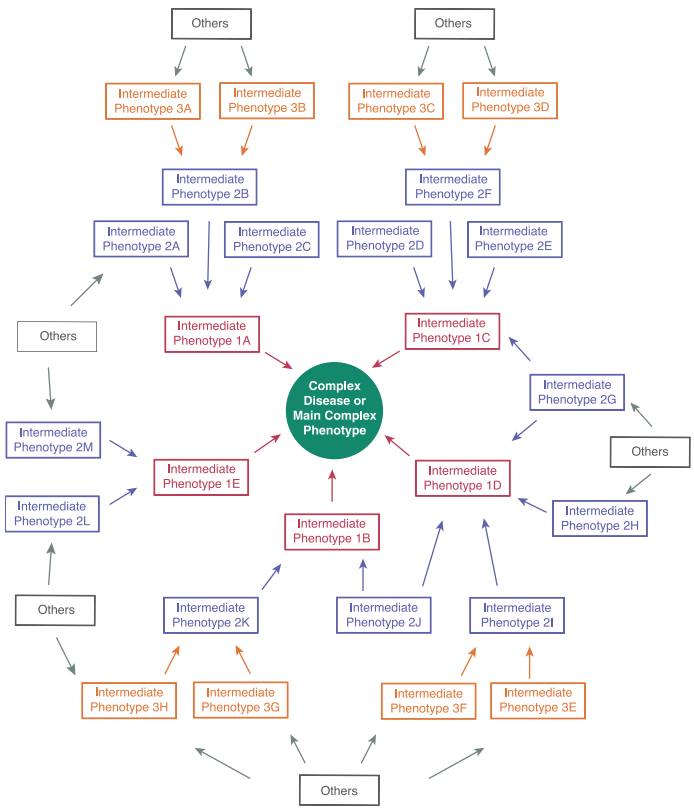
5 **Revisiting the impact of age and molecular subtype on overall survival after radiotherapy in breast cancer patients.** Mao JH, Diest PJV, Pérez-Losada J, Snijders AM. **Sci Rep. 2017 Oct 3;7(1):12587. doi: 10.1038/s41598-017-12949-5.** PMID: 28974723 **IF: 5.228 / Q1**



It is possible to dissect a complex disease in different pathophenotypes, and to identify a number of genetic determinants associated to the variability of these pathophenotypes in a population, that constitute the known proportion of the heritability of the disease. There are a number of intermediate phenotypes that contribute to the pathogenesis of the disease. The identification of genetic determinants that contribute to the variability of these intermediate phenotypes can be a global strategy to identify part of the missing heritability of complex diseases. iphQTL = intermediate phenotype QTL.

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Identificación de determinantes genéticos y moleculares comunes a la susceptibilidad de cáncer de mama y envejecimiento mediante una estrategia de Biología de Sistemas (SAF2014-56989-R)	Jesús Pérez Losada	Ministerio de Economía y Competitividad	2015-2017	145,200.00 €
CARdioToxicity In the Elderly pRogramme: the CARTIER project	Pedro Luis Sánchez Fernández (Investigator WP4: Jesús Pérez Losada	Instituto de Salud Carlos III	2015-2017	605,000.00 € (WP4: 80,000 €)
Infecciones, inflamación y cáncer: estudio de factores genéticos y moleculares asociados (IBY15/00003)	Antonio Muro (Collaborator: Jesús Pérez Losada)	Instituto de Salud Carlos III. Plan ayudas IBSAL	2016-2017	40,000.00 €
Estudio del desarrollo de las leucemias linfoblásticas agudas infantiles con el fin de establecer nuevas bases terapéuticas y profilácticas (CSI001U16)	Isidro Sánchez García (UIC17) (Collaborator: Jesús Pérez Losada)	Junta de Castilla y León, Consejería de Educación.	2017-2018	40,000.00 €



The grade of susceptibility and phenotypic variation in the presentation of complex diseases or complex traits depends on a number of intermediate phenotypes of second order that influence their pathogenesis; many of which are themselves complex phenotypes, which are in turn influenced by other intermediate phenotypes of third order. All of this creates a series of complex interactions between phenotypes. It must also be considered that the molecular and genetic determinants below each phenotype all acquire a structure of systems biology.

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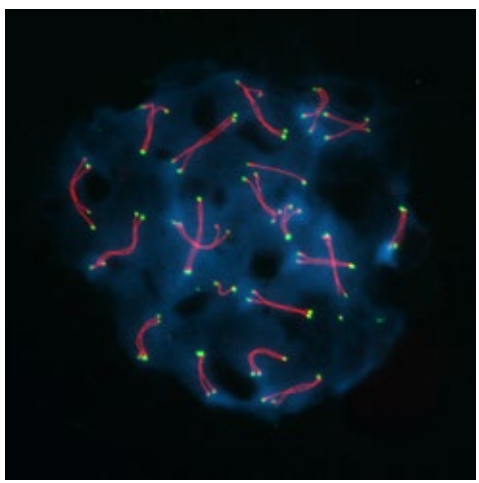
LABORATORY 9

CHROMOSOME SEGREGATION AND HUMAN DISEASE

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.

«Double Immunofluorescence of a Six6os1 - / - mouse spermatocytes arrested at pachytene. Red the synaptonemal complex protein 3 (SYCP3), a member of the axial element. RAP1, a telomeric protein, is labeled in green».



We had dissected in vivo the consequence of the lack of one protein, named Shugoshin-2, involved in the protection of the integrity of the Cohesin Complex. This protective system is essential for the faithful separation of homologous chromosomes during mitosis and meiosis which is the physical basis of Mendelian inheritance. More recently, we identified and characterized biochemically, cytologically, and functionally a new subunit of the -kleisin of the Cohesin Complex which is evolutionary conserved from fish to mammals. Through the development of a KO mouse of RAD21L1 we showed that whereas female mice deficient for RAD21L1 were fertile mutant males showed a severe meiotic arrest at late zygotene that ultimately led to azoospermia. Based on these results, we postulated that non obstructive azoospermia and POF can be due to genetic mutations in the cohesin pathway. To test this hypothesis, we undertook the genetic study of meiotic cohesins in human infertility by NGS of families affected of premature ovarian failure. In this respect, we identified in collaboration with the group of Dr. Vilain and Dr. Veitia a large consanguineous family with inherited premature ovarian failure. Using whole-exome sequence analysis we identified a homozygous 1-bp deletion inducing a frameshift mutation in the gene encoding the cohesin subunit STAG3. The pathogenicity of the STAG3 mutations was functionally validated with a ▸

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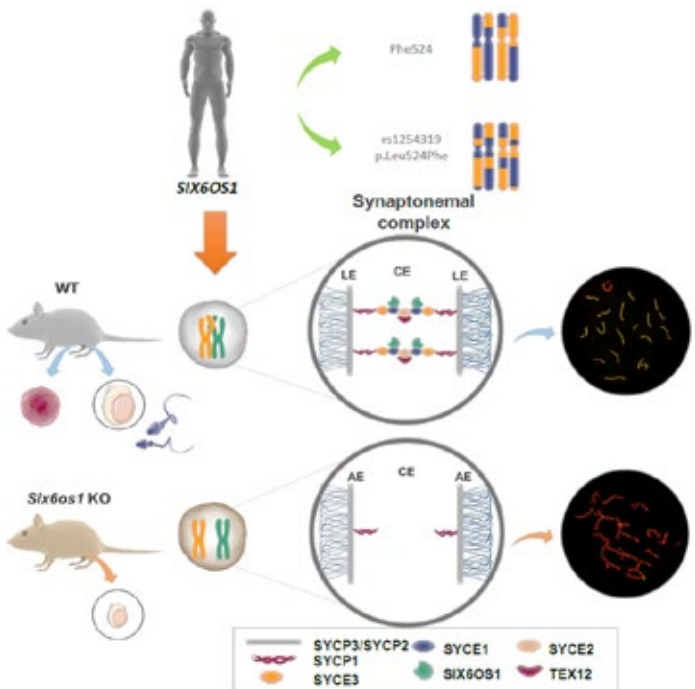
▸ loss-of-function mouse model for STAG3 in oogenesis. Female mice devoid of Stag3 were sterile, and their fetal oocytes were arrested at early prophase I, leading to oocyte depletion as early as at 1 week of age. However, and since none of the male members of this family was homozygous for the mutant allele, we made use of the mouse model to show that male mice devoid of Stag3 display a severe meiotic phenotype that includes a meiotic arrest at zygonema-like, demonstrating that STAG3 is a crucial cohesin subunit in mammalian gametogenesis and supporting our proposal that STAG3 is a strong candidate gene for human male infertility. Based on these results we postulate that the meiotic cohesins are responsible for a fraction of idiopathic human infertility syndromes and that meiotic genes are not haploinsuficient in humans as they are not also in mouse mutants.

More recently, we have initiated the characterization of anonymous loci from GWAS studies of human fertility such as the non-synonimous SNP rs1254319. We showed that this anonymous cSNP within the ORF named SIX6OS1, encodes a novel central element protein of the SC (2) that specifically interacts with the central element protein 1 (SYCE1). By using genomic editing techniques, we showed that mice lacking SIX6OS1 are defective in chromosome synapsis at meiotic prophase I, which provokes an arrest at the pachytene-like stage and results in infertility. In accordance with its role as a modifier of the human recombination rate, SIX6OS1 is essential for the appropriate processing of intermediate recombination nodules before crossover formation.



C14ORF39/SIX6OS1 encodes a component of the central element of the synaptonemal complex. Yeast two-hybrid analysis reveals that SIX6OS1 interacts with the well-established protein synaptonemal complex central element 1 (SYCE1). Mice lacking SIX6OS1 are defective in chromosome synapsis at meiotic prophase I, which provokes an arrest at the pachytene-like stage and results in infertility. In accordance with its role as a modifier of the human recombination rate, SIX6OS1 is essential for the appropriate processing of intermediate recombination nodules before crossover formation.

PUBLICATIONS

1 **Sororin loads to the synaptonemal complex central region independently of meiotic cohesin complexes.** Gómez R, Felipe-Medina N, Ruiz-Torres M, Berenguer I, Viera A, Pérez S, Barbero JL, Llano E, Fukuda T, Alsheimer M, Pendás AM, Losada A, Suja JA. **EMBO Rep. 2016 May;17(5):695-707. doi: 10.15252/embr.201541060. Epub 2016 Mar 7.** PMID: 26951638 **IF: 7.739 / D1**

2 **Distinct Roles of Meiosis-Specific Cohesin Complexes in Mammalian Spermatogenesis.** Biswas U, Hempel K, Llano E, Pendas A, Jessberger R. **PLoS Genet. 2016 Oct 28;12(10):e1006389. doi: 10.1371/journal.pgen.1006389. eCollection 2016 Oct.** PMID: 27792785 **IF: 6,661 / D1**

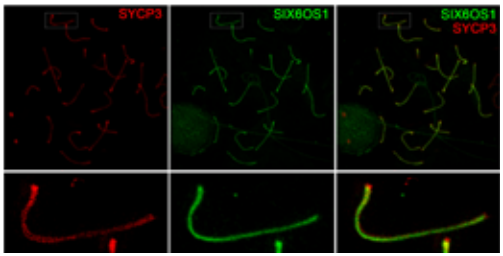
3 **C14ORF39/SIX6OS1 is a constituent of the synaptonemal complex and is essential for mouse fertility.** Gómez-H L, Felipe-Medina N, Sánchez-Martín M, Davies OR, Ramos I, García-Tuñón I, de Rooij DG, Dereli I, Tóth A, Barbero JL, Benavente R, Llano E, Pendas AM. **Nat Commun. 2016 Oct 31;7:13298. doi: 10.1038/ncomms13298.** PMID: 27796301 **IF: 11.329 / D1**

4 **piRNA-associated proteins and retrotransposons are differentially expressed in murine testis and ovary of aryl hydrocarbon receptor deficient mice.** Rico-Leo EM, Moreno-Marín N, González-Rico FJ, Barrasa E, Ortega-Ferrusola C, Martín-Muñoz P, Sánchez-Guardado LO, Llano E, Álvarez-Barrientos A, Infante-Campos A, Catalina-Fernández I, Hidalgo-Sánchez M, de Rooij DG, Pendás AM, Peña FJ, Merino JM, Fernández-Salguero PM. **Open Biol. 2016 Dec;6(12). pii: 160186. doi: 10.1098/rsob.160186.** PMID: 28003471 **IF: 4.822 / Q1**

5 **APC/CCdh1 Enables Removal of Shugoshin-2 from the Arms of Bivalent Chromosomes by Moderating Cyclin-Dependent Kinase Activity.** Rattani A, Ballesteros Mejia R, Roberts K, Roig MB, Godwin J, Hopkins M, Eguren M, Sanchez-Pulido L, Okaz E, Ogushi S, Wolna M, Metson J, Pendás AM, Malumbres M, Novák B, Herbert M, Nasmyth K. **Curr Biol. 2017 May 22;27(10):1462-1476.e5. doi: 10.1016/j.cub.2017.04.023. Epub 2017 May 11.** PMID: 28502659 **IF: 8.851 / D1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Biología funcional de la red meiótica (BFU2015- 71786-REDT)	Alberto Martín Pendás	Ministerio de Economía y Competitividad	2015-2016	47,000.00 €
Análisis funcional de la red de cohesinas en mamíferos (BFU2014- 59307-R)	Alberto Martín Pendás	Ministerio de Economía y Competitividad	2015-2017	411,400.00 €
Caracterización funcional de genes implicados en infertilidad humana (CSI052U16)	Alberto Martín Pendás	Consejería de Educación. Junta de Castilla y León	2016-2017	40,000.00 €
Analisis funcional de la gametogenesis en mamiferos (BFU2017-89408-R)	Alberto Martín Pendás	Ministerio de Economía y Competitividad	2018-2020	250,000.00 €



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LABORATORY 11

IMMUNOLOGY AND CANCER

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 t**o 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.

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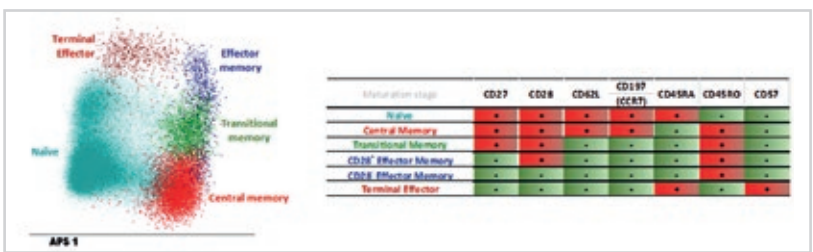
CHRONIC LYMPHOID NEOPLASMS: FACTORS INVOLVED IN ONTO-PATHOGENESIS AND TRANSFORMATION OF PRELEUKEMIC CONDITIONS INTO CLONAL/MALIGNANT DISEASES

«Immunology and Cancer» applied to hematological malignancies (leukemias and lymphomas) derived from mature B/T/NK lymphocytes, from the onto-pathogenesis to clinical settings, these latter including their potential application in diagnosis, classification and treatment monitoring of these neoplasms. **Major research activities:** 1) identification of mechanisms involved in the transformation/evolution of reactive to clonal and malignant conditions; 2) phenotypic, genetic/molecular and functional characterization of these cells; 3) translation to diagnosis, classification and treatment monitoring; 4) biological characterization of their normal (immune) cell counterparts; and 5) analysis of the role/alterations and monitoring of immune cells in other haematological malignancies, infectious diseases (HIV, Bp infection) and chronic alcoholism.

Her major contributions in the last two years have evidenced: i) the importance of an antigenic environment associated with monoclonal B lymphocytosis (-MBL-, condition that precedes chronic lymphatic leukemia –CLL-, Criado et al, Haematologica 2017); ii) the presence of altered numbers of immune cells from early stages of MBL, that could play a role in CLL progression (Criado et al, Leukemia 2018), and iii) low-count MBL subjects have a shorter overall survival (vs. age- and sex-matched controls) and suffer most frequently from infectious diseases (Criado et al, Haematologica 2018).

In the near future, her activities will focus on in-depth analyzing ontogenic factors of chronic B-cell lymphoid neoplasms, and translating it to chronic T-cell leukemias/lymphomas.



Identification of different maturational CD4+ T-cell subsets by multiparametric flow cytometry.

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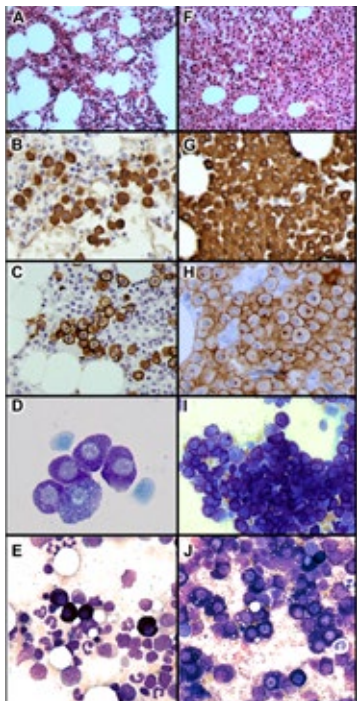
PHENOTYPIC AND MOLECULAR CHARACTERIZATION OF SYSTEMIC MASTOCYTOSIS: CORRELATION BETWEEN DISEASE PROGRESSION, IMMUNOPHENOTYPE AND THE SPECIFIC GENETIC BACKGROUND

Systemic mastocytosis (SM) are orphan diseases, indolent in most patients (ISM) that can progress to aggressive forms (ASM). Objective: To identify molecular patterns associated to the severity and evolution of SM to perform a predictive algorithm, with enough sensitivity and specificity, to obtain a prognostic stratification of the patients at diagnostic and follow-up.

Lines of Research: 1) Immunophenotypic characterization of pathologic mast cells (MC) in the different types of SM. 2) Transcriptomics and genomics of purified MC to identify molecular pathways altered in ASM vs ISM. 3) Correlation between molecular events, clinical data and environmental features to establish specific prognostic criteria. 4) Identification, using next generation sequencing (NGS) technologies, of somatic and/or germinal genetic variants responsible for the malignant transformation associated to the D816V KIT 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.



Images of representative histologic and cytomorphologic BM features in patients with WDSM. A-E, BM sections (A-C) and smears (D-E) showing small clusters of round mature-like MCs in a patient with mild BM MC infiltration (A, hematoxylin and eosin stain and 3200 magnification; B, tryptase stain and 3600 magnification; C, c-kit stain and 3600 magnification; D, toluidine blue stain and 31000 magnification; E, May-Gr€unwald-Giemsa stain and 3600 magnification). F-J, BM sections (F-H) and smears (I-J) showing a marked increase of round and well- granulated MCs diffusely infiltrating the BM in a patient fulfilling the criteria for MCL (F, hematoxylin and eosin stain and 3200 magnification; G, tryptase stain and 3600 magnification; H, c-kit stain and 3600 magnification; I, toluidine blue stain and 3600 magnification; J, May-Gr€unwald-Giemsa stain and 3600 magnification). (*Clinical, immunophenotypic, and molecular characteristics of well-differentiated systemic mastocytosis.* Álvarez-Twose I et al. J Allergy Clin Immunol. 2016 Jan;137(1):168-178.)

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

Novel ProteoGenomics approaches for identification of translational biomarkers in immune disorders, tumoral and hemopathologies.

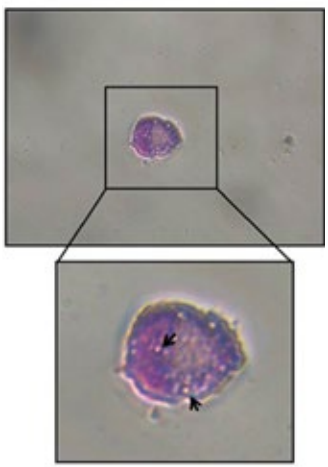
In post-Genome era having sequence the human genome, one of the most important pursuits is to understand the function of gene-expressed proteins. Despite the immense progress in molecular biology and genetics, only a small fraction of the proteome is understood at the biochemical level. Systems Biology and Proteomics (combine with nanotechnology) strive to create detailed predictive models for molecular pathways based upon the quantitative behavior of proteins. Understanding these dynamics networks provides clues into the consequence of aberrant interactions and why they lead to disease like cancer. Developments in different omics approaches have allowed incorporating the term «Proteogenomics» as the next step in the study and knowledge of cellular mechanisms and interactions between cells and the microenvironment in different situations (ie. tumoral pathologies,immune disorders,...).

This new approach will be very informative in the field of:

- Biological research: Proteogenomics has wide spectrum of applications, getting a better understanding of cellular and molecular biology.
- Biomedical research: Proteogenomics could support a customized clinical decision-making useful for diagnostic, prognostic and treatment election.

In summary, proteogenomics could become an indispensable tool which will allow complete the knowledge about cellular functions, pathways... and consequentially, over the understanding of physiopathologies development.

Our group is focused on design, developed and implemented these novel cutting-edge technologies, in order to provide new knowledge on the human immunome, immune system and immune response which could help to decipher the dynamics networks of cancer immunology to discover biomarkers or novel therapeutic agents, and to generate new biological hypothesis that could open new clinical trials.



PUBLICATIONS

1 **Diagnosis and classification of mastocytosis in non-specialized versus reference centres: a Spanish Network on Mastocytosis (REMA) study on 122 patients.** Sánchez-Muñoz L, Morgado JM, Álvarez-Twose I, Matito A, García-Montero AC, Teodosio C, Jara-Acevedo M, Mayado A, Mollejo M, Caldas C, González de Olano D, Escribano L, Orfao A. **Br J Haematol. 2016 Jan;172(1):56-63. doi: 10.1111/bjh.13789. Epub 2015 Oct 12.** PMID: 26456532 **IF: 5.812 / Q1**

2 **Minimal residual disease evaluation by flow cytometry is a complementary tool to cytogenetics for treatment decisions in acute myeloid leukaemia.** Vidriales MB, Pérez-López E, Pegenaute C, Castellanos M, Pérez JJ, Chandía M, Díaz-Mediavilla J, Rayón C, de Las Heras N, Fernández-Abellán P, Cabezudo M, de Coca AG, Alonso JM, Olivier C, Hernández-Rivas JM, Montesinos P, Fernández R, García-Suárez J, García M, Sayas MJ, Paiva B, González M, Orfao A, San Miguel JF; PETHEMA Programa para el Estudio de la Terapéutica en Hemopatías Malignas Cooperative Study Group. **Leuk Res. 2016 Jan;40:1-9. doi: 10.1016/j.leukres.2015.10.002. Epub 2015 Oct 22.** PMID: 26598032 **IF: 2.606 / Q3**

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6 **Phenotypic and genomic analysis of multiple myeloma minimal residual disease tumor cells: a new model to understand chemoresistance.** Paiva B, Corchete LA, Vidriales MB, Puig N, Maiso P, Rodríguez I, Alignani D, Burgos L, Sanchez ML, Barcena P, Echeveste MA, Hernández MT, García-Sanz R, Ocio EM, Oriol A, Gironella M, Palomera L, De Arriba F, Gonzalez Y, Johnson SK, Epstein J, Barlogie B, Lahuerta JJ, Blade J, Orfao A, Mateos MV, San Miguel JF; Spanish Myeloma Group / Program for the Study of Malignant Blood Diseases Therapeutics (GEM / PETHEMA) Cooperative Study Groups. **Blood. 2016 Apr 14;127(15):1896-906. doi: 10.1182/blood-2015-08-665679. Epub 2016 Jan 11.** PMID: 26755711 **IF: 11.847 / D1**

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12 **Spanish consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria.** Villegas A, Arrizabalaga B, Bonanad S, Colado E, Gaya A, González A, Jarque I, Núñez R, Ojeda E, Orfao A, Ribera JM, Vicente V, Urbano-Ispizua Á; Grupo de Trabajo de HPN de la Sociedad Española de Hematología y Hemoterapia. **Med Clin (Barc). 2016 Mar 18;146(6):278.e1-7. doi: 10.1016/j.medcli.2015.12.012. Epub 2016 Feb 17.** PMID: 26895645 **IF: 1.267 / Q2**

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15 **A genome-wide association study identifies SLC8A3 as a susceptibility locus for ACPA-positive rheumatoid arthritis.** Julià A, González I, Fernández-Nebro A, Blanco F, Rodríguez L, González A, Cañete JD, Maymó J, Alperi-López M, Olivé A, Corominas H, Martínez-Taboada V, Erra A, Sánchez-Fernández S, Alonso A, López-Lasanta M, Tortosa R, Codó L, Gelpi JL, García-Montero AC, Bertranpetit J, Absher D, Bridges SL Jr, Myers RM, Tornero J, Marsal S. **Rheumatology (Oxford). 2016 Jun;55(6):1106-11. doi: 10.1093/rheumatology/kew035. Epub 2016 Mar 15.** PMID: 26983453 **IF: 4.524 / Q1**

16 **Altered neutrophil immunophenotypes in childhood B cell precursor acute lymphoblastic leukemia.** Oliveira E, Bacelar TS, Ciudad J, Ribeiro MC, García DR, Sedek L, Maia SF, Aranha DB, Machado IC, Ikeda A, Baglioli BF, López-Duarte N, Teixeira LA, Szczepanski T, Silva ML, Land MG, Orfao A, Costa ES. **Oncotarget. 2016 Apr 26;7(17):24664-76. doi: 10.18632/oncotarget.8369.** PMID: 27028865 **IF: 5.008 / Q1**

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32 **Targeting of PI3K/AKT/mTOR pathway to inhibit T cell activation and prevent graft-versus-host disease development.** Herrero-Sánchez MC, Rodríguez-Serrano C, Almeida J, San Segundo L, Inogés S, Santos-Briz Á, García-Briñón J, Corchete LA, San Miguel JF, Del Cañizo C, Blanco B. **J Hematol Oncol. 2016 Oct 20;9(1):113.** PMID: 27765055 **IF: 6.263 / D1**

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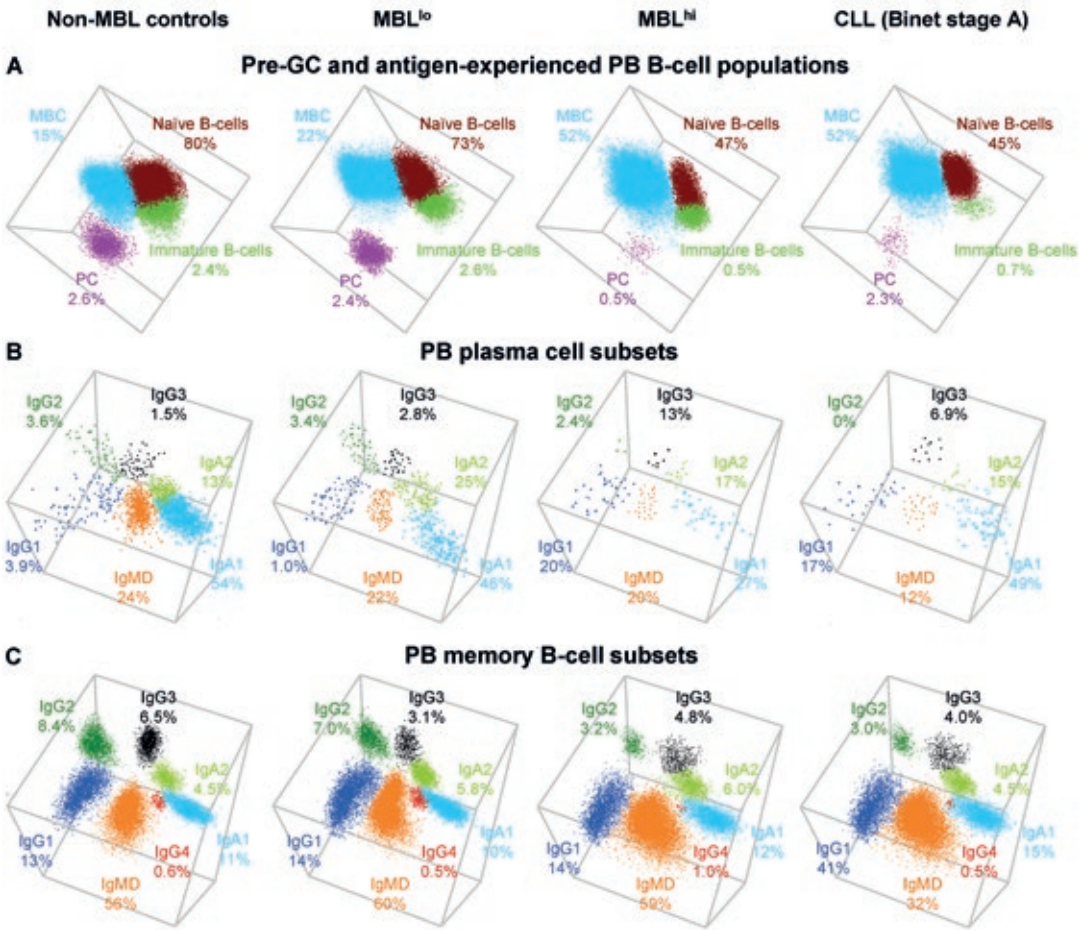

Relative distribution of distinct peripheral (PB) blood B-cell populations including the surface immunoglobulin heavy chain (sIgH)-isotype subclass subsets of memory B-cells and plasma cells in representative subjects from the non-MBL controls, MBLlo, MBLhi and Binet stage A CLL study groups. Panel A depicts the relative distribution (from total normal PB B-cells) of pre-germinal center (i.e. immature and naïve B-cells) vs. antigen-experienced B-cells (i.e. memory B-cells and plasma cells) for each of the four cases. **Panels B and C** show the relative (percent) distribution (from total PB plasma cells and total PB memory B-cells) of the different IgH-isotype subclass subsets of plasma cells and memory B-cells for each case, respectively. Each plot depicts 3-dimension automated population separator (APS) view -Principal Component 1 (PC1) vs. PC2 vs. PC3- dot plots obtained from a single representative case within each group of subjects included in this study.

38 **The myeloma stem cell concept, revisited: from phenomenology to operational terms.** Johnsen HE, Bøgsted M, Schmitz A, Bødker JS, El-Galaly TC, Johansen P, Valent P, Zojer N, Van Valckenborgh E, Vanderkerken K, van Duin M, Sonneveld P, Pérez-Andres M, Orfao A, Dybkær K. **Haematologica. 2016 Dec;101(12):1451-1459. Epub 2016 Nov 10. Review.** PMID: 27903712 **IF: 6.671 / D1**

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A, Almeida J; Primary Health Care Group of Salamanca for the Study of MBL. **Haematologica. 2017 Jul;102(7):1238-1246. doi: 10.3324/haematol.2016.159012. Epub 2017 Apr 6.** PMID: 28385786 **IF: 6.671 / D1**

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62 **Prognostic value of antigen expression in multiple myeloma: a PETHEMA/GEM study on 1265 patients enrolled in four consecutive clinical trials.** Arana P, Paiva B, Cedena MT, Puig N, Cordon L, Vidriales MB, Gutierrez NC, Chiodi F, Burgos L, Anglada LL, Martínez-López J, Hernández MT, Teruel AI, Gironella M, Echeveste MA, Rosiñol L, Martínez R, Oriol A, De la Rubia J, Orfao A, Blade J, Lahuerta JJ, Mateos MV, San Miguel JF. **Leukemia. 2017 Nov 3. doi: 10.1038/leu.2017.320.** PMID: 29099494 **IF: 12.104 / D1**

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64 **How to make usage of the standardized EuroFlow 8-color protocols possible for instruments of different manufacturers.** Nováková M, Glier H, Brdičková N, Vlková M, Santos AH, Lima M, Roussel M, Flores-Montero J, Szczepanski T, Böttcher S, van der Velden VHJ, Fernández P, Mejstříková E, Burgos L, Paiva B, van Dongen JJM, Orfao A, Kalina T. **J Immunol Methods. 2017 Nov 20. pii: S0022-1759(17)30139-4. doi: 10.1016/j.jim.2017.11.007.** PMID: 29154914 **IF: 1.858 / Q3**

65 **Efficacy and safety of native versus pegylated Escherichia coli asparaginase for treatment of adults with high-risk, Philadelphia chromosome-negative acute lymphoblastic leukemia.** Ribera JM, Morgades M, Montesinos P, Martino R, Barba P, Soria B, Bermúdez A, Moreno MJ, González-Campos J, Vives S, Gil C, Abella E, Guàrdia R, Martínez-Carballeira D, Martínez-Sánchez P, Amigo ML, Mercadal S, Serrano A, López-Martínez A, Vall-Llovera F, Sánchez-Sánchez MJ, Peñarrubia MJ, Calbacho M, Méndez JA, Bergua J, Cladera A, Tormo M, García-Belmonte D, Feliu E, Ciudad J, Orfao A; PETHEMA Group, Spanish Society of Hematology. **Leuk Lymphoma. 2017 Nov 22:1-10. doi: 10.1080/10428194.2017.1397661.** PMID: 29165013 **IF: 3.093 / Q2**

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67 **Molecular detection of minimal residual disease in multiple myeloma.** Bai Y, Orfao A, Chim CS. **Br J Haematol. 2017 Dec 19. doi: 10.1111/bjh.15075. Review.** PMID: 29265356 **IF: 5.812 / Q1**

68 **A Perspective on Proteomics of Infectious Diseases.** Venkatesh A, Gil C, Fuentes M, LaBaer J, Srivastava S. **Proteomics Clin Appl. 2017 Dec 28. doi: 10.1002/prca.201700139.** PMID: 29282898 **IF: 3.814 / Q1**

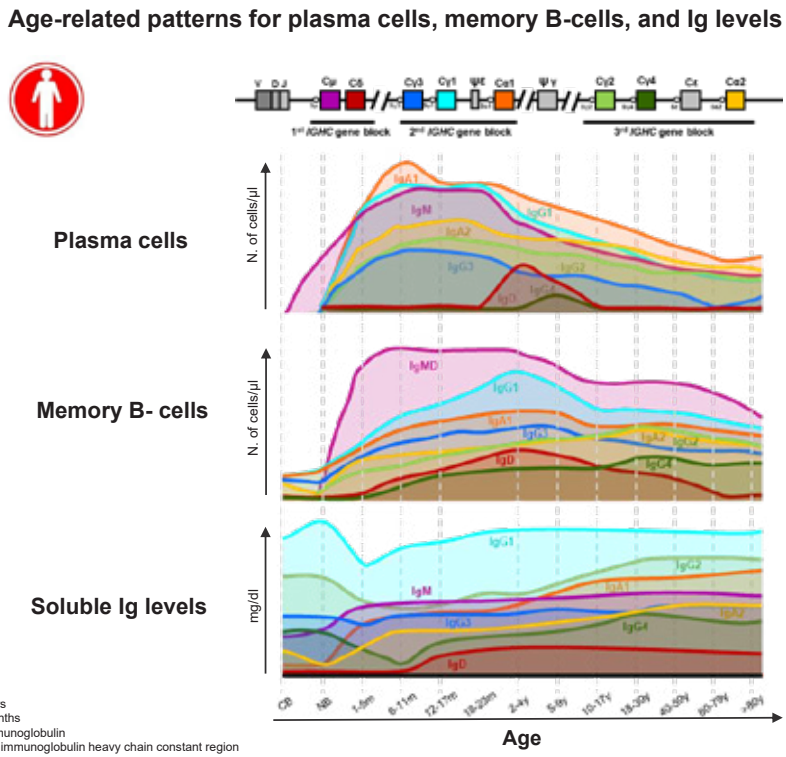
69 **Prognostic impact of a novel gene expression profile classifier for the discrimination between metastatic and non-metastatic primary colorectal cancer tumors.** Gutiérrez ML, Corchete LA, Sarasquete ME, Del Mar Abad M, Bengoechea O, Fermiñán E, Anduaga MF, Del Carmen S, Iglesias M, Esteban C, Angoso M, Alcazar JA, García J, Orfao A, Muñoz-Bellvís L, Sayagués JM. **Oncotarget. 2017 Nov 21;8(64):107685-107700. doi: 10.18632/oncotarget.22591. eCollection 2017 Dec 8.** PMID: 29296198 **IF: 5.008 / Q1**

70 **MRD detection in multiple myeloma: comparison between MSKCC 10-color single-tube and EuroFlow 8-color 2-tube methods.** Roshal M, Flores-Montero JA, Gao Q, Koeber M, Wardrope J, Durie BGM, Dogan A, Orfao A, Landgren O. **Blood Adv. 2017 May 3;1(12):728-732. doi: 10.1182/bloodadvances.2016003715. eCollection 2017 May 9.** PMID: 29296716 **IF: NI**

OTHER PUBLICATIONS & BOOK CHAPTERS

1 Peñalver FJ, De La Fuente A, Olave MT, Orfao A, Sancho JM **Diagnóstico, prevención y manejo terapeutico de la afectación del sistema nervioso central en pacientes con linfoma B difuso de célula grande. Guía de GELTAMO (Grupo Español de linfoma y trasplante de médula ósea), Sociedad Española de Hematología y Hemoterapia. Pp: 1-64, 2016.** ISNB 978-84-608-2837-2.

2 Flores-Montero J, Sanoja L, Pérez Jj, Pojero F, Puig N, Vidriales MB, Orfao A **Plasma cell disorders. En: «Manual of Molecular and Clinical Laboratory Immunology. Detrick B, Schmitz JL & Hamilton RG (Eds). 8th Edition, ASM Press, Washington DC (MA, USA). Pp: 235-250. 2016.** ISBN 9781555818722



Age-associated distribution of normal B-cell and plasma cell subsets in human peripheral blood. (Blanco, Pérez-Andres et al, J Allergy Clin Immunol. 2018)

y: years
m: months
Ig: immunoglobulin
IGHC: immunoglobulin heavy chain constant region

PATENTS

PATENT REFERENCE	TITLE	INVENTORS	PRIORITY DATE
US201715641743 20170705 EP20160382317 20160705	One step phagocytosis-cell activation-cell death assay	Fuentes García Manuel; Díez García Paula; Grunho Teodosio Cristina Isabel Gonçalves; Orfao de Matos Alberto; Jara Acevedo Ricardo; Applicant(s): Univ Salamanca; Immunostep S.L.	05/07/2016
13054EP00	Method of digital information classification	Juan Hernández, Rafael Fluxa, Alberto Orfao	12/2016

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Red Temática en Investigación Cooperativa en Cáncer. (RD12/0036/0048)	Alberto Orfao	Instituto de Salud Carlos III	2013-2016	273,125.00 €
Characterization of B cells CD5+/CD27+ in different developmental stages of monoclonal B lymphocytosis (MBL): From oligoclonal expansion of B cells CD5+/CD27+ to absolute lymphocitosis and chronic lymphocytic leukemia. (CLL) (PI12/00905)	Alberto Orfao	Instituto de Salud Carlos III	2013-2016	389,620.00 €
Minimal residual disease monitoring for multiple myeloma: automation of highly-sensitive conventional flow cytometric approaches and development of minimally invasive blood procedures	Alberto Orfao	International Myeloma Foundation USA	2013-2016	1.774,800.00 €
Caracterización fenotípica y funcional de los macrófagos tisulares circulantes: nueva estrategia de diagnóstico precoz y de monitorización de enfermedades. (PI13/01412)	Julia Almeida Parra	Instituto de Salud Carlos III	2014-2016	79,255.00 €
Monitorización de enfermedad mínima residual en neoplasias linfoides crónicas mediante la aplicación de estrategias novedosas de análisis automatizado de datos de citometría de flujo. (JCYL-SA 079U14)	Julia Almeida Parra	Consejería de Educación. Junta de Castilla y León	2014-2016	28,750.00 €
Plataforma de Bancos de Tumores (PT13/0010/0067)	Alberto Orfao	Instituto de Salud Carlos III	2014-2017	292,251.01 €
Plataforma de Recursos Biomoleculares y Bioinformáticos (PT13/0001/0037)	Alberto Orfao	Instituto de Salud Carlos III	2014-2017	1,197,989.56 €
Recursos Biomoleculares y Bioinformáticos (PRB2-ISCIII; PT13/0001/0003)	Manuel Fuentes García	Instituto de Salud Carlos III	2014-2018	184,481.00 €
Diseño y desarrollo de estrategias proteomicas de alto rendimiento para la caracterización de biomarcadores en líquido cefaloraquídeo en enfermedad leptomenígnea, linfoma non-hodgkin como modelo (BIO/SA07/15)	Manuel Fuentes García	Consejería de Sanidad/SACYL. Junta de Castilla y León	2015-2016	8,678.00 €
Identificación de alteraciones genéticas secundarias a la ruta c-Kit/SCF como factores necesarios para la progresión clínica de Mastocitosis Sistémica. Evaluación de la posible utilidad pronóstica». Ref. FS/22-2014	Andrés C. García Montero	Fundación Solórzano	2015-2016	3,845.00 €
Nuevas estrategias y aplicaciones clínicas en citometría de flujo	Julia Almeida Parra	Ministerio de Educación, Política Social y Deporte	2015-2016	9,500.00 €

PROJECT	PI	GRANT	TIME	FUNDING
Diseño y desarrollo de estrategias nanoproteómicas para la caracterización de biomarcadores en enfermedad leptomeningea, empleando linfoma non-Hodgkin como modelo (PI14/01538)	Manuel Fuentes García	Instituto de Salud Carlos III	2015-2017	120,000.00 €
Automated multidimensional flow cytometry for high-sensitive screening and to monitor response in AL amyloidosis	Alberto Orfao	International Myeloma Foundation USA	2015-2018	40,800.00 €
Nano-miR-Omics. Diseño y desarrollo de novedosas estrategias nanoproteómicas para el estudio del Interactoma miRNA-proteína en células patológicas hematopoyéticas como modelo (FS/23-2015)	Manuel Fuentes García	Fundación Solórzano	2016	4,096.00 €
Diseño, desarrollo y validación de un sistema automático de alto rendimiento para el análisis e interpretación de datos de citometria en el screening diagnóstico de hemopatías malignas (DTS15/00119)	Alberto Orfao	Instituto de Salud Carlos III	2016-2017	135,300.00 €
Programa Grupos Inv. Reconocidos. Programa XIII	Alberto Orfao	Universidad de Salamanca	2016-2017	50,121.42 €
Diseño y validación de un algoritmo genético para predecir la transformación maligna de mastocitosis indolentes a formas agresivas y otras hemopatías malignas (SA013U16)	Alberto Orfao	Junta de Castilla y León	2016-2018	120,000.00 €
AUTOMATISMO: automatización de fases pre-analiticas, analíticas y post-analíticas en citometria de flujo para ayuda en la toma de decisiones del experto en citometria (AEESD-IT de la Acción Estrategica de Economia y Sociedad Digital-Impulso Tecnológico. Cytognos / USAL)	Alberto Orfao	Ministerio de Economía y Competitividad	2016-2019	609,433.00 €
Desarrollo de una plataforma de software para gestión análisis y representación de datos provenientes de diferentes fuentes con aplicación a datos relevantes para el diagnóstico de enfermedades-MIDAS (Massive Information Data Analysis Software (RTC-2016-4865-1 RETOS de la Sociedad de la Acción Estrategica de Economia y Sociedad Digital-Impulso Tecnológico Cytognos/USAL)	Alberto Orfao	Ministerio de Economía y Competitividad	2016-2019	114,350.00 €
Identification of circulating tumor plasma cells in peripheral blood of multiple myeloma vs MGUS: clinical impact and implications in disease behavior	Alberto Orfao	International Myeloma Foundation USA	2016-2019	105,600.00 €
CYTOPREP: Metodología innovadora para el procesamiento de muestras en estudios multiparamétricos por citometria de flujo en el laboratorio clínico (RTC-2016-4707-1 RETOS de la Sociedad de la Acción Estrategica de Economia y Sociedad Digital-Impulso Tecnológico Inmunostep SL/USAL)	Alberto Orfao	Ministerio de Economía y Competitividad	2016-2019	111,393.00 €
«PERISCOPE: PERtussIS Correlates of Protection Europe0» (Innovative Medicines Initiative, de la Unión Europea en colaboración con la Fundación Bill y Melinda Gates)	Alberto Orfao	Union Europea	2016-2021	547,500.00 €
Papel del micro-medioambiente en las mastocitosis sistémicas y su potencias impacto en la progresión clínica de la enfermedad (SOL17-AMC)	Andrea Mayado Colino	Fundación Solórzano	2017	3,845.00 €
Diseño, evaluación técnica y validación clínica de un método de nueva generación para monitorización de enfermedad mínima residual en médula ósea y sangre en leucemias agudas (PI16/00787)	Alberto Orfao	Instituto de Salud Carlos III	2017-2019	212,052.00 €
Identificación de las alteraciones genéticas asociadas a la actividad oncogénica de la mutación D816V de KIT en neoplasias mieloides: la mastocitosis sistémica como modelo de estudio de la transformación maligna» Ref. PI16/00642	Andrés C. García Montero	Instituto de Salud Carlos III	2017-2020	122,815.00 €
Desarrollo de un prototipo de sistema multiplex por citometría de flujo para un novedoso diagnóstico etiopatogénico multiparamétrico del daño renal agudo (DTS 15/000166)	Manuel Fuentes García	Instituto de Salud Carlos III		96,918.00 €

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LABORATORY 12

ONCOHEMATOLOGY

The main characteristic of Prof González's group is the translational research, resulting 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 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.

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, applicability for diagnosis and Minimal Residual Disease.

3 To evaluate potential antitumoral targets in order 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.

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.

3 Cell Therapy and Transplantation.
- Study of hematopoiesis and bone marrow microenvironment in hematological disorders.
- Clinical investigation in haematopoietic transplantation. Novel procedures and complications.

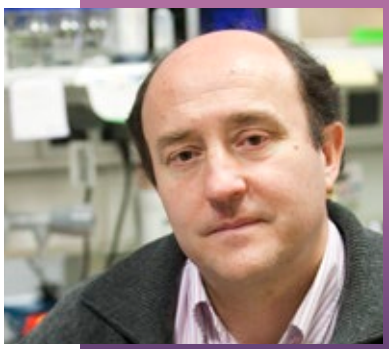
4 Novel Therapies in hematological malignancies.
- Preclinical development of novel antitumor drugs and new drug combinations.
- Molecular mechanisms of drug resistance: genomic, epigenetic, clonal heterogeneity and interactions with the bone marrow microenvironment.

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 abnormalities in MM, 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).

FUTURE CHALLENGES

- To deepen into the genomic mechanisms responsible for the development of haematological neoplasms. 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 Antigen Receptor) T-cells and NK-cells, BAR (B-cell Antigen Receptor) T-cells.



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SENIOR RESEARCHER

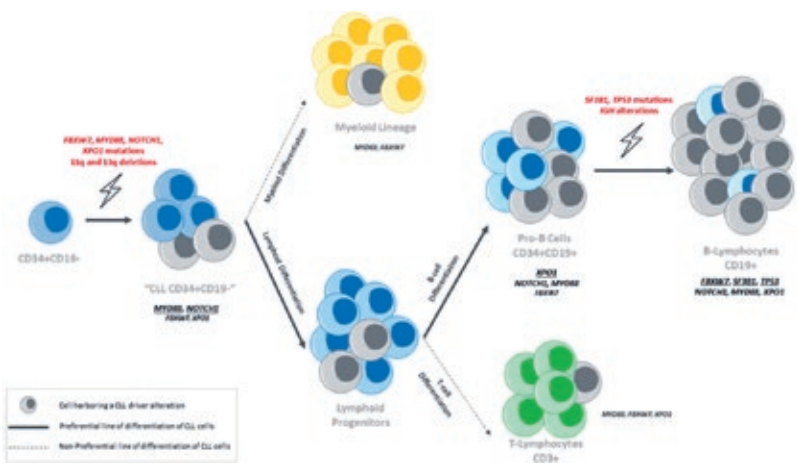
GENETICS IN ONCOHEMATOLOGY

This group is focused in the cytogenetic and molecular characterization of cancer. The scientific contribution of this line of research is competitive and internationally recognized. The **main lines of research** being developed are the following:

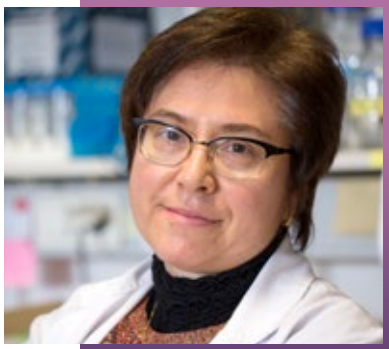
A) The comprehensive genomic analysis by integrating copy number variations, expression profiling by high-density microarrays and Next Generation Sequencing (NGS) of hematological malignancies.
B) The genomic and epigenomic studies on solid tumors.
C) Pharmacogenomics of new drugs used in cancer therapy.
D) Functional analysis by using CRISPR approaches.

The **future challenges** of the group will be the integration of data obtained on the different research lines in order to provide a personalized medicine in cancer therapy. In addition, implementation of the new tools, including Next Generation Sequencing (NGS), and the translation to the clinical setting is a main goal of the group. More specifically, the future challenges are the following:

- To analyze the mechanisms responsible for the development of drug-resistance using high-throughput CRISPR/Cas9 technology
- Generation of new leukemia-derived cell lines and animal models harboring specific mutations and reproducing the genomic heterogeneity seen in hematological malignancies, by using the CRISPR/Cas9 technology
- *In vitro* and *In vivo* assessment of CRISPR/Cas9 to the targeted cancer cells translating this tool for novel therapeutic approaches
- *To use Big Data* to deliver information that will help to improve the care of patients with hematologic malignancies. This will be achieved by gathering, integrating and analyzing 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.



Schematic model of events in hematopoiesis in CLL patients. Red gene names indicate the moment of appearance of mutations. Black names indicate the presence of a gene mutation in an specific cell population whereas underlined black gene names indicate the moment of expansion of tumor cells harboring these gene mutations during B-CLL differentiation. [from Quijada-Alamo et al. J Hematolo Oncol 2017; 11;10(1):83. doi: 10.1186/s13045-017-0450-y].



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SENIOR RESEARCHER

BONE MARROW MICROENVIRONMENT IN MULTIPLE MYELOMA AND BONE LESIONS

Our group has focused on the study of the role of the bone marrow microenvironment in the pathogenesis of multiple myeloma and in the development of bone lesions associated to this disease and other malignancies. We are also involved in preclinical studies of anti-myeloma agents with a specific effect on the bone marrow microenvironment: either overcoming the proliferative advantage conferred to myeloma cells and/or having a beneficial effect on osteolytic lesions. Besides, we are exploring the role of exosomes (50-100 nm vesicles) in the intercellular communication between myeloma cells and other cells in the bone marrow microenvironment.

LINES OF RESEARCH AND STRATEGIC OBJECTIVES

1) Comparative study (gene expression, epigenetics, functional) of bone marrow stromal cells (MSCs) at different stages of the disease and after anti-myeloma treatment, with the aim of identifying the putative contribution of these cells of the microenvironment in the onset of symptomatic myeloma, myeloma progression and/or in the development of osteolytic lesions.
2) To study the interactions of myeloma cells and MSCs, and to determine the gene expression/epigenetic/functional changes in both types of cells after those interactions and their role in myeloma pathophysiology.
3) To elucidate the role of exosomes as paracrine signaling mediators in myeloma bone marrow microenvironment.
4) To characterize the efficacy and mechanism of action (*in vitro* and *in vivo* models) of specific agents with anti-myeloma and bone anabolic/ anti-resorptive effects.

FUTURE CHALLENGES

- To identify mechanisms by which the bone marrow microenvironment mediates therapeutic resistance and survival to myeloma cells.
- To characterize the effects and mechanism of action of new immunotherapeutic agents alone and in combination with standard agents in multiple myeloma, using both *in vitro* and *in vivo* models.
- To explore the potential biomarker value of circulating exosomal microRNAs from myeloma patients.

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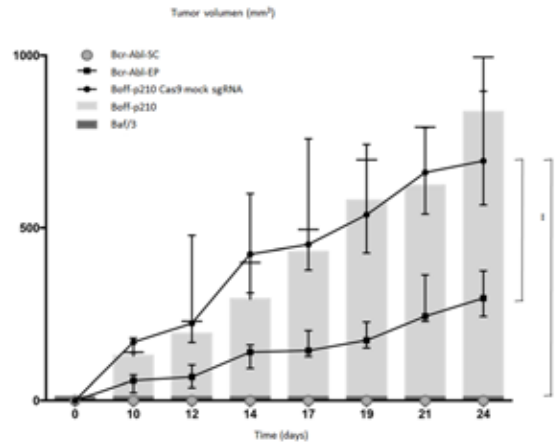
A



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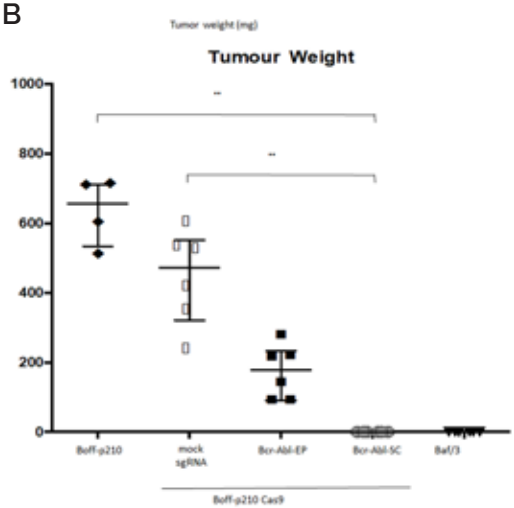
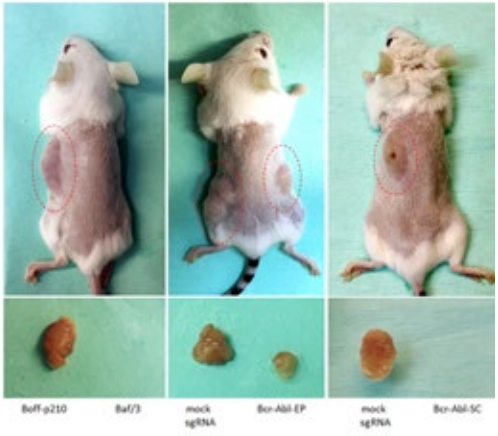


C



***In vivo* effects of CRISPR-mediated editing of the BCR/ABL oncogene. A)** Tumor growth (mm3) over the 24 days following subcutaneous cell injection. Similar tumor growth was observed in Boff-p210 (grey bars) and Boff-p210 Cas9 mock sgRNA (black dots line) injected cells. Tumors formed by Bcr-Abl-EP cells (black squares line) were half the size of those induced previously. Tumor growth was observed when the single edited cell-derived cells were injected (grey dotted line), as well Baf/3 cells (dark grey bars). The plot shows medians and ranges; ***$p < 0.001$. **B)** After 24 days, mice were sacrificed and their tumor mass measured. The final tumor mass was reduced by half in the case of the edited pool cells (black squares), relative to controls (black dots). Bcr-Abl-SC (grey dots) and Baf/3 (black triangles) cells were unable to form a subcutaneous tumor. The plot shows medians and ranges; **$p < 0.05$. **C)** External appearance of mice and developed tumors 24 days after subcutaneous cell injection. [from García-Tuñón I et al. Oncotarget 2017; 8:26027-26040. doi: 10.18632/oncotarget.15215].

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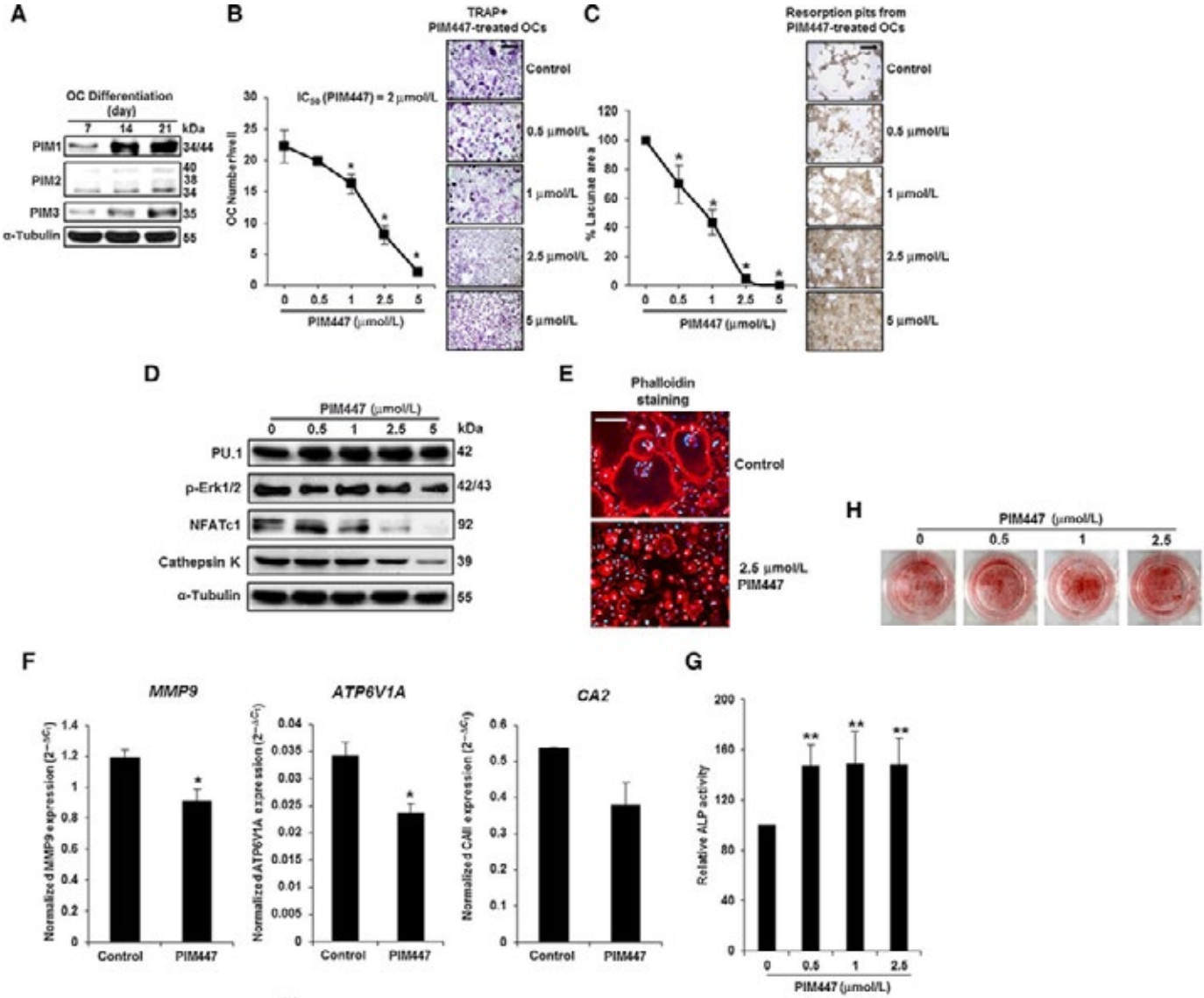

The novel pan-Pim kinase inhibitor, PIM447, inhibits in vitro OC formation and resorption and increases OB differentiation and activity. A) PBMCs were differentiated in osteoclastogenic medium for the indicated times. PIM1, PIM2, and PIM3 expression was analyzed by Western blot. **B)** OC formation was evaluated by the mean number of TRAP+ multinucleated cells (≥3 nuclei) per well after PIM447 treatment of osteoclastogenic cultures for 21 days. IC50 of PIM447 was calculated using SigmaPlot graphing software. **C)** To test the effect of PIM447 on OC resorption, PBMCs were cultured on calcium-coated slides in the presence of osteoclastogenic medium and PIM447 treatment as indicated. After 17 days, OCs were removed and the area of resorbed lacunae analyzed. **D)** PBMCs were differentiated in osteoclastogenic medium and exposed to different concentrations of PIM447. The levels of PU.1, phospho Erk1/2, and NFATc1 at day 7 and Cathepsin K at day 14 were analyzed by Western blot. **E)** Pre-OCs differentiated under PIM447 exposure for 14 days were stained with rhodamine-conjugated phalloidin and examined by fluorescence microscopy to visualize the F-actin ring. **F)** Relative gene expression of several molecules implicated in OC resorption after osteoclastogenic differentiation of PBMCs for 21 days in the presence of PIM447 (2.5 μmol/L) was assessed by real-time RT-PCR. **G)** Primary bone marrow MSCs from myeloma patients (n = 5) were maintained in osteogenic medium in the presence of indicated PIM447 concentrations, and ALP activity (nmol/L/min/μg protein) was measured at day 11. **H)** Representative micrographs of matrix mineralization by Alizarin Red staining in OBs derived from MSCs from a multiple myeloma patient (21 days of osteogenic differentiation in the presence of PIM447). [modified from Paino T et al. Clin Cancer Res. 2017; 23:225-238. doi: 10.1158/1078-0432.CCR-16-0230].

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201 Prevention and management of adverse events of Novel agents in multiple myeloma: A consensus of the european myeloma network. Ludwig H, Delforge M, Facon T, Einsele H, Gay F, Moreau P, Avet-Loiseau H, Boccadoro M, Hajek R, Mohty M, Cavo M, Dimopoulos MA, San-Miguel JF, Terpos E, Zweegman S, Garderet L, Mateos MV, Cook G, Leleu X, Goldschmidt H, Jackson G, Kaiser M, Weisel K, van de Donk NWCJ, Waage A, Beksac M, Mellqvist UH, Engelhardt M, Caers J, Driessen C, Sonneveld P. **Leukemia. 2017 Dec 18. doi: 10.1038/leu.2017.353. Review.** PMID: 29251284 **IF: 12.104 / D1**

202 Hemorrhagic pericardial effusion as the debut of acquired hemophilia in a chronic lymphocytic leukemia patient: A case report, and a review of acquired hemophilia A-related hematological malignancies. Bastida JM, Cano-Mozo MT, López-Cadenas F, Vallejo VE, Merchán S, Santos-Montón C, González-Calle D, Carrillo J, Martín AA, Torres-Hernández JA, González M, Martín-Herrero F, Pabón P, González-Porras JR. **Medicine (Baltimore). 2017 Nov;96(47):e8669. doi: 10.1097/MD.0000000000008669.** PMID: 29381944 **IF: 2.133 / Q2**

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204 Unmet needs in histological transformation of follicular lymphoma: a clinical and biological review. Alcoceba M, Alonso-Álvarez S, García-Álvarez M, Martín A, Caballero MD. **Ann Lymphoma 2017.** 1: 11 **IF: NI**

OTHER PUBLICATIONS & BOOK CHAPTERS

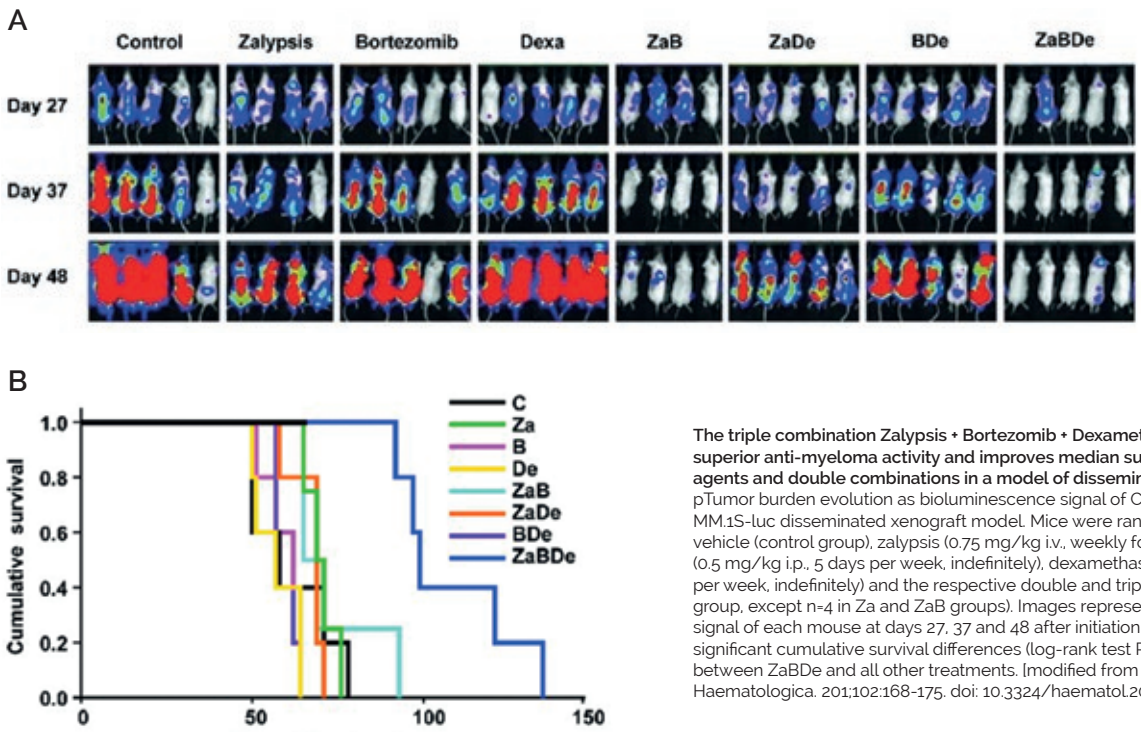
1 Sanchez-Guijo F. **Trasplante de sangre de cordón intramedular. En Carreras E (ed): Manual de trasplante hematopoyético. Barcelona, Ediciones Escofet Zamora, 2016.** ISBN: 978-84-88825-21-6

2 Prosper F, Sanchez-Guijo F, del Cañizo C. **Terapia celular en el TPH y otras aplicaciones. En Carreras E (ed): Manual de trasplante hematopoyético. Barcelona, Ediciones Escofet Zamora, 2016.** ISBN: 978-84-88825-21-6

3 Francisco Javier Peñalver, Adolfo de la Fuente, Mª Teresa Olave, Alberto Orfao, Juan Manuel Sancho, Alejandro Martín, Carlos Panizo, Elena Pérez Ceballos, Antonio Salar. **Diagnóstico, prevención y manejo terapéutico de la afectación del sistema nervioso central en pacientes con linfoma B difuso de célula grande.** ISBN: 978-84-617-7738-9. Depósito Legal: M-1032-2017

4 Mónica Coronado, Fátima de la Cruz, Antonio Manuel Gutiérrez, Alejandro Martín, Silvana Novelli. **Guía de GELTAMO para el diagnóstico y tratamiento de linfomas los T.** ISBN: 978-84-697-3652-4. Depósito Legal: M-16552-2017

5 Beatriz Albarrán, Dolores Caballero, Miguel Cabezudo, Erik de Cabo, Borja Cidoncha, Francisco Javier Díaz, Silvia Fernández, Ramón García, Marcos González, Tomás José González-López, Roberto Hernández, Jorge Labrador, Alejandro Martín, Marta Megido, Emilia Pardal, Mª Jesús Peñarrubia, José Antonio Queizán, Alicia Smucler, Mª Jesús Vidal. **Guía de Linfomas. Sociedad de Hematología y Hemoterapia de Castilla y León (SCLHH).**



The triple combination Zalypsis + Bortezomib + Dexamethasone (ZaBDe) has superior anti-myeloma activity and improves median survival compared with single agents and double combinations in a model of disseminated multiple myeloma. A) pTumor burden evolution as bioluminescence signal of CB17-SCID mice bearing the MM.1S-luc disseminated xenograft model. Mice were randomly assigned to receive vehicle (control group), zalypsis (0.75 mg/kg i.v., weekly for three doses), bortezomib (0.5 mg/kg i.p., 5 days per week, indefinitely), dexamethasone (1 mg/kg i.p., 2 days per week, indefinitely) and the respective double and triple combinations (n=5 per group, except n=4 in Za and ZaB groups). Images representing the bioluminescence signal of each mouse at days 27, 37 and 48 after initiation of treatment. **B)** Statistically significant cumulative survival differences (log-rank test P<0.05) were found between ZaBDe and all other treatments. [modified from López-Iglesias AA et al. Haematologica. 201;102:168-175. doi: 10.3324/haematol.2016.146076].

PATENTS

PATENT REFERENCE	TITLE	INVENTORS	PRIORITY DATE
17382601.7- 1408	New treatments of multiple myeloma.	Esteban Martín, Santiago (IDP Discoveery Pharma SL.); Nevola, Laura (IDP Discovery Pharma SL); Ocio San Miguel, Enrique María (Fundación de Investigación del Cáncer. Universidad de Salamanca); Krezeminski, Patryck (Fundación de Investigación del Cáncer. Universidad de Salamanca); Garayoa, Mercedes (Fundación de Investigación del Cáncer. Universidad de Salamanca).	

GRANTS FOR RESEARCH IN PROGRESS

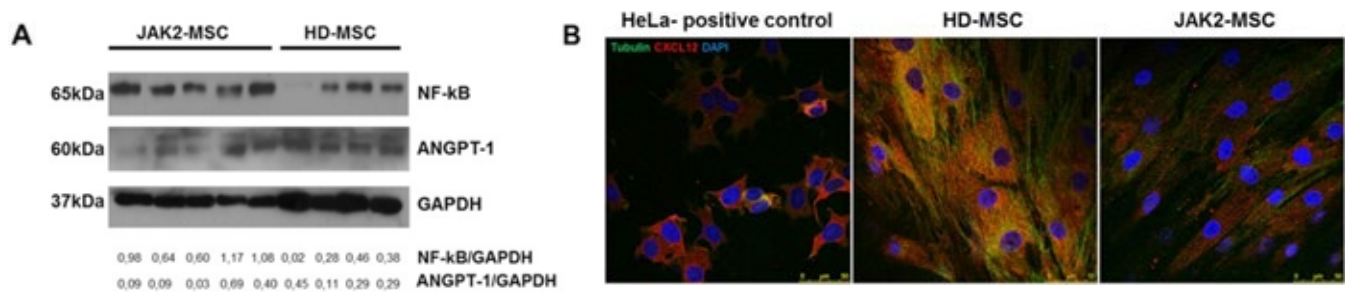
PROJECT	PI	GRANT	TIME	FUNDING
Análisis de marcadores de resistencia en mieloma múltiple y desarrollo de alternativas terapéuticas para superarla: proyecto basado en dos ensayos nacionales (GCB120981SAN)	Ramón García Sanz y Juan José Lahuerta Palacios	Spanish Association against Cancer (AECC)	2012-2017	418,837.00 €
Nodo 13 perteneciente a la «Red Nacional de Terapia Celular-TerCel» (RD12/0017/0019)	Mª Consuelo del Cañizo Fernández Roldán	Instituto de Salud Carlos III	2013-2016	331,200.00 €
Red Temática de Investigación Cooperativa en Cáncer (RD12/0036/0069)	Marcos González Díaz	Instituto de Salud Carlos III	2013-2016	330,180.00 €
Investigación del splicing del RNA y de su regulación en el mieloma múltiple (PI13/00111)	Norma C Gutiérrez Gutiérrez	Instituto de Salud Carlos III	2014-2016	67,155.00 €
Genómica funcional de Células Stem Mesenquimales (MSC) de individuos normales y pacientes con mieloma múltiple (FIC335U14)	Mercedes Garayoa Berrueta	Consejería de Educación. Junta de Castilla y León	2014-2017	29,000.00 €
Mecanismos moleculares responsables de la transformación histológica del linfoma folicular. Implicaciones pronosticas (GRS 1180/A/15)	Marcos González Díaz	Gerencia Regional de Salud. Junta de Castilla y León	2015-2016	20,000.00 €
Desarrollo de estrategias para vencer la resistencia a inhibidores del proteasoma en mieloma múltiple (GRS 1175/A/15)	Enrique M. Ocio San Miguel	Gerencia Regional de Salud. Junta de Castilla y León	2015-2016	19,000.00 €
Influencia de ruxolitinib (INC424) en el perfil de expresión génica de pacientes con mielofibrosis (GRS 1172/A/15)	Jesús Mª Hernández Rivas	Gerencia Regional de Salud. Junta de Castilla y León	2015-2016	19,700.00 €
Estudio de vesículas extracelulares plasmáticas como biomarcadores de síndromes mielodisplásicos y leucemias agudas mieloblásticas (GRS 1201/A/15)	Mª Consuelo del Cañizo Fernández Roldán	Gerencia Regional de Salud. Junta de Castilla y León	2015-2016	18,960.00 €
Evaluación de la actividad antitumoral de la amilorida en modelos pre-clínicos de mieloma múltiple (BIO/SA22/15)	Irena Misiewicz-Krzeminska	Consejería de Sanidad. Junta de Castilla y León	2015-2016	30,667.00 €
Evaluación preclínica de mecanismos de resistencia a fármacos anti-mieloma (Inhibidores del proteasoma e inmunomoduladores) y desarrollo de estrategias destinadas a vencerla	Enrique M Ocio San Miguel	Instituto de Salud Carlos III	2015-2017	159,115.00 €

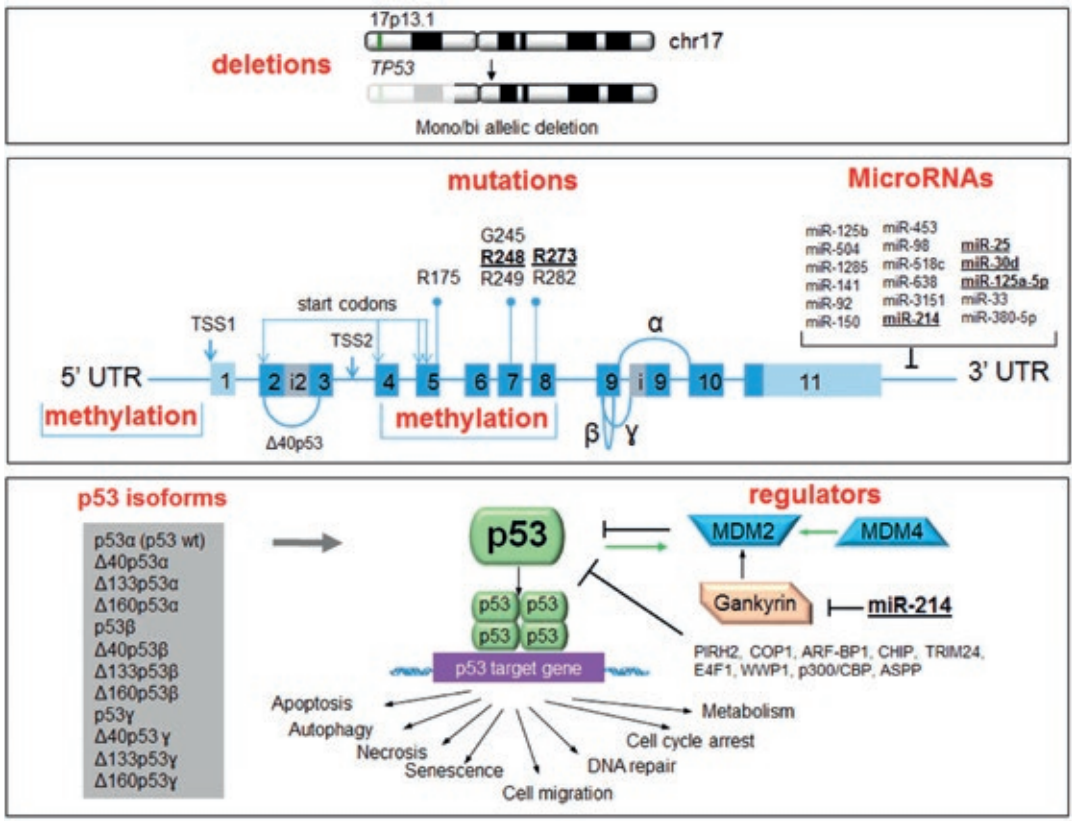
PROJECT	PI	GRANT	TIME	FUNDING
CARdioToxicity In the Elderly pRogramme: the CARTIER Project (CARTIER)	Fermín Sánchez-Guijo (WP-8)	Instituto de Salud Carlos III	2015-2017	50,000.00 €
Nodo 16 del Consorcio RETHRIM (Restoring tissue regeneration in patients with visceral graft versus host disease; proposal number 643580) (H2020-PHC-2014-single-stage_RTD, actividad PCH-15-2014)	Fermín M. Sánchez-Guijo	Unión Europea	2015-2019	314,850.00 €
Providing the right care to the right patient with MyeloDysplastic Syndrome at the right time (Ref. MDS-RIGHT) ((H2020-PHC-2014, Topic: PHC-17-2014 / 634789-2)	Jesús Mª Hernández Rivas	Unión Europea	2015-2020	35,145.00 €
Optimization and validation of an automated capillary immunoelectrophoresis technology to quantify the expression of essential proteins in the pathogenesis of multiple mieloma. IMF	Norma C Gutiérrez Gutiérrez	International Myeloma Foundation	2016	100,000.00 $
Caracterización funcional de genes desregulados en el mieloma múltiple: significado biológico e identificación de nuevas dianas para el tratamiento de la enfermedad (FS/25-2015)	Ana Belén Herrero Hernández	Fundación D Manuel Solórzano Barruso	2016	5,308.00 €
Estudio del exoma en muestras pareadas al diagnóstico y transformación a linfoma difuso de célula B grande en Macroglobulinemia de Waldenström (FS/26-2015)	Mª Dolores Caballero Barrigón	Fundación D Manuel Solórzano Barruso	2016	5,077.00 €
Evaluación del efecto sinérgico del inhibidor pan-PIM kinasa, PIM447, en combinación con terapias estándar en modelos preclínicos de mieloma múltiple (FS/22-2015)	Teresa Paíno Gómez	Fundación D Manuel Solórzano Barruso	2016	4,096.00 €
Inmunoterapia en mieloma múltiple: evaluación preclínica y clínica de nuevos tratamientos (BIO16/00007)	Teresa Paíno Gómez	IBSAL – Junta de Castilla y León	2016	25,000.00 €
Estudio del exoma en muestras pareadas al diagnóstico y transformación a linfoma difuso de célula B grande en Macroglobulinemia de Waldenström (FUCALHH 2015)	Ramón García Sanz	Asociación Castellano-Leonesa de Hematología y Hemoterapia	2016	6,000.00 €
Papel de la sobrecarga férrica en el daño del estroma en los Síndromes Mielodisplásicos (BIO16/00005).	Sandra Muntión	Consejería de Sanidad de la Junta de Castilla y León	2016	25,000.00 €
Design and standardization of a new NGS approach for integrated evaluation of IGH somatic hypermutation, gene mutations and copy-number variations in patients with CLL (GLD15/00348)	Marcos González Díaz	Instituto de Salud Carlos III	2016	44,405.00 €
Efecto de la dosis de exosomas derivados de células mesenquimales en la función hematopoyética in vitro e in vivo (GRS1348/A/16).	Fermín Sánchez-Guijo	Gerencia Regional de Salud. Junta de Castilla y León	2016-2017	16,539.00 €
Evaluación de biomarcadores de respuesta al inhibidor de check-point inmune pembrolizumab (AcMo anti-PD-1) en mieloma múltiple. GRS 1339/A/16	Enrique M. Ocio San Miguel	Gerencia Regional de Salud. Junta de Castilla y León	2016-2017	18,876.00 €
Papel de la vitamina D en mieloma múltiple: implicaciones clínico-biológica. GRS/ 1340/A/16	María-Victoria Mateos Manteca	Gerencia Regional de Salud. Junta de Castilla y León	2016-2017	18,315.00 €
Perfil de microRNAs de exosomas de plasma de pacientes con mieloma tratados según el ensayo CLARIDEX. Valor diagnóstico, pronóstico y/o marcador de respuesta (IBY15/00004)	Marcos González Díaz (IP CANC-17) Mercedes Garayoa (IP CANC-17) Norma C Gutiérrez (IP CANC-03 Mª Consuelo del Cañizo (IP CANC-05)	Proyecto integrado grupos del IBSAL; convocatoria competitiva	2016-2017	40,000.00 €

PROJECT	PI	GRANT	TIME	FUNDING
Biología molecular y celular en hemopatías. Programa XIII de la USAL para la Financiación de Grupos de Investigación Reconocidos (GIR 184086/ 463AC01)	Marcos González Díaz	Universidad de Salamanca	2016-2017	20,202.57 €
Estudio mediante secuenciación masiva y PCR-digital de las mutaciones de los genes implicados en mielofibrosis (GRS 1343/A/16)	Jesús Mª Hernández Rivas	Gerencia Regional de Salud. Junta de Castilla y León	2016-2017	16,966.00 €
Impacto pronostico del perfil mutacional de las celulas blasticas quimioresistentes en pacientes con neoplasias mieloides sometidos a trasplante alogenico (GRS1346/A/16)	Marcos González Díaz	Gerencia Regional de Salud. Junta de Castilla y León	2016-2017	16,517.00 €
Evaluación ultra-sensible de enfermedad mínima residual como biomarcador de curabilidad en dos modelos de mieloma múltiple (sintomático y quiescente de alto riesgo). PI15/02049	María-Victoria Mateos Manteca	Instituto de Salud Carlos III	2016-2018	94,380.00 €
Regulación del microambiente en el mieloma múltiple por microRNAs: papel en la enfermedad y posibilidades terapéuticas (PI15/02156)	Mercedes Garayoa Berrueta	Instituto de Salud Carlos III	2016-2018	110,715.00 €
IDP4MM - Desarrollo de fármacos en nuevas dianas terapéuticas IDP para el tratamiento del mieloma múltiple (RTC-2016-5056-1)	Enrique M. Ocio San Miguel	Ministerio de Economía y Competitividad	2016-2018	86,350.00 €
Análisis genómico y funcional de la evolución clonal en los enfermos con leucemia linfática crónica y en un modelo «in vitro» de modificación genética dirigida (PI15/01471)	Jesús Mª Hernández Rivas	Instituto de Salud Carlos III	2016-2018	134,915.00 €
Mecanismos moleculares de la transformación clínico-histológica del Linfoma Folicular a Linfoma agresivo. Implicaciones pronósticas y su aplicación en el diseño de nuevas terapias (PI15/01393)	Mª Dolores Caballero (IP) y Miguel Alcoceba	Instituto de Salud Carlos III	2016-2018	50,215.00 €
Estrategias de nueva generación para la caracterización molecular global del clon tumoral en el mieloma múltiple: implicaciones en diagnóstico clínico y patogenia de la enfermedad (PI15/01956)	Ramón García Sanz	Instituto de Salud Carlos III	2016-2018	87,120.00 €
Análisis de la leucemia aguda linfoblástica mediante un estudio transcriptómico (RNA-SEQ) y funcional (CRISPR), en un entorno BIG DATA (SA085U16)	Jesús Mª Hernández Rivas	Junta de Castilla y León, Consejería de Educación	2016-2018	120,000.00 €
Caracterización genómica de la leucemia mieloblástica aguda. Utilidad clínica del perfil genético al diagnóstico y en la monitorización terapéutica (PI15/01706)	Marcos González Díaz	Instituto de Salud Carlos III	2016-2018	56,265.00 €
Impacto pronóstico de mutaciones genéticas en pacientes con leucemia aguda linfoblástica infantil tratados según el protocolo SEHOP-PETHEMA 2013: proyecto colaborativo del Comité de Estudios Biológicos del Grupo de Leucemias de la Sociedad Española de Hemato-Oncología Pediátrica	Jesús María Hernández Rivas (IP: Mireia Camós)	Fundación Unoentrecienmil	2016-2018	100,000.00 €
Función, valor diagnóstico e inhibición farmacológica de R-RAS2, un nuevo «driver» oncogénico (GC16173472GARC)	Mª Dolores Caballero (IP-3)	Asociación Española Contra el Cáncer	2016-2021	197,500.00 €
Genética Molecular en Oncohematología. Programa XIII	Jesús Mª Hernández Rivas	Universidad de Salamanca	2017	19,611.00 €
Análisis funcional in vivo del truncamiento del gen ATM en células stem hematopoyéticas humanas mediante la tecnología de edición genómica CRISPR/Cas9: Implicaciones en leucemia linfática crónica.	Josefa Verónica Alonso Pérez	Fundacion Solórzano	2017	1,500.00 €

PROJECT	PI	GRANT	TIME	FUNDING
CIBER. Incorporación de nuevas áreas temáticas y nuevos grupos al consorcio CIBER, de la convocatoria 2016 de la Acción Estratégica en Salud 2013 – 2016. ÁREA TEMÁTICA DE CÁNCER (CB16/12/00233)	Marcos González Díaz	Instituto de Salud Carlos III	2017	300,260.00 €
Waldenstrom Macroglobulinemia transformed into agressive forms of disease: Evaluation of diagnostic and therapeutic possibilities of genomic changes (GLD16/12/00233)	Ramón García Sanz	Gilead	2017-2018	46,728.00 €
From preclinical models to the patient: a holistic investigation of immunotherapies in multiple myeloma (FRA 16/003)	Enrique M. Ocio San Miguel	Fundación Ramón Areces	2017-2019	119,998,50 €
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)	Mª Carmen Chillón	Fondo de investigaciones sanitarias / ISCIII	2017-2019	141,570.00 €
Estudio del estado funcional de p53 en el mieloma múltiple y de su repercusión en la respuesta terapéutica y en la supervivencia de los pacientes. (PI16/01074)	Norma C Gutiérrez Gutiérrez	Instituto de Salud Carlos III	2017-2019	154,275.00 €
Tratamiento de enfermedades inmunes/inflamatorias con vesículas extracelulares derivadas de células mesenquimales pre- estimuladas: la enfermedad injerto contra huésped como modelo para el desarrollo clínico (PI16/01407)	Fermín Sánchez-Guijo	Instituto de Salud Carlos III	2017-2019	62,315.00 €
Optimización de las células mesenquimales para su empleo en trastornos inmunes: estudio in vitro e in vivo financiado por la (CAS079P17)	Fermín Sánchez-Guijo	Consejería de Educación de la Junta de Castilla y León	2017-2019	118,600.00 €
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	Unión Europea	2017-2021	2,200,000.00 €

Protein expression of NF-kB, ANGPT-1 and CXCL12 in mesenchymal stromal cells from patients with myeloproliferative neoplastic diseases (MPN-MSC). A) Western Blot of NF-kB and ANGPT-1 in MPN and HD-MSC. **B)** Representative image of CXCL12 expression in MSCs by immunofluorescence. HD-MSCs show higher expression of CXCL12 (red) than MPN-MSCs. Green fluorescence shows tubulin. Scale: 0–50µm. [from Ramos TL et al. PLoS One 2017; 12:e0182470. doi: 10.1371/journal.pone.0182470].





Mechanisms of p53 regulation in cancer. p53 can be attenuated directly, by mutation or deletion, or indirectly through alterations in methylation, miRNAs, isoform expression and p53 regulators. Six TP53 hotspot mutations and regions potentially affected by methylation are indicated. p53 isoforms arise from the use of two alternative transcription start sites (TSS1 and TSS2), four start codons and alternative splicing, which originates the isoforms **α**, **β** and **γ**. miRNAs and regulators reported to affect p53 expression are shown. Alterations reported in MM are highlighted in bold and underlined. [from Herrero AB et al. Int J Mol Sci. 2016 Nov 30;17(12). pii: E2003. Review].

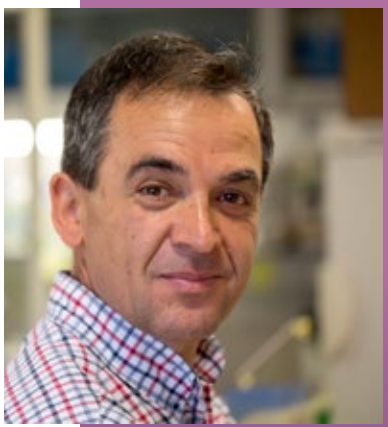
OTHER ACTIVITIES & RELEVANT FACTS

SCIENTIFIC NETWORKS AND INTERNATIONAL PLATFORMS

- Aristotele-Assessing the Risk of Transformation of Follicular Lymphoma in the Immunochemotherapy Era, and its Outcome (ELI). Estudio europeo observacional retrospectivo sobre la transformación de los linfomas indolentes (linfoma folicular) a linfoma agresivo. Promotor: European Lymphoma Institute (ELI): PI: M. Dolores Caballero and M. Federico. Collaborators: Sara Alonso and Miguel Alcoceba.
- ERIC-TP53 Network– Proyecto Europeo de estandarización de las técnicas moleculares de identificación de mutaciones de TP53. Promotor: European Research Initiative on CLL (ERIC). Coordinator: P. Ghia. PI Reference Center in Spain: Marcos González. Collaborators: Miguel Alcoceba and Ramón García-Sanz.
- Euroclonality (EC), EC-MRD, EC-NGS - Proyecto Europeo de estandarización de técnicas moleculares (análisis de clonalidad, estudio de reordenamientos de las inmunoglobulinas y receptor de células T, y paneles de alteraciones genéticas) incluido su empleo y análisis mediante NGS. Promotor: Euroclonality/ BIOMED-2 consortium. Collaborators: Ramón García-Sanz, Cristina Jiménez, M. Eugenia A. Sarasquete, M. Carmen Chillón, Miguel Alcoceba and Alejandro Medina.
- EuroMRD Consortium. Grupo europeo para el estudio de enfermedad minima residual en LLA ALL Ph+ (ESG-MRD-ALL). Collaborator: M. Carmen Chillón.
- EuroFlow – Proyecto Europeo de estandarización de la citometría de flujo de nueva generación. Promotor: Euroclonality/BIOMED-2 consortium. Collaborator: M. Belén Vidriales.

SPANISH NETWORKS SCIENTIFIC AND PLATFORMS:

- RTICC - Red Temática de Investigación Cooperativa en Cáncer – Marcos González Coordinator Hematological Tumors Program and PI RD12/0036/0069 group.
- CIBERONC – Marcos González Coordinator Hematological Tumors Program and PI CB16/12/00233 group.
- GEL-LFT-2014-1 - Estudio observacional retrospectivo sobre la transformación de los linfomas indolentes (linfoma folicular) a linfoma agresivo – Promotor: GELTAMO. PI: M. Dolores Caballero. Collaborators: Alejandro Martín, Marcos González, Sara Alonso, Miguel Alcoceba and María García Álvarez.
- PlatafoLMA - Desarrollo de una plataforma de diagnóstico y seguimiento integrales para medicina personalizada en la leucemia mieloblástica aguda - Red Nacional para el análisis de mutaciones al diagnóstico de la leucemia mieloblástica aguda. Promotor: Pethema. Collaborators: M. Belén Vidriales and M. Carmen Chillón.
- LMC – Estudio nacional para el evaluar el impacto de las mutaciones en el dominio quinasa de ABL1 detectadas mediante NGS en la respuesta a los inhibidores tirosin quinasa en la LMC y en las LLA Ph+. Promotor: Fundación Española de Hematología y Hemoterapia. Collaborators: M. Carmen Chillón and Ramón García-Sanz.
- NGS-LMA - Desarrollo de una plataforma de diagnóstico integral y rápido para medicina personalizada en la leucemia mieloblástica aguda. Promotor: Pethema. Collaborators: M. Carmen Chillón, M. Isabel Prieto-Conde.
- RED53 – Red Nacional para el análisis de las mutaciones de TP53 y de la hipermutación somática de las inmunoglobulinas. Promotor: Janssen. PI Salamanca: Marcos González. Collaborators: Miguel Alcoceba, Ana Balanzategui and Ramón García-Sanz.
- Centro en Red de Medicina Regenerativa y Terapia Celular de Castilla y León (Grupo Centro de Investigación del Cáncer). Junta de Castilla y León, Consejería de Sanidad y Gerencia Regional de Salud. PI Salamanca: Fermín Sánchez-Guijo and Mercedes Garayoa. Collaborators: Sandra Muntión, Teresa Paíno, Silvia Preciado, Ana Rico, E Macarena Algarín and Andrea Díaz.
- Centro en Red de Medicina Regenerativa y Terapia Celular de Castilla y León (Grupo Hospital Universitario de Salamanca). Junta de Castilla y León, Consejería de Sanidad y Gerencia Regional de Salud. PI Salamanca: Consuelo del Cañizo and Fermín Sánchez-Guijo.



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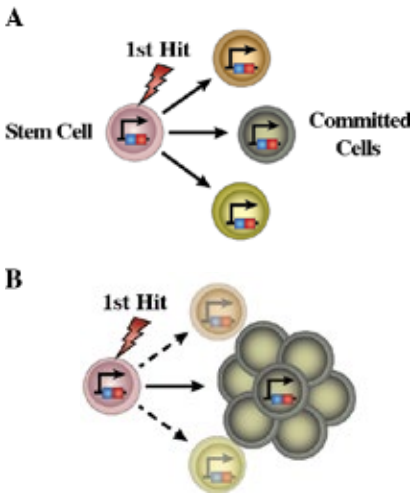
LABORATORY 13

STEM CELLS, CANCER STEM CELLS AND CANCER BIOLOGY



Schematic representation of the emergence of LSCs in human leukemia. A) A mutation occurs in HSCs leading to the emergence of aberrant pre-leukemic HSCs. These aberrant pre-leukemic HSCs self-renew and expand within the HSC compartment. Pre-leukemic HSCs give rise to a high number of lineage-committed progenitors harboring the identical mutations. This leads to an increased chance of acquiring the additional oncogenic events, which finally transform the aberrant progenitor cells from pre-leukemic HSCs into the leukemic stem cells (LSCs). **B)** Loss of differentiation potentials is essential for the emergence of LSCs. These sequential leukemia progression models are commonly accepted as to the development process of human acute malignancies

The elucidation of the molecular mechanisms that underlie tumor development remains a tremendous challenge for basic science, but also represents an essential step in the development of new drugs. The origin of cancer within a particular tissue is often impossible to determine, due to the advanced stages when patients enter the clinic. Our knowledge about the etiology of cancer is therefore derived from animal models that recapitulate human disease.

Due to the clonal nature of human cancer evolution, all tumoral cells carry the same cancer-initiating genetic lesions, independently of the intrinsic tumoral cellular heterogeneity. However, our latest findings have shown that the mode of action of oncogenes is not homogeneous throughout the developmental history of the tumor. Studies on different types of hematopoietic tumors have shown that the contribution of oncogenes to cancer development is mainly mediated through the epigenetic reprogramming of the cancer-initiating target cell.

This driving of cancer by a malignant epigenetic stem cell rewiring is however not exclusive of the hematopoietic system, but rather represents a common tumoral mechanism that is also at work in epithelial tumors. Tumoral epigenetic reprogramming is therefore a new type of interaction between genes and their target cells, in which the action of the oncogene modifies the epigenome to prime cancer development by establishing a new pathological tumoral cellular identity.

This reprogramming may remain latent until it is afterwards triggered by either endogenous or environmental stimuli. This new view on oncogenesis not only reveals a novel function for oncogenes in cancer, but also provides evidence for a previously unconsidered model of tumorigenesis, in which the programming of the cancerous cellular identity has already occurred at the level of stem cells, therefore showing a role for oncogenes in the timing of cancer initiation. These findings on the mechanisms of cellular commitment to a tumoral fate are relevant also to regenerative medicine, since it will be essential to have full control over the potential malignancy of reprogrammed cells.

Our CSC-based mouse models are unique tools to address this challenge, and they will be used by our research team as the basis for understanding the molecular mechanisms that govern the development of cancer cells as a result of a reprogramming-like mechanism. We hope this investigation will result not only in new concepts in cancer biology and development, but it will also provide the basis for the development of both a new strategy in cancer therapy and new methods for assessing treatment efficacy.

PUBLICATIONS

1 **Extremely low-frequency magnetic fields and risk of childhood leukemia: A risk assessment by the ARIMMORA consortium.** Schüz J, Dasenbrock C, Ravazzani P, Röösli M, Schär P, Bounds PL, Erdmann F, Borkhardt A, Cobaleda C, Fedrowitz M, Hamnerius Y, Sanchez-García I, Seger R, Schmiegelow K, Ziegelberger G, Capstick M, Manser M, Müller M, Schmid CD, Schürmann D, Struchen B, Kuster N. **Bioelectromagnetics. 2016 Mar 15. doi: 10.1002/bem.21963.** PMID:26991812 **IF: 1.583 / Q2**

2 **Comparative dosimetry for children and rodents exposed to extremely low-frequency magnetic fields.** Gong Y, Capstick M, Dasenbrock C, Fedrowitz M, Cobaleda C, Sánchez-García I, Kuster N. **Bioelectromagnetics. 2016 Jul;37(5):310-22. doi: 10.1002/bem.21976. Epub 2016 May 13.** PMID: 27176719 **IF: 1.583 / Q2**

3 **Could Vitamin D Analogues Be Used to Target Leukemia Stem Cells?** García-Ramírez I, Martín-Lorenzo A, González-Herrero I, Rodríguez-Hernández G, Vicente-Dueñas C, Sánchez-García I. **Int J Mol Sci. 2016 Jun 6;17(6). pii: E889. doi: 10.3390/ijms17060889. Review.** PMID: 27275819 **IF: 3.257 / Q2**

4 **Homeobox NKX2-3 promotes marginal-zone lymphomagenesis by activating B-cell receptor signalling and shaping lymphocyte dynamics.** Robles EF, Mena-Varas M, Barrio L, Merino-Cortes SV, Balogh P, Du MQ, Akasaka T, Parker A, Roa S, Panizo C, Martin-Guerrero I, Siebert R, Segura V, Agirre X, Macri-Pellizeri L, Aldaz B, Vilas-Zornoza A, Zhang S, Moody S, Calasanz MJ, Tousseyn T, Broccardo C, Brousset P, Campos-Sanchez E, Cobaleda C, Sanchez-García I, Fernández-Luna JL, García-Muñoz R, Pena E, Bellosillo B, Salar A, Baptista MJ, Hernández-Rivas JM, Gonzalez M, Terol MJ, Climent J, Ferrandez A, Sagaert X, Melnick AM, Prosper F, Oscier DG, Carrasco YR, Dyer MJ, Martínez-Climent JA. **Nat Commun. 2016 Jun 14;7:11889. doi: 10.1038/ncomms11889.** PMID: 27297662 **IF: 11.329 / D1**

5 **Metabolic gatekeeper function of B-lymphoid transcription factors.** Chan LN, Chen Z, Braas D, Lee JW, Xiao G, Geng H, Cosgun KN, Hurtz C, Shojaee S, Cazzaniga V, Schjerven H, Ernst T, Hochhaus A, Kornblau SM, Konopleva M, Pufall MA, Cazzaniga G, Liu GJ, Milne TA, Koeffler HP, Ross TS, Sánchez-García I, Borkhardt A, Yamamoto KR, Dickins RA, Graeber TG, Müschen M. **Nature. 2017 Feb 23;542(7642):479-483. doi: 10.1038/nature21076. Epub 2017 Feb 13.** PMID: 28192788 **IF: 38.138 / D1**

6 **Crebbp loss cooperates with Bcl2 overexpression to promote lymphoma in mice.** García-Ramírez I, Tadros S, González-Herrero I, Martín-Lorenzo A, Rodríguez-Hernández G, Moore D, Ruiz-Roca L, Blanco O, Alonso-López D, Rivas JL, Hartert K, Duval R, Klinkebiel D, Bast M, Vose J, Lunning M, Fu K, Greiner T, Rodrigues-Lima F, Jiménez R, Criado FJG, Cenador MBG, Brindle P, Vicente-Dueñas C, Alizadeh A, Sánchez-García I, Green MR. **Blood. 2017 May 11;129(19):2645-2656. doi: 10.1182/blood-2016-08-733469. Epub 2017 Mar 13.** PMID: 28288979 **IF: 11.847 / D1**

7 **Prolonged intracellular accumulation of light-inducible nanoparticles in leukemia cells allows their remote activation.** Boto C, Quartin E, Cai Y, Martín-Lorenzo A, Cenador MBG, Pinto S, Gupta R, Enver T, Sánchez-García I, Hong D, Pires das Neves R, Ferreira L. **Nat Commun. 2017 May 11;8:15204. doi: 10.1038/ncomms15204.** PMID: 28492285 **IF: 11.329 / D1**

8 **Infection exposure promotes ETV6-RUNX1 precursor B cell leukemia via impaired H3K4 demethylases.** Rodríguez-Hernández G, Hauer J, Martín-Lorenzo A, Schäfer D, Bartenhagen C, García-Ramírez I, Auer F, Gonzalez-Herrero I, Ruiz-Roca L, Gombert M, Okpanyi V, Fischer U, Chen C, Dugas M, Bhatia S, Linka RM, García-Suquia M, Rascón-Trincado MV, García-Sanchez A, Blanco O, García-Cenador MB, García-Criado FJ, Cobaleda C, Alonso-López D, De Las Rivas J, Müschen M, Vicente-Dueñas C, Sánchez-García I, Borkhardt A. **Cancer Res. 2017 Jun 19. pii: canres.0701.2017. doi: 10.1158/0008-5472.CAN-17-0701.** PMID: 28630052 **IF: 8.556 / D1**

9 **Activation-induced cytidine deaminase prevents pro-B cell acute lymphoblastic leukemia by functioning as a negative regulator in Rag1 deficient pro-B cells.** Auer F, Ingenhag D, Pinkert S, Kracker S, Hacein-Bey-Abina S, Cavazzana M, Gombert M, Martin-Lorenzo A, Lin MH, Vicente-Dueñas C, Sánchez-García I, Borkhardt A, Hauer J. **Oncotarget. 2017 Sep 7;8(44):75797-75807. doi: 10.18632/oncotarget.20563. eCollection 2017 Sep 29.** PMID: 29100269 **IF: 5.008 / Q1**

10 **Modeling the process of childhood ETV6-RUNX1 B-cell leukemias.** Rodríguez-Hernández G, Schäfer D, Gavilán A, Vicente-Dueñas C, Hauer J, Borkhardt A, Sánchez-García I. **Oncotarget. 2017 Sep 27;8(60):102674-102680. doi: 10.18632/oncotarget.21281. eCollection 2017 Nov 24. Review.** PMID: 29254279 **IF: 5.008 / Q1**

OTHER PUBLICATIONS & BOOK CHAPTERS

1 Editors: Dr. Geoffrey Brown and Dr. Isidro Sanchez-García. **Diversity, Versatility, and Leukaemia. Nova Science Publishers, Inc., New York, NY 11788-3619, USA Series: Cancer Etiology, Diagnosis and Treatments Pub. Date: 2016 - 2nd Quarter https://www.novapublishers.com/catalog/product_info.php?products_id=57649** ISBN: 978-1-63484-781-0

2 Geoffrey Brown and Dr. Isidro Sanchez-García. **Chapter 1: The diversity of blood cells. In: Title - Diversity, Versatility, and Leukaemia. Nova Science Publishers, Inc., New York, NY 11788-3619, USA.** ISBN: 978-1-63484-781-0

3 Geoffrey Brown and Dr. Isidro Sanchez-García. **Chapter 2: The conventional viewpoint to hematopoiesis. In: Title - Diversity, Versatility, and Leukaemia. Nova Science Publishers, Inc., New York, NY 11788-3619, USA.** ISBN: 978-1-63484-781-0

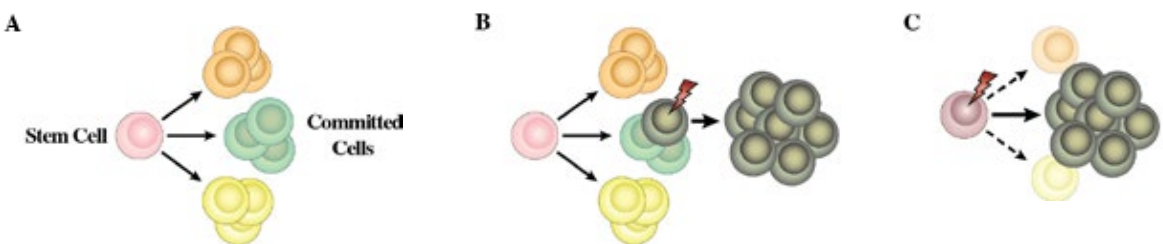
4 Geoffrey Brown and Dr. Isidro Sanchez-García. **Chapter 3: Revision to the model of hematopoiesis. In: Title - Diversity, Versatility, and Leukaemia. Nova Science Publishers, Inc., New York, NY 11788-3619, USA.** ISBN: 978-1-63484-781-0

5 Geoffrey Brown and Dr. Isidro Sanchez-García. **Chapter 4: Classifying the various leukaemias/hematopoietic cancers. In: Title - Diversity, Versatility, and Leukaemia. Nova Science Publishers, Inc., New York, NY 11788-3619, USA.** ISBN: 978-1-63484-781-0

6 Geoffrey Brown and Dr. Isidro Sanchez-García. **Chapter 5: Leukaemia/ hematopoietic cancer-initiating cellular events. In: Title - Diversity, Versatility, and Leukaemia. Nova Science Publishers, Inc., New York, NY 11788-3619, USA.** ISBN: 978-1-63484-781-0

7 Geoffrey Brown and Dr. Isidro Sanchez-García. **Chapter 6: Leukemia/ hematopoietic cancers and lineage commitment. In: Title - Diversity, Versatility, and Leukaemia. Nova Science Publishers, Inc., New York, NY 11788-3619, USA.** ISBN: 978-1-63484-781-0

8 Geoffrey Brown and Dr. Isidro Sanchez-García. **Chapter 7: The prospect of new treatments for leukaemia and other cancers. In: Title - Diversity, Versatility, and Leukaemia. Nova Science Publishers, Inc., New York, NY 11788-3619, USA.** ISBN: 978-1-63484-781-0



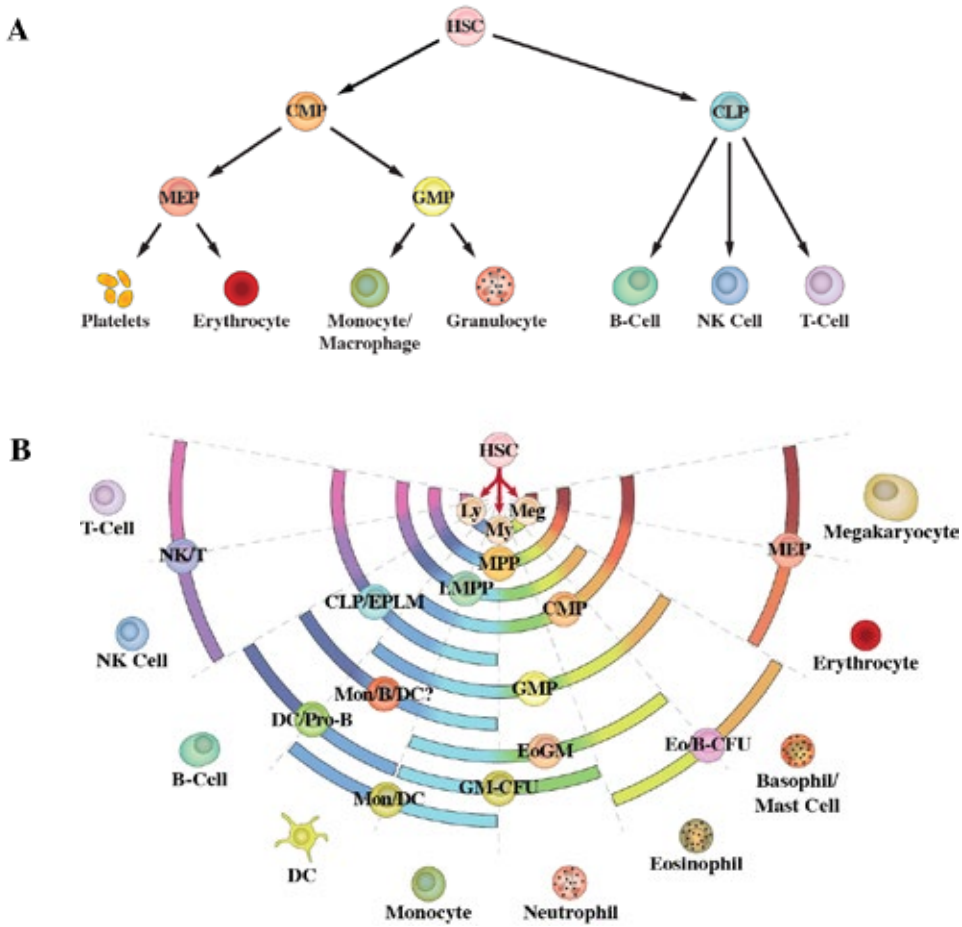
A new concept of the human leukemia as a result of a restriction of lineage options during stem cell transformation. A) Scheme of the normal differentiation program from stem cells. Normal stem cells give rise to transit cells (lobulated in the scheme) which expand to give rise to terminally differentiated cells. **B)** Human leukemia is a genetic disease originated by several possible types of genetic/ epigenetic alterations. LSC give rise to transit-amplifying cells (lobulated in the scheme) that would expand and originate the main and highly expansive tumor cell mass (spiked cells). All human leukemic cells carry the oncogenic alteration, from the cell-of-origin to the more differentiated cancer cells, though the role of this oncogene may be different at different stages of leukemia differentiation, and these mutations might become carrier mutations rather than driving ones depending on the cellular context. **C)** Based on the reprogramming nature of oncogenes, restricting expression of the oncogenic alterations to the stem cell compartment is all that is needed to recapitulate the heterogeneity of leukemia. Using a stem-cell restricted transgenic expression system, the expression of the oncogene in the reprogramming-prone stem cells and progenitors allows the development of all of the cells that compose the leukemia mass. The modified gene is present in all the mouse cells but the oncogene impact is limited to the stem/progenitor compartment. This is similar to what happens in other cases of reprogramming, where the reprogramming factor(s) does not need to be present anymore once the initial fate-inducing change as taken place (for example, induced pluripotency).

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Mecanismos moleculares que gobiernan en el desarrollo de las células madre cancerígenas como resultado del proceso de reprogramación: implicaciones en el desarrollo y tratamiento (SAF2012-32810)	Isidro Sánchez García	Ministerio de Economía y Competitividad	2013-2016	230,000.00 €
About Decision-making within cells and differentiation entity therapies (DECIDE) (GRANT AGREEMENT: nº 315902)	Isidro Sánchez García	European Union (Marie Curie initial training programme	2013-2016	
The elucidation of the molecular mechanisms that govern the development of Cancer Stem Cells as a result of a reprogramming-like mechanism: implications in tumor development and treatment (SECRET) (SAF2012-32810)	Isidro Sánchez García	Ministerio de Economía y Competitividad	2013-2016	269,100.00 €
Development of a novel in vivo model to elucidate the genetic determinants of childhood precursor B-cell acute lymphoblastic leukaemia (pB-ALL) with TEL-AML1 (ETV6/Runx1) rearrangement (DJCLS R13/26)	Isidro Sánchez García & Arndt Borkhardt	German Carreras Foundation (DJCLS)	2014-2016	366,000.00 €
Biología del cáncer (SAF2014-57791-REDC)	Isidro Sánchez García	Ministerio de Economía y Competitividad	2015-2016	45,000.00 €
Del desarrollo de las leucemias linfoblásticas agudas infantiles tel-aml1 con el fin de establecer nuevas bases terapéuticas y profilácticas.	Isidro Sánchez García	Fundación Inocente Inocente	2015-2016	30,000.00 €
Chemotherapy cardiotoxicity in the elderly: a translational and personnel approach. CARTIER (CARdioToxicity In the Elderly progRamme) (PIE 14/00066)	Isidro Sánchez García	Instituto de Salud Carlos III	2015-2017	605,000.00 €
Convenio para la información y asesoramiento sobre el estado del arte de la investigación científica relativa al impacto de las emisiones radioeléctricas de radiofrecuencia en los seres humanos, la salud y el medioambiente	Isidro Sánchez García	Telefonica Moviles España SA	2016	10,000.00 €
Estudio del desarrollo de las leucemias linfoblásticas agudas infantiles con el fin de establecer nuevas bases terapéuticas y profilácticas (CSI001U16)	Isidro Sánchez García	Consejería de Educación. Junta de Castilla y León	2016-2017	40,000.00 €
Infecciones, inflamación y cáncer: estudio de factores genéticos y moleculares asociados. (IBY15/00003)	Isidro Sánchez García	Instituto de Salud Carlos III	2016-2017	40,000.00 €
Mecanismos moleculares responsables de la reprogramación tumoral de progenitores hematopoyéticos mediada por Bcl6 (TAMARA) (SAF2015-64420-R)	Isidro Sánchez García	Ministerio de Economía y Competitividad	2016-2018	290,400.00 €
Infectious trigger in childhood pB-ALL – new approaches for leukemia prevention. (DJCLS 02R/2016)	Isidro Sánchez García	German Carreras Foundation (DJCLS)	2016-2019	367,767.00 €
Identifying and targeting mechanisms of CREBBP mutation-driven lymphomagenesis (1R01CA201380-01A1)	Isidro Sánchez García	National Health Insitute. Universidad de Nebraska	2016-2021	237,600.00 €
Convenio para la información y asesoramiento sobre el estado del arte de la investigación científica relativa al impacto de las emisiones radioeléctricas de radiofrecuencia en los seres humanos, la salud y el medioambiente	Isidro Sánchez García	Telefonica Moviles España SA	2017	10,000.00 €
Leukämie im Kindesalter – Einfluss des Immunnsystems auf die Entstehung der Erkankrung experimentelle Studie am einem geeigneten Tiernmodell (FRAUNHOFER-ITEM17-ISG)	Isidro Sánchez García	Fraunhofer Institut für Toxikologie und Experimentelle Medizin	2017-2018	50,000.00 €

OTHER ACTIVITIES & RELEVANT FACTS

- Director del grupo CANC-15 del IBSAL - Salamanca Institute for Biomedical Research (ibsal). 2012-present.
- Reconocimiento de la condición de Unidad de Investigación Consolidada de Castilla y León Inscribir a dicha unidad en el Registro de Unidades de investigación Consolidada de Castilla y León, con el número UIC 017, integrada por los doctores Francisco Javier García-Criado, Rafael Jiménez, Jesús Pérez-Losada, Pedro Lazo, Rogelio González-Sarmiento, Carolina Vicente-Dueñas, Juan Jesús Cruz e Isidro Sánchez-García (en calidad de Director de la misma). 29.07.2015.



Schematic representations of haematopoiesis. A) Depicts the classic model in which the haematopoietic stem cell make an irrevocable choice between the myeloid and lymphoid pathways. **B)** Depicts the pair-wise model. Differentiation options are envisaged as a series of invariant pair-wise developmental relatinships with cells becoming gradually biased towards producing one cell type or another.

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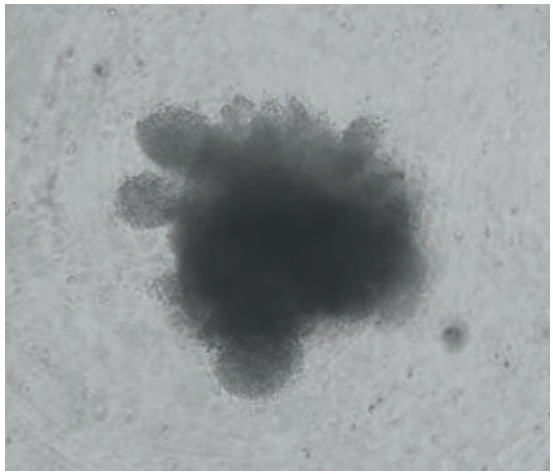
LABORATORY 14

HEREDITARY CANCER

The first aim of the laboratory 14 is the characterization of molecular abnormalities in patients with familiar cancer within the program of Genetic Counseling in Hereditary Cancer supported by the Junta de Castilla y León. Within this project, the laboratory is also 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. We are also characterizing low penetration mutations in women with breast cancer under 40 years old as well as novel mutations in males with breast cancer. In colon cancer, our secondary aim is to characterize the frequency of mutation in patients with colon cancer under 40 years old. We are also trying to perform functional characterization of unknown significance mutations. Finally we a reference in Castilla y León for genetic analysis of all hereditary cancer syndromes.

A second aim of the laboratory is the characterization of molecular abnormalities in brain and endometrial tumors and correlate them with abnormalities in colon cancer within Lynch Syndrome. In this aim we are collaborating with the Service of Neurosurgery of the Hospital Son Llatzer and with the Departments of Obstetrics and Gynecology, and pathology of the University Hospital of Salamanca.

A third aim is the analysis of the modifications induced in cell lines derived from different tumor after incubation with new drugs, some of them developed by the Department Pharmaceutical Chemistry of the University of Salamanca.



Finally, we are collaborating in a multicentric trial analyzing SNPs in candidate genes that could increase the risk to suffer head and neck cancer and characterizing novel mutations in these tumors.

All these projects are developed in collaboration with the Department of Oncology of the University Hospital of Salamanca directed by Prof. JJ Cruz.

PUBLICATIONS

1 **Influence of UGT2B7, CYP3A4, and OPRM1 Gene Polymorphisms on Transdermal Buprenorphine Pain Control in Patients with Critical Lower Limb Ischemia Awaiting Revascularization.** Blanco F, Muriel C, Labrador J, Gonzalez-Porras JR, Gonzalez-Sarmiento R, Lozano FS. **Pain Pract. 2016 Sep;16(7):842-9. doi: 10.1111/papr.12343. Epub 2015 Sep 26.** PMID: 26407542 **IF: 2.317 / Q2**

2 **Two Cases of Autosomal Recessive Congenital Ichthyosis due to CYP4F22 Mutations: Expanding the Genotype of Self-Healing Collodion Baby.** Noguera-Morel L, Feito-Rodríguez M, Maldonado-Cid P, García-Miñaur S, Kamsteeg EJ, González-Sarmiento R, De Lucas-Laguna R, Hernández-Martín A, Torrelo A. **Pediatr Dermatol. 2016 Mar-Apr;33(2):e48-51. doi: 10.1111/pde.12740. Epub 2015 Dec 9.** PMID: 26646773 **IF: 1.163 / Q3**

3 **Alcoholic liver disease and hepatitis C virus infection.** Novo-Veleiro I, Alvela-Suárez L, Chamorro AJ, González-Sarmiento R, Laso FJ, Marcos M. **World J Gastroenterol. 2016 Jan 28;22(4):1411-20. doi: 10.3748/wjg.v22.i4.1411. Review.** PMID: 26819510 **IF: 2.787 / Q2**

4 **The presence of CFH, HTRA1, ARMS2, VEGF-A and VEGF-R and the appearance of age-related macular degeneration sub-types.** Cruz-González F, Cabrillo Estévez L, Cañete Campos C, Sánchez-Jara Sánchez A, Juan Marcos L, González-Sarmiento R. **Arch Soc Esp Oftalmol. 2016 Apr;91(4):177-83. doi: 10.1016/j.oftal.2015.12.016. Epub 2016 Feb 3.** PMID: 26850328 **IF: NI**

5 **Comment on «Wild-type APC prediction of poor prognosis in microsatellite-stable proximal colorectal cancer differs according to the age of onset».** Perea J, Arriba M, Rueda D, Sánchez R, García JL, Pérez J, Rodríguez Y, González-Sarmiento R, Urioste M. **Br J Cancer. 2016 May 10;114(10):e7. doi: 10.1038/bjc.2016.53. Epub 2016 Apr 26.** PMID: 27115472 **IF: 5.569 / Q1**

6 **Novel mutations in FATP4 gene in two families with ichthyosis prematurity syndrome.** Bueno E, Cañueto J, García-Patos V, Vicente MA, Bodet-Castillo D, Hernández-Ruíz ME, González-Sarmiento R. **J Eur Acad Dermatol Venereol. 2017 Jan;31(1):e11-e13. doi: 10.1111/jdv.13584. Epub 2016 May 11.** PMID: 27168232 **IF: 3.029 / Q1**

7 **VAV3 Gene Polymorphism Is Associated with Paget's Disease of Bone.** Usategui-Martín R, Calero-Paniagua I, García-Aparicio J, Corral-Gudino L, Del Pino Montes J, González Sarmiento R. **Genet Test Mol Biomarkers. 2016 Jun;20(6):335-7. doi: 10.1089/gtmb.2015.0292. Epub 2016 May 12.** PMID: 27172236 **IF: 1.297 / Q4**

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20 **Correction: Study of Association between Pre-Senile Cataracts and the Polymorphisms rs2228000 in XPC and rs1042522 in p53 in Spanish Population.** López Valverde G, García Martin E, Larrosa Povés JM, Polo Llorens V, Fernández Mateos J, Pablo Júlvez LE, Sarmiento RG. **PLoS One. 2017 Jan 26;12(1):e0171395. doi: 10.1371/journal.pone.0171395. eCollection 2017.** PMID: 28125715 **IF: 3.057 / Q1**

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28 **Analysis of autophagy gene polymorphisms in Spanish patients with head and neck squamous cell carcinoma.** Fernández-Mateos J, Seijas-Tamayo R, Klain JCA, Borgoñón MP, Pérez-Ruiz E, Mesía R, Del Barco E, Coloma CS, Dominguez AR, Daroqui JC, Fernández Ruiz E, Cruz-Hernández JJ, González-Sarmiento R. **Sci Rep. 2017 Jul 31;7(1):6887. doi: 10.1038/s41598-017-07270-0.** PMID: 28761177 **IF: 5.228 / Q1**

29 **Identification of a novel locus on chromosome 2q13, which predisposes to clinical vertebral fractures independently of bone density.** Alonso N, Estrada K, Albagha OME, Herrera L, Reppe S, Olstad OK, Gautvik KM, Ryan NM, Evans KL, Nielson CM, Hsu YH, Kiel DP, Markozannes G, Ntzani EE, EvÁngelou E, Feenstra B, Liu X, Melbye M, Masi L, Brandi ML, Riches P, Daroszewska A, Olmos JM, Valero C, Castillo J, Riancho JA, Husted LB, Langdahl BL, Brown MA, Duncan EL, Kaptoge S, Khaw KT, Usategui-Martín R, Del Pino-Montes J, González-Sarmiento R, Lewis JR, Prince RL, D'Amelio P, García-Giralt N, Nogués X, Mencej-Bedrac S, Marc J, Wolstein O, Eisman JA, Oei L, Medina-Gómez C, Schraut KE, Navarro P, Wilson JF, Davies G, Starr J, Deary I, Tanaka T, Ferrucci L, Gianfrancesco F, Gennari L, Lucas G, Elosua R, Uitterlinden AG, Rivadeneira F, Ralston SH. **Ann Rheum Dis. 2018 Mar;77(3):378-385. doi: 10.1136/annrheumdis-2017-212469. Epub 2017 Nov 23.** PMID: 29170203 **IF: 5.228 / D1**

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GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Estudio de polimorfismos de genes implicados en autofagia y susceptibilidad a padecer enfermedades. Estudio del gen y proteínas SQSTM17P62 en enfermedad (PI13/01741)	Rogelio González Sarmiento	Instituto de Salud Carlos III	2014-2016	113,740.00 €
Correlación clínico-molecular del receptor de andrógenos y sus isoformas en pacientes con cáncer de próstata metastásico y resistente a castración farmacológica	Rogelio González Sarmiento	Asociación Española Contra el Cáncer	2016-2018	

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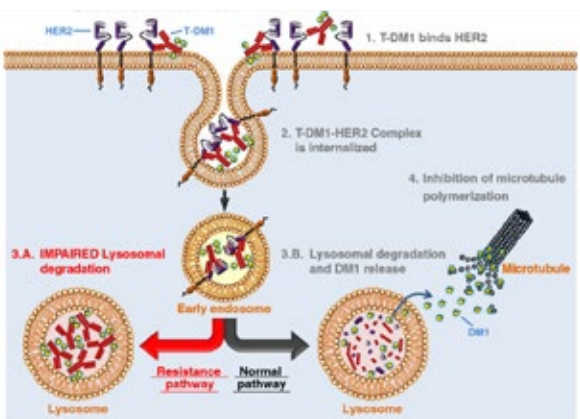
LABORATORY 15

KINASES IN ONCOLOGY. SIGNALING BY RECEPTOR TYROSINE KINASES

Schematic representation of a proposed T-DM1–resistance model. T-DM1 binds HER2 on the plasma membrane, followed by entry of HER2–T-DM1 complexes into the cell via receptor-mediated endocytosis. The internalized complexes are initially contained within endocytic vesicles, which fuse to become early endosomes. The load of these endosomes can be recycled back to the plasma membrane or early endosomes can mature to lysosomes. In the normal pathway, the acidic lysosomal proteases degrade the antibody moiety of the T-DM1, releasing the payload. Intracellular Lys-MCC-DM1 inhibits microtubule polymerization, inducing mitotic arrest, apoptosis, mitotic catastrophe, and disrupted intracellular trafficking. In the resistance pathway, altered lysosomal pH could restrict the intrinsic proteinase activities of lysosomal enzymes impairing proteolytic cleavage of endocytosed T-DM1. The ADC would be retained inside the lysosomes and the payload would not reach its target.



During the last few years our research has been centered in the understanding of the role of several receptor tyrosine kinases and their signal transduction routes in cell proliferation.

Interest in the activation of RTKs by membrane anchored ligands has been a major focus of our laboratory with special emphasis on the study of the mechanisms responsible for the solubilization of membrane-anchored growth factors, and the biological properties of these factors in the membrane-anchored conformation. In addition, the role of novel RTK signaling intermediates, such as P-Rex1 is being analyzed.

In this area of research an effort is being paid to an integral understanding of the role of RTKs, especially those of the ErbB/HER family in cancer by analyzing how their activating ligands act, and how downstream signaling molecules participate in proliferative responses to RTK activation. Studies with drugs (small molecule kinase inhibitors as well as monoclonal antibodies) that target these receptors or their signal transduction pathways are carried out in parallel with biological studies.

Besides, during the last few years we have become especially interested in the major clinical problem of the establishment of resistances to targeted therapies, especially in the context of HER2 positive breast cancer. In line with this, we have made an effort to generate new in vitro and in vivo models of resistance to anti-HER2 therapies and have identified novel mechanisms of acquired resistance to these drugs. Taking all these into consideration we are investigating and developing new therapeutic approaches to be used in this context.

Future aims: to increase our knowledge on the role of different signaling molecules in sustaining cancer cell survival.

We are also interested in defining molecular alterations whose targeting may result in efficient antitumoral therapies.

In line with this, the identification of new targets and the development of new therapeutic agents against them is, in this moment, an important goal in our team.

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SENIOR RESEARCHER

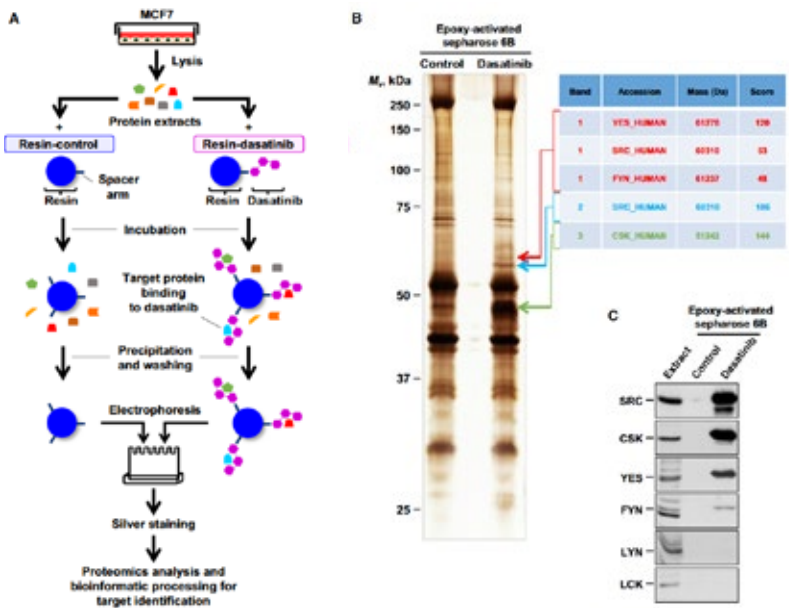
THE MEK5/ERK5 PATHWAY IN CANCER

Mitogen-activated protein kinases (MAPKs) control multiple essential biological processes. In mammals, several MAPK families have been described. In the last years, the MEK5/ERK5 pathway has been reported to be deregulated in various types of cancer. However, whether activation of this route is sufficient to drive tumorigenesis was unknown. To answer this question, we generated a transgenic mouse engineered to express a constitutively active form of MEK5, and we show that this route contributes to the pathogenesis of lung cancer, opening the possibility of its targeting with therapeutic purposes.

Now, we are trying to:

i) Gain insights into the mechanism of activation of the MEK5 / ERK5 pathway in lung cancer. This will open new options for future clinical applications.
ii) Analyze the regulation of gene expression by MEK5 in lung cancer and determine if there is any type of molecular signature associated with the MEK5 activation.

On the other hand, proteomic studies from our group identified several ERK5-interacting proteins, some of them related to the intermediate metabolism, which may represent interesting anticancer targets. The role of those proteins in the actions of ERK5 is being unveiled.



Aldentification of dasatinib-binding proteins in MCF7 cells. **A)** Schematic representation of the chemical proteomics approach used for dasatinib-binding protein identification in MCF7 cells. **B)** Silver-stained SDS/PAGE of protein–resin complexes. MCF7 cell lysates were incubated with dasatinib coupled to epoxy-activated Sepharose 6B medium (dasatinib-resin) or to uncoupled epoxy activated Sepharose 6B medium (control resin). Bands of interest were excised from the gel, and the proteins from these bands were analyzed by MALDI-TOF. Main proteins identified in bands 1–3 across SwissProt database are shown in the table to the right, together with the proteins' molecular weight and the proteins' score Mascot reported. M r refers to molecular mass (kDa). **C)** Western blotting analysis of the interaction of SRC, CSK, YES, FYN, LYN, and LCK with dasatinib by pulldown experiments with the resins mentioned in (B). Cell extracts were used to detect total protein levels. Data information: In (B,C), results from a representative experiment that was repeated twice are shown.

PUBLICATIONS

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2 **Transcriptomic analyses identify association between mitotic kinases, PDZ-binding kinase and BUB1, and clinical outcome in breast cancer.** Ocaña A, Pérez-Peña J, Díez-González L, Sánchez-Corrales V, Templeton A, Seruga B, Amir E, Pandiella A. **Breast Cancer Res Treat. 2016 Feb;156(1):1-8. doi: 10.1007/s10549-016-3720-4. Epub 2016 Feb 20.** PMID: 26897635 **IF: 4.085 / Q2**

3 **In silico analyses identify gene-sets, associated with clinical outcome in ovarian cancer: role of mitotic kinases.** Ocaña A, Pérez-Peña J, Alcaraz-Sanabria A, Sánchez-Corrales V, Nieto-Jiménez C, Templeton AJ, Seruga B, Pandiella A, Amir E. **Oncotarget. 2016 Apr 19;7(16):22865-72. doi: 10.18632/oncotarget.8118.** PMID: 26992217 **IF: 5.008 / Q1**

4 **Neuregulin expression in solid tumors: prognostic value and predictive role to anti-HER3 therapies.** Ocaña A, Díez-González L, Esparís-Ogando A, Montero JC, Amir E, Pandiella A. **Oncotarget. 2016 Jul 19;7(29):45042-45051. doi: 10.18632/oncotarget.8648.** PMID: 27074567 **IF: 5.008 / Q1**

5 **Interaction between Hormonal Receptor Status, Age and Survival in Patients with BRCA1/2 Germline Mutations: A Systematic Review and Meta-Regression.** Templeton AJ, Gonzalez LD, Vera-Badillo FE, Tibau A, Goldstein R, Seruga B, Srikanthan A, Pandiella A, Amir E, Ocana A. **PLoS One. 2016 May 5;11(5):e0154789. doi: 10.1371/journal.pone.0154789. eCollection 2016. Review.** PMID: 27149669 **IF: 3.057 / Q1**

6 **In Silico Analysis Guides Selection of BET Inhibitors for Triple-Negative Breast Cancer Treatment.** Pérez-Peña J, Serrano-Heras G, Montero JC, Corrales-Sánchez V, Pandiella A, Ocaña A. **Mol Cancer Ther. 2016 Aug;15(8):1823-33. doi: 10.1158/1535-7163.MCT-16-0004. Epub 2016 Jun 2.** PMID: 27256375 **IF: 5.579 / Q1**

7 **Targeting the EGF/HER Ligand-Receptor System in Cancer.** Esparís-Ogando A, Montero JC, Arribas J, Ocaña A, Pandiella A. **Curr Pharm Des. 2016;22(39):5887-5898.** PMID: 27426127 **IF: 3.052 / Q2**

8 **Antiproliferative Effect of Synadenium grantii Hook f. stems (Euphorbiaceae) and a Rare Phorbol Diterpene Ester.** Campos A, Vendramini-Costa DB, Longato GB, Zermiani T, Ruiz AL, de Carvalho JE, Pandiella A, Cechinel Filho V. **Int J Toxicol. 2016 Nov;35(6):666-671. Epub 2016 Jul 27.** PMID: 27466346 **IF: 1.077 / Q4**

9 **DNA-damage related genes and clinical outcome in hormone receptor positive breast cancer.** Nieto-Jiménez C, Alcaraz-Sanabria A, Páez R, Pérez-Peña J, Corrales-Sánchez V, Pandiella A, Ocaña A. **Oncotarget. 2016 Jul 28. doi: 10.18632/oncotarget.10886.** PMID: 27486818 **IF: 5.008 / Q1**

10 **CM363, a novel naphthoquinone derivative which acts as multikinase modulator and overcomes imatinib resistance in chronic myelogenous leukemia.** Guerra B, Martín-Rodríguez P, Díaz-Chico JC, McNaughton-Smith G, Jiménez-Alonso S, Hueso-Falcón I, Montero JC, Blanco R, León J, Rodríguez-González G, Estévez-Braun A, Pandiella A, Díaz-Chico BN, Fernández-Pérez L. **Oncotarget. 2017 May 2;8(18):29679-29698. doi: 10.18632/oncotarget.11425.** PMID: 27557509 **IF: 5.008 / Q1**

11 **ODZ1 allows glioblastoma to sustain invasiveness through a Myc-dependent transcriptional upregulation of RhoA.** Talamillo A, Grande L, Ruiz-Ontañon P, Velasquez C, Mollinedo P, Torices S, Sanchez-Gomez P, Aznar A, Esparis-Ogando A, López-López C, Lafita C, Berciano MT, Montero JA, Vazquez-Barquero A, Segura V, Villagra NT, Pandiella A, Lafarga M, Leon J, Martínez-Climent JA, Sanz-Moreno V, Fernández-Luna JL. **Oncogene. 2017 Mar 23;36(12):1733-1744. doi: 10.1038/onc.2016.341. Epub 2016 Sep 19.** PMID: 27641332 **IF: 7.932 / D1**

12 **Multisite phosphorylation of P-Rex1 by protein kinase C.** Montero JC, Seoane S, García-Alonso S, Pandiella A. **Oncotarget. 2016 Nov 22;7(47):77937-77949. doi: 10.18632/oncotarget.12846.** PMID: 27788493 **IF: 5.008 / Q1**

13 **Targeting basal-like breast tumors with bromodomain and extraterminal domain (BET) and polo-like kinase inhibitors.** Nieto-Jiménez C, Alcaraz-Sanabria A, Pérez-Peña J, Corrales-Sánchez V, Serrano-Heras G, Galán-Moya EM, Serrano-Oviedo L, Montero JC, Burgos M, Llopis J, Pandiella A, Ocaña A. **Oncotarget. 2017 Mar 21;8(12):19478-19490. doi: 10.18632/oncotarget.14465.** PMID: 28061448 **IF: 5.008 / Q1**

14 **Targeting oncogenic vulnerabilities in triple negative breast cancer: biological bases and ongoing clinical studies.** Ocana A, Pandiella A. **Oncotarget. 2017 Mar 28;8(13):22218-22234. doi: 10.18632/oncotarget.14731. Review.** PMID: 28108739 **IF: 5.008 / Q1**

15 **Impact of Availability of Companion Diagnostics on the Clinical Development of Anticancer Drugs.** Tibau A, Díez-González L, Navarro B, Galán-Moya EM, Templeton AJ, Seruga B, Pandiella A, Amir E, Ocana A. **Mol Diagn Ther. 2017 Jun;21(3):337-343. doi: 10.1007/s40291-017-0267-y.** PMID: 28247182 **IF: 1.909 / Q3**

16 **Mitotic read-out genes confer poor outcome in luminal A breast cancer tumors.** Pérez-Peña J, Alcaraz-Sanabria A, Nieto-Jiménez C, Páez R, Corrales-Sánchez V, Serrano-Oviedo L, Wali VB, Patwardhan GA, Amir E, Győrffy B, Pandiella A, Ocaña A. **Oncotarget. 2017 Mar 28;8(13):21733-21740. doi: 10.18632/oncotarget.15562.** PMID: 28423514 **IF: 5.008 / Q1**

17 **Transcriptomic immunologic signature associated with favorable clinical outcome in basal-like breast tumors.** Martínez-Canales S, Cifuentes F, López De Rodas Gregorio M, Serrano-Oviedo L, Galán-Moya EM, Amir E, Pandiella A, Győrffy B, Ocaña A. **PLoS One. 2017 May 4;12(5):e0175128. doi: 10.1371/journal.pone.0175128. eCollection 2017.** PMID: 28472085 **IF: 3.057 / Q1**

18 **Resistance to the antibody-drug conjugate T-DM1 is based in a reduction in lysosomal proteolytic activity.** Ríos-Luci C, García-Alonso S, Díaz-Rodríguez E, Nadal-Serrano M, Arribas J, Ocaña A, Pandiella A. **Cancer Res. 2017 Jul 7. pii: canres.3127.2016. doi: 10.1158/0008-5472.CAN-16-3127.** PMID: 28687619 **IF: 8.556 / D1**

19 **Antitumoral effect of Ocoxin in hepatocellular carcinoma.** Díaz-Rodríguez E, El-Mallah AM, Sanz E, Pandiella A. **Oncol Lett. 2017 Aug;14(2):1950-1958. doi: 10.3892/ol.2017.6440. Epub 2017 Jun 21.** PMID: 28781639 **IF: 1.390 / Q4**

20 **Neutrophils in cancer: prognostic role and therapeutic strategies.** Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. **Mol Cancer. 2017 Aug 15;16(1):137. doi: 10.1186/s12943-017-0707-7. Review.** PMID: 28810877 **IF: 6.024 / Q1**

21 **Defective Cyclin B1 Induction in Trastuzumab-emtansine (T-DM1) Acquired Resistance in HER2-positive Breast Cancer.** Sabbaghi M, Gil-Gómez G, Guardia C, Servitja S, Arpí O, García-Alonso S, Menendez S, Arumi-Uria M, Serrano L, Salido M, Muntasell A, Martínez-García M, Zazo S, Chamizo C, González-Alonso P, Madoz-Gúrpide J, Eroles P, Arribas J, Tusquets I, Lluch A, Pandiella A, Rojo F, Rovira A, Albanell J. **Clin Cancer Res. 2017 Nov 15;23(22):7006-7019. doi: 10.1158/1078-0432.CCR-17-0696. Epub 2017 Aug 18.** PMID: 28821558 **IF: 8.738 / D1**

22 **Synthetic Lethality Interaction Between Aurora Kinases and CHEK1 Inhibitors in Ovarian Cancer.** Alcaraz-Sanabria A, Nieto-Jiménez C, Corrales-Sánchez V, Serrano-Oviedo L, Andrés-Pretel F, Montero JC, Burgos M, Llopis J, Galán-Moya EM, Pandiella A, Ocaña A. **Mol Cancer Ther. 2017 Nov;16(11):2552-2562. doi: 10.1158/1535-7163.MCT-17-0223. Epub 2017 Aug 28.** PMID: 28847989 **IF: 5.579 / Q1**

23 **Regulation of the prometastatic neuregulin-MMP13 axis by SRC family kinases: therapeutic implications.** Orive-Ramos A, Seoane S, Ocaña A, Pandiella A, Montero JC. **Mol Oncol. 2017 Dec;11(12):1788-1805. doi: 10.1002/1878-0261.12145. Epub 2017 Oct 31.** PMID: 29032615 **IF: 5.367 / Q1**

24 **BET inhibitors as novel therapeutic agents in breast cancer.** Ocaña A, Nieto-Jiménez C, Pandiella A. **Oncotarget. 2017 Aug 1;8(41):71285-71291. doi: 10.18632/oncotarget.19744. eCollection 2017 Sep 19. Review.** PMID: 29050361 **IF: 5.008 / Q1**

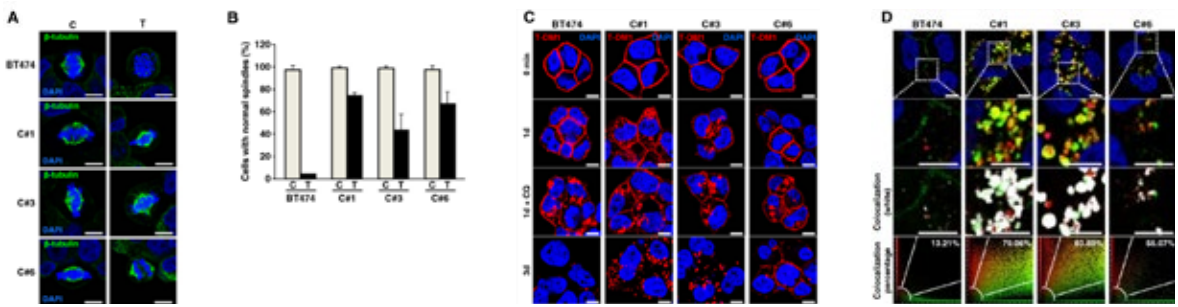
25 **A phase I study of the SRC kinase inhibitor dasatinib with trastuzumab and paclitaxel as first line therapy for patients with HER2-overexpressing advanced breast cancer.** GEICAM/2010-04 study. Ocana A, Gil-Martin M, Martín M, Rojo F, Antolín S, Guerrero Á, Trigo JM, Muñoz M, Pandiella A, Diego NG, Bezares S, Caballero R, Carrasco E, Urruticoechea A. **Oncotarget. 2017 Apr 14;8(42):73144-73153. doi: 10.18632/oncotarget.17113. eCollection 2017 Sep 22.** PMID: 29069857 **IF: 5.008 / Q1**

26 **Ubiquitin-conjugating enzyme E2T (UBE2T) and denticleless protein homolog (DTL) are linked to poor outcome in breast and lung cancers.** Pérez-Peña J, Corrales-Sánchez V, Amir E, Pandiella A, Ocana A. **Sci Rep. 2017 Dec 13;7(1):17530. doi: 10.1038/s41598-017-17836-7.** PMID: 29235520 **IF: 5.228 / Q1**

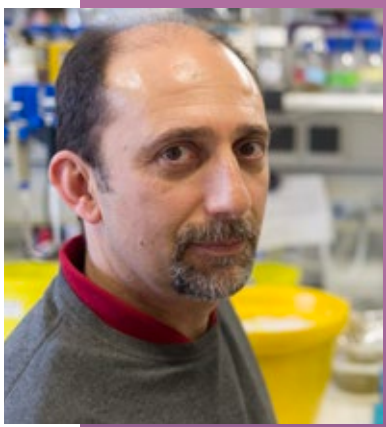
27 **Transcriptome evolution from breast epithelial cells to basal-like tumors.** Santpere G, Alcaráz-Sanabria A, Corrales-Sánchez V, Pandiella A, Győrffy B, Ocaña A. **Oncotarget. 2017 Dec 8;9(1):453-463. doi: 10.18632/oncotarget.23065. eCollection 2018 Jan 2.** PMID: 29416627 **IF: 5.008 / Q1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Nuevas estrategias para tratar el cáncer de mama positivo para HER2	Atanasio Pandiella Alonso (Coordinated with Joaquín Arribas)	Spanish Association against Cancer (AECC)	2012-2018	600,000.00 €
Red Temática de Investigación Cooperativa en Cáncer (RD12/0036/0003)	Atanasio Pandiella Alonso	Instituto de Salud Carlos III	2013-2016	332,000.00 €
Nuevas terapias en cáncer de ovario	Atanasio Pandiella Alonso	CRIS Foundation	2015-2018	18,000.00 €
La ruta de MEK5/ERK5 como diana terapéutica en cáncer (PI15/01180)	Azucena Esparís Ogando	Instituto de Salud Carlos III	2016-2018	110,715.00 €
Búsqueda de nuevas dianas moleculares en cáncer de mama triple negativo (PI15/00684)	Juan Carlos Montero	Instituto de Salud Carlos III	2016-2018	92,565.00 €
Señalización por receptores ERBB/HER en cáncer (BFU2015-71371-R)	Atanasio Pandiella Alonso	Ministerio de Economía y Competitividad	2016-2019	369,050.00 €
Señalización por receptores ERBB/HER en cáncer (CSI002U16)	Atanasio Pandiella Alonso	Junta de Castilla y León	2016-2018	120,000.00 €
Caracterización de nuevos mecanismos de resistencia a terapias anti-her2 en Cáncer de mama: muerte inducida por trail (SOL17-EDR)	Elena Díaz	Fundacion Solorzano	2017	2,750.00 €
Búsqueda de nuevas dianas moleculares en cáncer de mama triple negativo (SOL17-JCM)	Juan Carlos Montero	Fundacion Solorzano	2017	2,750.00 €



Effect of T-DM1 on spindle assembly. A) Action of T-DM1 on mitotic spindle formation. Cell lines were treated, fixed, stained for ß-tubulin (green) and DAPI (blue), and representative images taken. Scale bar,7.5µm. **B)** Quantitative analysis of mitotic cells with normal spindles. Bipolar spindles were evaluated in mitotic cells of the different cell lines treated or not with T-DM1. The bar graphs show the mean ± SD of two independent experiments, calculated as follows: (number of mitotic cells with normal spindles/total number of mitotic cells) x 100 (%). **C)** T-DM1 staining in the different cell lines. Cells seeded on coverslips were pulsed with 10nmol/L T-DM1 (15 min. at 37ºC), and chased for the indicated times. CQ, chloroquine (50mmol/L). **D)** Colocalization of T-DM1 with the acidic vesicle indicator Lysotracker. Cells were pulsed as in C, chased for 3 days, and costained with Anti-Human-Dylight 488 (T-DM1; green) and the acidic vesicle indicator LysoTracker red. Boxed areas define higher magnifications (second row). Colocalization between T-DM1 and LysoTracker is shown in white (third row). Image-generated scatter plots of acquired images for colocalization analysis were processed by the LAS AF software (last row). Pure red and green pixels are between abscissa/ordinate and white lines; colocalizating pixels are found inside central region of the plot (between white lines). LysoTracker/T-DM1 colocalization, calculated as the ratio of the area of colocalizing signals with respect to total fluorescence area, is indicated. Scale bars, 7.5µm.



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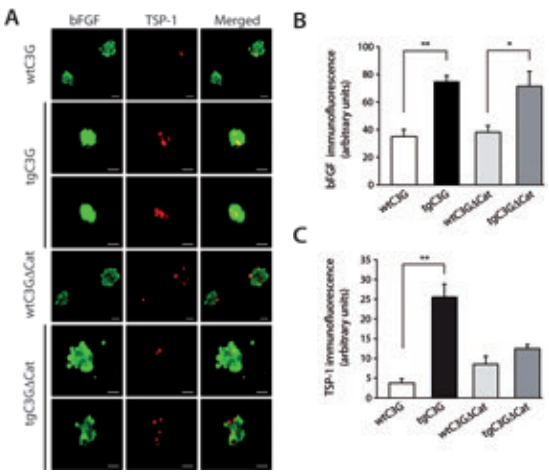
LABORATORY 17

STRUCTURAL BIOLOGY OF CELL ADHESION AND SIGNALING



Transgenic C3G expression prevents the release of thrombospondin-1 (TSP-1) and bFGF from thrombin-stimulated mouse platelets. A) Representative confocal microscopy images of the subcellular distribution of TSP-1 and bFGF in thrombin-activated platelets of the indicated genotypes. All micrographs were taken at the same exposure time. Scale bars: 0.4 µm. The graphs show arbitrary values of immunofluorescence intensity (mean ± SEM) for bFGF **B)** or TSP-1 **C)** in each genotype. *p < 0.05; **p < 0.01. Tg: transgenic; wt: wild-type; Cat: C3G mutant lacking the catalytic domain.

Our group is interested in understanding the structural and mechanistic basis of the function of proteins involved in cell adhesion, and how they are altered in human diseases such as tumoral processes. To this end, we apply mutidisciplinary approaches that include complementary structural biology methods and the use of quantitative biophysical and biochemical techniques.

In one of our research lines we study the architecture and regulation of hemidesmosomes, which are multiprotein adhesion complexes that mediate the stable attachment of epithelial cells to the basement membrane. We also study other roles of hemidesmosomal proteins. For example, in healthy epithelia integrin 64 is an essential component of hemidesmosmes, while in carcinoma cells, were hemidesmosomes become disorganized, 64-mediated signaling favors migration, invasion, and survival. We have extensively characterized the structure of the cytoplasmic region of the 4 subunit, which mediates most of the interactions of 64 both in hemidesmosomes and in pro-migration signaling. We have elucidated the 3D structure of the region of 4 that includes the 3rd and 4th FnIII domains (FnIII-3,4). The FnIII-3,4 of 4 mediates the binding to the protein BPAG1e in hemidesmosomes. We are currently characterizing the structural basis of the interaction between 64 and BPAG1e, a member of the plakin protein family, and potential mechanisms that may inhibit binding.

Plectin and BPAG1e are the two plakins that tether intermediate filaments to hemidesmosomes. We have extensively characterized plectin, which serves as a model for other plakins. Recently, we have elucidated the complete 3D structure of the plakin domain of plectin. This is a 1000-resdiues long domain in the amino terminal region of the molecule that harbors binding sites for other proteins. The plakin domain has a rod-like shape formed by a series of spectrin repeats in tandem. The continuous structure suggests that the plakin domain of plectin might act as a molecular shock absorber. Plectin also connects intermediate filaments to the nuclear envelope and to other organelles. We have collaborated in the characterization of the mechanical properties of the interaction of plectin with isolated nucleus.

In a second research line we are characterizing the mechanisms of autoinhibition and regulation of a C3G a guanine nucleotide exchange factor that activates Rap1, a small GTPase involved in the regulation of cell adhesion.

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C3G REGULATION OF PLATELET FUNCTION USING ANIMAL MODELS AND ITS IMPACT ON CORONARY SYNDROME AND TUMOR METASTASIS

During the last years, our group has been focused on the role of C3G in platelet function and its relationship with tumor development and metastasis. The relevance of C3G in cell adhesion, together with the known role of its effector Rap1 in the platelet function, prompted us to study a possible role of C3G in platelet physiology. Using transgenic models with specific expression of C3G in megakaryocytes and platelets, we have uncovered a new role for C3G in platelet homeostasis by regulating platelet activation and aggregation triggered by different agonists. Mechanistically, C3G contributes to the activation of the platelet integrin aIIbß3 induced by thrombin, through a PKC-C3G-Rap1 pathway. In addition, C3G participates in the regulation of platelet -granule secretion through its interaction with the v-SNARE VAMP-7. Specifically, C3G controls the secretion of pro- and anti-angiogenic factors from thrombin- or ADP-stimulated mouse platelets, which results in the modulation of angiogenesis, both in vivo and in vitro, including tumor angiogenesis and metastasis. Moreover, C3G also participates in megakaryocyte differentiation and proplatelet formation. Based on this novel role of C3G in the regulation of the biology of platelets, our future goal will be to study a possible involvement of C3G in the thrombotic disease.

PUBLICATIONS

1 **Purification and Structural Analysis of Plectin and BPAG1e.** Manso JA, García Rubio I, Gómez-Hernández M, Ortega E, Buey RM, Carballido AM, Carabias A, Alonso-García N, de Pereda JM. **Methods Enzymol. 2016;569:177-96. doi: 10.1016/bs.mie.2015.05.002. Epub 2015 May 29.** PMID: 26778559 **IF: 2.088 / Q3**

2 **C3G knock-down enhances migration and invasion by increasing Rap1-mediated p38 activation, while it impairs tumor growth through p38-independent mechanisms.** Priego N, Arechederra M, Sequera C, Bragado P, Vázquez-Carballo A, Gutiérrez-Uzquiza Á, Martín-Granado V, Ventura JJ, Kazanietz MG, Guerrero C, Porras A. **Oncotarget. 2016 Jul 19;7(29):45060-45078. doi: 10.18632/oncotarget.9911.** PMID: 27286263 **IF: 5.008 / Q1**

3 **The Structure of the Plakin Domain of Plectin Reveals an Extended Rod-like Shape.** Ortega E, Manso JA, Buey RM, Carballido AM, Carabias A, Sonnenberg A, de Pereda JM. **J Biol Chem. 2016 Sep 2;291(36):18643-62. doi: 10.1074/jbc.M116.732909. Epub 2016 Jul 13.** PMID: 27413182 **IF: 4.258 / Q1**

4 **A New Member of the Thioredoxin Reductase Family from Early Oxygenic Photosynthetic Organisms.** Buey RM, Galindo-Trigo S, López-Maury L, Velázquez-Campoy A, Revuelta JL, Florencio FJ, de Pereda JM, Schürmann P, Buchanan BB, Balsera M. **Mol Plant. 2017 Jan 9;10(1):212-215. doi: 10.1016/j.molp.2016.06.019. Epub 2016 Jul 12.** PMID: 27418374 **IF: 7.142 / D1**

5 **The CRISPR/Cas9 system efficiently reverts the tumorigenic ability of BCR/ABL in vitro and in a xenograft model of chronic myeloid leukemia.** García-Tuñón I, Hernández-Sánchez M, Ordoñez JL, Alonso-Pérez V, Álamo-Quijada M, Benito R, Guerrero C, Hernández-Rivas JM, Sánchez-Martín M. **Oncotarget. 2017 Apr 18;8(16):26027-26040. doi: 10.18632/oncotarget.15215.** PMID: 28212528 **IF: 5.008 / Q1**

6 **A nucleotide-controlled conformational switch modulates the activity of eukaryotic IMP dehydrogenases.** Buey RM, Fernández-Justel D, Marcos-Alcalde Í, Winter G, Gómez-Puertas P, de Pereda JM, Luis Revuelta J. **Sci Rep. 2017 Jun 1;7(1):2648. doi: 10.1038/s41598-017-02805-x.** PMID: 28572600 **IF: 5.228 / Q1**

7 **The nesprin-cytoskeleton interface probed directly on single nuclei is a mechanically rich system.** Balikov DA, Brady SK, Ko UH, Shin JH, de Pereda JM,

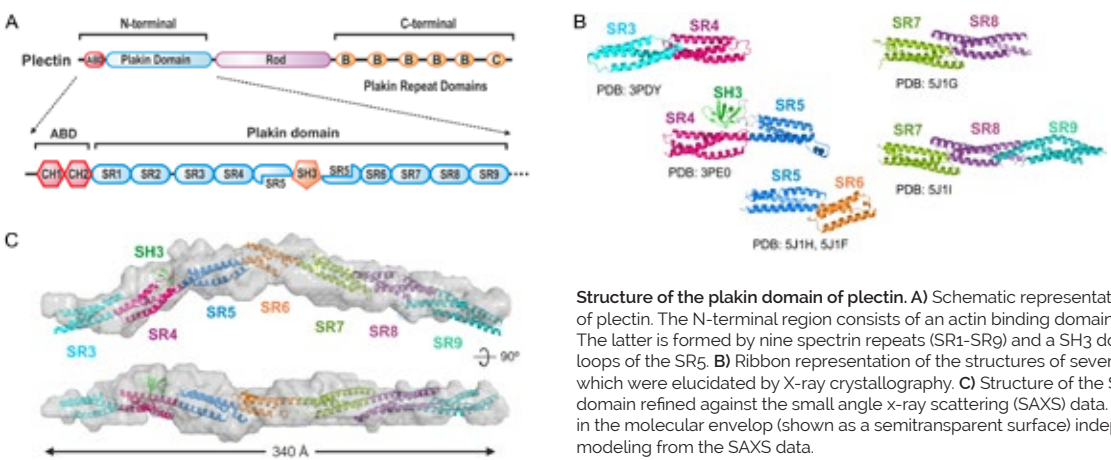
Sonnenberg A, Sung HJ, Lang MJ. **Nucleus. 2017 Jun 22:1-14. doi: 10.1080/19491034.2017.1322237.** PMID: 28640691 **IF: 2.387 / Q3**

8 **Unprecedented pathway of reducing equivalents in a diflavin-linked disulfide oxidoreductase.** Buey RM, Arellano JB, López-Maury L, Galindo-Trigo S, Velázquez-Campoy A, Revuelta JL, de Pereda JM, Florencio FJ, Schürmann P, Buchanan BB, Balsera M. **Proc Natl Acad Sci U S A. 2017 Nov 28;114(48):12725-12730. doi: 10.1073/pnas.1713698114. Epub 2017 Nov 13.** PMID: 29133410 **IF: 9.423 / D1**

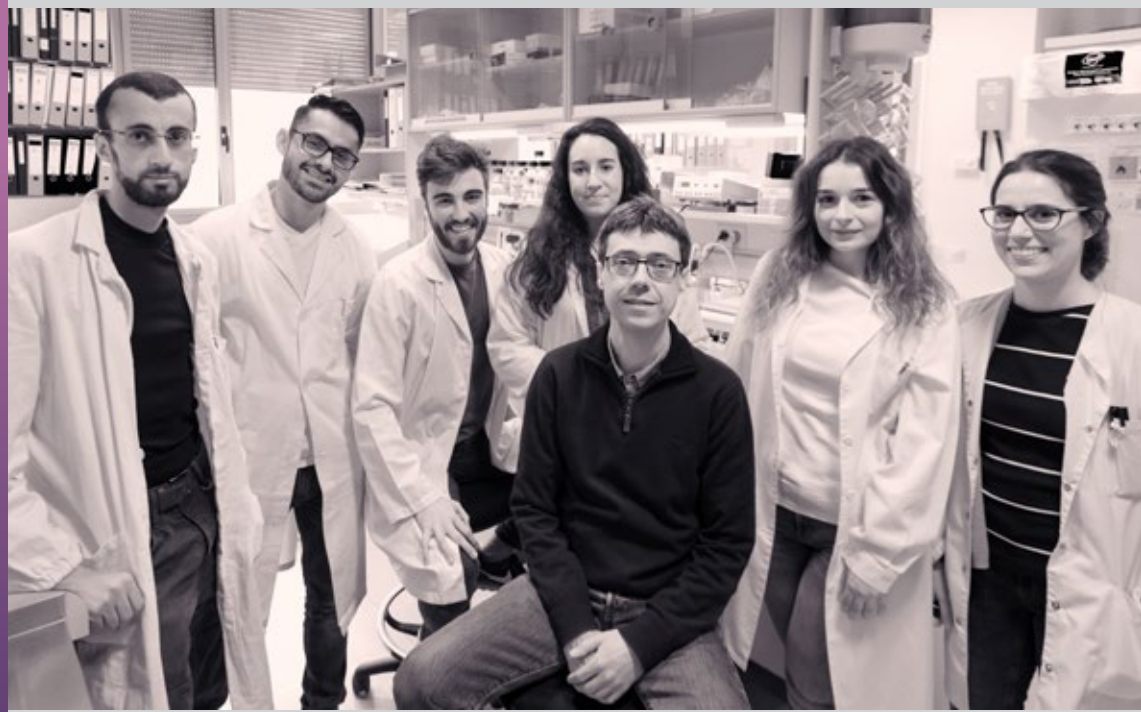
9 **C3G promotes a selective release of angiogenic factors from activated mouse platelets to regulate angiogenesis and tumor metastasis.** Martín-Granado V, Ortiz-Rivero S, Carmona R, Gutiérrez-Herrero S, Barrera M, San-Segundo L, Sequera C, Perdiguero P, Lozano F, Martín-Herrero F, González-Porras JR, Muñoz-Chápuli R, Porras A, Guerrero C. **Oncotarget. 2017 Nov 6;8(67):110994-111011. doi: 10.18632/oncotarget.22339. eCollection 2017 Dec 19.** PMID: 29340032 **IF: 5.008 / Q1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Análisis in vitro e in vivo de la función de C3G en diferentes tipos celulares y su impacto en patologías cardiovasculares y en metástasis (SAF2013-48210-C2-1-R)	Carmen Guerrero Arroyo	Ministerio de Economía y Competitividad	2014-2016	133,100.00 €
Mecanismos de señalización en enfermedades cardiovasculares y otras patologías: de la investigación básica a la clínica (Programa XIII Grupos de Investigación Reconocidos)	Carmen Guerrero Arroyo	Universidad de Salamanca	2016	1,666.10 €
Bases estructurales y mecanísticas de la regulación del activador de RAP1 C3G (BFU2015-69499-P)	Jose María de Pereda	Ministerio de Economía y Competitividad	2016-2018	130,438.00 €
Papel de C3G en la regulación de la función plaquetaria: implicaciones en angiogénesis y aplicación al diagnóstico y tratamiento de la enfermedad trombótica (SA017U16)	Carmen Guerrero Arroyo	Consejería de educación. Junta de Castilla y León	2016-2018	119,999.00 €
Función de C3G en el desarrollo tumoral y en la patofisiología del hígado. Implicación del C3G plaquetario en la angiogénesis y en enfermedades hepáticas y cardiovasculares (SAF2016-76588-C2-2-R)	Carmen Guerrero Arroyo	Ministerio de Economía y Competitividad	2016-2018	121,000.00 €
Mecanismos de señalización en enfermedades cardiovasculares y otras patologías: de la investigación básica a la clínica (Programa XIII Grupos de Investigación Reconocidos)	Carmen Guerrero Arroyo	Universidad de Salamanca	2017	1,774.00 €



Structure of the plakin domain of plectin. A) Schematic representation of the domain organization of plectin. The N-terminal region consists of an actin binding domain (ABD) and a plakin domain. The latter is formed by nine spectrin repeats (SR1-SR9) and a SH3 domain inserted in one of the loops of the SR5. **B)** Ribbon representation of the structures of several overlapping fragments, which were elucidated by X-ray crystallography. **C)** Structure of the SR3-SR9 segment of the plakin domain refined against the small angle x-ray scattering (SAXS) data. The atomic structure is docked in the molecular envelop (shown as a semitransparent surface) independently obtained by ab initio modeling from the SAXS data.



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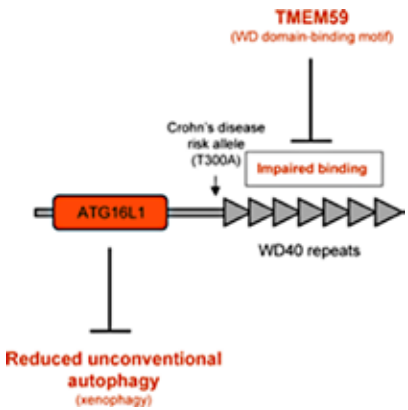
LABORATORY 18

UNCONVENTIONAL AUTOPHAGY IN HEALTH AND DISEASE

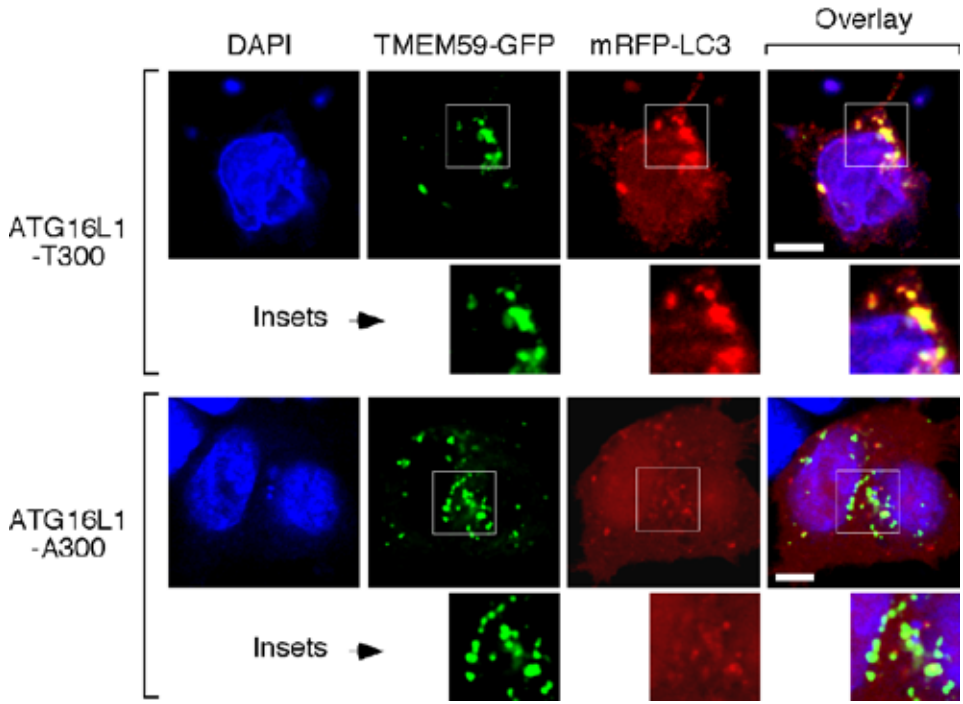


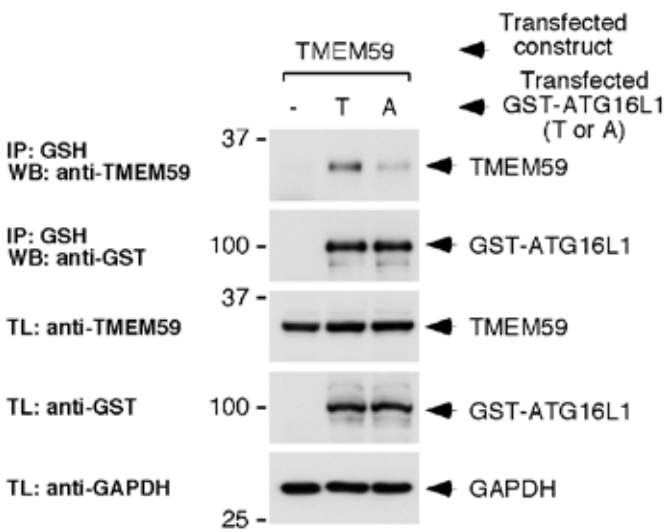
The main focus of our laboratory is the study of unconventional forms of autophagy and the implications that this growing collection of processes may have in human disease.

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.


DAPI
TMEM59-GFP
mRFP-LC3
Overlay
ATG16L1
-T300
Insets
ATG16L1
-A300
Insets


TMEM59
Transfected construct
- T A
Transfected GST-ATG16L1 (T or A)
IP: GSH
WB: anti-TMEM59
37 -
TMEM59
IP: GSH
WB: anti-GST
100 -
GST-ATG16L1
37 -
TL: anti-TMEM59
TMEM59
TL: anti-GST
100 -
GST-ATG16L1
TL: anti-GAPDH
GAPDH
25 -

PUBLICATIONS

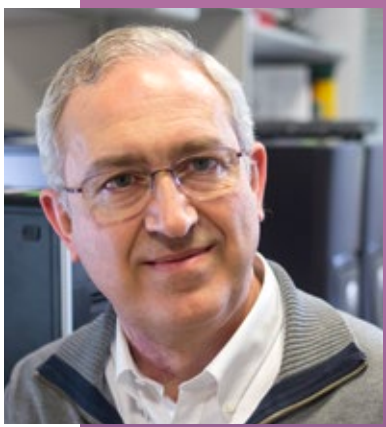
1 **Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition).** Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, ..., Pierrefite-Carle V, Pietrocola F, Pimentel-Muiños FX, Pinar M, Pineda B, Pinkas-Kramarski R, ..., Zhuang SM, Zhuang X, Ziparo E, Zois CE, Zoladek T, Zong WX, Zorzano A, Zughaier SM. **Autophagy. 2016;12(1):1-222. doi: 10.1080/15548627.2015.1100356. Erratum in: Autophagy. 2016;12(2):443. Selliez, Iban [corrected to Seiliez, Iban] Autophagy. 2016;12(1):1-222. doi: 10.1080/15548627.2015.1100356.** PMID: 26799652 **IF: 9.108 / D1**

2 **The T300A Crohn's disease risk polymorphism impairs function of the WD40 domain of ATG16L1.** Boada-Romero E, Serramito-Gómez I, Sacristán MP, Boone DL, Xavier RJ, Pimentel-Muiños FX. **Nat Commun. 2016 Jun 8;7:11821. doi: 10.1038/ncomms11821.** PMID: 27273576 **IF: 11.329 / D1**

3 **Unconventional autophagy mediated by the WD40 domain of ATG16L1 is derailed by the T300A Crohn disease risk polymorphism.** Serramito-Gómez I, Boada-Romero E, Pimentel-Muiños FX. **Autophagy. 2016 Nov;12(11):2254-2255. Epub 2016 Aug 19.** PMID: 27541200 **IF: 9.108 / D1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Papel de la autofagia no convencional en inmunidad innata, homeostasis intestinal y enfermedad de Crohn (SAF2014-53320)	Felipe X. Pimentel Muiños	Ministerio de Economía y Competitividad	2015-2017	133,100.00 €
Red de Excelencia para el Estudio de la Autofagia (Participación como miembro del equipo de investigación) (NEAR) (BFU2015-71869-REDT)	Felipe X. Pimentel Muiños	Ministerio de Economía y Competitividad	2015-2017	42,000.00 €
Transautophagy European Network (Participación como miembro del equipo de investigación) (COST Action; CA15138)	Felipe X. Pimentel Muiños	Union Europea	2016-2018	500,000.00 €
Nuevas actividades del regulador autofágico ATG16L1 y su relevancia en patología (SAF2017-88390-R)	Felipe X. Pimentel Muiños	Ministerio de Economía y Competitividad	2018-2020	205,700.00 €



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Jorge Martínez Romero

LABORATORY 19

BIOINFORMATICS AND FUNCTIONAL GENOMICS OF CANCER

A) Barplot presenting the number of research articles per country published by scientists from 19 countries of LA on bioinformatics and computational biology in 25 years (from 1991 to 2016). The total number found was: 2119. **B)** Word cloud derived from the titles of top 500 most highly cited research articles within the total list of 2119 papers. **C)** Selection of some of the organisms studied by scientists of LA. **De Las Rivas J et al. (2017)** ***Brief Bioinform***

Research framed within the field of Bioinformatics and Functional Genomics applied to the biomedical area of Cancer and Oncology:

- **Functional Genomics:** development of methods and strategies for the analysis of genomic data derived from different types of high throughput technologies (high-density microarrays, and deep DNA- and RNA-sequencing) to determine expression of genes, miRNAs and ncRNAs, splicing, copy-number alteration, methylation, etc; and to achieve statistically robust assignment of signal values to biological entities to identify gene sets, profiles and signatures associated to specific biological or pathological processes. Focus on cancer samples from patients to study onco-hematological diseases, adenocarcinomas and tumor metastasis in collaboration with medical groups.
- **Proteomics, Interactomics and Integrative Bioinformatics:** Development of an integrated 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 and to allow drug-target predictions.
- **Cancer Computational Omics:** Application of Machine and Deep Learning (M/DL) and Reverse Engineering (RE) methods to genomic and proteomic cancer data to discover the biomolecular signatures associated to specific cancer states and to build prognosis predictors derived from cancer survival analysis. Studies focused mainly on onco-hematological diseases, in collaboration with medical groups.

PUBLICATIONS

1 **Microvesicles from Mesenchymal Stromal Cells Are Involved in HPC-Microenvironment Crosstalk in Myelodysplastic Patients.** Muntión S, Ramos TL, Diez-Campelo M, Rosón B, Sánchez-Abarca LI, Misiewicz-Krzeminska I, Preciado S, Sarasquete ME, De Las Rivas J, González M, Sánchez-Guijo F, Del Cañizo MC. **PLoS One. 2016 ; 11(2):e0146722. doi: 10.1371/journal.pone.0146722.** PMID: 26836120 **IF: 3.057 / Q1**

2 **APID interactomes: providing proteome-based interactomes with controlled quality for multiple species and derived networks.** Alonso-López D, Gutiérrez MA, Lopes KP, Prieto C, Santamaría R, De Las Rivas J. **Nucleic Acids Res. 2016 ; 44(W1):W529-35. doi: 10.1093/nar/gkw363.** PMID: 27131791 **IF: 10.162 / D1**

3 **Matrix-Gla protein promotes osteosarcoma lung metastasis and associates with poor prognosis.** Zandueta C, Ormazábal C, Perurena N, Martínez-Canarias S, Zalacaín M, Julián MS, Grigoriadis AE, Valencia K, Campos-Laborie FJ, De Las Rivas J, Vicent S, Patiño-García A, Lecanda F. **J Pathol. 2016 ; 239(4):438-449. doi: 10.1002/path.4740.** PMID: 27172275 **IF: 7.381 / D1**

4 **Evolutionary hallmarks of the human proteome: chasing the age and coregulation of protein-coding genes.** Lopes KP, Campos-Laborie FJ, Vialle RA, Ortega JM, De Las Rivas J. **BMC Genomics. 2016 ; 17(Suppl 8):725.** PMID: 27801289 **IF: 3.867 / Q1**

5 **Path2enet: generation of human pathway-derived networks in an expression specific context.** Droste C, De Las Rivas J. **BMC Genomics. 2016; 17(Suppl 8):731.** PMID: 27801297 **IF: 3.867 / Q1**

6 **Insights into the human mesenchymal stromal/stem cell identity through integrative transcriptomic profiling.** Roson-Burgo B, Sanchez-Guijo F, Del Cañizo C, De Las Rivas J. **BMC Genomics. 2016 ; 17(1):944.** PMID: 27871224 **IF: 3.867 / Q1**

7 **Identification of expression patterns in the progression of disease stages by integration of transcriptomic data.** Aibar S, Abaigar M, Campos-Laborie FJ, Sánchez-Santos JM, Hernández-Rivas JM, De Las Rivas J. **BMC Bioinformatics. 2016 ; 17(Suppl 15):432. doi: 10.1186/s12859-016-1290-4.** PMID: 28185568 **IF: 2.435 / Q1**

8 **MicroRNA (miR)-203 and miR-205 expression patterns identify subgroups of prognosis in cutaneous squamous cell carcinoma.** Cañueto J, Cardeñoso-Álvarez E, García-Hernández JL, Galindo-Villardón P, Vicente-Galindo P, Vicente-Villardón JL, Alonso-López D, De Las Rivas J, Valero J, Moyano-Sanz E, Fernández-López E, Mao JH, Castellanos-Martín A, Román-Curto C, Pérez-Losada J. **Br J Dermatol. 2017 ; 177(1):168-178. doi: 10.1111/bjd.15236.** PMID: 27943259 **IF: 4.317 / D1**

9 **Linking amyotrophic lateral sclerosis and spinal muscular atrophy through RNA-transcriptome homeostasis: a genomics perspective.** Gama-Carvalho M, L García-Vaquero M, R Pinto F, Besse F, Weis J, Voigt A, Schulz JB, De Las Rivas J. **J Neurochem. 2017 ; 141(1):12-30. doi: 10.1111/jnc.13945. Review.** PMID: 28054357 **IF: 3.842 / Q2**

10 **Epidermal Growth Factor Signaling towards Proliferation: Modeling and Logic Inference Using Forward and Backward Search.** Riesco A, Santos-Buitrago B, De Las Rivas J, Knapp M, Santos-García G, Talcott C. **Biomed Res Int. 2017; 2017:1809513. doi: 10.1155/2017/1809513.** PMID: 28191459 **IF: 2.134 / Q3**

11 **Ten simple rules for forming a scientific professional society.** Gaëta BA, De Las Rivas J, Horton P, Meysman P, Mulder N, Romano P, Welch L. **PLoS Comput Biol. 2017; 13(3):e1005226. doi: 10.1371/journal.pcbi.1005226.** PMID: 28333920 **IF: 4.587 / D1**

12 **Crebbp loss cooperates with Bcl2 overexpression to promote lymphoma in mice.** García-Ramírez I, Tadros S, González-Herrero I, Martín-Lorenzo A, Rodríguez-Hernández G, Moore D, Ruiz-Roca L, Blanco O, Alonso-López D, De Las Rivas J, Hartert K, Duval R, Klinkebiel D, Bast M, Vose J, Lunning M, Fu K, Greiner T, Rodrigues-Lima F, Jiménez R, Criado FJG, Cenador MBG, Brindle P, Vicente-Dueñas C, Alizadeh A, Sánchez-García I, Green MR. **Blood. 2017; 129(19):2645-2656. doi: 10.1182/blood-2016-08-733469.** PMID: 28288979 **IF: 13.164 / D1**

13 **Screening and Validation of Novel Biomarkers in Osteoarticular Pathologies by Comprehensive Combination of Protein Array Technologies.** Sierra-Sánchez Á, Garrido-Martín D, Lourido L, González-González M, Díez P, Ruiz-Romero C, Sjöber R, Droste C, De Las Rivas J, Nilsson P, Blanco F, Fuentes M. **J Proteome Res. 2017 ; 16(5):1890-1899. doi: 10.1021/acs.jproteome.6b00980.** PMID: 28379711 **IF: 4.173 / Q1**

14 **Infection Exposure Promotes ETV6-RUNX1 Precursor B-cell Leukemia via Impaired H3K4 Demethylases.** Rodríguez-Hernández G, Hauer J, Martín-Lorenzo A, Schäfer D, Bartenhagen C, García-Ramírez I, Auer F, González-Herrero I, Ruiz-Roca L, Gombert M, Okpanyi V, Fischer U, Chen C, Dugas M, Bhatia S, Linka RM, García-Suquia M, Rascón-Trincado MV, García-Sanchez A, Blanco O, García-Cenador MB, García-Criado FJ, Cobaleda C, Alonso-López D, De Las Rivas J, Müschen M, Vicente-Dueñas C, Sánchez-García I, Borkhardt A. **Cancer Res. 2017 ; 77(16):4365-4377. doi: 10.1158/0008-5472.CAN-17-0701.** PMID: 28630052 **IF: 9.122 / D1**

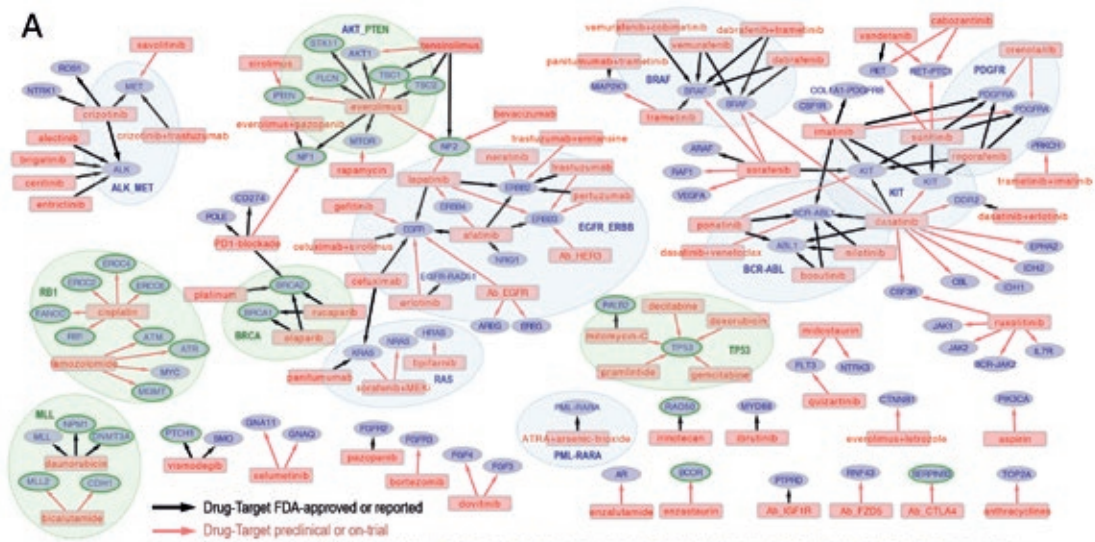
15 **Mesenchymal stromal cells (MSC) from JAK2+ myeloproliferative neoplasms differ from normal MSC and contribute to the maintenance of neoplastic hematopoiesis.** Ramos TL, Sánchez-Abarca LI, Rosón-Burgo B, Redondo A, Rico A, Preciado S, Ortega R, Rodríguez C, Muntión S, Hernández-Hernández Á, De Las Rivas J, González M, González Porras JR, Del Cañizo C, Sánchez-Guijo F. **PLoS One. 2017 ; 12(8):e0182470. doi: 10.1371/journal.pone.0182470.** PMID: 28796790 **IF: 3.057 / Q1**

16 **Bioinformatics in Latin America and SoIBio impact, a tale of spin-off and expansion around genomes and protein structures.** De Las Rivas J, Bonavides-Martínez C, Campos-Laborie FJ. **Brief Bioinform. 2017 ; 18(6):1091. doi: 10.1093/bib/bbx114.** PMID: 28968628 **IF: 8.399 / D1**

GRANTS FOR RESEARCH IN PROGRESS

PROJECT	PI	GRANT	TIME	FUNDING
Fly-SMALS: Common RNA-dependent pathways for motor neuron degeneration in spinocerebellar muscular atrophy and amyotrophic lateral sclerosis. (Project Refs. AC14/00024 and JPND_CD_FP-688-085)	Javier De Las Rivas	EU Joint Programme - Neurodegenerative Disease Research (JPND) & Ministerio de Sanidad y Consumo - ISCIII	2015-2018	49,610.00 €
Genómica y proteómica integrativa de hemopatías malignas mieloides y mieloma múltiple: estudio bioinformático de datos ómicos de muestras clínicas de pacientes (Project Ref. PI15/00328)	Javier De Las Rivas	Instituto de Salud Carlos III	2016-2018	92,565.00 €
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	Union Europea – Horizonte 2020	2017-2020	452,375.00 €
Plataforma de Bioinformática: Bioinformatics and Functional Genomics in Cancer (Project Ref. PT17/0009/0008)	Javier De Las Rivas	Instituto de Salud Carlos III	2017-2019	31,899.00 €

A



13 major cancer druggable modules: AKT_PTEN, ALK_MET, BCR-ABL, BRAF, BRCA, EGFR_ERBB, KIT, MLL, PDGFR, PML-RARA, RAS, RB1, TP53

B

Drugs	Degree	Genes	Degree
dasatinib	11	EGFR	7
everolimus	9	ERBB2	7
imatinib	7	BCR-ABL1	6
sorafenib	6	BRAF	6
sunitinib	6	KIT	6
cisplatin	6	ALK	5
afatinib	5	BRAF	5
lapatinib	5	TP53	5
ruxolitinib	5	Drugs & Genes with ≥ 5 interactions	

C

Tumor Supressor Cancer Genes (loss-of-function): 27 genes		
ATM	ERCC6	PTCH1
ATR	FANCC	PTEN
BCOR	FLCN	RAD50
BRCA1	MGMT	RB1
BRCA2	MLL2	SERPINB3
CDH1	NF1	STK11
DNMT3A	NF2	TP53
ERCC2	NPM1	TSC1
ERCC4	PALB2	TSC2

Cancer protein–drug bipartite network including 92 cancer driver genes/proteins and 83 selected drugs that interact with such proteins. **A)** Visualization of the network that includes 176 directed interactions, showing with black arrows the links corresponding to drugs approved by FDA and with pale red arrows the links corresponding to drugs that are still on-trial or preclinical use. **B)** Table showing the degree of the proteins and the drugs that have the highest number of interactions (5). **C)** Table showing the list of 27 proteins that are tumor suppressors. **De Las Rivas J et al. (2017)** ***Adv Protein Chem Struct Biol***

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Beatriz María Rivas López

Nurse
Aline Rodrigues Françoso

Administrative Staff
Felicidad Alisente Frías

ONCOLOGY SERVICE

CLINICAL AND MOLECULAR ANALYSIS OF SOLID TUMORS

The research group collaborate with the main national and international cooperative groups such as GEICAM (Spanish research group in breast cancer), SOLTI (Spanish group treatment of solid tumors), TTD (Spanish group treatment of gastrointestinal tumors), Group ONCOPAZ, BCIRG (Breast Cancer International Research Group), the Spanish Group for Head and Neck Cancer (TTCC), GECP (Spanish Group for Lung Cancer), BCIRG (Breast Cancer International Research Group) among others.

Research in hereditary cancer. It is carried out by our group in collaboration with the group of Dr. González Sarmiento, having a clinical unit of genetic counseling and the laboratory 14 of the Cancer Research Center (CIC / IBSAL) for molecular studies. These studies have focused on the clinical-pathological characteristics and their correlation with molecular alterations, mainly in the syndrome of hereditary breast and ovarian cancer and in Lynch Syndrome.

Translational research lines in head and neck tumors. Polymorphism studies in relation to the susceptibility and response to medical and radiotherapy treatment of Head and Neck tumors. Coordinating studies at the national level. Polymorphism studies are carried out in collaboration with the Molecular Medicine Unit of Prof. González Sarmiento. Following the previous line, we have initiated other projects: studies of genetic mutations through massive sequencing

techniques in head and neck tumors and their relationship with response and survival in patients with a pre-established treatment, in collaboration with the Molecular Medicine Unit of Prof. González Sarmiento and with the HUSA Cytogenetics Unit of Prof. Hernández Rivas.

Study of circulating tumor cells, as prognostic and possibly predictive factors of response in patients with breast, colon and prostate cancer. We began this line 15 years ago with the CIC / IBSAL group led by Dr. Isidro Sánchez, and since two years ago it is our own independent line that we developed within our group, since Dr. Juan joined us. Luis García, in collaboration with Dr. Isidro Sánchez and other clinical units. We have currently started a multi-center project with hospitals in Castilla y León. Last year, a collaborative project with the CNIO (prostate group headed by Dr. Olmos) on circulating cells in prostate cancer has begun.

These projects are giving rise to the implementation of Liquid BIOPSY, (colon cancer, lung cancer, and prostate) which is one of our flagship projects and which we hope to be able to implement in the clinic briefly, in collaboration with the Service of AP directed by Dr. Ludeña and in collaboration with the Pharmaceutical industry(CollaborationAgreementAMGEN - Biocartis).

Characterization of the molecular subtypes of breast cancer, in collaboration with the Pathological Anatomy Service directed by Dr. Ludeña, through the agreement of the Regional Health and Prosignation Management. It is coordinated from our service for the entire community of Castilla y León. The first results were presented at the next congress of the SEOM to be held in Madrid in October.

PUBLICATIONS

1 **SIADH-related hyponatremia in hospital day care units: clinical experience and management with tolvaptan.** De las Peñas R, Ponce S, Henao F, Camps Herrero C, Carcereny E, Escobar Álvarez Y, Rodríguez CA, Virizuela JA, López López R. **Support Care Cancer. 2016 Jan;24(1):499-507. doi: 10.1007/s00520-015-2948-6. Epub 2015 Oct 2.** PMID: 26431960 **IF: 2.698 / Q1**

2 **Management of infection and febrile neutropenia in patients with solid cancer.** Virizuela JA, Carratalà J, Aguado JM, Vicente D, Salavert M, Ruiz M, Ruiz I, Marco F, Lizasoain M, Jiménez-Fonseca P, Gudiol C, Cassinello J, Carmona-Bayonas A, Aguilar M, Cruz JJ. **Clin Transl Oncol. 2016 Jun;18(6):557-70. doi: 10.1007/s12094-015-1442-4. Epub 2015 Nov 17.** PMID: 26577106 **IF: 2.075 / Q3**

3 **Do new cancer drugs offer good value for money? The perspectives of oncologists, health care policy makers, patients, and the general population.** Dilla T, Lizan L, Paz S, Garrido P, Avendaño C, Cruz-Hernández JJ, Espinosa J, Sacristán JA. **Patient Prefer Adherence. 2015 Dec 18;10:1-7. doi: 10.2147/PPA.S93760. eCollection 2016.** PMID: 26719677 **IF: 1.732 / Q3**

4 **Spanish consensus on the risks and detection of antipsychotic drug-related hyperprolactinaemia.** Montejo ÁL, Arango C, Bernardo M, Carrasco JL, Crespo-Facorro B, Cruz JJ, Del Pino J, García Escudero MA, García Rizo C, González-Pinto A, Hernández AI, Martín Carrasco M, Mayoral Cleries F, Mayoral van Son J, Mories MT, Pachiarotti I, Ros S, Vieta E. **Rev Psiquiatr Salud Ment. 2016 Jul-Sep;9(3):158-73. doi: 10.1016/j.rpsm.2015.11.003. Epub 2016 Feb 24. English, Spanish.** PMID: 26927534 **IF: 2.227 / Q3**

5 **Epidemiological characteristics of a Spanish cohort of patients diagnosed with squamous cell carcinoma of head and neck: distribution of risk factors by tumor location.** Seijas-Tamayo R, Fernández-Mateos J, Adansa Klain JC, Mesía R, Pastor Borgoñón M, Pérez-Ruiz E, Vázquez Fernández S, Salvador Coloma C, Rueda Domínguez A, Taberna M, Martínez-Trufero J, Bonfill Abella T, Vázquez Estévez S, Pollán M, Del Barco Morillo E, Cruz-Hernández JJ. **Clin Transl Oncol. 2016 Nov;18(11):1114-1122. Epub 2016 Apr 25.** PMID: 27112939 **IF: 2.075 / Q3**

6 **Quality Indicators to Assure and Improve Cancer Care in Spain Using the Delphi Technique.** Camps C, Albanell J, Antón A, Aranda E, Carrato A, Cassinello J, Castellano D, Cruz JJ, Garrido P, Guillem V, Grávalos C, López G, Llorente C, Lorenzo A, Lluch A, Ignacio E, Díaz-Rubio E. **J Natl Compr Canc Netw. 2016 May;14(5):553-8.** PMID: 27160233 **IF: 4.262 / Q1**

7 **A nomogram for predicting complications in patients with solid tumours and seemingly stable febrile neutropenia.** Fonseca PJ, Carmona-Bayonas A, García IM, Marcos R, Castañón E, Antonio M, Font C, Biosca M, Blasco A, Lozano R, Ramchandani A, Beato C, de Castro EM, Espinosa J, Martínez-García J, Ghanem I, Cubero JH, Manrique IA, Navalón FG, Sevillano E, Manzano A, Virizuela J, Garrido M, Mondéjar R, Arcusa MÁ, Bonilla Y, Pérez Q, Gallardo E, Del Carmen Soriano M, Cardona M, Lasheras FS, Cruz JJ, Ayala F. **Br J Cancer. 2016 May 24;114(11):1191-8. doi: 10.1038/bjc.2016.118. Epub 2016 May 17.** PMID: 27187687 **IF: 5.569 / Q1**

8 **Anti-HER2 Therapy Beyond Second-Line for HER2-Positive Metastatic Breast Cancer: A Short Review and Recommendations for Several Clinical Scenarios from a Spanish Expert Panel.** Martínez-Jañez N,

9 Chacón I, de Juan A, Cruz-Merino L, Del Barco S, Fernández I, García-Teijido P, Gómez-Bernal A, Plazaola A, Ponce J, Servitja S, Zamora P. **Breast Care (Basel). 2016 Apr;11(2):133-8. doi: 10.1159/000443601. Epub 2016 Feb 8.** PMID: 27239176 **IF 1.553 / Q3**

10 **Equity, barriers and cancer disparities: study of the Spanish Society of Medical Oncology on the access to oncologic drugs in the Spanish Regions.** Salvador J, Aparicio J, Baron FJ, García-Campelo R, García-Carbonero R, Lianes P, Llombart A, Isla D, Piera JM, Munoz M, Puente J, Rivera F, Rodríguez CA, Virizuela JA, Martin M, Garrido P. **Clin Transl Oncol. 2017 Mar;19(3):341-356. doi: 10.1007/s12094-016-1535-8. Epub 2016 Aug 25. Erratum in: Clin Transl Oncol. 2017 Apr;19(4):525. multiple author names corrected.** PMID: 27562312 **IF: 2.075 / Q3**

11 **New clinical trials regulation in Spain: analysis of royal decree 1090/2015.** Martin Jiménez M, Calvo Ferrandiz A, Aparicio Urtasun J, García-Campelo R, Gonzalez-Flores E, Lazaro Quintela M, Muñoz Mateu M, Rodríguez Sanchez CA, Santaballa Bertran A, Sepulveda Sanchez JM, Vera García R, Virizuela Echaburu JA, Segui Palmer MA. **Clin Transl Oncol. 2017 Mar;19(3):291-300. doi: 10.1007/s12094-016-1550-9. Epub 2016 Oct 7.** PMID: 27718157 **IF: 2.075 / Q3**

12 **Perceptions of Oncologists, Healthcare Policy Makers, Patients and the General Population on the Value of Pharmaceutical Treatments in Oncology.** Sacristán JA, Lizan L, Comellas M, Garrido P, Avendaño C, Cruz-Hernández JJ, Espinosa J, Dilla T. **Adv Ther. 2016 Nov;33(11):2059-2068. Epub 2016 Oct 7.** PMID: 27718158 **IF: 1.745 / Q2**

13 **A definition for aggressive disease in patients with HER-2 negative metastatic breast cancer: an expert consensus of the Spanish Society of Medical Oncology (SEOM).** González A, Lluch A, Aba E, Albanell J, Antón A, Álvarez I, Ayala F, Barnadas A, Calvo L, Ciruelos E, Cortés J, de la Haba J, López-Vega JM, Martínez E, Muñoz M, Peláez I, Redondo A, Rodríguez Á, Rodríguez CA, Ruíz A, Llombart A. **Clin Transl Oncol. 2017 May;19(5):616-624. doi: 10.1007/s12094-016-1571-4. Epub 2016 Nov 16. Review.** PMID: 27853985 **IF: 2.075 / Q3**

14 **Phase II study of panitumumab and paclitaxel as first-line treatment in recurrent or metastatic head and neck cancer. TTCC-2009-03/VECTITAX study.** Del Barco Morillo E, Mesía R, Adansa Klain JC, Vázquez Fernández S, Martínez-Galán J, Pastor Borgoñon M, González-Rivas C, Caballero Daroqui J, Berrocal A, Martínez-Trufero J, Vera R, Cruz-Hernández JJ; Spanish Head And Neck Cancer Cooperative Group (TTCC). **Oral Oncol. 2016 Nov;62:54-59. doi: 10.1016/j.oraloncology.2016.09.009. Epub 2016 Oct 8.** PMID: 27865372 **IF: 4.286 / Q1**

15 **SEOM Clinical Guideline for bone metastases from solid tumours (2016).** Grávalos C, Rodríguez C, Sabino A, Seguí MÁ, Virizuela JA, Carmona A, Cassinello J, Isla D, Jara C, Martín M. **Clin Transl Oncol. 2016 Dec;18(12):1243-1253. Epub 2016 Nov 28.** PMID: 27896639 **IF: 2.075 / Q3**

16 **SEOM Clinical Guideline update for the prevention of chemotherapy-induced nausea and vomiting (2016).** de Las Peñas R, Blasco A, De Castro J, Escobar Y, García-Campelo R, Gúrpide A, López-López R, Majem M, Rodríguez CA, Virizuela JA. **Clin Transl Oncol. 2016 Dec;18(12):1237-1242. Epub 2016 Nov 28.** PMID: 27896642 **IF: 2.075 / Q3**

17 **Epidermal growth factor receptor (EGFR) pathway polymorphisms as predictive markers of cetuximab toxicity in locally advanced head and neck squamous cell carcinoma (HNSCC) in a Spanish population.** Fernández-Mateos J, Seijas-Tamayo R, Mesía R, Taberna M, Pastor Borgoñón M, Pérez-Ruiz E, Adansa Klain JC, Vázquez Fernández S, Del Barco Morillo E, Lozano A, González Sarmiento R, Cruz-Hernández JJ; Spanish Head and Neck Cancer Cooperative Group (TTCC). **Oral Oncol. 2016 Dec;63:38-43. doi: 10.1016/j.oraloncology.2016.10.006. Epub 2016 Nov 12.** PMID: 27938998 **IF: 4.286 / Q1**

18 **Familial clustering of nasopharyngeal carcinoma in non-endemic area. Report of three families.** Paredes-Durán LM, Del Barco-Morillo E, Baldeón-Conde MJ, Medina-Valdivieso S, Guillen-Sacoto MC, Cruz-Hernández JJ. **Acta Otorrinolaringol Esp. 2017 May - Jun;68(3):164-168. doi: 10.1016/j.otorri.2016.07.006. Epub 2016 Dec 9. English, Spanish.** PMID: 27939110 **IF: NI**

19 **Medical oncology future plan of the Spanish Society of Medical Oncology: challenges and future needs of the Spanish oncologists.** Rivera F, Andres R, Felip E, García-Campelo R, Lianes P, Llombart A, Piera JM, Puente J,

Rodríguez CA, Vera R, Virizuela JA, Martin M, Garrido P. **Clin Transl Oncol. 2017 Apr;19(4):508-518. doi: 10.1007/s12094-016-1595-9. Epub 2016 Dec 22. Review.** PMID: 28005259 **IF: 2.075 / Q3**

20 **Could the Addition of Cetuximab to Conventional Radiation Therapy Improve Organ Preservation in Those Patients With Locally Advanced Larynx Cancer Who Respond to Induction Chemotherapy? An Organ Preservation Spanish Head and Neck Cancer Cooperative Group Phase 2 Study.** Mesia R, García-Saenz JA, Lozano A, Pastor M, Grau JJ, Martínez-Trufero J, Lambeaz J, Martínez-Galán J, Mel JR, González B, Vázquez S, Mañós M, Taberna M, Cirauqui B, Del Barco E, Casado E, Rubió-Casadevall J, Rodríguez-Jaráiz A, Cruz JJ; Spanish Head And Neck Cancer Cooperative Group (Study TTCC-2007/02). **Int J Radiat Oncol Biol Phys. 2017 Mar 1;97(3):473-480. doi: 10.1016/j.ijrobp.2016.11.016. Epub 2016 Nov 17.** PMID: 28011050 **IF: 5.133 / Q1**

21 **Plitidepsin: design, development, and potential place in therapy.** Alonso-Álvarez S, Pardal E, Sánchez-Nieto D, Navarro M, Caballero MD, Mateos MV, Martín A. **Drug Des Devel Ther. 2017 Jan 19;11:253-264. doi: 10.2147/DDDT.S94165. eCollection 2017. Review.** PMID: 28176904 **IF: 2.822 / Q2**

22 **Multidisciplinary consensus on the therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotics.** Montejo ÁL, Arango C, Bernardo M, Carrasco JL, Crespo-Facorro B, Cruz JJ, Del Pino-Montes J, García-Escudero MA, García-Rizo C, González-Pinto A, Hernández AI, Martín-Carrasco M, Mayoral-Cleries F, Mayoral-van Son J, Mories MT, Pachiarotti I, Pérez J, Ros S, Vieta E. **Front Neuroendocrinol. 2017 Apr;45:25-34. doi: 10.1016/j.yfrne.2017.02.003. Epub 2017 Feb 21. Review.** PMID: 28235557 **IF: 9.425 / D1**

23 **A novel capillary nano-immunoassay for assessing androgen receptor splice variant 7 in plasma. Correlation with CD133 antigen expression in circulating tumor cells. A pilot study in prostate cancer patients.** García JL, Lozano R, Misiewicz-Krzeminska I, Fernández-Mateos J, Krzeminski P, Alfonso S, Marcos RA, García R, Gómez-Veiga F, Virseda Á, Herrero M, Olmos D, Cruz-Hernández JJ. **Clin Transl Oncol. 2017 Jun 9. doi: 10.1007/s12094-017-1675-5.** PMID: 28600675 **IF: 2.075 / Q3**

24 **Analysis of autophagy gene polymorphisms in Spanish patients with head and neck squamous cell carcinoma.** Fernández-Mateos J, Seijas-Tamayo R, Klain JCA, Borgoñón MP, Pérez-Ruiz E, Mesía R, Del Barco E, Coloma CS, Dominguez AR, Daroqui JC, Fernández Ruiz E, Cruz-Hernández JJ, González-Sarmiento R. **Sci Rep. 2017 Jul 31;7(1):6887. doi: 10.1038/s41598-017-07270-0.** PMID:28761177 **IF: 5.228 / Q1**

25 **Spontaneous nasal perforation in a bevacizumab-treated patient with metastatic breast cancer.** Rodríguez CA, Martin T, Lozano R, Gomez A, Cruz JJ. **Breast J. 2017 Nov;23(6):745-746. doi: 10.1111/tbj.12913. Epub 2017 Aug 27.** PMID: 28845572 **IF: 2.297 / Q2**

26 **Should clinically meaningful outcomes in cancer be based on individual survival rather than median overall survival?** Sacristán JA, Dilla T, Garrido P, Avendaño C, Cruz-Hernández JJ, Espinosa J, Comellas M, Lizán L. **J Comp Eff Res. 2017 Sep;6(6):491-495. doi: 10.2217/cer-2016-0081. Epub 2017 Sep 29.** PMID: 28959896 **IF: 1.204 / Q4**

27 **Oncologist's knowledge and implementation of guidelines for breakthrough cancer pain in Spain: CONOCE study.** López López R, Camps Herrero C, Khosravi-Shahi P, Guillem Porta V, Carrato Mena A, García-Foncillas J, Cruz Hernández JJ, Gascón Vilaplana P, Antón Torres A, Díaz-Rubio E, Feyjoo Saus M, Aranda Aguilar E. **Clin Transl Oncol. 2017 Oct 3. doi: 10.1007/s12094-017-1756-5.** PMID: 28975575 **IF 2.075 / Q3**

28 **SEOM clinical guidelines for the treatment of head and neck cancer (2017).** Iglesias Docampo LC, Arrazubi Arrula V, Baste Rotllan N, Carral Maseda A, Cirauqui Cirauqui B, Escobar Y, Lambea Sorrosal JJ, Pastor Borgoñón M, Rueda A, Cruz Hernández JJ. **Clin Transl Oncol. 2018 Jan;20(1):75-83. doi: 10.1007/s12094-017-1776-1. Epub 2017 Nov 20.** PMID: 29159792 **IF 2.075 / Q3**

29 **Cumplimiento de las recomendaciones sobre estilos de vida saludables en mujeres en seguimiento tras un cáncer de mama.** Labrador Ortega M., Rodríguez Sánchez CA, Rodríguez García B. Revista Enfermería CyL Vol 9, Nº 1 (2017) 54-62 **IF: NI**

30 **Grupo Español de tratamiento de tumores de cabeza y cuello (TTCC): 15 años de historia (2001-2016).** JJ Cruz Hernández, R. Mesiá, JC Adansa Klain. Rev Cancer Vol. 30 Nº 3, 85-92 2016 **IF: NI**

GRANTS FOR RESEARCH IN PROGRESS

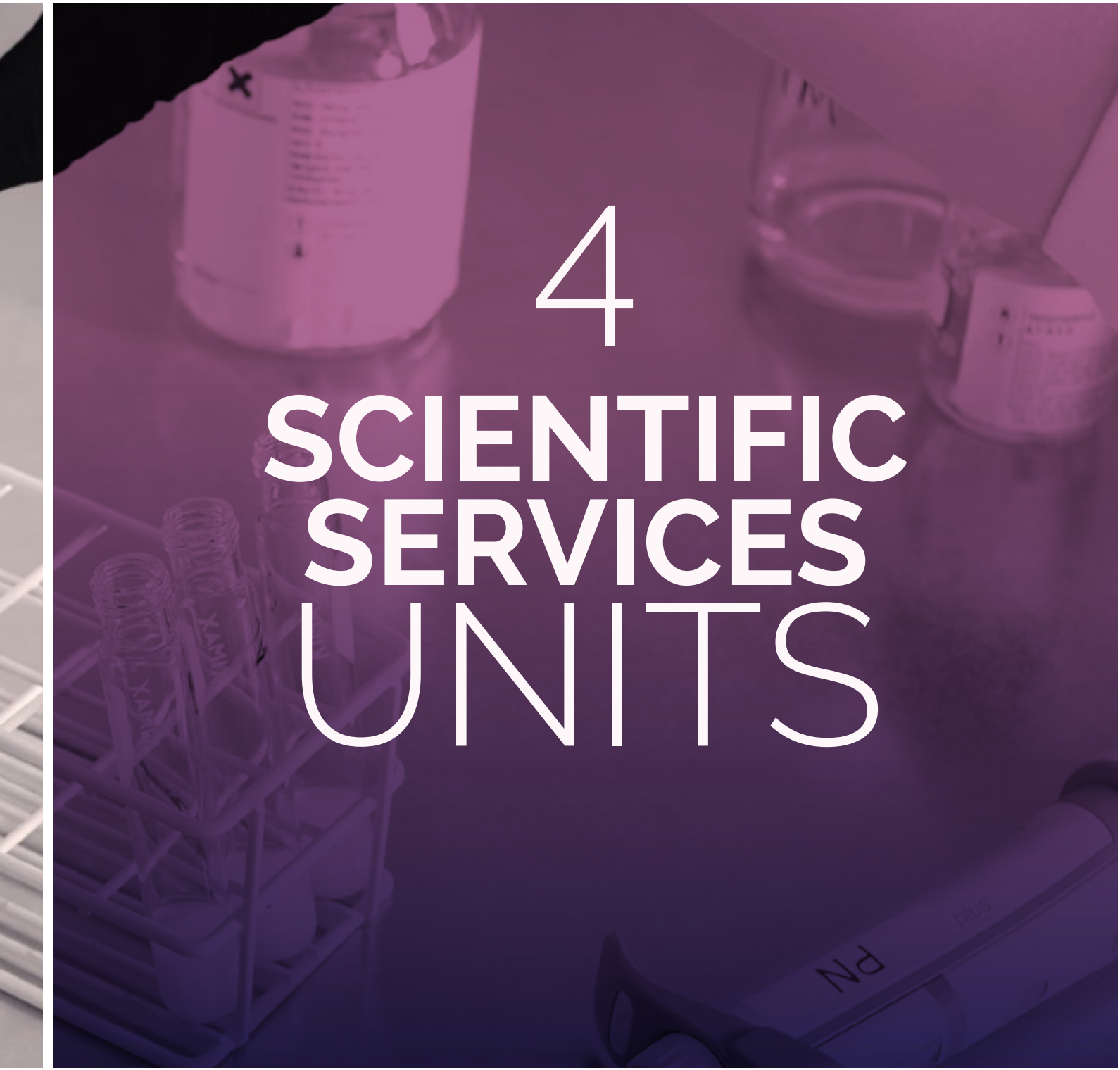
PROJECT	PI	GRANT	TIME	FUNDING
Análisis multinacional en cáncer epidermoide de cabeza y cuello. Implicaciones pronosticas y predictivas de respuesta en el ensayo clínico fase III. (PI14/00071)	Juan Jesús Cruz Hernández	Instituto de Salud Carlos III	2015-2017	91,500.00 €
CARdioToxicity Um the Elderly pRogramme: the CARTIER Project (PIE14/00066)	Juan Jesús Cruz Hernández	Instituto de Salud Carlos III	2015-2017	550,000.00€
Caracterización del virus del papiloma humano (VPH) en cáncer de cabeza y cuello en población española. Implicaciones clínicas GRS1385/A/16	Juan Jesús Cruz Hernández	Gerencia Regional de Salud. Consejería de Sanidad de la Junta de Castilla y León	2016-2017	13,236.00 €
Análisis mutacional de BRCA1/BRCA2 en línea somática en cáncer de ovario. Evaluación de implicaciones pronósticas y terapéuticas GRS1637/A/17	Teresa Martín Gómez	Gerencia Regional de Salud. Consejería de Sanidad de la Junta de Castilla y León	2017-2019	13,710.00 €

OTHER ACTIVITIES & RELEVANT FACTS

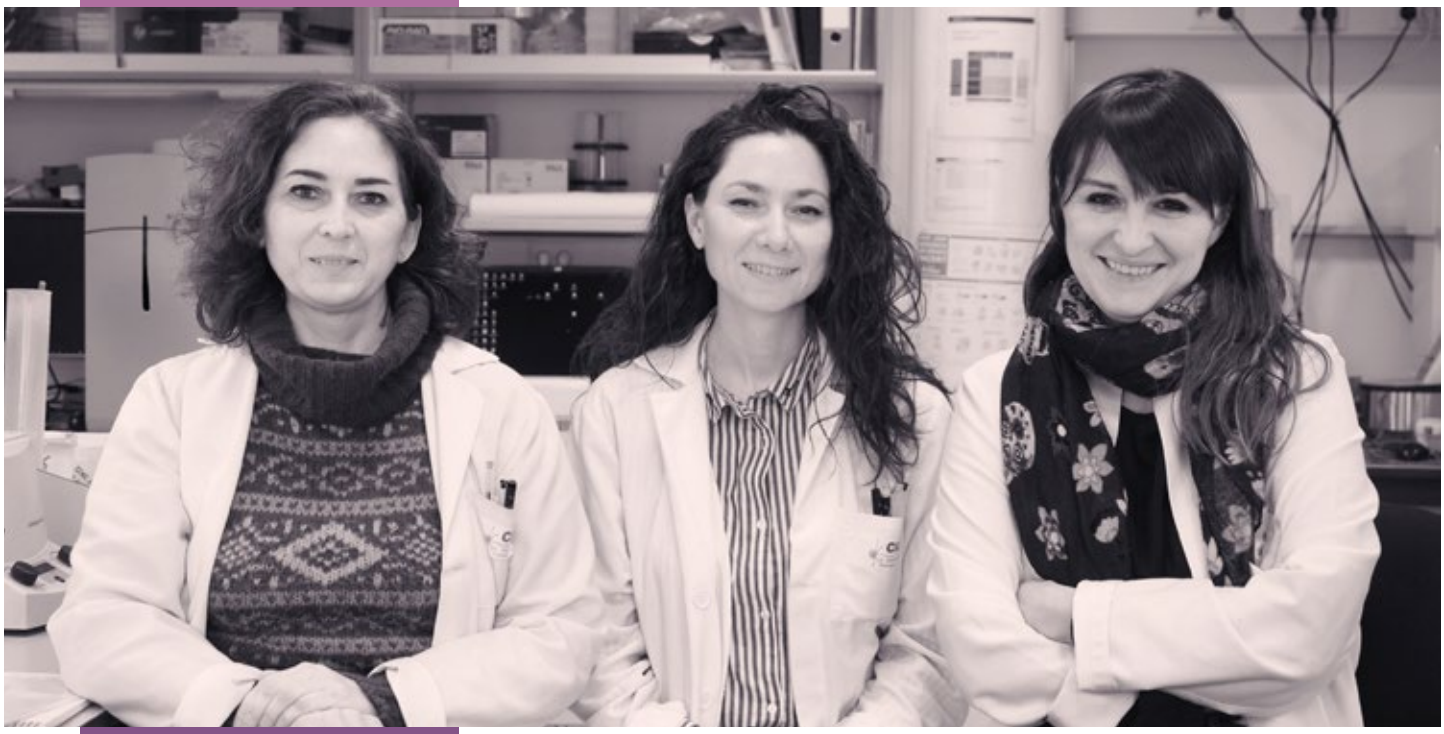
PARTICIPATION IN CLINICAL TRIALS

- A phase II randomized, doublé-blind, placebo-controlled trial of radium-223 dichloride versus placebo when adminitered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases treated with hormonal treatment background therapy BAY 88-8223/1698 Sponsor: Bayer Pharma AG. Principal Investigator Dr. César A. Rodríguez Sánchez. 2016.
- Determination of RAS Mutation Status in Liquid Biopsies in Subjects With RAS Wild-type Colorectal Cancer in First-line Treatment: a Prospective, Observational Multi-centre Study in Spain. PERSEIDA Study. 20140381-AMG-RAS-2015-01 Perseida. Amgen S.A. Principal Investigator Dr. Juan Jesús Cruz Hernández. 2016.
- A Study Evaluating The Clinical Utility Of The Health-Related Quality-Of-Life QLQ-GINET21 Questionnaire In The Treatment Of Patients With Gastrointestinal Neuroendocrine Tumours QUALINETS Study. QUALINETS (IPS-ANT-2015-01). Sponsor Ipsen Farma. Principal Investigator Dr. Miguel Navarro Martín. 2016.
- Registry of thoracic tumors. Sponsor Spanish Lung Cancer Group GECP. Principal Investigator Dra. Elvira del Barco Morillo. Año 2016.
- Analysis of Soluble Mediators, Cytokines, and Circulating Angiogenic Factors (FACs) as Potential Predictors / Prognostic Factors in Antiangiogenic Therapy Following Failure of First-line Chemotherapy in Advanced Non-squamous Lung Carcinoma. GECP 16/02 SELINA (SEcond/Third LInes Angiogenesis). Sponsor Grupo Español de Cáncer de Pulmón GECP. Principal Investigator Dra. Elvira del Barco Morillo. 2016.

- Observational, retrospective study to assess the long-term efficacy of induction chemotherapy followed by chemo-radiotherapy alone in the treatment of patients with locally advanced, unresectable squamous cell carcinoma of the head and neck. QUIRAD2503-TTCC-2015-02. Sponsor Spanish Group of Treatment of head and neck tumors Principal Investigator Dr. Juan Jesús Cruz Hernández Año 2016.
- Validation of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Prognostic Classification for Targeted Therapies (TKI/mTOR Inhibitors) in Second Line After First Line Treatment With Pazopanib. SPAZO-2. SOGUG-2016-A-IEC(REN)-4. Sponsor Grupo Español de Tumores Genitourinarios (SOGUG) Principal Investigator Dra. Rocío García Domínguez. 2017.
- A Phase III, Open-Label, Randomized Study of Atezolizumab (MPDL3280A, Anti-Pd-L1 Antibody) in Combination With Carboplatin or Cisplatin + Pemetrexed Compared With Carboplatin or Cisplatin + Pemetrexed in Patients Who Are Chemotherapy-Naive and Have Stage IV Non-Squamous Non-Small Cell Lung Cancer. GO29438. Sponsor F. Hoffmann-La Roche Ltd. Principal Investigator Dra. Lorena Bellido Hernández. 2017.
- Retrospective observational study on the treatment of metastatic colorectal cancer (mCRC) in Spain. BAY-ONC-2016-01. STREAM Sponsor Bayer Hispania S.L. Principal Investigator Dra. Teresa Martín Gómez. Año 2017.
- A Prospective Registry Study in Patients With Unresectable Locally Advanced or Metastatic Breast Cancer (MBC). RegistEM. GEICAM 2014-03. Sponsor Fundación Grupo Español de Investigación en cáncer de mama (GEICAM). Principal Investigator Dr. César A. Rodríguez. 2017.
- Global treatment patterns, health care resource utilization, and survival outcomes among patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. GLANCE H&N MSD-CCE-2016-01. Sponsor Merck Sharp & Dohme Corp. Principal Investigator Dra. Elvira del Barco Morillo. 2017.
- COMPLEEMENT-1: An Open-label, Multicenter, Phase IIIb Study to Assess the Safety and Efficacy of Ribociclib (LEE011) in Combination With Letrozole for the Treatment of Men and Pre/Postmenopausal Women With Hormone Receptor-positive (HR+) HER2-negative (HER2-) Advanced Breast Cancer (aBC) With no Prior Hormonal Therapy for Advanced Disease. CLEE011A2404 (Compleement). Sponsor Novartis Farmacéutica,S.A. Principal Investigator Dr. César A. Rodríguez. 2017.
- Neo-Adjuvant chemo/Immunotherapy for the treatment of resectable stage IIIA non small cell lung cancer (NSCLC): A phase II multicenter exploratoty study. NADIM (GECP 16/03) Sponsor Grupo Español de Cáncer de Pulmón GECP Principal Investigator Dra. Elvira del Barco Morillo. 2017.
- A Randomized, Open-Label, Phase 3 Study of Abemaciclib Combined With Standard Adjuvant Endocrine Therapy Versus Standard Adjuvant Endocrine Therapy Alone in Patients With High Risk, Node Positive, Early Stage, Hormone Receptor Positive, Human Epidermal Receptor 2 Negative, Breast Cancer. Monarch. I3Y-MC-JPCF. Sponsor Eli Lilly and Co. Principal Investigator Dr. César A. Rodríguez. Año 2017.
- A phase III clinical of intra-arterial TheraShere® in the treatment of patients with unresectable hepatocellular carcinoma (HCC) TS-103 STOP-HCC. Sponsor BIG Co-Investigador: Dr. Miguel Navarro Martín. Año 2017.
- Prospective Multi-centre Study of Prognostic Factors in Castration-Resitant Prostate Cancer Patients Treated With Radium-223. PRORADIUM (IBIMA-CNIO-CP-03-2015). Sponsor Fundación Centro Nacional de Investigación Oncológica (CNIO). Instituto de Salud Carlos III. Principal Investigator Dra. Rocío García Domínguez. Año 2017.
- Prospective Multi-Centre Study of Prognostic Factors in Castration-Resistant Prostate Cancer Patients Treated With Enzalutamide. PROSENZA (IBIMA-CNIO-CP-01-2016). Sponsor Fundación Centro Nacional de Investigación Oncológica (CNIO) Principal Investigator Dra. Rocío García Domínguez. Año 2017.
- Prospective study of the usefulness of liquid biopsy as a predictor and prognostic factor in patients with metastatic urothelial carcinoma progression after platinum-based chemotherapy. SOG-PLA-2016-01. Sponsor Grupo Español de Tumores Genitourinarios (SOGUG) Principal Investigator Dra. Rocío García Domínguez. Año 2017.
- Observational study: Measurement of quality of life (QOL LS) in long survivors of cancer in the Spanish population. Validation of the measuring instrument. Principal Investigator Dra. Rosario Vidal Tocino. Año 2017.
- Study to Evaluate the Use of Resources and the Costs Associated With Controlled or Uncontrolled Carcinoid Syndrome in Patients With Neuroendocrine Tumours (NETs) in Spain. (RECOSY) IPS-SOM-2017-01/A-ES-52030-367. Principal Investigator Dr. Miguel Navarro Martín. Año 2017.



4 SCIENTIFIC SERVICES UNITS



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SCIENTIFIC SERVICE UNITS

GENOMICS

In this Facility we provide complete services for: a) Analysis of expression profiles and genotyping using Affymetrix technology. b) Printing and processing of home-made chips. c) Sequencing. d) Genomics related techniques such as 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 (total RNA, genomic DNA), we carry out all the genomics steps, including technical advice about the design of the experiment, quality control of the samples provided, microarray analysis, and a standard bioinformatics analysis.

The facility itself and its experimental protocols have been certified by ISO9001. The Occupational Health and Safety Management System of the facility has been also certified using the OHSAS18001 system.

SERVICES

- DNA Sequencing. Sequencing of DNA contained in plasmids or PCR fragments using ABI-3130xl sequencer (Applied Biosystems). This system is able to do both genotyping and SNPs analysis.

- Genomics studies using Affymetrix technology. The main services includes in this category are: – Analysis of expression profiles using Gene Chip System of Aff ymetrix in different organisms. The main arrays used 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 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 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 by inmunoprecipitation (ChIP on chip) and other kind of studies which involve complete genome. 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.
- Analysis of polymorphisms (SNPs) and copy number studies. 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.
- Analysis of miRNAs and its precursors. The main arrays used are:
  - Gene Chip miRNA 2.0, 3.0 and 4.0 Array.

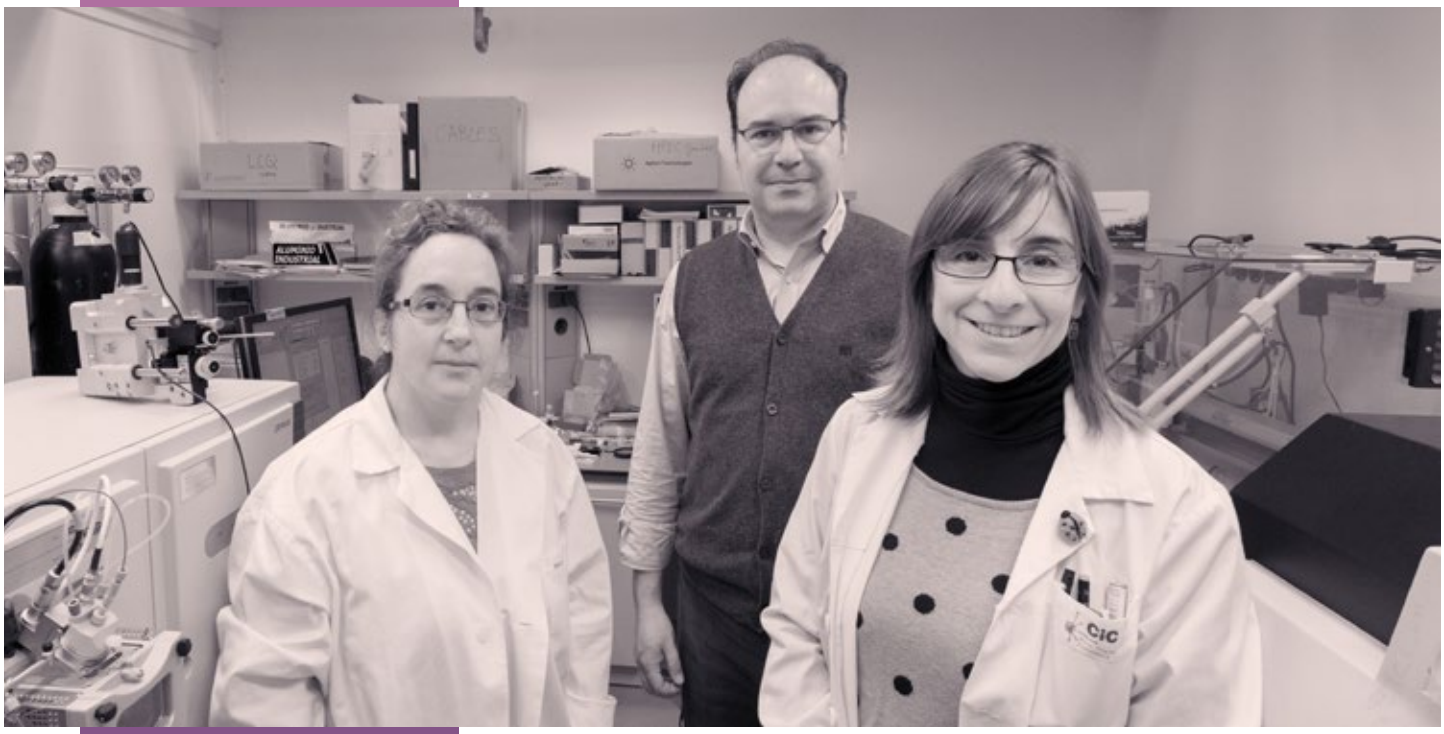
For more information visit www.affymetrix.com

- Printing and processing home-made chips:
  We provide a system to prepare home-made microarrays using the MGII Arrayer of Biorobotics. The samples are provided by the user (oligonucleotides, cDNAs, DNA cloned in BACs, antibodies, purified proteins or cellular lysates). These microarrays are hybridized using the automatized system hs4800pro (Tecan). Finally, the microarrays are scanned using the GenePix4000 system of Axon.

Our Unit provides the files to be analyzed with bioinformatics tools.

EQUIPMENT

- Analysis of RNA quality:
  - Agilent 2100 Bioanalyzer.
- Platform for the analysis of Affymetrix arrays:
  - GeneChip Hybridization Oven 640.
  - GeneChip Fluidics Station 450.
  - Gene Array Scanner 3000 7G.
- Platform for the manufacture of home-made arrays
  - Biorobot 3000 (Qiagen).
  - Arrayer (Biorobotics).
  - HS4800Pro Hybridization Station (Tecan).
  - GenePix 4000B (Axon).
- Automatic sequencer, 16-capillary ABI Prism 3130xl (Applied Biosystems).



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SCIENTIFIC SERVICE UNITS

PROTEOMICS

In this Facility we strive to provide investigators with access to the latest proteome analysis technologies.

These technologies are implemented with a broad spectrum of techniques for protein and peptide separation as well as mass spectrometry-based techniques to characterize and quantify analytes from complex biological samples.

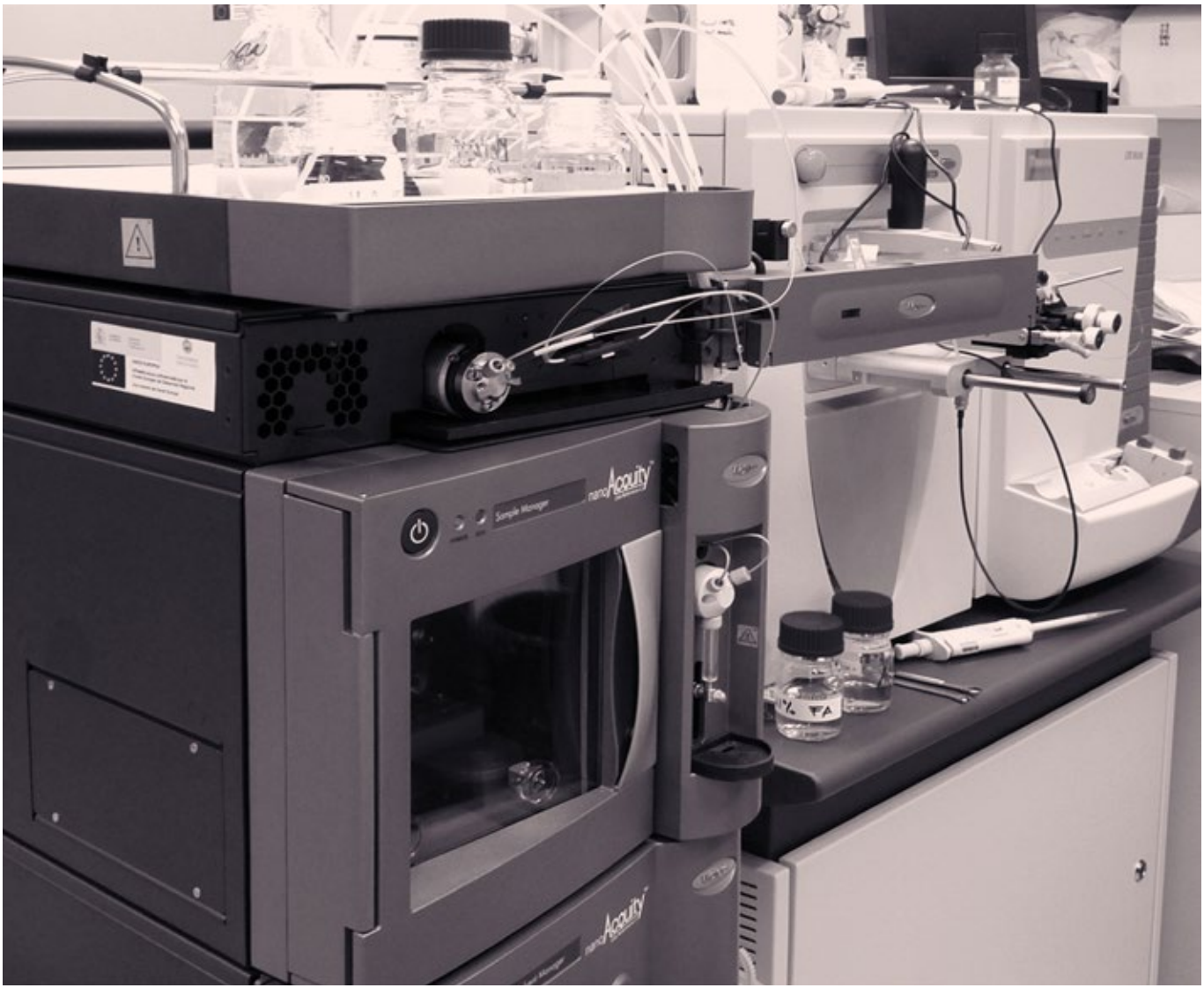
We provide services for: a) Protein separation, b) Protein identification, c) Analysis of posttranslational modifications, d) Characterization of proteome dynamics and e) Protein-protein interaction studies.

The philosophy of this Resource is to provide full services to both internal and external customers. We provide technical advice about proteomics experimental design and carry out quality control of the processes undertaken. Through our involvement in ProteoRed and ABRF multicentric studies we contribute to the evaluation and set up of new proteomic approaches.

The facility itself and its experimental protocols have been certified by ISO9001. The Occupational Health and Safety Management System of the facility has been also certified using the OHSAS18001 system.

SERVICES

- Protein separation by electrofocusing in IPG strips. Separation of proteins according to their pI is done in an Ettan IPGphor.
  http://www5.gelifesciences.com/aptrix/upp01077.nsf/Content/2d_electrophoresis~2delectrophoresis_handbook
- Protein separation by SDS-PAGE. Separation of proteins in a SDS-acrylamide:bis-acrylamide denaturing gel according to their molecular weight.
  http://www5.gelifesciences.com/aptrix/upp01077.nsf/Content/2d_electrophoresis~2delectrophoresis_handbook
- Protein separation by 2D-electroforesis. Protein separation by electrofocusing in IPG strips is followed by SDS-PAGE separation.
  http://www5.gelifesciences.com/aptrix/upp01077.nsf/Content/2d_electrophoresis~2delectrophoresis_handbook
- Gel staining with Coomassie. Staining of gel separated proteins with Coomassie brilliant blue G-250.
- Gel staining with silver. Staining of gel separated proteins with silver using a modification of Heukeshoven and Dernick protocol, Electrophoresis 6, 103-112, (1988), mass spectrometry compatible.
- Protein or peptide fractionation by in solution IEF. Protein or peptide in solution fractionation by IEF using the 3100 OFFGEL fractionator.
  http://www.chem.agilent.com/Library/usermanuals/Public/G3100-90001_OFFGEL_UserManual_ ebook.pdf
- Protein or peptide fractionation by HPLC. Protein or peptide separation by gel filtration, ion exchange or reverse phase chromatography using HPLC 1100.
- Enrichment of phosphopeptides by IMAC. Phosphopeptides are enriched by Fe^{3+} chromatography following SIMAC procedure. (Thingholm et al. Molecular & Cellular Proteomics 7:661-671,2008.).
- Enrichment of phosphopeptides by TiO_2. Phosphopeptides are enriched by TiO_2.
- In gel protein digestion. Digestion with trypsin of a protein gel spot or band. (Schevchenko et al. Anal. Chem. 1996, 68, 850-858.).
- In solution protein digestion. Digestion with trypsin of a protein sample in solution.
- Desalting and concentration of peptide digests by C18. Low abundance or dirty tryptic peptide samples are cleaned and concentrated using reverse phase C18 columns before MS analysis.(Rappsilber J, Anal Chem. 2003 Feb 1;75(3):663-70.).
- Peptide Mass Fingerprinting analysis by MALDI-TOF MS. Identification of a protein by peptide mass fingerprinting analysis. The masses of the tryptic peptides generated by digestion of single protein are analyzed by a MALDI-TOF mass spectrometer. The pattern of masses obtained is compared against the pattern of masses of each protein in a database of the same organism digested «in silico» with the same endoprotease. (Pappin et al. Current Biol. 1993, 3, 327-332.).
- Protein analysis by LC-MS/MS of low, medium or high complexity protein samples. Peptides derived from digested protein mixtures will be separated by reverse phase chromatography using a nanoUPLC coupled to the mass spectrometer. Different gradient lengths are used depending on the complexity of the protein sample. Eluting peptides are directly analyzed by MS/MS with the LTQ-Orbitrap velos (Olsen et al. Mol Cell Proteomics. 2009 Dec;8(12):2759-69.
- Relative quantitation of protein samples by label free and SILAC based mass spectrometry analysis.
- Bioinformatics analysis.
  - Identification of posttranslational modifications.
  - Differential proteomics.
  - De novo sequencing.
  - Protein and Peptide Molecular Weight Analysis.
  - Molecular weight analysis of purified proteins or peptides by MALDI-TOF.
- Analysis of protein interaction by SPR. Interaction analysis of proteins by BIACORE X.
- Quantization of nucleotides by HPLC.
- Protein Microarrays.
- IVTT protein expression .
- >9000 human proteins already cloned (in Gateway System) and sequence-validated.


nanoAcquity
Sample Manager
nanoAcquity

EQUIPMENT

Electrophoresis 2D
- Ettan IPGphor (Amersham,, GE Healthcare).
- Ettan Dalt-6 Electrophoresis system (Amersham).
- Hoefer miniVE electrophoresis (Amersham).
- Hoefer SE 600 Ruby (Amersham).

Image acquisition
- Escaner Epson perfection 1640SU (Proteineersp, Bruker).
- Escaner FLA-3000 Series, (Filtros: Y520, O580, R675Laser: 473nm, 633nm) (Fujifilm).

Spot picking and sample digestion robots
- Proteineersp, SPOTPICKER (Bruker).
- Proteineerdp, DIGESTOR (Bruker)

HPLC
- HPLC1100 (Agilent).
- Surveyor LC pump (ThermoFinnigan) coupled with the LCQ-DECA XP.
- NanoAcquity UPLC (Waters) coupled with the LTQ Orbitrap velos.

In solution IEF
- 3100 OFF GEL fractionator (Agilent).

Mass Spectrometers
- MALDI-TOF (Bruker).
- LCQ-DECA XP (ThermoFinnigan).
- LTQ-Orbitrap velos with ETD (ThermoScientific).

Protein interaction
- Biacore X (Biacore, GE Healthcare).

Protein Microarrays
- Ultra-Marathon Microarray Printer (Arrayjet).
- Scanner Sensovation.
- Array Processor M2.

PUBLICATIONS

1 **A multicentric study to evaluate the use of relative retention times in targeted proteomics.** Vialas V, Colomé-Calls N, Abian J, Aloria K, Álvarez-Llamas G, Antúnez O, Arizmendi JM, Azkargorta M, Barceló-Batllori S, Barderas MG, Blanco F, Casal JI, Casas V, de la Torre C, Chicano-Gálvez E, Elortza F, Espadas G, Estanyol JM, Fernández-Irigoyen J, Fernández-Puente P, Fidalgo MJ, Fuentes M, Gay M, Gil C, Hainard A, Hernaez ML, Ibarrola N, Kopylov AT, Lario A, López JA, López-Lucendo M, Marcilla M, Marina-Ramírez A, Marko-Varga G, Martín L, Mora MI, Morato-López E, Muñoz J, Odena MA, de Oliveira E, Orera I, Ortea I, Pasquarello C, Ray KB, Rezeli M, Ruppen I, Sabidó E, Del Pino MMS, Sancho J, Santamaría E, Vazquez J, Vilaseca M, Vivanco F, Walters JJ, Zgoda VG, Corrales FJ, Canals F, Paradela A. **J Proteomics. 2017 Jan 30;152:138-149. doi: 10.1016/j.jprot.2016.10.014. Epub 2016 Oct 29.** PMID: 27989941 **IF: 3.867 / Q1**

2 **Methods for Selecting Phage Display Antibody Libraries.** Jara-Acevedo R, Diez P, Gonzalez-Gonzalez M, Degano RM, Ibarrola N, Gongora R, Orfao A, Fuentes M. **Curr Pharm Des. 2016;22(43):6490-6499. doi: 10.2174/1381612822666161007153127. Review.** PMID: 27748198 **IF : 3.052 / Q2**

OTHER ACTIVITIES & RELEVANT FACTS

- Proteomics Unit belongs to «Plataforma de Recursos Biomoleculares y BioInformaticos» (www.prb3.org) and «ProteoRed» of Instituto de Salud Carlos III. (www.proteored.org) (Ref. PT17/0019/0023).
- Organization and participation on the VI International Workshop on Protein Arrays. Financed by ISCIII.

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Traslational Oncopharmacology Unit
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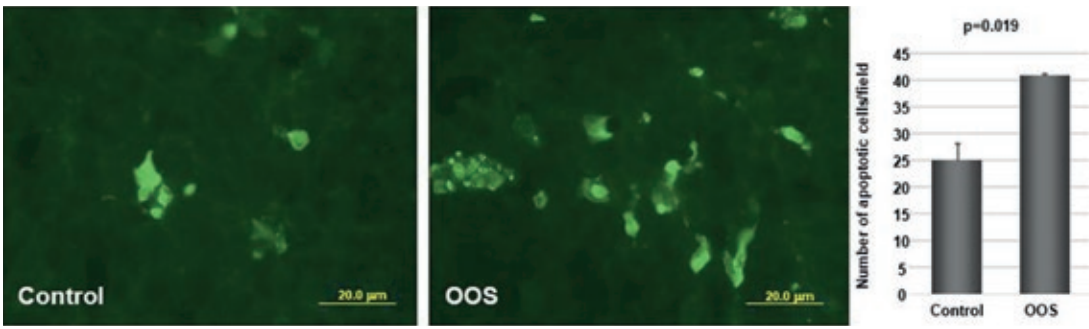
SCIENTIFIC SERVICE UNITS

TRASLATIONAL ONCOPHARMACOLOGY

The traslational oncopharmacology laboratory was created (april 2007) in response to the needs of several groups of our institute that work on antitumor drug development. This unit performs screening of antitumoral activities of drugs, in solid tumors and hematological disorders. The unit has given support to both internal research groups, but also to some pharma and biotech companies, as well as to researchers from other academic/ government institutions outside our Institute.

SERVICES

- MTT uptake assay in 24w, 48 w and 96 w microtiter plates. MTT uptake experiments are used to initially assess drug activity on tumoral cells.
- BrdU Cell Proliferation Assay. BrdU uptake experiments are used sporadically to assess drug activity on tumoral cells.
- Bioluminescence Assay. Two types of protocols are usually performed. One is based on the incubation of the agent of interest in the presence of bone marrow cells. In this case, BM cells from patients or the HS-5 cell line can be used. The latter is preferred



Ocoxin® Oral solution (OOS) induces an increase in cell death and a decrease in proliferation in vivo. At the time of sacrifice, part of the tumors from control or OOS treated animals were fixed and included in paraffin for further analysis For each experimental condition, two tumors were randomly processed for IHC analysis and apoptotic cells were detected by TUNEL staining. Images of representative fields stained for this marker are shown. Besides, the number of apoptotic cells per field was quantified for each condition and its mean number ± SD is shown in the graph.

as it gives more consistent and less variable results. The second experimental setting consists on the incubation of the agent together with growth factors, such as IL-6 or IGF-I. Both protocols are designed to test whether drug was able to overcome the protective effect of the BM microenvironment.

- Apoptosis assays (Annexin V-FITC). Annexin V staining experiments are used to initially asses the action of drugs on apoptosis of tumoral cells.
- Cell cycle analyses (Propidium Iodide). Cell cycle experiments are used to initially assess whether a drug interferes with cell cycle progression.
- Western blot. The effect induced by the drug(s) treatment on the most important cell signaling and proliferation pathways as Erk, PI3K/AKT, NFkB or JAK/STAT are evaluated by Western-Blot.
- Analyses of the results. Once the data are available, most of the external customers ask for counseling about how to further proceed based on the data generated.
- Antibody generation. If required, rabbit polyclonal antibodies will be prepared and affinity purified following protocols previously optimized in our laboratory. Their performance in several experimental settings will also be determined.
- Murine Model Assay. In vivo studies of the activity of some drugs and drug combinations using mouse models may be required. Usually a set is required for control, placebo-treated animals, and several additional sets for different doses of a single drug or combination of drugs.
- Design of strategic assays (advice and acquisition of material and reagents) In addition to the advice once the data have been generated, sometimes new and specialized assays have to be set-up. This, together with counseling for unexperienced customers, is required.

A detailed description of the experimental protocols is listed as Standard Operating Procedure (SOP) of the unit.

A web page is already prepared detailing the services offered by the unit. http://www.cicancer.org/lot/screening.php

The facility itself and its experimental protocols have been certified by ISO9001. The Occupational Health and Safety Management System of the facility has been also certified using the OHSAS18001 system.

STRATEGIC OBJECTIVES

We offer a suitable service to the demand that allows the translation into the clinics of new clinical antitumor drugs acting on different cellular targets. In addition, an increase in the ability to predict their biological behavior in different tumor types is also pursued.

ACHIEVEMENTS

In addition to counseling services performed and conducted by staff of the unit it has also been implemented in 2009 the Quality Certification ISO 9001 to improve the scientific output of the unit and provide reliability and traceability studies.

GOALS FOR THE FUTURE

To ensure quality services and fulfill the purpose of the LOT indicated above in this document.

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SCIENTIFIC SERVICE UNITS

BIOINFORMATICS

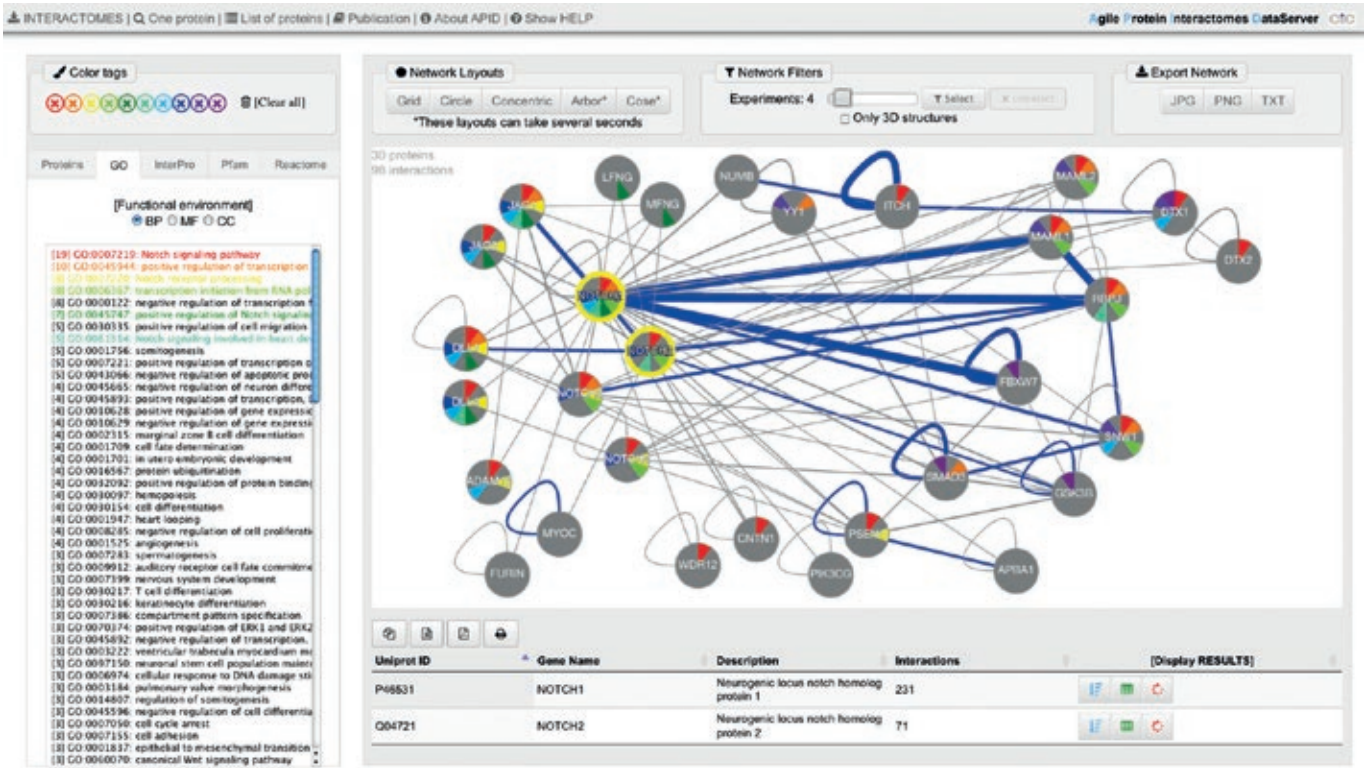
The Bioinformatics Unit works in the CiC-IBMCC with the help and support of the Bioinformatics and Functional Genomics Research Group, to provide technical and scientific service on bioinformatics data analyses to scientists and research groups from the CiC, the University of Salamanca or from outside. The Unit has major expertise in the analysis of genomic and transcriptomic data and biological networks.

The Bioinformatics Unit was launched to provide services in June 2008 and in the last decade has performed different analyses of biological data from more than 3000 samples coming from different labs and research centers in Spain.

Description of some common services provided:

SERVICES

- **Multivariate analyses and comparison of two or more states using omic data.** Analysis to search and identify genes (or other biomolecular entities such as miRNAs, ncRNAs, proteins, etc.) that show statistical significant changes using robust techniques of differential contrast of two states (Normal versus Altered) or between different classes.



- **Biomarker profiling.** 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.
- **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 data.** 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: NCBI-GEO, NCBI-SRA, Bioconductor, GSEA, etc.
  - Open Access Software developed within the CiC-IBMCC: GATExplorer, GeneTerm-Linker, FGNet, APID Interactomes, DECO, 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.

MOLECULAR & CELLULAR DIAGNOSTICS

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Cytometry Service
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Miriam Santos

CYTOMETRY SERVICE

The Cytometry Service (SGC) is a common research platform of open use to all members of the Institute (Cancer Research Centre) 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 parallel, at the SGC there are several ongoing technologically oriented research projects. Finally, the SGC has an important role in education in Cytometry with more than 35 researches from all over the world being trained during the last year, and more than 350 in the last 15 years.

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.

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 gamma-delta T cells lymphoid neoplasms by flow cytometry.
- Immunophenotypic characterization of mature T and NK-cell 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 paroxymal nocturnal hemoglobinuria.
- 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...

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Molecular Cytogenetic Service
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Sara González Briones

Mª Ángeles Hernández García
María Almudena Martín Martín
Mª Ángeles Ramos Rodríguez
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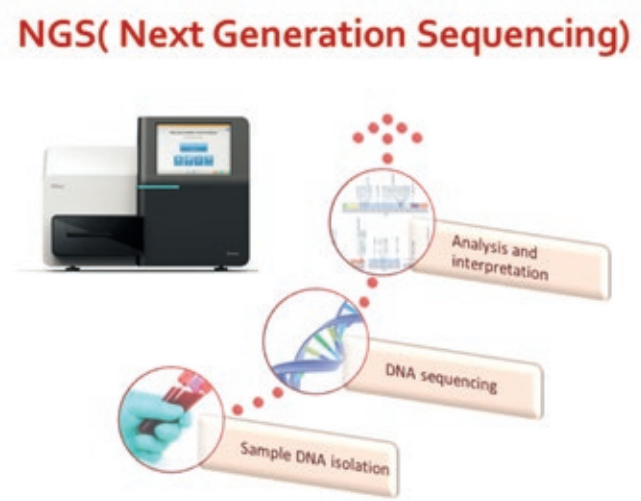
Isabel Mª Isidro Hernández
Vanesa Gutiérrez Moreta
Mª Teresa Prieto Martín
Sandra Santos
Sandra Pujante

CYTOGENETIC SERVICE

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 to expression microarrays (MILE), genomic microarrays (EuGESMA), next generation sequencing (IRON, ELAN, NGS-PTL), and the European project HARMONY, which through



the use of Big Data will help improve the care of patients with hematologic malignancies.

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.
- Comparative Genomic Hybridization: Test to analyse global gains and losses of genetic material in tumour cells.
- Genomic microarrays.
- Pharmacogenetic microarrays.
- 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 next-gen sequencing.
- 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 (Illumina), MiSeq sequencer.

MOLECULAR BIOLOGY SERVICE

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Molecular Biology Service
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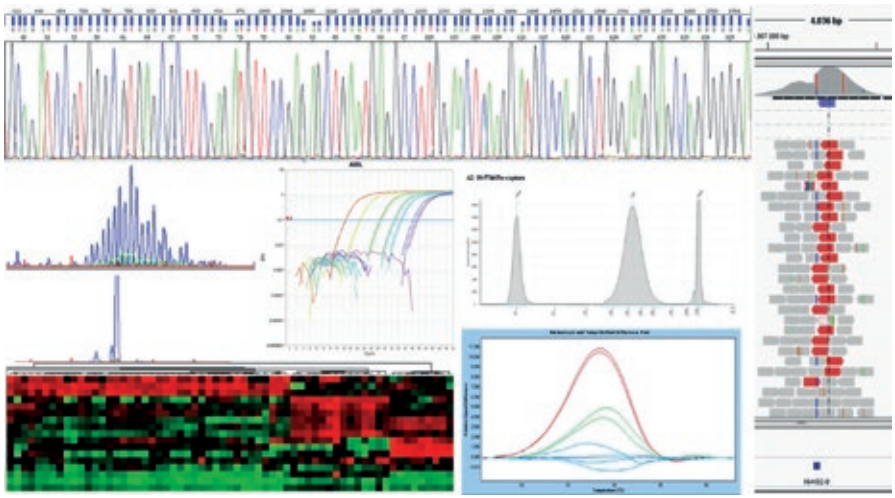
Verónica González de la Calle

The Molecular Biology Service (MBU) is a facility with the aim of the molecular analysis of cancer patients, with special focus on patients with haematological malignancies (leukaemias and lymphomas). In addition, the MBU carry out chimerism studies in patients who underwent allogeneic stem-cell transplantation and molecular studies in coagulopathies. The MBU is the reference centre for Castilla y León Hospitals. Furthermore, more than 50 hospitals in Spain, and occasionally others foreign institutions, have used the MBU services. The Unit actively collaborates with the most relevant Spanish groups in the treatment of the haematological malignancies such as Pethema, GEL-TAMO, GEM, or GETH, providing characterization of the molecular abnormalities and carrying out studies on molecular monitoring of drug efficacy (Minimal Residual Disease -MRD- Studies) in the patients included in



clinical trials. In addition, the MBU have participated in various international projects focused on different methodologies standardization (Biomed I, Biomed II, Europe Against Cancer and Eurochimerism projects), and it is involved in several international projects related to clonality (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).

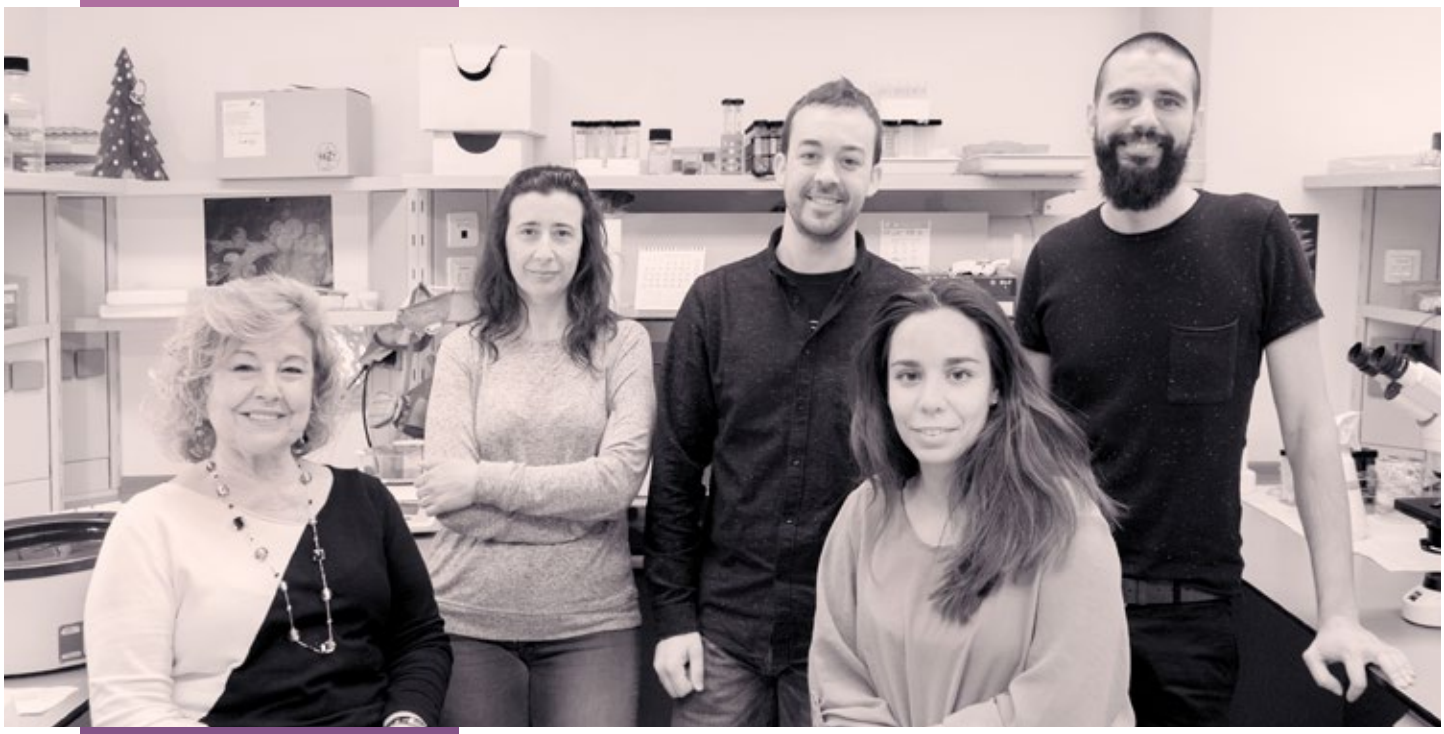
The total number of samples received in 2016 and 2017 were 13309 and 15978, respectively.

SERVICES

- 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.
- Screening and quantification of chromosomal translocations (qualitative and real-time quantitative PCR, RT-PCR) for diagnosis and MRD monitoring in hematological malignancies.
- Analysis of somatic mutations: prognostic value, screening of potential MRD markers and/or identification of therapeutic targets.
- Gene expression: RT-PCR for diagnosis, prognosis and MRD detection.
- Next generation sequencing: Analysis of genetic alterations using commercial kits (i.e. AML panel) and custom panels for diagnosis and prognostic value.
- 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.
- Fragment analysis and Sanger sequencing.
- Low and high resolution HLA typing: donor typing, disease association.
- Hematopoietic chimerism analysis with STR polymorphisms.
- Digital PCR for low allele frequency mutation detection.

EQUIPMENT

- Real-time quantitative (4): One7900HT, two StepOnePlus (Applied Biosystems) and one LightCycler (Roche Diagnostics).
- Next generation sequencing systems: MiSeq Dx 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 (2): ABI3500 XL (16-capillary, Applied Biosystems).
- Fluoroanalyzer (1): Luminex XYP (Luminex Corp.).
- Thermocyclers (8) : four 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): two Maxwell16 (Promega).



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SCIENTIFIC SERVICE UNITS

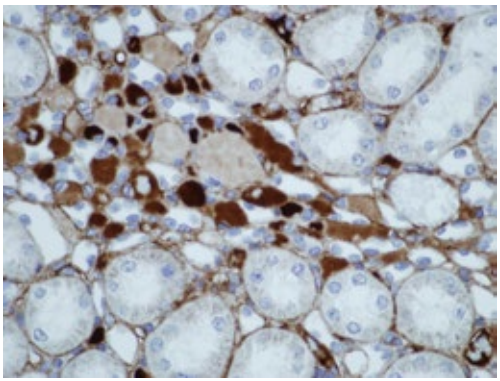
COMPARATIVE MOLECULAR PATHOLOGY

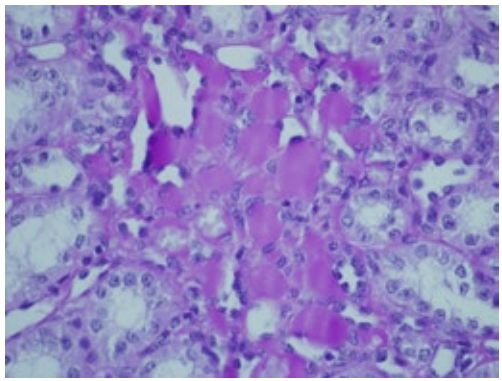
This is a core lab with two different aims:

1 It serves as the Coordinating Node for the Biobank Network Oncological Diseases of Castilla and León, managing all tissue transactions between Hospitals of the Network (n=7) and researchers inside or outside the region. About 10 requests for tumor samples are received/served per year, which represents about 300 samples/year.

2 Support service, to all the Centers on the Campus, as well as to a «NUCLEUS», from this year as an Associated Unit. as a Comparative Pathology Service, analyzing samples of transgenic animal models that offer a complete range of histological, immunohistochemical and molecular analyzes designed and adapted to order. Approximately 5.240 samples are processed per year, from 556 job applications.

ISO Certifications: ISO9001:2008

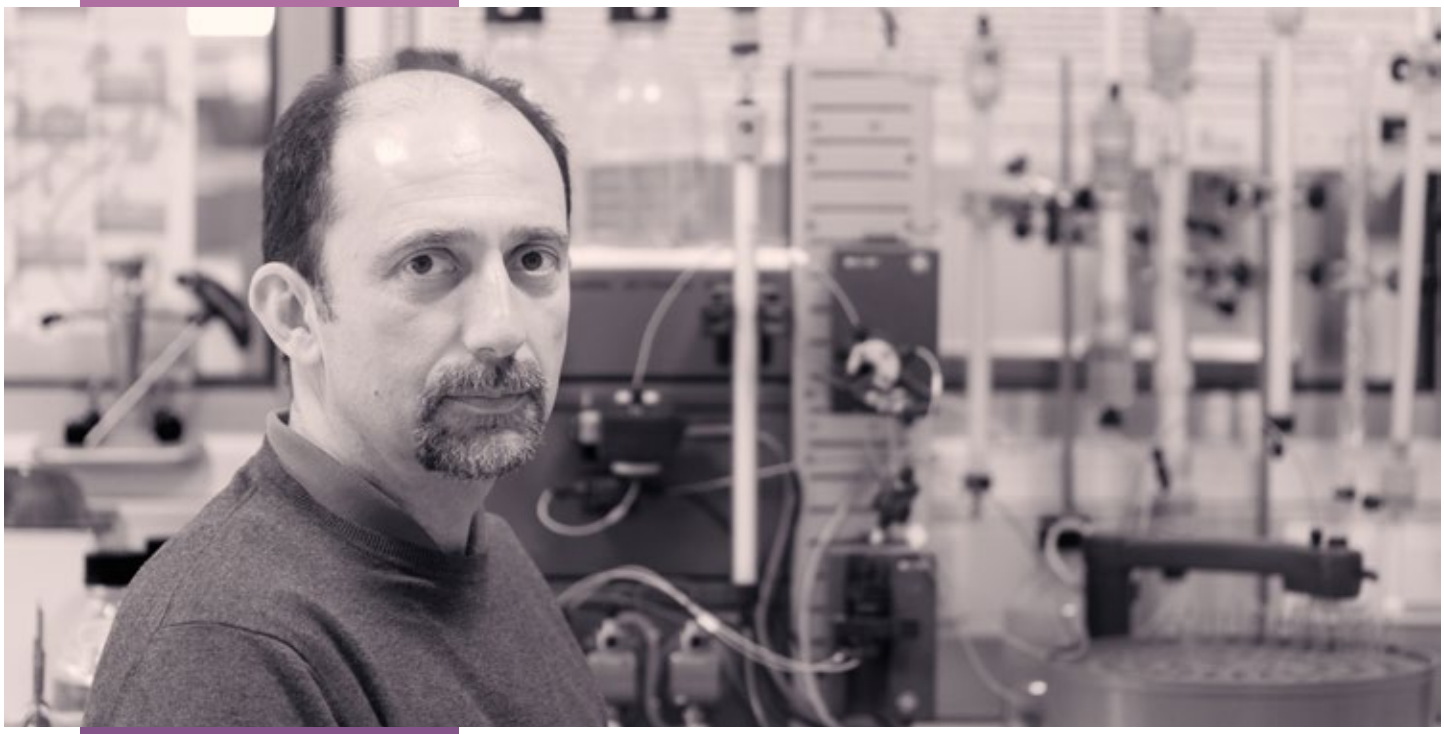




SERVICES

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.

- 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. In the last two years, 41 antibodies have been prepared for murine tissues, at the request of the different researchers from both the CIC and the rest of the Units of Campus.
- 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 biopses.
- 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.
- 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.



SCIENTIFIC SERVICE UNITS

STRUCTURAL BIOLOGY

The primary mission of the Macromolecular Crystallography Facility (MXF) is to provide access to x-ray crystallography methods to researchers that aim at elucidating the 3D atomic structure of macromolecules of biological relevance.

SERVICES

Crystallization: the MXF offers dedicated space for setting up and for storage of crystallization experiments in temperature controlled environments (Fig 1). The Facility has stereo microscopes for visualization and manipulation of crystals. Equipment for cooling, storage, and transportation of crystals at cryo-temperatures (liquid nitrogen) is also available at the MXF.

Data collection and analysis: the MXF provides access to equipment for X-ray data collection and analysis from macromolecular crystals. The Facility houses a Microstar (Bruker AXS) rotating anode micro-focus x-ray generator equipped with a large-area Image-plate detector mar345 (Marresearch) and a Cryostream 700 low temperature system (Oxford Cryosystems). The MXF also provides consultations and assistance on optimization of crystallization, data collection and processing, and structure solution.

Scientific Coordinator
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Structural Biology Unit
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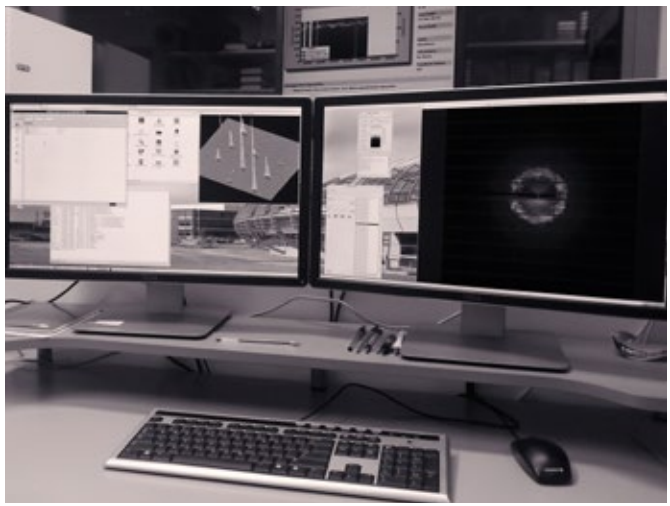
Remote data collection: The MXF is equipped with a computer setup for remote data collection at synchrotron laboratories. Since 2016 the Facility has been extensively used to easily collect data at the synchrotrons ALBA (Barcelona, Spain) and Diamond Light Source (Didcot, UK). In early 2017, a two-monitor setup has been installed (Fig 2). This large desktop area has greatly improved the remote operation of the synchrotron beamlines.

The activities at the MXF during this period have resulted in 12 protein structures solved with the support from the Facility (Table 1). All these structures are freely available in the Protein Data Bank.

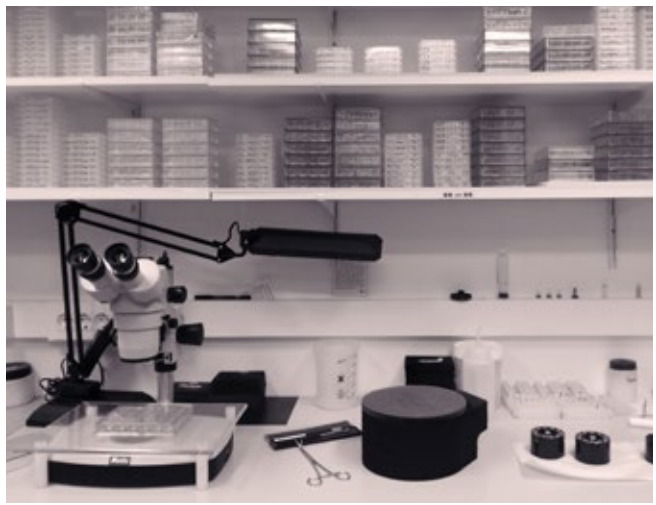
Protein structures solved with support from the Facility, published in the Protein Data Bank (PDB) in this period.

PDB CODE	DESCRIPTION	REFERENCE
5JRI 5K0A	Oxidoreductase from Synechocystis sp. PCC6803	Buey RM et al. (2017) PNAS 114 12725-12730
5N0J 5ODE	Novel oxidoreductase from G. violaceus	Buey RM et al. (2017) PNAS 114 12725-12730
5MCP	IMP dehydrogenase from A. gossypii bound to ATP	Buey RM et al. (2017) Sci Rep 7 2648-2648
5TC3	IMP dehydrogenase from A. gossypii bound to ATP and GDP	Buey RM et al. (2017) Sci Rep 7 2648-2648
5J60	Thioredoxin reductase from G. violaceus	Buey RM et al. (2017) Mol Plant 10 212-215
5J1F 5J1H	Spectrin repeats 5 and 6 of human plectin	Ortega E et al. (2016) J Biol Chem 291 18643-18662
5J1G	Spectrin repeats 7 and 8 of human plectin	Ortega E et al. (2016) J Biol Chem 291 18643-18662
5J1I	Spectrin repeats 7, 8 and 9 of human plectin	Ortega E et al. (2016) J Biol Chem 291 18643-18662
4ZN0	NADPH-dependent thioredoxin reductase from M. mazei	To be published

Computer setup at the Facility for remote operation of synchrotron beamlines.



Equipment for crystallization experiments and for the manipulation of protein crystals at the MXF.



SCIENTIFIC SERVICE UNITS

MICROSCOPY

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Personnel
Ángel Luis Prieto Martín
Ana Isabel García Vega

The CIC-IBMCC Microscopy and Cytometry Unit has tried during these last two years to improve their services. Accordingly, the facility has acquired a new super-resolution equipment that will allow to get new images with an unprecedented sharpness.

In addition to the new service, the CIC-IBMCC Microscopy and Citometry Unit provides the following services:

1. Confocal microscopy (Leica SP5 and Zeiss LSM510), that provides services to internal and external users. Running timelapse, Z-Series, colocalization, FRAP and FRET experiments. Web based management allows remote communication with the service for reservations.
2. Flow cytometry: sorting and immunophenotypic analysis of different cell populations, independently of complexity and/or staining. Running and maintenance of the BDFACS-Aria-III system. Configuration of FACSDiva software.
3. Preventative and corrective maintenance of Accuri-C6 flow cytometer. Training and advising about Accuri-C6 use to the researchers so they can reach full autonomy. In addition, the Unit personnel prepare and refill the sheath solution and cleaning solutions when needed in order to keep the system in the optimum conditions.

4 Live cell imaging: designing timelapse experiments and processing images and videos. Running Olympus IX71 and Nikon Eclipse TE2000 microscopes, both with CO2 and temperature controlled, and the software attached-Delta-Vision and Metamorph. Deconvolution of images available upon request.

5 Conventional microscopy: 9 fluorescence microscopes, 10 inverted microscopes for cell culture, 1 microinjector, 1 microscope for cytogenetic and 1 microscope for histological analysis.

6 Monthly revisions of the microscopes, including phase adjustment, Kohler adjustment, objective cleaning and weekly revisions of the different microscopy rooms (material reposition). Adjustment and maintenance of mercury and halogen lamps.

7 Training and advising about image capture software and hardware (Metamorph, Leica LAS AF, LSM Image Browser, ImageJ, Openlab, etc.). Solving inquiries about image analysis.

8 Creating, updating and maintaining the Web Unit, including updates of technical specifications or new equipment incorporated by the Center. Edition of guides and tutorials about de instructions, basic configuration and software.

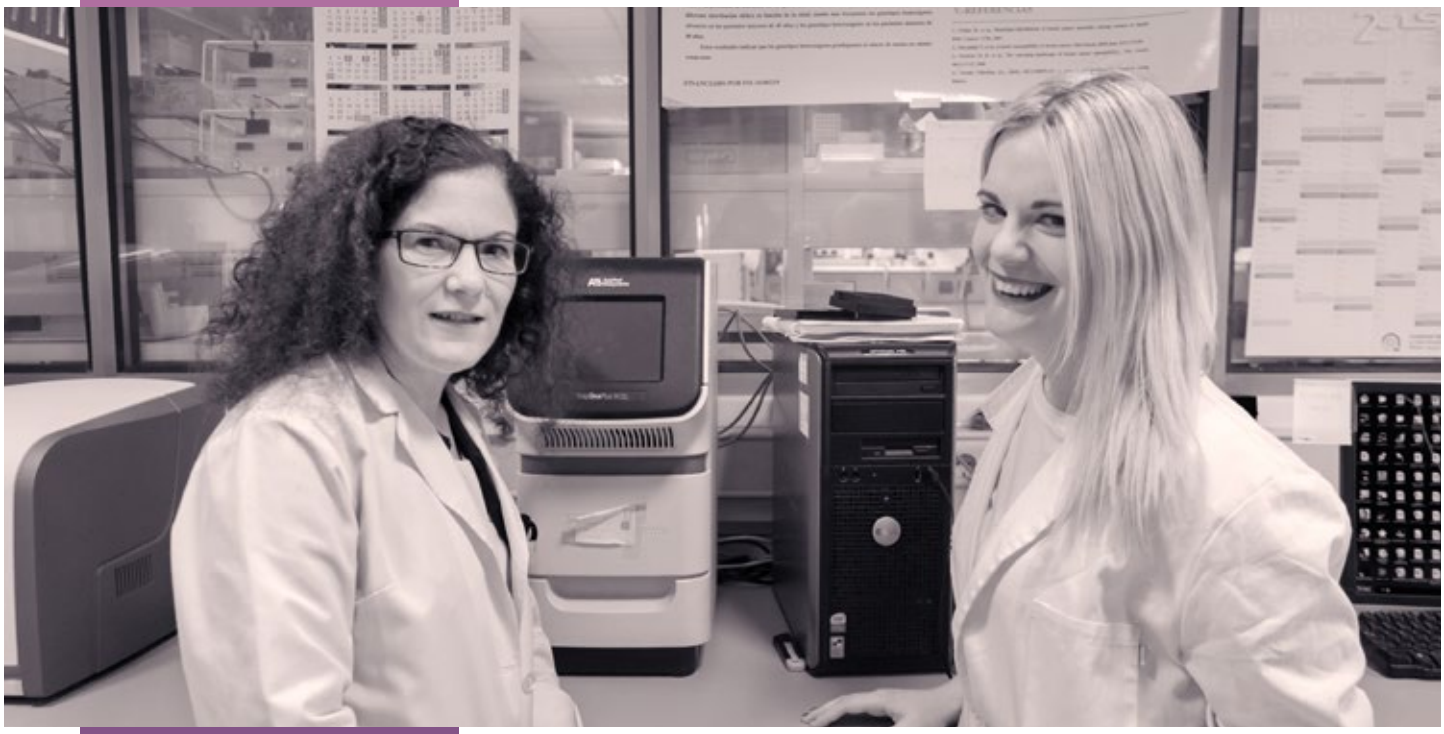
9 Quality assessment. Certifications: ISO-9001 and Ohsas -18001.

EQUIPMENT

The Microscopy Unit of the Cancer Research Centre with its variety of equipments offers a high range of possibilities. There are seven main equipments:

- Laser Scan Confocal Microscopy Leica SP5: the machine was funded by FEDER, Ministerio de Sanidad y Consumo and Instituto de Salud Carlos III. The microscope 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. Aditionally, due to its software and the motorized stage, FRAP, FRET or co-localization analysis can be performed as well.
- Flow cytometer and sorter BD FACS-AriaIII: co-funded by CSIC-MINECO and FEDER. It is one of the most advanced cytometry system available nowadays. It supports up to 6 excitation lasers combined with 20 detectors. This feature allows the staining with complex dye configurations. Furthermore, the cell damage is minimized by a temperature controlled system, increasing cell viability and process efficiency.
- Live Cell Microscopy Delta-Vision: acquired with FEDER and CSIC founding, this equipment is mainly used for in vivo time-lapse experiments. The microscopy main advantages are the ultra-precise stage; the lighting system which combines a xenon lamp with an excitation filters wheel; and a high sensitive CCD camera. Thus, low exposition times are required reducing cell damage. In addition, the deconvolution module contributes to a more complex image processing.
- Laser Scan Confocal Microscopy Zeiss LSM 510: mainly used when the demand is over possibilities of Leica confocal and for external users.
- Microscope Nikon TE2000 for in vivo analysis: this microscope is combined with Metamorph, a very powerful software tool in microscopy. Metamorph provides several applications such as transforming images or quantization.
- Cell analyzer cytometer BD Accuri-C6®: co-founded by CSIC-MINECO and FEDER. Despite Accuri-C6® is a simple and easy to use platform, it offers an optimum configuration which detects four fluorochromes simultaneously. Researchers can perform immunophenotipycal analysis, cell-cycle analysis, etc. Furthermore, different cellular models can be used, from yeast to mammals.
- Laser Scan Confocal Microscopy Leica SP8: the equipment was co-founded by FEDER, Ministerio de Economía, Industria y Competitividad and Universidad de Salamanca. The microscope has a powerfull white laser that is able to excite ever wavelength into a width range. This, in combination with the spectral detection technology, allows any fluorochrome to be detected in the visible range. In addition two lasers can make the fluorescence depletion and the system provides hi-resolution images. Using this technology we can decrease the microscopy resolution limit to 50 nanometres. Moreover, the equipment is completed with a Huygens Deconvolution Software. The Huygens deconvolution provides a significant increase in the contrast and resolution, which significantly improves the visualization and analysis.

In the next two years we´ll work in a hard way to improve the services that we provide, in microscopy and flow cytometry areas to help and facilitate the CIC- IBMCC scientists job.



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Hereditary Cancer & Genetic Counseling
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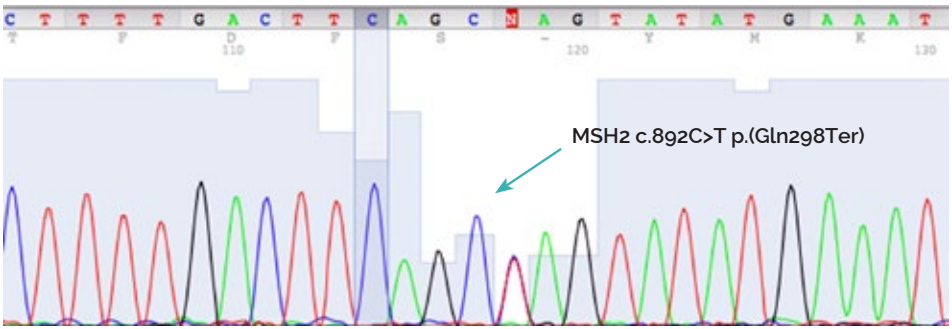
Teresa Martín Gómez
Rosario Vidal Tocino
Elena Bueno Martínez

SCIENTIFIC SERVICE UNITS

HEREDITARY CANCER & GENETIC COUNSELING

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.


5
TECHNICAL
SUPPORT
UNITS

Personnel
Gerardo Arévalo Vicente

TECHNICAL SUPPORT UNITS
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
Javier Beltrán Lurueña
Antonio Mata Domínguez
Cristina Santos Gallego
Álvaro Menéndez Sánchez
Margarita Villamor Carba
Miguel Ángel Moreno Valle
María Manuela Calvo González

TECHNICAL SUPPORT UNITS
ADMINISTRATION

The Administration Unit offers its services in various areas related to the three different institutions supporting the Institute: National Research Council (CSIC), University of Salamanca (USAL) and Foundation for Cancer Research (FICUS):

- 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
Nuria Morán Aguirre

TECHNICAL SUPPORT UNITS
SECRETARY

- Secretarial support and assistance to the Institute Direction.
- Administrative and logistic assistance to the personnel and visitors (travels, meetings, events, bookings...).
- Processing of internship programs for students in the center.
- Preparation of semi-annual reports of activities of the center.

Personnel
Sonia Pedraza Flores
Pablo González Delgado

TECHNICAL SUPPORT UNITS
INFORMATION TECHNOLOGIES SERVICES (IT)

The Computer Service is responsible for the development, maintenance, manage-ment, 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).

Personnel
Almudena Timón Sánchez

TECHNICAL SUPPORT UNITS

COMMUNICATION & MARKETING

The mission of the Communication & Marketing Unit is to cover dissemination activities, dissemination and popularization of science center centralizing information on scientific and social interest for dissemination through CIC web page, social networks and media, addressing researchers, educators, high school students and society at large.

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

- Social Marketing to achieve specific 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: (i) Media Relations, (ii) Press releases, (iii) Press conferences, (iv) Social networking services and (v) Media monitoring and evaluation.
- Internal Communications.

SERVICES

- CIC Scientific seminars series
- Attention to the guided tours requested to visit of schools, university students and society in general
- Follow up of news published in newspapers and journals.
- Promotion of the scientific culture through educational projects.
- Internal support to the meetings organized by the scientists at the center.
- Elaboration of press releases and organization of press conferences.
- Management of the scientific culture unit (belonging UCC + I Network) of the Cancer Research Center.
- Attention to the consults and managements of the donations to the CIC through its foundation (FICUS).
- Attention to the media.

Personnel
Celso Collazo López
Carlos Miguel de los Dolores Redondo

TECHNICAL 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 Certifications: ISO 9001 and OSHAS 18001.

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, CO_2 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 Benéitez

TECHNICAL SUPPORT UNITS

QUALITY CONTROL & RISK PREVENTION

The Quality & Risk Unit Labor is responsible for:

- Management of ISO 9001 and OSHAS 18001 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 OHSAS 18001 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.

Personnel
María Sonia Pérez Díez
Mª Eugenia Fernández de la Torre

TECHNICAL SUPPORT UNITS

CENTRAL WAREHOUSE & RADIOLOGICAL PROTECTION

SERVICES

- Supply of fungible material, reactive materials, solvents and monitoring of user expenses, internal invoicing and information. Files and acquisitions of inventorial material.
- Management of the acquisition of radioisotopes and means, equipment and instruments of prevention and protection. Acquisition of safety equipment and edition of procedures.
- Management of hazardous waste. Controlled disposal of disclassified radioactive waste.
- Evaluations, previous and periodic, of biological, chemical and radiological risk. Maintenance of medical and dosimetric reports of the exposed personnel.
- Acting in radiological incidents, accidents or emergency situations following the previously established procedures.
- Training, information, safety, health seminars and permanent practical advising for the personnel exposed to potential risk agents.
- The unit has the ISO Certification: ISO 9001:2000 y OHSAS 18001:2007 since 2007 and it having succesfully passed the sucessive external audits required.

Personnel
Ana Brufau Redondo
Mª del Rosario García Rubia
Vanessa Centeno Talayero

TECHNICAL SUPPORT UNITS

GLASSWARE CLEANING, MEDIA/ SOLUTIONS PREPARATION & STERILIZATION

The Glassware Cleaning, Media/Solutions Preparation & Sterilization unit performs its services for the research units and service units of the institute in the following areas:

- Ordering and storage of reagents and research materials. Stock management.
- Decontamination, cleaning of labware and sterilization of material.
- Preparation of different media and solutions usually required in the laboratories of our center, and some media and solutions specifically required from certain laboratories.

The unit has the ISO Certification: ISO 9001:2000 since 2007and it having successfully passed the successive external audits required.

SERVICES

- Sterilization of biological waste.
- Media preparation.
- Cleaning and sterilization of material needed in laboratories.
- Stocking of research material.
- Management of dangerous waste biohazard disposal.
- Competent cell preparation.

6 SCIENTIFIC ACTIVITIES

LIST OF JOURNALS

This list reflects all the journal in which the investigators of the CIC-IBMCC have published original articles during 2016-2017. The publications with an impact factor over 10 points are highlighted.

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Acta Haematologica	1	1,205	1,205	Q4
Acta Otorrinolaringológica Española	1	NI	NI	NI
Advances in Experimental Medicine and Biology	3	1,953	5,859	Q2
Advances in Therapy	1	1,745	1,745	Q2
Aging (Albany NY)	1	3,979	3,979	Q2
American Journal of Hematology	3	5,000	15,000	Q1
American Journal of Pathology	2	4,206	8,412	Q1
American Society of Clinical Oncology Educational Book	1	NI	NI	NI
Annals of Hematology	8	3,022	24,176	Q2
Annals of Oncology	1	9,269	9,269	Q1/D1
Annals of the Rheumatic Diseases	**1**	**12,384**	**12,384**	**Q1/D1**
Archivos de la Sociedad Española de Oftalmología	1	NI	NI	NI
Arthritis & Rheumatology	1	6,009	6,009	Q1
Autophagy	2	9,108	18,216	Q1/D1
Best Practice & Research Clinical Haematology	1	2,740	2,740	Q2
Biochimica et Biophysica Acta (BBA) - Molecular Cell Research	1	5,261	5,261	Q1
Bioconjugate Chemistry	1	4,818	4,818	Q1
Bioelectromagnetics	2	1,583	3,166	Q2
Bioessays	1	4,725	4,725	Q1
Biology of Blood and Marrow Transplantation	3	3,980	11,940	Q2
Biomed Research International	1	2,134	2,134	Q3
Blood	**18**	**11,847**	**213,246**	**Q1/D1**
Blood Advances	1	NI	NI	NI

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Blood Cancer Journal	1	4,411	4,411	Q1
BMC Bioinformatics	2	2,435	4,870	Q1
BMC Genomics	3	3,867	11,601	Q1
BMJ Open	1	2,562	2,562	Q1
Bone Marrow Transplantation	5	3,636	18,180	Q2
Breast Cancer Research and Treatment	1	4,085	4,085	Q2
Breast Care	1	1,553	1,553	Q3
Breast Journal	1	2,297	2,297	Q2
Briefings in Bioinformatics	1	8,399	8,399	Q1/D1
British Journal of Cancer	3	5,569	16,707	Q1
British Journal of Clinical Pharmacology	1	3,830	3,830	Q1
British Journal of Dermatology	4	4,317	17,268	Q1/D1
British Journal of Haematology	19	5,812	110,428	Q1
Cancer Cell	**1**	**27,407**	**27,407**	**Q1/D1**
Cancer Letters	1	5,992	5,992	Q1
Cancer Medicine	2	3,362	6,724	Q2
Cancer Research	4	8,556	34,224	Q1/D1
Cancer Treatment and Research	2	NI	NI	NI
Case Reports in Hematology	1	NI	NI	NI
Cell Communication and Signaling	1	3,661	3,661	Q2
Cell Death & Disease	1	5,378	5,378	Q1
Cell Reports	1	7,870	7,870	Q1
Cell Signal	1	4,191	4,191	Q2
Clinical & Translational Oncology	12	2,075	24,900	Q3
Clinical Advances in Hematology & Oncology	1	NI	NI	NI
Clinical and Experimental Rheumatology	1	2,634	2,634	Q3
Clinical Cancer Research	6	8,738	52,428	Q1/D1
Clinical Case Reports	1	NI	NI	NI
Clinical Chemistry and Laboratory Medicine	1	3,432	3,432	Q1
Clinical Colorectal Cancer	1	3,090	3,090	Q2

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Clinical Lymphoma Myeloma & Leukemia	1	2,316	2,316	Q3
Clinical Ophthalmology	1	NI	NI	NI
Clinical Rheumatology	1	2,042	2,042	Q3
Current Biology	1	8,851	8,851	Q1/D1
Current Opinion in Genetics & Development	1	5,825	5,825	Q1
Current Pharmaceutical Design	2	3,052	6,104	Q2
Cytometry Part B: Clinical Cytometry	4	2,822	11,288	Q1
Cytotherapy	1	3,625	3,625	Q1
Drug Design Development and Therapy	2	2,822	5,644	Q2
Drug Metabolism and Personalized Therapy	1	NI	NI	NI
Drugs	1	5,000	5,000	Q1/D1
EBioMedicine	1	NI	NI	NI
EMBO Reports	1	7,739	7,739	Q1/D1
European Journal of Haematology	3	2,544	7,632	Q3
Experimental Eye Research	1	3,332	3,332	Q1
Expert Opinion on Biological Therapy	1	3,684	3,684	Q1
Expert Review of Proteomics	2	3,465	6,930	Q2
F1000Research	2	NI	NI	NI
Frontiers in Neuroendocrinology	1	9,425	9,425	Q1/D1
Frontiers in Oncology	1	NI	NI	NI
Gene	1	2,319	2,319	Q3
Genes Chromosomes & Cancer	1	3,960	3,960	Q1
Genetic Testing and Molecular Biomarkers	1	1,297	1,297	Q4
Haematologica	12	6,671	80,052	Q1/D1
Haemophilia	1	2,673	2,673	Q2
Hematological Oncology	4	3,494	13,976	Q2
Hematology-American Society of Hematology Education Program	1	2,016	2,016	Q2
Human Pathology	1	2,791	2,791	Q2
International Journal of Cancer	1	5,531	5,531	Q1
International Journal of Molecular Sciences	2	3,257	6,514	Q2

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
International Journal of Ophthalmology	1	0,939	0,939	Q4
International Journal of Radiation Oncology Biology Physics	1	5,133	5,133	Q1
International Journal of Toxicology	1	1,077	1,077	Q4
Investigative Ophthalmology & Visual Science	1	3,303	3,303	Q1
Journal of Biological Chemistry	1	4,258	4,258	Q1
Journal of Cell Science	1	4,706	4,706	Q2
Journal of Clinical Oncology	**3**	**20,982**	**62,946**	**Q1/D1**
Journal of Comparative Effectiveness Research	1	1,204	1,204	Q4
Journal of Cutaneous Pathology	1	1,409	1,409	Q3
Journal of Hematology & Oncology	4	6,263	25,052	Q1/D1
Journal of Immunological Methods	4	1,858	7,432	Q3
Journal of Investigative Dermatology	1	6,915	6,915	Q1/D1
Journal of Materials Science-Materials in Medicine	1	2,325	2,325	Q2
Journal of Molecular Diagnostics	1	5,201	5,201	Q1/D1
Journal of Neurochemistry	1	3,842	3,842	Q2
Journal of Pathology	1	7,381	7,381	Q1/D1
Journal of Proteome Research	1	4,173	4,173	Q1
Journal of Proteomics	2	3,867	7,734	Q1
Journal of the European Academy of Dermatology and Venereology	1	3,029	3,029	Q1
Journal of the National Comprehensive Cancer Network	1	4,262	4,262	Q1
Journal of Thrombosis and Haemostasis	2	5,565	11,130	Q1/D1
Journal of Translational Medicine	1	3,786	3,786	Q1
Lancet	**2**	**47,831**	**95,662**	**Q1/D1**
Lancet Oncology	**3**	**26,509**	**79,527**	**Q1/D1**
Leukemia	**17**	**12,104**	**205,768**	**Q1/D1**
Leukemia & Lymphoma	9	3,093	27,837	Q2
Leukemia Research	4	2,606	10,424	Q3
Medicina Clinica	6	1,267	7,602	Q2
Medicine	2	2,133	4,266	Q2
Metallomics	2	3,540	7,080	Q2

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Methods in Enzymology	1	2,088	2,088	Q3
Methods in Molecular Biology	2	NI	NI	NI
Molecular and Cellular Endocrinology	1	3,859	3,859	Q2
Molecular and Cellular Neuroscience	1	3,084	3,084	Q2
Molecular Cancer	1	6,024	6,024	Q1
Molecular Cancer Therapeutics	2	5,579	11,158	Q1
Molecular Diagnosis & Therapy	1	1,909	1,909	Q3
Molecular Oncology	1	5,367	5,367	Q1
Molecular Plant	1	7,142	7,142	Q1/D1
Nanoscale	1	7,367	7,367	Q1
Nature	**1**	**38,138**	**38,138**	**Q1/D1**
Nature Communications	**4**	**11,329**	**45,316**	**Q1/D1**
Nature Genetics	**1**	**31,616**	**31,616**	**Q1/D1**
Nature Medicine	**1**	**29,886**	**29,886**	**Q1/D1**
Nature Reviews Disease Primers	1	6,389	6,389	Q1/D1
Neoplasia	1	4,509	4,509	Q1
New England Journal of Medicine	**3**	**59,558**	**178,674**	**Q1/D1**
Nucleic Acids Research	**1**	**10,162**	**10,162**	**Q1/D1**
Nucleus	1	2,387	2,387	Q3
Oncogene	3	7,932	23,796	Q1/D1
Oncologist	1	4,789	4,789	Q2
Oncology Letters	1	1,390	1,390	Q4
Oncotarget	36	5,008	180,288	Q1
Open Biology	1	4,822	4,822	Q1
Ophthalmic Genetics	1	1,886	1,886	Q2
Oral Oncology	2	4,286	8,572	Q1
Pain Practice	1	2,317	2,317	Q2
Patient Preference and Adherence	1	1,732	1,732	Q3

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Pediatric Dermatology	1	1,163	1,163	Q3
Pharmaceutical Biology	1	1,546	1,546	Q2
Platelets	2	2,465	4,930	Q3
Plos Computational Biology	1	4,587	4,587	Q1/D1
Plos Genetics	1	6,661	6,661	Q1/D1
PLoS One	12	3,057	36,684	Q1
Proceedings of the National Academy of Sciences of the United States of America	2	9,423	18,846	Q1/D1
Proteomics	1	4,079	4,079	Q1
Proteomics Clinical Applications	1	3,814	3,814	Q1
Rev Cancer	1	NI	NI	NI
Revista de Psiquiatría y Salud Mental	1	2,227	2,227	Q3
Revista Enfermería CyL	1	NI	NI	NI
Revista Española de Cardiología (Engl Ed).	2	4,485	8,970	Q2
Revista Española de Medicina Nuclear e Imagen Molecular	1	0,951	0,951	Q4
Rheumatology	1	4,524	4,524	Q1
RNA	1	4,605	4,605	Q1
Science Translational Medicine	**1**	**16,264**	**16,264**	**Q1/D1**
Scientific Reports	7	5,228	36,596	Q1
Seminars in Ophthalmology	1	1,184	1,184	Q4
Small GTPases	1	NI	NI	NI
Stem Cell Reports	1	7,338	7,338	Q1
Stem Cell Research	1	3,963	3,963	Q1
Supportive Care in Cancer	1	2,698	2,698	Q1
Thrombosis and Haemostasis	1	5,255	5,255	Q1
Thrombosis Research	2	2,650	5,300	Q2
World Journal of Gastroenterology	1	2,787	2,787	Q2
World Neurosurgery	1	2,685	2,685	Q1

CIC-IBMCC PUBLICATIONS BY QUARTILE 2007-2017

SCIENTIFIC ACTIVITIES

NATIONAL AND INTERNATIONAL COLLABORATIONS

NATIONAL COLLABORATIONS

CENTER	PROVINCE	RESEARCHERS
Centro Nacional de Microbiología, ISCIII	Madrid	J M Rojas
Instituto de Biomedicina y Biotecnología de Cantabria (IBBTEC)	Santander	P. Crespo
Univ. Alcalá de Henares	Madrid	P. de la Villa
Instituto de Neurociencias de Castilla y León (INCYL)	Salamanca	A. Porteros, C. Lillo
Instituto Investigación Sanitaria Gregorio Marañón (IISGM)	Madrid	J. Vaquero
Instituto de Biología y Genética Molecular (IBGM)	Valladolid	C. Villalobos / Andrés Alonso
Centro de Biología Molecular Severo Ochoa (CBMSO)	Madrid	J. M. Cuezva / Paulino Gómez Puertas / César Cobaleda
Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)	Cordoba	Marco A. Calzado Canale
IBIS-Hospital Universitario Virgen del Rocío-Universidad de Sevilla	Sevilla	Francisco M. Vega
Hospital Infantil St Joan de Deu-Universidad de Barcelona	Barcelona	Carme Fons
Instituto de Investigación Biomédica de Bellvitge (IDIBELL) Epigenetics and Cancer Biology Program	Barcelona	Manel Esteller
Centro de Investigaciones Biológicas (CIB)	Madrid	Rodrigo Bermejo / J Teixidó
Centro Nacional de Investigaciones Oncológicas (CNIO)	Madrid	Marcos Malumbres / Maríano Barbacid
Centro Nacional de Microelectrónica (CNM-CSIC)	Madrid	José Antonio Plaza
Universidad Autónoma de Madrid	Madrid	Julián Aragonés / Francisco Sánchez-Madrid
Centro Nacional de Biotecnología (CNB)	Madrid	Mario Mellado
Instituto de Investigaciones Biomédicas «Alberto Sols» (IIBM)	Madrid	Jorge Martín Pérez
Centro de Investigación Médica Aplicada (CIMA)	Navarra	José Ángel Martínez-Climent / F Prosper /JF San Miguel
Universidad de Salamanca (USAL)	Salamanca	Francisco Javier García-Criado / Rafael Jiménez Fernández / Rubén Martínez Buey / Manuel A. Sánchez Martín /Francisco S. Lozano Sánchez
Instituto de Biología Funcional y Genómica (IBFG)	Salamanca	Dionisio Martín-Zanca
Hospital Universitario Marqués de Valdecilla / Fundación IFIMAV	Santander	Miguel A. Piris
Instituto de Biomedicina de Salamanca (IBSAL)	Salamanca	Antonio Muro
Vall D´Hebron Institute of Oncology (VHIO)	Barcelona	Joaquín Arribas
Institut Hospital del Mar d´Investigacions Mèdiques (IMIM)	Barcelona	Joan Albanell

CENTER	PROVINCE	RESEARCHERS
Universidad de Castilla-La Mancha	Albacete	Alberto Ocaña
Instituto de Biología y Genética Molecular (IBGM)	Valladolid	Andrés Alonso
Instituto de Recursos Naturales y Agrobiología (IRNASA)	Salamanca	Mónica Balsera
Universidad Complutense de Madrid (UCM)	Madrid	Almudena Porras
Universidad de Málaga	Malaga	Ramón Muñoz Chápuli
Hospital Universitario de Salamanca	Salamanca	José Ramón González Porras / Francisco Martín Herrero
Universidad de Zaragoza	Zaragoza	Inés García Rubio
Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS).	Barcelona	J. Bladé

INTERNATIONAL COLLABORATIONS

CENTER	PROVINCE	RESEARCHERS
Fondazione Italiana per la Ricerca sul Cancro- International Foundations of Medicine (FIRC-IFOM), Milano	Italy	G. Scita
National Cancer Institute (NCI)-National Institutes of Health (NIH) , Bethesda	USA	L Samelson, C. Kortum
Central Institute of Mental Health (CIMH), Heidelberg University	Germany	R. Spanagel
Institute of Psychiatry, Psychology & Neuroscience, King´s College, London	UK	G. Schumann, C. Müller
Babraham Institute, Cambridge	UK	S.Suire
Institute of Medical Genetics, Shaare-Zedek Hospital, Hebrew University Medical School	Israel	Ephrat Levy-Lahad / Paul Renbaum
University of Michigan	USA	Daniel J. Klionsky
Stem Cell Research Institute of New York, New York	USA	Ana Sevilla
École Polytechnique de Paris, Paris	France	Alexis Gautreau
Institute for Medical Informatics and Biometry, Medical School, University of Technology Dresden	Germany	Lars Kaderalli
Hutchison/MRC Research Centre, Cambridge	United Kingdom	Ashok Venkitaraman
Life Sciences Division. Lawrence Berkeley National Laboratory (LBNL). University of California, Berkeley	USA	Jian Hua Mao
University of Bayreuth	Germany	Olaf Stemmann
French National Centre for Scientific Research-CNRS, Paris	France	Katja Wassmann
Paris Diderot University, Paris	France	Reiner Veitia
University of Cambridge, Cambridge	UK	Owen Davies
Oxford University, Oxford	UK	Kim Nasmyth
University of Düsseldorf, Düsseldorf	Germany	Arndt Borkhardt / Julia Hauer

CENTER	PROVINCE	RESEARCHERS
University of California, San Francisco (UCSF), San Francisco	USA	Allan Balmain / Markus Muschen
Stanford University	USA	Ash Alizadeh
Sanger Center, Cambridge	United Kingdom	Natalie Conte / Allan Bradley
Cornell Institute, NY	USA	Ari Melnick
University of Miami Sylvester Comprehensive Cancer Center, Florida	USA	Izidore Lossos
Imperial College London, London, UK		Cristina Lo Celso
University of Nebraska Medical Center (UNMC) , Nebraska	USA	Michael Green
Massachusetts General Hospital (MGH)- Harvard Medical School, (HMS) Harvard, Boston,	USA	Hanno Reinhard Hock
Magna Graecia University,	Italy	Daniele Torella
Kings College, London	UK	Bernardo Nadal-Ginard
University Health Network/University of Toronto, Toronto	Canada	Eitan Amir
Netherlands Cancer Institute-NKI, The Hague	The Netherlands	Arnoud Sonnenberg
Vanderbilt University,	USA	Adrian Olivares / Mathew Lang
University of Porto, Porto	Portugal	Sandra Macedo-Ribeiro
Center for Cancer Systems Biology (CCSB) at the Dana-Farber Cancer Institute, Harvard Medical School (DFCI-HMS), Boston	USA	Marc Vidal
Biological Systems and Integrative Sciences Institute (BioISI), Faculty of Sciences, University of Lisbon (ULISBOA), Lisbon	Portugal	Margarida Gama-Carvalho
Laboratoire Cell Growth and Tissue Repair (CRRET, CNRS 9215), Université Paris-Est Créteil Val-de-Marne (UPEC) Paris	France	Dulce Papy-García
Computational Genomics, Center for Genomic Sciences (CCG), Universidad Nacional Autonóma de México (UNAM) Cuernavaca	Mexico	Julio Collado-Vides
Charité University Medicine, Berlin	Germany	Lars Bullinger
Queen´s University Belfast, Belfast	United Kingdom	Ken Mills
Universidad de Iberoamerica (UNIBE)	Costa Rica	Christian Uriel Blanco
Universidad de Coimbra, Coimbra	Portugal	Fernando Regateiro
EUROFLOW CONSORTIUM - Leiden University Medical Center, Leiden - Erasmus MC, Rotterdam - Instituto Portugués de Oncologia, Lisbon - University of Schleswig-Holstein - Campus Kiel, Kiel - Hôpital Necker-Enfants Malades, Paris - Charles University, Prague - Medical University of Silesia, Zabrze - Federal University of Rio de Janeiro, Rio de Janeiro - Dutch Childhood Oncology Group, The Hague - Centro Hospitalar do Porto / University of Porto, Porto - Universitätmedizin Rostock – Rostock	The Netherlands / Portugal /Germany / France / Czech Republic / Poland / Brasil	J.J.M. van Dongen / M. van der Burg / V.H.J van der Velden / A. Medina Almeida / M. Kneba /E. Macintyre / J. Trka /T. Szczepanski / C.E. Pedreira / E. Sonneveld / M. Lima / S. Böttcher

CENTER	PROVINCE	RESEARCHERS
PERISCOPE CONSORTIUM - Radboud University Medical Center - University of Oxford - Public Health England - Institut Pasteur de Lille - Trinity College Dublin - University of Turku - Commissariat à l'énergie atomique et aux energies alternatives - Imperial College London - National Institute for Public Health and the Environment (RIVM) - Institute of Microbiology of the CAS, v. v. i. - University of Basel Children's Hospital - University of Bath - Leiden University Medical Center - Université Libre de Bruxelles - Hospice Cantonaux - University of Southampton - Q-Biologicals NV - Medical Research Council Unit The Gambia - European Research and Project Office GmbH - Sanofi Pasteur - GSK Vaccines	United Kingdom / The Netherlands / France / Ireland / Finland / c Switzerland / Belgium / Gambia	Ronald de Groot / Dominic Kelly / Andrew Gorringe / Camille Locht / Kingston Mills / Qiushui He / Roger Le Grand / Beate Kampmann / Cécile van Els / Guy Berbers / Peter Sebo / Ulrich Heininger / Andrew Preston / Jacques J.M. van Dongen / Françoise Mascart / Giuseppe Pantaleo / Robert Read / Annie Van Broekhoven / Beate Kampmann / Patricia Londoño-Hayes / Philippe Denoel
ARIMMORA CONSORTIUM - Foundation for Research on Information Technologies in Society - University of Basel, Department of Biomedicine - Swiss Tropical and Public Health Institute - Weizmann Institute of Science - Fraunhofer-Institute of Toxicology and Experimental - University of Veterinary Medicine Hannover, Foundation - Schmid & Partner Engineering AG, Zürich - Centre International de Recherche sur le Cancer - Consiglio Nazionale delle Ricerche	Czech Republic / Germany / Israel / Switzerland / France / Italy	Niels Kuster / Primo Schär / Martin Röösli / Rony Seger / Clemens Dasenbrock / Maren Fedrowitz / Katja Pokovic / Joachim Schüz / Paolo Ravazzani
DECIDE CONSORTIUM - Consortium GARR - Consiglio Nazionale delle Ricerche - COMETA; Consorzio Multi Ente per la Promozione e l'Adozione di Tecnologie di Calcolo Avanzato - IT Sicilian Grid computing consortium - Provincia Lombardo Veneta Ordine Ospedaliero di San Giovanni di Dio Fatebenefratelli - Università Vita-San Raffaele - Università degli Studi di Genova - Università degli Studi di Foggia - Fondazione SDN - Maat France - Imperial College of Science, Technology and Medicine - Uniwersytet Warszawsky - Centre Hospitalier Universitaire de Toulouse (Gérontopôle) - Alzheimer Europe - King's College London	Italy/ France / United Kingdom / Poland / Luxembourg	

SCIENTIFIC ACTIVITIES

SPANISH COOPERATIVE CANCER RESEARCH NETWORK (RTICC)

The Spanish Cooperative Cancer Research Network (RTICC) is one of the RETICS (Networks for Cooperative Research in Health) formed through association to the Instituto de Salud Carlos III of a range of multidisciplinary research centers and groups in cancer research dependent on different public administrations or on the private sector, belonging to at least four Autonomous Communities, which seek to conduct cooperative research projects of general interest in cancer. They respond to the priorities of the National Plan for Scientific and Technical Research and Innovation 2013-2016 in the health care sector and integrate different types of research as a strategy to shorten the gap between the production of new knowledge and the transfer and application of this knowledge to medical practice.

The mission of RTICC is to implement a functional network matrix of scientific Programs structured at the national level that is geared at improving the integration, synergization and enhancement of the quality of cancer research performed by individual, internationally competitive cancer research groups distributed throughout the different Spanish Autonomous Regions. This Network structure should make it possible the multidisciplinary study of cancer at the basic, translational, epidemiological and clinical levels and, in addition, should facilitate the efficient transfer of results from the lab bench to the society. Specific goals linked to this general mission include at least the following: (i) To create an environment of research excellence that allows Spanish cancer researchers to compete in equal terms with other national and international cancer networks; (ii) To promote synergistic cooperation among basic, clinical, and translational laboratories in Spain; (iii) To conduct a multifaceted study of the tumorigenic process at the basic, translational, and clinical level; (iv) To develop new diagnostic and prognostic tools of application to cancer patients; (v) To put in motion technical and diagnostic facilities that favor cancer diagnostics, prognostics and the development of new anti-tumor approaches and therapies; (vi) To promote interactions with other national and international cancer networks as well as with the biopharmaceutical industry; (vii) To train specialized personnel at the technical, graduate, and postdoctoral level in molecular, translational, and clinical oncology.

The vision of RTICC is to become a permanent network research structure within the Spanish biomedical research system (long term «Stable Networked Research Structures» of the ISCIII) that allows the top leading Spanish cancer researchers and research centers to carry out interdisciplinary, internationally competitive studies on cancer in Spain. This structure has to promote and facilitate dynamic and fluid interaction between groups of excellence at the basic, translational, and clinical level in hospitals and other specialized cancer research centers throughout our country. In addition, it must act as a catalyzer for cancer research in Spain by promoting the establishment of networks between clinical and academic departments in Spain. Finally, it has to foster new technological advances in cancer research by making available state-of-the-art technologies to individual researchers and the overall Spanish R+D system.

Since January 2013 until December 2017 a total of 72 groups, structured into eight specific programs: (i) Molecular mechanisms: molecular characterization of tumors, cancer genomics and biomarkers, (ii) Epidemiology and Prevention of cancer, (iii) Hematological tumors, (iv) Breast cancer, (v) Colon and Gastrointestinal cancer, (vi) Lung and Upper Respiratory tract, (vii) Other Solid and pediatric tumors and finally (viii) a transversal program of Formation and Coordination, with more than 1200 researchers in 40 institutions (universities, public research institutions and hospitals) distributed in 9 different autonomous communities of Spain have been working in the Spanish Cancer Network coordinated by Dr. Eugenio Santos from Cancer Research Center of Salamanca. Five groups of the CIC-IBMCC, led by Dr. Eugenio Santos, Xosé R. Bustelo, Alberto Orfao, Marcos González and Atanasio Pandiella have been involved in five of the eight programs of the RTICC.

ONCOLOGY BIOMEDICAL RESEARCH NETWORKING CENTER (CIBERONC)

CIBER (Biomedical Research Networking Centers) 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 with the aim of promoting research of excellence in priority areas of Biomedicine and Health Science, carried out in the National Health System and in the National Science and Technology System. The importance of this goal for science, health and society as a whole requires the ISCIII to undertake the promotion and financial support of these CIBER.

Currently, the consortia CIBER (www.ciberisciii.es) and CIBERNED (www.ciberned.es) consist of over 400 research groups working in 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.

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) of the CIBER of ISCIII.

The main aim of the Consorcio Centro de Investigación Biomédica en Red de Cáncer (CIBERONC) is to promote excellence in oncology research in Spain, as well as to incorporate new findings to clinical practice. In order to attain excellence, CIBERONC promotes the cooperation of 50 of the best national research groups in cancer. CIBERONC pursues also an increase in the quality of its researchers by means of a transversal training and mobility program.

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, the CIBERONC center wishes to narrow the gap between scientific knowledge and society and clearly explain the benefits of our research to the general public by means of different endeavors.

CIBERONC has 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.

Five groups of the CIC-IBMCC, led by Dr. Eugenio Santos, Xosé R. Bustelo (Coordinator of the Tumour Progression Mechanisms program), Alberto Orfao, Marcos González (Coordinator of the Haematological Tumours program) and Atanasio Pandiella are involved in several programs of the CIBERONC.

SCIENTIFIC ACTIVITIES

AWARDS AND RECOGNITIONS

In 2016-2017 period the work of several scientists at the Cancer Research Center (CIC-IBMCC) has been recognized through scientific awards, appointments and recognition as detailed below:

- Second prize to the communication «*Identification of genetic determinants associated with heart damage caused by anthracyclines through analysis of DNA damage/genotoxicity pathways as subphenotypes*». VIII Simposium Bases Biológicas del Cáncer y Terapias Personalizadas. Salamanca (Spain). May 2016.
- International Award for Research in Leukaemia-LADY TATA MEMORIAL TRUST Winners of the Academic Year 2016 - 2017 to Dr. Carolina Vicente-Dueñas. 2016.
- Premio de Investigación en Innovación y Tecnología de la Junta de Castilla y León to Dr. Juan Jesús Cruz. 2016.
- Prize of the German Carreras Foundation (DJCLS) to Dr. Isidro Sanchez García. 2016.
- Funding: Boehringer Ingelheim Fonds Travel Grant to Dr. Adrián Blanco Gómez. 2016.
- Extraordinary Doctorate Award USAL PhD Thesis University of Salamanca «*Transcriptomic characterization of Human Mesenchymal Stromal/Stem Cells*» to Dr. Beatríz Rosón Burgo. Mentors: Dr. Javier De Las Rivas, Dra. Consuelo del Cañizo and Dr. Fermín Sánchez-Guijo. 2016.
- Extraordinary Thesis Award to Dr. María del Mar Sáez Freire. Salamanca 2016.
- The Halifax Group received a Cancer Prevention Award 2015 to Dr. Isidro Sanchez García (it was a unanimous choice of the Prevent Cancer Now Board of Directors). 2016.
- GETH Award from the Grupo Español de Trasplante Hematopoyético y Terapia Celular to the best publication in 2016 on clinical research whose first author is from Spain, to the work «*Immunomodulatory effect of vitamin D after allogeneic stem cell transplantation: results of a prospective multicenter clinical trial*» published in Clin Cancer Res 2016: 22: 5673-5681, by: Caballero-Velázquez T, Montero I, Sánchez-Guijo F, Parody R, Saldaña R, Valcárcel D, López-Godino O, Ferra i Coll C, Carrillo-Vico A, Cuesta M, Sánchez-Abarca LI, López-Corral L, Márquez-Malaver F, Pérez-Simón JA. 2016.
- Award best oral communication «*Identification and enumeration of distinct subsets of monocyte-macrophages in different human tissues throughout life using 9-color flow cytometry*». Dr. J. Almeida, Dr. A. Orfao, Dr. M. Pérez Andrés. Congreso de la Sociedad Ibérica de Citometría 2017. Lisboa, May 2017.
- Best Poster Award, at the 14th International Symposium on Stem Cell Therapy and Cardiovascular Innovations for the poster «*Study of the effect of extracellular vesicles from mesenchymal stromal cells (MSC-VE) on cardiotoxicity induced by doxorrubicin*», by Rico A, Muntión S, Preciado S, Moyano C, Ocio E, Sánchez-Guijo F, Sánchez PL, Cañizo MC. Madrid (Spain), June 2017.
- Best Oral Communication Award from the Spanish Foundation of Hematology and Hemotherapy (FEHH), at the LIX National Congress SEHH - XXXIII National Congress SETH,. «*El pan-inhibidor de Pim kinasas, PIM447, potencia el efecto de pomalidomida y dexametasona en myeloma múltiple*», by Paíno T, San Segundo L, Hernández García S, Gonzáles Méndez L, Algarín EM, López Iglesias AA, Mogollón P, Martín Sánchez M, Díaz Tejedor A, Gutiérrez N, Mateos MV, Garayoa M, Ocio EM. Málaga (Spain) October 2017.
- Distinguished Speaker's Lecture to Dr. Xosé R. Bustelo. Sylvester Comprehensive Cancer Center, Univ. of Miami. Miami, FL (USA). 2017.
- Award María de Maeztu from Salamanca University a la Excelencia Científica to Dr. Andrés Avelino Bueno. Salamanca. 2017.
- «We can be heroes» Foundation grant to Dr. Adrián Blanco Gómez. 2017.
- Award «Innovador 2017» from the «El Mundo of Castilla y León» newspaper to Dr. Alberto Martín Pendás. 2017.
- Extraordinary Doctorate Award 2016/2017. PhD Thesis University of Salamanca: «*Nuevas estrategias terapéuticas en neoplasias hematológicas*» to Dr. Ana Alicia López Iglesias. Mentors: Dr. Enrique Ocio San Miguel; Mercedes Garayoa Berrueta, Marcos González Díaz. 2017.
- VII Prize to Research «Profesor Garmedia» to Sonia Gómez. September 2017.


Centrifuge 5415 R

SCIENTIFIC ACTIVITIES

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

Nº	PI	RESEARCHERS
002	**Xosé Ramón García Bustelo**	María Josefa Montero Gómez / Mercedes Dosil Castro / María Ángeles Sevilla Toral / Javier Robles Valero / Myriam Cuadrado López / María Isabel Fernández Pisonero
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 / Pedro Alfonso Lazo-Zbikowski Taracena / Rogelio González Sarmiento / Juan Jesús Cruz Hernández
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 / Carmela Gómez Rodríguez
106	**Mª del Carmen Guerrero Arroyo**	José Ramón González Porras / Francisco Santiago Lozano Sánchez / Francisco Martín Herrero / José María de Pereda Vega / Almudena Porras Gallo
110	**Norma Carmen Gutiérrez Gutiérrez**	María Victoria Mateos Manteca / Enrique María Ocio San Miguel / Mercedes Garayoa Berrueta / Noemí Puig Morón / Ana Belén Herrero Hernández / Irena Misiewick-Krzeminska / María Teresa Paíno Gómez
143	**Jesús María Hernández Rivas**	Juan Luis García Hernández / Cristina Robledo Montero / Ana Eugenia Rodríguez Vicente / M. Rocío Benito Sánchez / 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 / José María Sayagués Manzano
155	**Marcos González Díaz**	Ramón García Sanz / María Dolores Caballero Barrigón / María del Carmen Chillón Santos / María Eugenia Alonso Sarasquete / Miguel Alcoceba Sánchez / Luis Alberto Marín Rubio / María Belén Vidriales Vicente / Alejandro Martín García-Sancho / María Pilar Tamayo Alonso
252	**Andrés Avelino Bueno Núñez**	Felipe Xosé Pimentel Muiños / María Sacristán Martín / Rodrigo Bermejo Moreno

CIC-IBMCC GROUPS RECOGNIZED AS «GRUPO DE INVESTIGACIÓN RECONOCIDA» (GIR) BY SALAMANCA UNIVERSITY (USAL)

NAME	PI	RESEARCHERS	COLLABORATORS	RESEARCH LINES
Señalización, División y Crecimiento Celular	Dosil Castro, Mercedes	Sacristán Martín, Mª Paz / Llano Cuadra, Elena	Martín Pendás, Alberto / García Bustelo, Xosé Ramón / Pimentel Muiños, Felipe X.	– Papeles de moléculas de señalización celular en procesos tumorales y en otras enfermedades de alta incidencia. – Regulación de la tolerancia al daño en el DNA durante su replicación y relación con la estabilidad del genoma. – 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. – División celular y estabilidad genómica: papel de las proteínas fosfatasas Cdc14 en la regulación del ciclo de división celular y en la respuesta de daño al DNA
Biología Molecular y Celular en Hemopatías	González Díaz, Marcos	García Sanz, Ramón / Caballero Barrigón, Mª Dolores / Chillón Santos, Mª del Carmen / Alonso Sarasquete, Mª Eugenia / Alcoceba Sánchez, Miguel / Marín Rubio, Luis A. / Vidriales Vicente, Mª Belén / Martín García-Sancho, Alejandro / Tamayo Alonso, Mª Pilar		– 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.

NAME	PI	RESEARCHERS	COLLABORATORS	RESEARCH LINES
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 / Gutiérrez Herrero, Sara / Ortiz Rivero, Sara	Porras Gallo, Almudena / Perdiguero Martín, Pedro Daniel / Pereda Vega, José María de / Martin Granado, Victor Miguel	– 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.
Genética Molecular en Oncohematología	Hernández Rivas, Jesús Mª	Robledo Montero, Cristina / Rodríguez Vicente, Ana / E. Benito Sánchez, M. Rocío / Rey González, Mónica del	Lumbreras González, Eva / Hernández Sánchez, María / Montaño Brioso, Adrián / Janusz, Kamila Quijada Álamo, Miguel / Martín Izquierdo, Marta / Hernández Sánchez, Jesús María	– 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 hemopatía - 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		– Identificación de patrones de expresión proteica 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
GTPASAS y Cáncer: Señalización mediada por RAS	Santos de Dios, Eugenio	Rivas Sanz, Javier de las / Fernández Medarde, Alberto / Gómez Rodríguez, Carmela		

7 TRAINING ACTIVITIES

POSTGRADUATE PROGRAM: MASTER DEGREE IN «BIOLOGY AND CLINIC OF CANCER»

The Master «Biology and Clinic of Cancer» is the adaptation and adjustment to the European Higher Education Doctoral Program that, under the same title, has been providing the IBMCC Institute from 2000 to present.

This Master Program focuses on specialized graduate training aimed at getting graduates and physicians specializing in basic, clinical or bioinformatics research level in any aspect of molecular, cellular biology and cancer clinic. This is a distinctly Masters Research aimed at the basic training necessary for graduates with an interest in Cancer Biology without prior experimental experience in the fields of molecular and cell biology that allow students to continue doctoral studies in the field.

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 disease clinically. The study of cancer from the molecular point of view is a new discipline that has developed a specialized manner only during the last two decades. The knowledge generated in this field of study areas ranges from basic research (in the microbiological, biochemical or molecular biology fields) to clinical research areas related to diagnosis, prognosis and experimental treatment. This knowledge breaks down barriers between traditionally separated biomedical fields such as Medicine, Pharmacy and Biology. 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.

In general, this Master degree provides an introduction to the study of tumor processes through an integrated approach that begins with an analysis of these processes at the molecular level and continues with the application of these basic skills to the clinic. The integration of molecular content with clinical content in the same Master gives an extremely unique character and training key for future researchers in this field. Furthermore, the Master´s Program is taught professors and researchers specialized in each of the subjects, most of them belonging to the CIC-IBMCC but also visiting researchers, invited for that purpose. In addition, it has a high practical profile, which constitutes one of its most attractive points. Thus, of its 60 total ECTS, 18 of them correspond to the subject «Practicum Biology

and Cancer Clinic» in which the student carries out, under the direct supervision of a tutor, a research project in one of the CIC-IBMCC research groups throughout the academic year.

The orientation of this teaching is therefore essentially a postgraduate research program, which aims to prepare students for inclusion in doctoral programs and the completion of the doctoral thesis. 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 «Biology and Clinic of Cancer» maintains from 2000 to present an average enrollment of 85% of the places offered; and it has been considered by the national press «El Mundo» one of the five best Masters taught by Spanish Universities, Companies or Institutions, in the field of Medical Specialties within the Health Area in 2017 (http://www.elmundo.es/especiales/mejores-masters/)

Finally, emphasize that this title is related to the degrees taught in the Faculties of Biology (Biology and Biotechnology degrees), Medicine and Pharmacy, which could be called powers of the biomedical area.

The title of this Master is comparable (and in this academic context, compatible) with other programs in Master in Molecular Oncology currently offered in different Spanish and European Research or Academic Centers.

TRAINING ACTIVITIES

STUDENTS MASTER PROGRAM

2015/2016

Jesús Antolín Sáiz
Regina Bou Puerto
Rocío Fuentes Mateo
Raúl García González
Sonia Gómez Gaspar
Luis Hernández Cano
Rodrigo Hernando Llorente
Carla Ijurko Valeta
Juan Carlos Marín Payá
Marta Martín Izquierdo
Saúl Martín Sánchez
Alejandro Medina Herrera
Pedro Mogollón Arroyo
Adrián Montaño Brioso
Haidi Jazmín Moreno Rodríguez
Daniel Murciano Trigo
Celia Nieto Jiménez
Rubén Picón Murillo
Miguel Quijada Alamo
Dolores Rivero Megías
Laura Rollán Manso

2016/2017

Pablo Antonio Antón García
Roberto Corchado Cobos
Hipólito Nicolás Cuesta Hernández
María Delgado Pérez
Andrea Díaz Tejedor
Soraya García Sorribes
Mª de los Ángeles Gómez Muñoz
Sara González De Tena-Dávila
Ana Marín Quílez
Abel Jesús Martel Martel
Cristina Medina Menéndez
Patricia Morejón García
María Ovejero Sánchez
María Paniagua Sancho
Daniela Pinto Damásceno
Sara del Mar Rodríguez Escobar
Mª José Ruiz Vasconez
Rachid Taouil
Maríana Vega Céspedes
Darnel Marchena Mendoza

2017/2018

Jorge Alejo Mateo
Sara Armenteros González
Esla Natividad Astorga Simón
Judith Jeniffer Azaña Yupanqui
Marina Belver Jiménez
Beatriz Benayas López
Ana Casado García
Claudia Cifuentes Caballero
Cristina Fernández Infante
Natalia Fernández Parejo
Blanca Fuentes Herrero
Natalia García Sancha
Nerea Gestoso Uzai
Luis González Moreno
Calos Gutiérrez Cerrajero
Marta López Yus
Gerardo Javier Martí Chillón
María Millán Salanova
Guillermo Oliva Ariza
Ana Ordiales Talavero
Niyireth Peñaloza Castañeda
Claudia Pérez Carretero
Claudia María Rejano Gordillo
Antonio Rodríguez Blázquez
Laura Sánchez Díaz
Tania Sánchez-Bayuela Recio
Laura Silva Sousa

MASTER THESES

MASTER STUDENT	DIRECTOR	TITLE MASTER THESES	DATE
Adrián Montaño Brioso	Jesús M. Hernández Rivas / María Hernández	Estudio de mutaciones del gen Notch1 en pacientes con leucemia linfática crónica mediante técnicas de secuenciación masiva	July 2016
Alejandro Medina Herrera	Marcos González Díaz	Análisis molecular del reordenamiento VDJ del gen de la cadena pesada de inmunoglobulinas en mieloma múltiple	July 2016
Carla Ljurko Valeta	María Consuelo del Cañizo	NADPH oxidasas como dianas terapéuticas en leucemia mieloide aguda	July 2016
Celia Nieto Jiménez	Eva M. Martín del Valle/ Atanasio Pandiella	Preparación, caracterización y validación in vitro de nanopartículas de alginato y piperacina, vectorizadas para el tratamiento del cáncer de mama HER2-positivo	July 2016
Daniel Murciano Trigo	Alberto Orfao/ Julia Almeida Parra	Caracterización de monocitos y células dendríticas de sangre periférica de pacientes con mastocitosis sistémica	July 2016
Dolores Rivero Megías	Atanasio Pandiella Alonso	Therapeutic targets of the novel compound CM-728 in triple negative breast cancer	July 2016
Haidi Jazmin Moreno Rodríguez	Fermín Sánchez-Guijo Martín / Consuelo del Cañizo	Leucemia mieloide crónica, inhibidores de tirosina quinasa y angiogénesis: el papel de las vesículas extracelulares	July 2016
Jesús Antolín Sáiz	Javier De Las Rivas	Análisis bioinformático de la diferenciación hematopoyética humana	July 2016
Juan Carlos Marín Paya	Alberto Orfao/ Arancha Rodríguez Caballero	Vías de diferenciación B en médula ósea y su relación con diferenciación B en la leucemia linfoblástica aguda B	July 2016
Laura Rollán Manso	Rogelio González Sarmiento	Caracterización de variantes alélicas y variaciones en el número de copias en cáncer de mama en varón	July 2016
Luis Hernández Cano	Manuel Sánchez/Carmen Guerrero	Generación de nuevos modelos animales para el estudio de la participación de C3G en leucemia mieloide crónica	July 2016
Marta Martín Izquierdo	Jesús M. Hernández Rivas	Evolución clonal de las mutaciones en la progresión de los SMD a LAM mediante secuenciación masiva	July 2016
Miguel Quijada Alamo	Jesús M. Hernández Rivas	Integrative analysis of NGS and FISH show the presence of both gene mutations and chromosomal abnormalities in hematopoietic progenitors of patients with chronic lymphocytic leukemia	July 2016
Pedro Mogollón Arroyo	Rogelio González Sarmiento	Análisis de amplicones por ultrasecuenciación en tumores escamosos de cabeza y cuello	July 2016
Raúl García González	Pedro A. Lazo-Zbikowski Taracena	Implicación de la quinasa VRK1 en la regulación epigenetica y estabilización de p53 durante la respuesta al daño génico inducido por Doxorrubicina	July 2016
Regina Bou Puerto	Xosé R. Bustelo / Myriam Cuadrado	Role of the oncogene VAV2 in lung tumorigenesis	July 2016
Rocío Fuentes Mateos	Eugenio Santos / Alberto Fernández Medarde	La eliminación combinada de las proteínas H-RAS y N-RAS en ratones provocan inmadurez pulmonar, fallo respiratorio y muerte neonatal	July 2016
Rodrigo Hernando Llorente	Xosé R. Bustelo / Javier Robles Valero	Functional characterization of the first oncogenic mutations found for the VAV1 oncogene in human tumors	July 2016
Rubén Picón Murillo	José M de Pereda	Análisis de la interacción entre el factor de intercambio de nucleótido de guanina C3G y E-cadherina	July 2016
Saúl Martín Sánchez	Avelino Bueno/María Sacristán	Análisis del papel de HCDC14 en el checkpoint de replicación: estudios de complementación en Schizosaccharomyces pombe	July 2016
Sonia Gómez Gaspar	Mercedes Dosil	Compartimentalización de la maquinaria de síntesis de ribosomas dentro del núcleo celular	July 2016

MASTER STUDENT	DIRECTOR	TITLE MASTER THESES	DATE
Abel Jesús Martel Martel	Pedro A. Lazo-Zbikowski Taracena	Regulación de la expresión del gen VRK1 por la ruta mitogénica de las MAPKs	July 2017
Alicia Landeira Viñuela	Manuel Fuentes García	Caracterización diferencial de perfiles de expresión proteica en leucemia linfoide crónica de células B mediante aproximaciones ómicas de análisis masivo	July 2017
Ana Marín Quílez	Isidro Sánchez García	Consecuencias de la expresión de bcl6 en células ProB	July 2017
Andrea Díaz Tejedor	Teresa Paíno / Enrique M. Ocio San Miguel	Estudio del posible efecto inmunomodulador de panobinostat en mieloma múltiple	July 2017
Ángel Pablo Barrera del Pozo	Manuel Fuentes García / Javier De Las Rivas	Estrategia Proteo-Genómica para la caracterización de monocitos-macrófagos de origen humano	July 2017
Clara Llorente González	Miguel Vicente-Manzanares	Linear actin bundles transmit non-muscle myosin II-dependent contractile forces at a distance to control cellular traction and adhesion dynamics	July 2017
Cristina Medina Menéndez	Felipe Pimentel	Evaluación de un posible ligando de la proteína autofágica tmem59	July 2017
Daniela Pinto Damásceno	Alberto Orfao/ Julia Almeida Parra	Distinct subsets of monocyte-macrophages in different human tissues throughout life	July 2017
Mª de los Ángeles Gómez Muñoz	Fermín Sánchez-Guijo Martín / Sandra Muntión Olave	Caracterización, cuantificación y comparación de vesículas extracelulares procedentes de células mesenquimales de pacientes con síndromes mielodisplásicos de bajo y alto riesgo	July 2017
Mª José Ruiz Vasconez	Alberto Orfao	Estudio de precursores B de Médula Ósea Normal y de pacientes con Leucemia Linfoblástica Aguda B mediante citometría de flujo de alto rendimiento para la identificación de nuevos marcadores pan-B tempranos para estudio de enfermedad mínima residual	July 2017
María Delgado Pérez	Rogelio González Sarmiento	Estudio de genes de penetrancia intermedia y baja en pacientes con Síndrome de cáncer de mama y ovario hereditario	July 2017
María Loreto Megido Domínguez	Manuel Fuentes García	Diseño y desarrollo de una metodología multi-paramétrica para la evaluación de la función biológica en compuestos químicos de alto valor añadido	July 2017
María Ovejero Sánchez	Rogelio González Sarmiento	Establecimiento de nuevos modelos tridimensionales in vitro para el estudio del cáncer	July 2017
Maríana Vega Céspedes	Alberto Orfao / Julia Almeida Parra	Caracterización fenotípica y genotípica de las subpoblaciones funcionales de linfocitos T CD4+ en sangre periférica humana	July 2017
Nicolás Cuesta Hernández	José M de Pereda	Activación del factor de intercambio de nucleótidos de guanina C3G por fosforilación con la quinasa c-Src	**July 2017**
Pablo Antonio Antón García	Mercedes Garayoa Berrueta / Enrique M. Ocio San Miguel / Marcos González Díaz	Isolation and study of multiple myeloma cell line-derived exosomes	July 2017
Patricia Morejón García	Pedro A. Lazo-Zbikowski Taracena	Caracterización del complejo proteico vrk1-smn coilina-vcp implicado en procesos neurodegenerativos	July 2017
Rachid Taouil	Felipe Pimentel	Efecto de ATG16L1 sobre la actividad autofágica de las integrinas 2 y 7	July 2017
Roberto Corchado Cobos	Jesús Pérez Losada	Identificación de determinantes genéticos y moleculares asociados a la cardiotoxicidad por antraciclinas	July 2017
Sara González De Tena-Dávila	Rogelio González Sarmiento	Estudio genético en pacientes diagnosticados de poliposis con apc/myh negativos	July 2017
Sara Rodríguez Escobar	Julia Almeida Parra	Caracterización fenotípica y genotípica de los linfocitos T colaboradores foliculares de sangre periférica	July 2017
Soraya García Sorribes	Isidro Sánchez García	Efecto de la expresión de BCL6 en células B del centro germinal	July 2017
Yunaira Méndez	Miguel Vicente-Manzanares	Mechanical control of stem cell lineage commitment	July 2017

POSTGRADUATE: PhD PROGRAM ENTITLED «BIOSCIENCE: BIOLOGY AND CLINIC OF CANCER AND TRANSLATIONAL MEDICINE»

The PhD program entitled «Biology and Clinic of Cancer» presented by the Institute CIC-IBMCC from the academic year 2001-2002 (teaching and research periods) has continued its activities until 2010, year in which the new Master called «Biology and Clinic of Cancer» was approved which involves the adaptation to the Education European Space of the PhD program above mentioned. In the same year, 2010, a new PhD program entitled «Bioscience: «Biology and Clinic of Cancer» and Translational Medicine» was presented to fulfill such legal requirements.

This program, which contained different courses and topics in their teaching period, was academically sponsored by the Department of Microbiology and Genetics (Faculty of Biology) and the Department of Medicine (Medical School). The program had among its objectives to provide the students an introduction to the study of the tumoral processes through an integrated approach that start with the analysis of this process at the molecular level and continues after with their application in the clinic.

It is the aim of these programs to approach the study of cancer from a molecular point of view and also to offer the students a compilation of the knowledge generated in this field of study in recent years (ranging from basic research to areas of clinical research related with the diagnosis, prognosis and experimental treatments). We believe that this view will jump the barriers between traditionally separate different biomedical areas such as Medicine, Pharmacy and Biology. In this sense, the study of the program requires an interdisciplinary approach and it is indeed of interest to professionals in the area and to academics in the medical, pharmaceutical or biological fields.

As pointed above, the contents integrate «molecular» and «clinical» approaches with an emphasis on the molecular links with the disease. The PhD program structure containing a first set of courses focused on topics related to cellular and molecular biology of cancer, which gave way to another block of courses focused on the use of basic knowledge level for diagnosis and prognosis and cancer treatment, along with

courses that examined genetics, development, and clinical pathology of various human solid tumors or hematologic. On the other hand, it also offers a series of experimental content courses primarily among which included a course of instrumental techniques required in the pre-doctoral work at the Cancer Research Center and a specialized course in Bioinformatics and use in the analysis of problems related to cancer, to conclude with workshops on the use of cytogenetic techniques or flow cytometry in the study of tumors. Significantly, the PhD program has been awarded with a Golden Quality Stamp by the Spanish Ministry of Education and Science since its second biennium and such recognition has been renewed continuously since then until today.

TRAINING ACTIVITIES

STUDENTS PhD PROGRAM

2015/2016

Adrián Sánchez Fernández
Alba Quesada Moreno
Alejandro Rolo Ramírez
Alexis E. Morales Boscán
Alfonso Fernandes De Abreu Alves Chaves
Alicia Alonso Jiménez
Aline Rodrigues
Ana África Martín López
Ana Alejandra Cordero Vaquero
Ana Alicia López Iglesias
Ana Isabel Sánchez Marcos
Ana María Mateos Díaz
Ana María Orive Ramos
Ana Rico Sorli
Andrea Silvana Prolo Acosta
Andrés Julián Plata Izquierdo
Aránzazu García Mateo
Arturo Carabias Del Rey
Blanca Nieto Bernáldez
Blanca Rodríguez Martín
Carlos Fabián Castaño Romero
Conrado Jorge Finnigan
Cristina Blanco Dorado
Cristina Cantero Diez
Cristina Egido Turrión
Cristina Sofía Baz Villoria
Dalia Salim Quwaider
Daniela Pinto Damasceno
David Barreda Gago
Diego Sánchez Nieto
Elena Díaz Peláez
Elena Martín Doncel
Elisa Calvo Jiménez
Elizabeta De Los Ángeles Rojas Ricardo
Esperanza Macarena Algarín Pachón
Ester Laso Lucas
Eva García Piney
Eva María Diez Baeza
Fátima Méndez Ambel
Francisco Javier García Palomo
Francisco Javier Ortega García
Francisco José Campos Laborie
Guillermo Rodríguez Hernández
Henar Pérez Ramos
Ignacio Campillo Marcos
Inmaculada Serramito Gómez
Isora Follana Neira
Javier Ignacio Muñoz González
Jesús Manuel González Santiago
Jesús María Hernández Sánchez
Jose Manuel Iglesias Clemente
Josepa Sebastia Morant
Juan Carlos Caballero Berrocal
Juan Francisco Soto Delgado
Juan Luis Muñoz Sánchez
Julie Milena Galvis Jiménez
Julio Davila Valls
Laura Gómez Hernández
Laura Ruiz Remolina
Luis Francisco Lorenzo Martín
Luis López Mesonero
Luis Martínez Roldán
Luzalba Del Carmen Sanoja Flores
M. De La Paz Vaquero Herrero
Mª Concepción Piñero Pérez
Magdalena Janusz Kamila
Marco López Zubizarreta
María Amparo Mateos Diego
María De Los Ángeles De Pedro Muñoz
María Elena Pérez Losada
María Esther Ramos Araque
María Fernández Regueras
María García Álvarez
María González-Tablas Pimenta
María Isabel Prieto Conde
María Teresa Cano Mozo
María Teresa González Sánchez
Marta Fernández Prieto
Mercedes Garzón Martínez
Miriam López Parra
Mónica Morais Gomes Ferreira
Natalia Felipe Medina
Natalia Sánchez Aguadero
Noemí Muñoz García
Oriana López Godino
Pablo Segovia Alonso
Pedro Daniel Perdiguero Martín
Pilar Costa Alba
Raquel Moreno Mayordomo
Rebeca Sánchez González
Ronald Paul Macías Casanova
Ruslan Alali
Santiago José Bueno Fortes
Sara Alonso Álvarez
Sara García Alonso
Sara Gutiérrez Herrero
Sergio Cadenas Menéndez
Silvia Preciado Pérez
Silvio Ragozzino
Soledad Medina Valdivieso
Sonia Rodríguez Fernández
Soraya Jodra Sánchez
Soraya Merchán Gómez
Susana Hernández García

Svetlana Zhilina
Ventura Idania De Los Santos
Verónica González De La Calle
Víctor Miguel Martín Granado
Yazmine Bejarano Condezo
Yolanda María Guillén Pérez
Yuliana Mónica Jamanca Poma

2016/2017

Adrián Blanco Gómez
Adrián Ricardo Montaño Brioso
Adrián Sánchez Fernández
Adriana Cosano Quero
Aitor Uribarri González
Alba Iglesias Ceacero
Alba Quesada Moreno
Alba Vicente Cornejo
Alberto Martín Lorenzo
Aldo Bruno Fiorini Talavera
Alejandro Hernández Delgado
Alejandro Medina Herrera
Alejandro Rolo Ramírez
Alexis E.Morales Boscán
Alfonso Fernandes De Abreu Alves Chaves
Aline Rodrigues
Ana África Martín López
Ana Alejandra Cordero Vaquero
Ana Alicia López Iglesias
Ana Isabel Sánchez Marcos
Ana María Mateos Díaz
Ana María Orive Ramos
Andrea Silvana Prolo Acosta
Andrés Barbosa Ventura
Ángel Pinto Bruno
Aránzazu García Mateo
Ariana Centa
Arturo Carabias Del Rey
Atenea Pascual Rodríguez
Aurora Gómez Vecino
Beatriz Saenz Narciso
Bianca Paz Renau Mínguez
Blanca Nieto Bernáldez
Blanca Rodríguez Martín
Carlos Alberto Lugo Godoy
Carlos Fabián Castaño Romero
Carlos Llanes Álvarez
Carlos María Fernández Giménez
Catia Daniela Quintás Faria
Conrad Friedrich Droste
Conrado Jorge Finnigan
Cristina Blanco Dorado
Cristina Carbonell Muñoz
Cristina Cigarral García
Cristina Egido Turrión
Cristina Jiménez Sánchez
Cristina Robles Lázaro
Cristina Sofía Baz Villoria
Dalia Salim Quwaider
Daniela Pinto Damasceno
David Barreda Gago
Elena Blanco Álvarez
Elena De Dios Rodríguez
Elena Díaz Peláez
Elena Martín Doncel
Elisa Calvo Jiménez
Elizabeta De Los Ángeles Rojas Ricardo
Esperanza Macarena Algarín Pachón
Ester Laso Lucas
Eva García Piney
Eva María Diez Baeza
Eva María Rodríguez Beltrán
Félix López Cadenas
Francisco Javier Ortega García
Francisco José Campos Laborie
Giselle Castillo Villa
Guillermo Rodríguez Hernández
Idania De Los Santos Ventura
Idoia García Ramírez
Ignacio Campillo Marcos
Ignacio Criado García
Inmaculada Serramito Gómez
Irene Andrés Ramos
Javier Fernández Mateos
Javier Ignacio Muñoz González
Jendri Manuel Pérez Perozo
Jésica Pérez García
Jesús María Hernández Sánchez
Josepa Sebastia Morant
Juan Alejandro Cascón Hernández
Juan Carlos Caballero Berrocal
Juan Luis Muñoz Sánchez
Julie Milena Galvis Jiménez
Julio Davila Valls
Kamila Magdalena Janusz
Laura Clavaín Mateo
Laura Gómez Hernández
Laura Manzanedo Bueno
Laura Ruiz Remolina
Leticia Gómez Sánchez
Lidia Iglesias Bayo
Lorena Bellido Hernández
Lucia Pinzón Uribe
Lucía Ruiz Roca
Luis Francisco Lorenzo Martín
Luis García Martín
Luis Hernández Cano
Luis Martínez Roldán
Luzalba Del Carmen Sanoja Flores
M.De La Paz Vaquero Herrero
Mª Concepción Piñero Pérez
Manuel Domínguez Gómez
Marco López Zubizarreta
María Amparo Mateos Diego
María Carmela Rodríguez Martín
María De Los Ángeles De Pedro Muñoz
María Del Pilar Leoz
María Fernández Regueras
María García Álvarez

María González González
María González Muñoz
María González-Tablas Pimenta
María Hernández Sánchez
María Isabel Prieto Conde
María Luisa Pérez García,
María Mercedes Alperi López
María Pilar Liceras Boillos
María Teresa Cano Mozo
María Teresa González Sánchez
Marta Gómez Iglesias
Marta Martín Izquierdo
Martina Vanova
Mercedes Garzón Martínez
Miguel Quijada Alamo
Miriam López Parra
Mónica Morais Gomes Ferreira
Natalia Felipe Medina
Natalia Sánchez Aguadero
Noelia Dasilva Freire
Noemí Muñoz García
Oriana López Godino
Óscar González Velasco
Óscar José Ferré Bermejo
Pablo Álvarez Vega
Pablo Segovia Alonso
Paola María Fradejas Salazar
Paula Díez García
Pedro Daniel Perdiguero Martín
Pedro Mogollón Arroyo
Rafael Hipola Muñoz
Ramón Rodríguez Borrego
Raquel Moreno Mayordomo
Raquel Villamuera Del Sordo
Raúl García González
Raúl García Marcos
Rebeca Sánchez González
Rocío Fuentes Mateos
Ronald Paul Macías Casanova
Rosario Alonso Domínguez
Rubén Fernández Caloto
Santiago José Bueno Fortes
Sara García Alonso
Sara Gutiérrez Herrero
Sara Ortiz Rivero
Silvia Preciado Pérez
Silvio Ragozzino
Soledad Medina Valdivieso
Sonia Gómez Gaspar
Sonia Rodríguez Fernández
Soraya Jodra Sánchez
Soraya Merchán Gómez
Susana Hernández García
Svetlana Zhilina
Vanesa Álvarez Álvarez
Verónica González De La Calle
Verónica Temprado Moreno
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2017/2018

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Ana María Orive Ramos
Ana Marín Quilez
Ana Rico Sorli
Andrea Díaz Tejedor
Andrés Achury Murcia,Carlos
Andres Barbosa Ventura
Aránzazu García Mateo
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Isabel Valriberas Herrero
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Jose Javier Garrido Sánchez
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María Isabel Prieto Conde
María Jesús Canal Boyero
María Mercedes Alperi López
María Teresa Cano Mozo
María Teresa González Sánchez
Marta Alonso Fernández De Gatta
Marta Gómez Iglesias
Marta Martín Izquierdo
Martina Vanova
Mercedes Garzón Martínez
Miguel Quijada Álamo
Miriam López Parra
Monica Baile González
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Natalia Eugenia Espinosa Lara
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Pablo Segovia Alonso
Pamela Vázquez Cárdenas
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Rachid Taouil
Rafael Hipola Muñoz
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Rosa Ana Marcos Sánchez
Rosario Alonso Domínguez
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Sara Teresa González De Tena-Dávila
Silvia Preciado Pérez
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Svetlana Zhilina
Tamara Jiménez Solas
Vega Riesco Cuadrado
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Yuliana Mónica Jamanca Poma

TRAINING ACTIVITIES

DOCTORAL THESES

PhD STUDENT	DIRECTOR	TITLE	DATE
Carmen González Payo	Rogelio González Sarmiento / Emilia Fernández López	Estudio clínico y genético en carcinoma basocelular esporádico y asociado a síndrome de Gorlin	16/01/2016
José Ignacio Martín González	José Ignacio Herrero Herrero / Rogelio González Sarmiento	Distribución de polimorfismos de genes de la autofagia y reparadores del DNA en una población anciana hospitalizada	27/01/2016
Jorge Labrador Gómez	José Ramón González Porras /Mª Dolores Caballero Barrigón	Complicaciones trombóticas y hemorrágicas relacionadas con el trasplante alogénico de progenitores hematopoyéticos. Incidencia, factores de riesgo y significado pronóstico	27/01/2016
Elena Sebastián Pérez	Marcos González Díaz / Miguel Alcoceba Sánchez / Ramón García Sanz	Polimorfismos genéticos, alteraciones moleculares y reordenamientos clonotípicos en el linfoma B difuso de célula grande. Correlaciones clínico-biológicas	01/02/2016
Ana Cristina Antoli Royo	Ángel Sánchez Rodríguez / Rogelio González Sarmiento	Correlación fenotipo-genotipo de variantes génicas en el Síndrome Metabólico	02/02/2016
María Jara Acevedo	Alberto Orfao de Matos / Andrés Celestino García Montero	Mastocitosis sistémica y mutación de Kit: Frecuencia, grado de afectación de la hematopoyesis y comportamiento clínico y biológico de la enfermedad	03/02/2016
Juan Flores Montero	José Alberto Orfao de Matos Correia e Vale	Nuevas estrategias metodológicas y de análisis de datos de citometría de flujo aplicadas al diagnóstico y clasificación de hemopatías malignas.	04/02/2016
Ismael Calero Paniagua	Javier del Pino Montes / Rogelio González Sarmiento	Polimorfismos de los genes reguladores de la angiogénesis en la enfermedad ósea de Paget	04/02/2016
Rosa Ana Iglesias López	Rogelio González Sarmiento / José Manuel Miralles García	Estudio de polimorfismos genéticos en tiroiditis autoinmune	05/02/2016
José Ángel Martín Oterino	Rogelio González Sarmiento / Francisco Javier Martín Vallejo	Caracterización genotípica de SNPs de PPAR?, endotelina, VAV-3, IL-10, IL-12B y GNB3, asociados a factores clínicos y bioquímicos como predictores de la evolución de la hipertensión arterial	08/02/2016
Ricardo Usategui Martín	Rogelio González Sarmiento / Javier del Pino Montes	Estudio molecular de la enfermedad ósea de Paget	25/02/2016
Eduardo Ávila Espinoza	Juan Jesús Cruz Hernández / Feliciano Sánchez Domínguez	Funcionalidad familiar y calidad de vida en pacientes oncológicos que reciben cuidados paliativos. Un estudio epidemiológico	04/03/2016
María del Mar Sáez Freire	María Eugenia Muñoz Bermejo / Jesús Pérez Losada	Identificación de determinantes genéticos comunes a la susceptibilidad del cáncer de mama y al envejecimiento mediante una estrategia de biología de sistemas	11/03/2016
Miguel Ángel González Hierro	Rogelio González Sarmiento	La gestión de la Incapacidad Temporal, veinte años de reformas normativas	18/03/2016
Marta Fernández Prieto	Rogelio González Sarmiento	Estudio de la ruta de la autofagia en carcinoma de endometrio esporádico	08/04/2016
David da Silva Moura	Pedro A. Lazo-Zbikowski Taracena	Roles of human VRK1 Ser-Thr kinase in the regulation of cell proliferation	08/04/2016
Marta González de Arriba	Emilia Fernández López /Mª Belén Vidriales Vicente	Caracterización inmunofenotípica del sistema inmune en pacientes con vitíligo y/o halo nevus	09/05/2016

PhD STUDENT	DIRECTOR	TITLE	DATE
María Lourdes Martín Martín	Alberto Orfao de Matos Correia e Vale / Julia Almeida Parra	Caracterización clínica y biológica de la neoplasia de célula dendrítica plasmocitoide blástica y comparación con su contrapartida celular normal	10/05/2016
Sara Alonso Álvarez	Marcos González Díaz / Miguel Alcoceba Sánchez / Mª Dolores Caballero Barrigón / Ramón García Sanz.	Caracterización clínica y biológica del proceso de transformación de los síndromes linfoproliferativos indolentes: Análisis histológico, fenotípico y molecular	31/05/2016
Luis Alberto Guardado Sánchez	Dolores Caballero Barrigón/ Juan Luis Gómez González/ Alejandro Martín García-Sancho	Estudio clínico-biológico de los linformas No Hodgkin con afectación nodal y extranodal en cabeza y cuello	02/06/2016
Jesús Orejuela Rodríguez	Juan Jesús Cruz Hernández / José Ignacio Calvo Arenillas / Ana Mª Martín Nogueras	Influencia de las técnicas de facilitación neuromuscular propioceptiva sobre la musculatura respiratoria en una población de mujeres mayores	23/07/2016
Teresa Da Conceiçao Lopes Ramos	Fermín Sánchez-Guijo Martín / Luis Ignacio Sánchez-Abarca Bernal / Mª Consuelo del Cañizo Fernández- Roldán	Role of Mesenchymal stromal cells and their extracellular vesicles microRNAs in JAK2 Myeloproliferative Neoplasms	05/09/2016
Ruslan Al-Ali	Rogelio González Sarmiento	Analysis of Autophagy in Lung Cancer N007345316	12/09/2016
María del Rosario Vidal Tocino	Juan Jesús Cruz Hernández/ Rogelio González Sarmiento	Caracterización clínico-biológica de pacientes con cáncer colorrectal. Cribado poblacional de síndrome de Lynch	13/09/2016
Mª Elena Pérez Losada	Miguel Cordero Sánchez / Jesús Pérez Losada / Carmen Patino Alonso.	Identificación de marcadores del pronóstico de sepsis en pacientes ingresados en la unidad de cuidados intensivos	16/09/2016
Elena Bueno Martínez	Rogelio González Sarmiento	Estudio de genes y proteínas de autofagia en tumores del sistema nervioso central	18/11/2016
Carlos Mª Fernández Giménez	Alberto Orfao /Sergio Matarraz Sudón	Caracterización biológica de hemopatías malignas mieloides frente a su contrapartida normal: relación con las vías de transformación maligna	19/12/2016
Vanesa Álvarez Álvarez	Andrés Avelino Bueno Núñez / María Sacristán Martín	Implicación de ubiquitín-proteasas en la regulación de PCNA en eucariotas unicelulares	17/03/2017
Alba Juanes García	Miguel Vicente-Manzanares	A regulatory motif in non-muscle myosin II-B controls its assembly and determines its role in plasma membrane protrusion, adhesion dynamics and migratory polarization	19/04/2017
María Hernández Sánchez	Jesús María Hernández Rivas /Ana Eugenia Rodríguez Vicente /María Rocío Benito	Analysis of the molecular heterogeneity and disease evolution in chronic lymphocytic leukemia by combining high-throughput genomic and transcriptomic technologies	31/05/2017
Alvaro Ortega Carrión	Miguel Vicente-Manzanares	Function of the molecular motor non-muscle myosin II-B in mechanical regulation of T cell activation and the immune synapse	23/06/2017
Cristina Jiménez Sánchez	Ramón García Sanz / Mª Eugenia Alonso Sarascate / Marcos González Díaz	Caracterización molecular de la macroglobulinemia de Waldenström: Implicaciones en el diagnóstico, pronóstico y transformación histológica	03/07/2017
Javier Fernández Mateos	Juan Jesús Cruz / Rogelio González Sarmiento	Estudio Molecular del carcinoma escamoso de cabeza y cuello en la población española	07/07/2017
Rocío Aguilar Cuenca	Miguel Vicente-Manzanares	New regulatory mechanisms of the cellular functions of non-muscle myosin II	10/07/2017
Carmen González Payo	Juan Jesús Cruz Hernández / Antonio Santamaría Abad	Estudio de la incidencia de tumores sólidos en la provincia de Salamanca durante el trienio 2009-2011	21/07/2017

PhD STUDENT	DIRECTOR	TITLE	DATE
Nerea Sánchez Sánchez	Juan Jesús Cruz Hernández / Feliciano Sánchez Domínguez	Análisis de los factores sociodemográficos que pueden influir en el lugar de fallecimiento de os pacientes con cáncer en la provincia de Salamanca durante el periodo 1998-2008	21/07/2017
Paula Díaz García	Manuel Fuentes / Alberto Orfao	Caracterización proteómica de la Célula B tumoral de la leucemia linfocítica crónica y su contrapartida	21/07/2017
Athenea Pascual Rodríguez	Rogelio González Sarmiento / Juan Luis García Hernández	Nuevas Aportaciones a la caracterización del cáncer de mama en mujeres jóvenes	27/07/2017
Pilar Liceras Boillos	Eugenio Santos / Fernando Calvo Baltanás	Estudio funcional de Sos1 y Sos2 in vivo e in vitro en la regulación de procesos fisiológicos y tumorales. Las proteínas Sos como dianas terapéuticas en cáncer	28/07/2017
Sara Ortiz Rivero	Carmen Guerrero Arroyo	Role of C3G in the diferentiation and maturation of Megakaryocytes	28/07/2017
Ana Alicia López Iglesias	Enrique Ocio San Miguel Mercedes Garayoa Berrueta / Marcos González Díaz	Evaluación preclínica de nuevas estrategias terapéuticas en neoplasias hematológicas	31/07/2017
Pedro Soria Carreras	Juan Jesús Cruz Hernández	Combinación de quimioterapia y radioterapia en el tratamiento del carcinoma de cérvix. Análisis de resultados en nuestro medio y estudio de la influencia de la duración del mismo en la supervivencia	01/09/2017
Diego García Cantero	Juan Jesús Cruz Hernández / Rosario Vidal Tocino	Evaluación de la situación física, psicosocial y laboral de los pacientes largos supervivientes de cáncer	04/09/2017
Beatriz Sáenz Narciso	Juan Cabello Pardos / Eva Mª Gómez Orte / María Sacristán Martín	C. elegans Integrator complex: Identification and analysis of a role beyond snRNA processing	04/09/2017
Conrad Friedrich Droste	Javier De Las Rivas	Bioinformatics to integrate protein and gene information in a relational context, application to human proteomic and transcriptomic data	04/09/2017
Blanca Rodríguez Martín	Juan Jesús Cruz	Deterioro Cognitivo inducido por la quimioterapia en pacientes diagnosticadas de cáncer de mama	05/09/2017
Adrián Blanco Gómez	Jesús Pérez Losada	Identificación de determinantes genéticos y moleculares de la evolución y la respuesta a la quimioterapia del cáncer de mama mediante el análisis de fenotipos intermedios	07/09/2017
Alberto Martín Lorenzo	Isidro Sánchez García	Estudio de la etiología de la leucemia linfoblástica aguda con el objetivo de establecer nuevas estrategias terapéuticas y profilácticas	07/09/2017
Purificación Sánchez Chaves	Juan Jesús Cruz Hernández / Feliciano Sánchez Domínguez	Análisis de la mortalidad por cáncer en la provincia de Salamanca durante el período 1999-2008	12/09/2017
Carlos Cruz Rodríguez	Juan Jesús Cruz Hernández / Dolores Ludeña de la Cruz	Alteraciones moleculares detectadas por inmunohistoquímica en cáncer epidermoides de cabeza y cuello	12/09/2017
Tatiana Elisabeth Carranco Medina	Javier del Pino Montes / Rogelio González Sarmiento	Síndrome de fragilidad en pacientes con fractura vertebral. Asociación con genes de autofagia	14/09/2017
Elisabet Martín García	Fermín Sánchez-Guijo Martín / Luis Ignacio Sánchez-Abarca / Emiliano Hernández Galilea /	Estudio de la capacidad terapéutica de las células mesenquimales administradas por vía subconjuntival en el tratamiento de la enfermedad injerto contra receptor ocular en un modelo murino optimizado	15/09/2017
María Luisa Pérez García	Rogelio González Sarmiento / Miguel Pericacho Bustos	Actualización Clínica y Molecular de la telangiectasia hemorrágica hereditaria en Salamanca	16/09/2017
Víctor Miguel Martín Granado	Carmen Guerrero Arroyo / José Ramón González Porras	Papel de C3G plaquetario en angiogénesis y metástasis tumoral	23/10/2017
Idoia García Ramírez	Isidro Sánchez García	Neoplasias Linfoides, célula de origen e identidad tumoral	15/12/2017

CONFERENCES MEETINGS & SCIENTIFIC COURSES

1 • VIII SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER Y TERAPIAS PERSONALIZADAS

(http://www.cicancer.org/es/eventos/176/viii-simposium-bases-biologicas-del-cancer-y-terapias-personalizadas)

Date: 19/05/2016 to 20/05/2016

Director: Prof. Juan Jesús Cruz Hernández (Hospital Clínico Universitario / Universidad de Salamanca)

Coordinator: Dr. César A. Rodríguez (Hospital Clínico Universitario / Universidad de Salamanca)

Place: Centro de Investigación del Cáncer de Salamanca. Salón de Actos, Campus Miguel de Unamuno s/n. Salamanca

Program: *(http://www.cicancer.org/uploads/archivos/ProgramaFinal_BasesBiologicas2016.pdf)*

MAY 19, 2016

10:00-10:15
BIENVENIDA Y PRESENTACIÓN
Prof. Juan Jesús Cruz, Hospital Clínico Universitario, Salamanca / Prof. Eugenio Santos de Dios, Centro de Investigación del Cáncer, Salamanca / Dr. Rogelio González Sarmiento, Departamento de Medicina, Universidad de Salamanca

10:15-11:00
CONFERENCIA INAUGURAL
Moderadores: Dr. Germán Martín, Hospital Clínico Universitario, Salamanca / Dr. Ramón Colomer, Hospital Universitario de La Princesa, Madrid / Prof. Rogelio Gonzalez Sarmiento, Director Instituto de Investigación Biomédica de Salamanca

Secuenciación Masiva en Oncología. ¿Lista para su uso en la Práctica Clínica? / Dr. Enrique de Álava, Hospital Universitario Virgen del Rocío, Sevilla, Área Sanitaria, Osuna

11:00-11:40
CONFERENCIA EDUCACIONAL 1
Moderadores: Dr. Rafael López, Complejo Hospitalario Universitario, Santiago de Compostela / Dr. Fernando Rivera, Hospital Universitario Marqués de Valdecilla, Santander

La Biopsia Líquida: Desarrollo Actual y Perspectivas Futuras / Dr. Jesús García Foncillas, Fundación Jiménez Díaz, Madrid

11:40-12:00 Visita a pósters expuestos

12:00-13:00
MESA REDONDA 1: Cáncer ginecológico
Moderadores: Dra. Beatriz Esteban, Complejo Asistencial de Segovia / Dr. José Valero Álvarez, Complejo Asistencial de Zamora

Cáncer de Ovario: De la Biología Molecular al Tratamiento Multidisciplinar / Dr. Andrés Redondo, Hospital Universitario La Paz, Madrid

Tratamiento del Cáncer de Cérvix en 2016 / Dra. Amalia Gómez Bernal, Hospital Clínico Universitario, Salamanca

13:00-13:45
CONFERENCIA EDUCACIONAL 2
Moderadores: Dr. Atanasio Pandiella, Centro de Investigación del Cáncer, Salamanca / Dr. Andrés García Palomo, Complejo Asistencial Universitario, León

Oncología Traslacional I: «Identificando vulnerabilidades oncogénicas en cáncer» / Dr. Alberto Ocaña, Hospital Universitario, Albacete

15:00-15:40
CONFERENCIA EDUCACIONAL 3
Moderadores: Dr. César A. Rodríguez, Hospital Clínico Universitario, Salamanca / Dr. Antonio Antón, Hospital Universitario Miguel Servet, Zaragoza

Plataformas Genómicas en Cáncer de Mama. Más allá de su uso en Adyuvancia / Dr. Emilio Alba, Hospital Clínico Virgen de la Victoria, Málaga

15:40-17:00
MESA REDONDA 2: Cáncer de mama
Moderadores: Prof. Juan Jesús Cruz, Hospital Clínico Universitario, Salamanca / Dra. Ana Lluch, Hospital Clínico Universitario, Valencia

Hormonoterapia y Nuevas Terapias Biológicas en Cáncer de Mama Avanzado: Una realidad / Dr. Diego Soto de Prado, Hospital Clínico Universitario, Valladolid

Cáncer de Mama HER2 positivo: Selección Personalizada del Tratamiento: ¿Es Posible? / Dr. César A. Rodríguez, Hospital Clínico Universitario, Salamanca

Redefiniendo el Papel de la Quimioterapia en Cáncer de Mama / Dr. Jesús García Mata, Hospital Santa María de Nai, Ourense

17:00-17:40
CONFERENCIA EDUCACIONAL 4
Moderadores: Dr. Guillermo López Vivanco, Hospital Universitario de Cruces, Bilbao / Dr. Rogelio González Sarmiento, Departamento de Medicina, Universidad de Salamanca

30 Años del Tratamiento Sistémico del Cáncer de Cabeza y Cuello Localmente Avanzado. Avances y Retos Pendientes / Dra. Elvira del Barco, Hospital Clínico Universitario, Salamanca

17:40-18:00 Visita a pósters expuestos

18:00-19:00
MESA REDONDA 3: Cáncer colorrectal
Moderadores: Dr. Eduardo Díaz Rubio, Hospital Clínico Universitario San Carlos, Madrid / Dr. Enrique Aranda, Hospital Universitario Reina Sofía, Córdoba

Clasificación Molecular del Cáncer de Colon: Una Visión Actualizada / Dr. Rodrigo Dienstmann, Hospital Universitari Vall d'Hebron, Barcelona

Estrategia Terapéutica del Cáncer Colorrectal Avanzado: Selección individualizada del Tratamiento / Dra. Pilar García Alfonso, Hospital General Universitario Gregorio Marañón, Madrid

19:00-20:00
MESA REDONDA 4: Cáncer de páncreas y net
Moderadores: Dr. Alfredo Carrato, Hospital Universitario Ramón y Cajal, Madrid / Dr. Emilio Fonseca, Hospital Clínico Universitario, Salamanca

Novedades en el Tratamiento del Cáncer de Páncreas Avanzado / Dr. Juan Carlos Torrego, Hospital Universitario Río Hortega, Valladolid

Abordaje Clínico de los Tumores Neuroendocrinos Gastroenteropancreáticos / Dr. Miguel Navarro, Hospital Clínico Universitario, Salamanca

MAY 20, 2016

09:20-10:40
MESA REDONDA 5: Melanoma maligno
Moderadores: Dr. Salvador Martín Algarra, Clínica Universitaria, Pamplona / Dr. Alberto Arízcun, Complejo Asistencial Universitario, Palencia

Inmunoterapia en Melanoma Maligno: Rompiendo Barreras / Dr. Alfonso Berrocal, Hospital General Universitario, Valencia

Nuevas Moléculas, Nuevas Combinaciones. Impacto en la Supervivencia / Dr. Enrique Espinosa, Hospital Universitario La Paz, Madrid

«En Resumen»: Visión Integral del Tratamiento en Pacientes con MM avanzado / Dra. Yolanda López Mateos, Complejo Asistencial de Zamora

10:40-12:00
MESA REDONDA 6: Cáncer de pulmón
Moderadores: Dr. Carlos Camps, Hospital General Universitario, Valencia / Dra. Pilar Garrido, Hospital Universitario Ramón y Cajal, Madrid

La Inmunoterapia como nuevo Paradigma en el Tratamiento del CPNM Avanzado / Dra. Enriqueta Felip, Hospital Universitari Vall d'Hebrón, Barcelona

Otras Terapias Biológicas en CPMN: Una visión actualizada / Dra. Dolores Isla, Hospital Clínico Universitario Lozano Blesa, Zaragoza

«En Resumen»: Visión Integral del Tratamiento en Pacientes con CPNM avanzado / Dr. Carlos García Girón, Complejo Asistencial Universitario, Burgos

12:00-12:20 Visita a posters expuestos

12:20-12:50
CONFERENCIA EDUCACIONAL 5
Moderadores: Dr. Javier Cassinello, Hospital General Universitario, Guadalajara / Dr. Isidro Sánchez, Centro de Investigación del Cáncer, Salamanca

Oncología Traslacional II / Dr. David Olmos, Unidad CNIO-IBIMA de Investigación en Cáncer de Próstata, Centro Nacional de Investigaciones Oncológicas, Madrid e Instituto de investigaciones Biomédicas, Málaga

12:50-13:50
MESA REDONDA 7: Cáncer genitourinario
Moderadores: Dr. Vicente Guillem, Instituto Valenciano de Oncología, Valencia / Dra. Rocío García Domínguez, Hospital Clínico Universitario, Salamanca

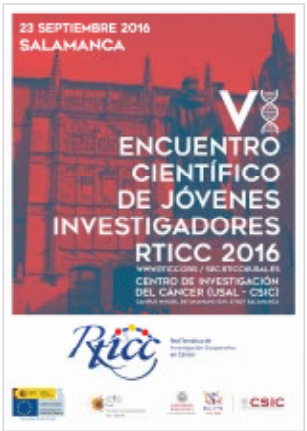
Cáncer de Próstata: Redefiniendo la Secuencia Óptima del Tratamiento / Dra. Rebeca Lozano, Hospital Clínico Universitario, Salamanca

Cáncer Renal: Completando el «Puzzle» de las Terapias Biológicas: ¿Faltan Piezas? / Dr. José Ángel Arranz, Hospital General Universitario Gregorio Marañón, Madrid

13:50-14:20
CONFERENCIA EDUCACIONAL 6
Moderador: Dr. José Enrique Alés, Hospital de Nuestra Señora de Sónsoles, Ávila

Cáncer y Eventos Óseos: ¿Del simple soporte al Aumento de Supervivencia? / Dra. Maribel Ruiz, Complejo Asistencial Universitario, Palencia

14:35-14:45
CONCLUSIONES Y CIERRE
Prof. Juan Jesús Cruz, Hospital Clínico Universitario, Salamanca / Dr. César A. Rodríguez, Hospital Clínico Universitario, Salamanca



2 • VI ENCUENTRO CIENTÍFICO DE JÓVENES INVESTIGADORES DE LA RED TEMÁTICA DE INVESTIGACIÓN COOPERATIVA EN CÁNCER 2016

(http://www.rticc.org/noticia20.php)

Date: 23/09/2016

Place: Centro de Investigación del Cáncer de Salamanca. Salón de Actos, Campus Miguel de Unamuno s/n. Salamanca

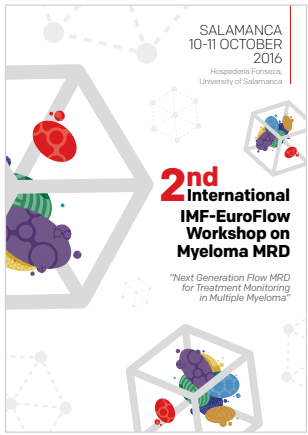
Summary: The Executive Committee of the RTICC a proposal of the coordinator of the Training and Mobility RTICC program has agreed to organize the VI Scientific Meeting of Young Researchers from the Spanish Cancer Network (RTICC) 2016.

The general objectives of the Training and Mobility RTICC program included in the application of the 2012 to funding a new Spanish Cancer Network are (i) to facilitate and to enhance collaborative research activities of the researchers of the RTICC; (ii) to optimize and to make efficient use of the budgetary resources available for training within of the cancer network, (iii) to improve the number and quality of training courses offered to the groups and institutions involved in RTICC, and finally (iv), to manage, call and finance various programs specifically designed to attain objectives mentioned above.

Specific objectives of the Training and Mobility RTICC program, are to promote and facilitate interaction of the youngest researchers working at RTICC groups and their participation in the dissemination of their results of your work within the RTICC. For this proposal RTICC organize an annual meeting of Young Researchers from RTICC, meeting wherein said researchers will present and discuss with the other groups the results obtained in their projects within the network and exchange experiences and proposals with other researchers from other groups to develop their project within the network.

With this meeting the Committee of the Training and Mobility RTICC program aims to provide a new opportunity to deepen these three goals: formation, participation and scientific interaction between groups. In short, this is an opportunity to learn and publicize the scientific work that young members RTICC been carried out in recent years. We hope that this activity is a success and serve as a platform to promote collaboration among the various groups in the network through knowledge and interaction among its younger members.

Program: *(http://www.rticc.org/docs/noticias/programa-vi-encuentro-cientifico-jovenes-investigadores-rticc.pdf)*



3 • 2ND INTERNATIONAL IMF-EUROFLOW WORKSHOP ON MYELOMA MRD «NEXT GENERATION FLOW MRD FOR TREATMENT MONITORING IN MULTIPLE MYELOMA»

http://www.cicancer.org/es/eventos/214/2nd-international-imf-euroflow-workshop-on-myeloma-mrd-next-generation-flow-mrd-for-treatment-monitoring-in-multiple-myeloma

Date: 10/10/2016 to 11/10/2016

Place: Hospedería Fonseca, University of Salamanca

Organizers: Prof. Dr. Alberto Orfao and Dr. Brian Durie. The International Myeloma Foundation (IMF) and the EuroFlow Consortium

Summary: The workshop aims to provide a space for the update and discussion of the new and recent advances in MM MRD monitoring, specially focusing on the innovative Next Generation Flow cytometry (NGF) approach developed through the collaborative work performed within the Black Swan Research Initiative.

Participants will have the opportunity to interact with world class speakers whose work contributes to define the standards in MM therapeutics and

after-treatment monitoring of myeloma patients.

In addition, there will be also the opportunity for a «hands-on» training on the NGF approach including instrument set-up, sample processing and data analysis.

Program: *(http://www.cicancer.org/uploads/archivos/Program__2nd_International_IMF-EuroFlow_Workshop.10-11_Oct._2016_(2).pdf)*


Seminario sobre Técnicas de Super Resolución

que tendrá lugar en el CENTRO DE INVESTIGACIÓN DEL CÁNCER el próximo día 11 de Enero de 2017 a las 12:30h

Ponente: Juan Luis Monteagudo, Product Manager de Microscopía Confocal y Sistemas de Super Resolución de Leica Microsistemas.

- Técnicas de Super Resolución.
- Soluciones Leica en Super Resolución:
- Sistema de Super Resolución Leica TCS SP8 STED 3X

http://www.leica-microsystems.com/products/confocal-microscopes/details/product/leica-tcs-sp8-sted-one/

- Resolución obtenida mediante métodos ópticos
- Resolución hasta 50 nm XY
- Aumento de resolución en XY y Z.
- Basado en la plataforma confocal Leica TCS SP8
- Total flexibilidad espectral
- Super resolución en microscopía de célula viva
- Sistema modular que puede ir creciendo según las necesidades.
- Abierto a futuras necesidades y aplicaciones. Actualizaciones sin restricciones in situ.
- Alta precisión y reproducibilidad

4 • TÉCNICAS DE SUPER RESOLUCIÓN

(http://www.cicancer.org/es/eventos/219/tecnicas-de-super-resolucion)

Date: 11/01/2017

Place: Centro de Investigación del Cáncer de Salamanca. Salón de Actos, Campus Miguel de Unamuno s/n. Salamanca

Speaker: Juan Luis Monteagudo (Leica Microsistemas)

Summary: Nanoscopy has revolutionized the study of subcellular architecture and dynamics and is on its way to becoming the new gold standard in fluorescence imaging.

The fully integrated STED (STimulated Emission Depletion) systems Leica TCS SP8 STED 3X and Leica TCS SP8 STED ONE meet the requirements of daily research and provide fast, intuitive, and purely optical access to structural details far beyond the diffraction limit.

Resolution becomes tunable in x, y and z.

Visualizing the precise 3D localization of molecules and structures is crucial for a better understanding of cellular processes. The Leica SR GSD 3D widefield fluorescence microscope based on GSD (Ground State Depletion) or dSTORM (Direct STochastical Optical Reconstruction Microscopy) technology offers not only 2D, but also 3D super-resolution imaging – with the highest precision, reproducibility and maximum possible resolution in widefield microscopy so far. The Leica SR GSD 3D is based on a fully automated TIRF system. As a multi-functional system, it gives researchers the freedom to tailor the system exactly to their applications in live cell or advanced fluorescence imaging.

HyVolution 2 is super-resolution for every specimen and every experiment. Study the rapid dynamics of living cells or colocalization. Image multiple fluorophores simultaneously and capture intracellular details with resolution down to 140 nm.

With HyVolution 2, the trade-off between imaging speed, resolution, or number of colors is a thing of the past. Now, all your confocal experiments are represented with the greatest level of detail.

Program: *http://www.cicancer.org/uploads/archivos/seminario_super_resolucion.pdf*

5 • ACTIVATE SCIENCE

(http://www.cicancer.org/es/eventos/223/humanity-in-a-dish-key-technologies-for-disease-modeling-with-human-pluripotent-stem-cells-cell-culture-environment-and-stemcells)

Date: 08/03/2017

Place: Centro de Investigación del Cáncer de Salamanca. Salón de Actos, Campus Miguel de Unamuno s/n. Salamanca

Summary: Activate Science events are aimed at all laboratory personnel, including anyone who uses or purchases products. It is a great opportunity to network and speak directly at a customer's location. Delegates have commented that they value being able to talk to suppliers in a relaxed atmosphere away from the laboratory. Attendees also attend seminars covering topics relevant to their work today, learning about new techniques and developments to enable them to make the world healthier, cleaner and safer.

Stands de los principales fabricantes del mercado: Thermo Fisher, Eppendorf, Ohaus-Metler Toledo, GE Healthcare, Corning-Falcon, Control Company, Acros Organics, Fisher Chemical, Fisher Bioreagents…

They are include
- Product exhibitions from leading scientific suppliers
- Showcasing equipment, plastics, reagents & kits
- Technical talks on Key Applications
- «Speed demos»
- Product samples
- Free refreshments

Lectures:
- Humanity in a dish. Key Technologies for disease modeling with human pluripotent stem cells
- 3D Cell Culture environment and Stemcells.

6 • IX SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER Y TERAPIAS PERSONALIZADAS

(http://www.cicancer.org/es/eventos/227/ix-simposium)

Date: 18/05/2017 to 19/05/2017

Director: Prof. Juan Jesús Cruz Hernández (Hospital Clínico Universitario / Universidad de Salamanca)

Coordinator: Dr. César A. Rodríguez (Hospital Clínico Universitario / Universidad de Salamanca)

Place: Centro de Investigación del Cáncer de Salamanca. Salón de Actos, Campus Miguel de Unamuno s/n. Salamanca

Program:

MAY 18, 2017

09:30-09:45
BIENVENIDA Y PRESENTACIÓN
Prof. Juan Jesús Cruz, Hospital Clínico Universitario, Salamanca / Dr. Rogelio González Sarmiento, Departamento de Medicina, Universidad de Salamanca

09:45-10:15
CONFERENCIA INAUGURAL
Prof. Eugenio Santos, Centro de Investigación del Cáncer, Salamanca

10:15-11:00
CONFERENCIA EDUCACIONAL 1. Bases biológicas de la moderna inmunoterapia en el tratamiento del cáncer
Moderadora: Dra. Ruth Vera, Complejo Hospitalario de Navarra, Pamplona / Dr. Fernando Rivera, Hospital Universitario Marqués de Valdecilla, Santander

La Biopsia Líquida: Desarrollo Actual y Perspectivas Futuras / Dr. Jesús García Foncillas, Fundación Jiménez Díaz, Madrid

11:00-11:40
CONFERENCIA EDUCACIONAL 2. Biopsia Líquida. ¿Lista para su uso en práctica clínica?
Moderador: Dr. Rafael López, Complejo Hospitalario Universitario de Santiago
Discusión: Dr. Jesús Pérez Losada, Instituto de Biología Molecular y Celular del Cáncer (IBMCC), CSIC-Universidad de Salamanca

Revisión de la evidencia / Dr. Ignacio Matos, Hospital Universitari Vall d'Hebron, Barcelona

Experiencia del Hospital Clínico Universitario de Salamanca / Dra. Rebeca Lozano, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid

12:00-13:10
MESA REDONDA 1: CÁNCER GINECOLÓGICO
Moderador: Dr. José Valero Álvarez, Complejo Asistencial de Zamora
Discusión: Dra. Beatriz Esteban, Complejo Asistencial de Segovia

Cáncer de ovario: De la biología molecular al tratamiento multidisciplinar en el año 2017 / Dr. Antonio González Martín, MD Anderson Cancer Center, Madrid

Avances terapéuticos en el cáncer de cérvix / Dra. Ana de Juan, Hospital Universitario Marqués de Valdecilla, Santander

13:00-13:55
CONFERENCIA EDUCACIONAL 3. Nuevas estrategias diagnósticas y terapéuticas de los tumores de origen desconocido
Moderador: Dr. Germán Martín, Hospital Clínico Universitario de Salamanca
Discusión: Dr. Carlos García Girón, Complejo Asistencial Universitario de Burgos
Ponente: Dr. Federico Longo, Hospital Universitario Ramón y Cajal, Madrid

15:00-15:40
CONFERENCIA EDUCACIONAL 4. Perfiles de expresión génica en cáncer de mama. Situación actual y vías de desarrollo
Moderador: Dr. Jesús García Mata, Hospital Santa María de Nai, Ourense
Discusión: Dr. Antonio Antón, Hospital Universitario Miguel Servet, Zaragoza
Ponente: Dr. Emilio Alba, Hospital Universitario Virgen de la Victoria, Málaga

15:40-17:00
MESA REDONDA 2: Cáncer de mama
Moderador: Miguel Martín, Hospital General Universitario Gregorio Marañón, Madrid
Discusión: Dra. Ana Lluch, Hospital Clínico Universitario de Valencia

Nuevas estrategias en el tratamiento de cáncer de mama hormonosensible / Dr. Andrés García Palomo, Complejo Asistencial Universitario de León

Cáncer de mama HER2 positivo. Situación actual y perspectivas de futuro / Dr. César A. Rodríguez, Hospital Clínico Universitario de Salamanca

Cáncer de mama triple negativo. Avances y retos / Dra. Eva Ciruelos, Hospital Universitario 12 de Octubre, Madrid

17:00-17:40
CONFERENCIA EDUCACIONAL 5. Cáncer de cabeza y cuello. Aportaciones del TTCC. 2001-17
Moderador: Dr. Ricard Mesia, ICO Hospital Duran i Reynals, l'Hospitalet de Llobregat
Discusión: Dra. Elvira del Barco, Hospital Clínico Universitario de Salamanca
Ponente: Dr. Juan J. Cruz Hernández, Hospital Clínico Universitario de Salamanca

18:10-19:10
MESA REDONDA 3: Cáncer colorrectal
Moderador: Dr. Eduardo Díaz-Rubio, Hospital Clínico Universitario San Carlos, Madrid
Discusión: Dr. Enrique Aranda, Hospital Universitario Reina Sofía, Córdoba

Cáncer de colon en 2017: De la biología a la Clínica / Dr. Rodrigo Dienstmann, Hospital Universitari Vall d'Hebron, Barcelona

Estrategia terapéutica del cáncer colorrectal avanzado: Selección del tratamiento / Dra. Pilar García-Alfonso, Hospital General Universitario Gregorio Marañón, Madrid

19:10-20:10
MESA REDONDA 4: Cáncer de pancreas y net
Moderador: Dr. Alberto Arízcun, Complejo Asistencial Universitario de Palencia
Discusión: Dr. Emilio Fonseca, Hospital Clínico Universitario de Salamanca

Bases biológicas y opciones terapéuticas del cáncer de páncreas avanzado / Dr. Juan Carlos Torrego, Hospital Universitario Río Hortega, Valladolid

Avances en el diagnóstico y tratamiento de los tumores neuroendocrinos gastropancreáticos / Dr. Miguel Navarro, Hospital Clínico Universitario de Salamanca

MAY 19, 2016

09:20-10:20
MESA REDONDA 5: Melanoma Maligno. Nuevos paradigmas de tratamiento
Moderador: Dr. Salvador Martín Algarra, Clínica Universidad de Navarra, Pamplona
Discusión: Dr. Guillermo López Vivanco, Hospital Universitario de Cruces

Inmunoterapia: Actualización de resultados / Dra. Lorena Bellido, Hospital Clínico Universitario de Salamanca

Otras moléculas y combinaciones / Dr. Enrique Espinosa, Hospital Universitario La Paz, Madrid

10:20-11:20
MESA REDONDA 6: Cáncer de pulmón
Moderador: Dr. Carlos Camps, Hospital General Universitario de Valencia
Discusión: Dra. Pilar Garrido, Hospital Universitario Ramón y Cajal, Madrid

La inmunoterapia en el tratamiento del CPNM avanzado. Impacto en la práctica clínica actual / Dra. Enriqueta Felip, Hospital Universitari Vall d'Hebron, Barcelona

Otras terapias biológicas en CPMN: Selección de tratamiento / Dra. Dolores Isla, Hospital Clínico Universitario Lozano Blesa, Zaragoza

11:50-12:20
CONFERENCIA EDUCACIONAL 6. Oncología traslacional
Moderador: Dr. Pedro Lazo-Zbikowski, Instituto de Biología Molecular y Celular del Cancer (CISC), Salamanca
Discusión: Dr. Javier Cassinello, Hospital General Universitario de Guadalajara
Ponente: Dr. David Olmos, Centro Nacional de Investigaciones Oncológicas, Madrid

12:20-12:50
CONFERENCIA EDUCACIONAL 7. Oncología básica
Moderador: Dr. José Enrique Alés, Hospital de Nuestra Señora de Sónsoles, Ávila
Discusión: Dr. Atanasio Pandiella, Centro de Investigación del Cáncer, Salamanca
Ponente: Dr. Isidro Sánchez, Centro de Investigación del Cáncer, Salamanca

12:50-13:50
MESA REDONDA 7: Cáncer genitourinario
Moderador: Dr. Vicente Guillem, Instituto Valenciano de Oncología, Valencia
Discusión: Dra. Rocío García Domínguez, Hospital Clínico Universitario, Salamanca

Cáncer de próstata avanzado. Secuencia óptima de tratamiento / Dra. Raquel Luque, Hospital Universitario Virgen de las Nieves, Granada

Optimización del tratamiento de cáncer renal avanzado con terapias biológicas / Dr. José Ángel Arranz, Hospital General Universitario Gregorio Marañón, Madrid

13:50-14:20
CONFERENCIA EDUCACIONAL 8. Cáncer y eventos óseos, más allá de un tratamiento de soporte
Moderador: Dr. Ignacio Chacón, Hospital Virgen de la Salud, Toledo
Discusión: Dr. Alfredo Carrato, Hospital Universitario Ramón y Cajal, Madrid
Ponente: Dra. Maribel Ruiz, Complejo Asistencial Universitario de Palencia

14:35-14:45
CONCLUSIONES Y CIERRE
Prof. Juan Jesús Cruz, Hospital Clínico Universitario, Salamanca / Dr. César A. Rodríguez, Hospital Clínico Universitario, Salamanca.

7 • NUEVAS HERRAMIENTAS EN LOS LABORATORIOS DE PATOLOGÍA. DIGITALIZACIÓN Y CUANTIFICACIÓN DE IMÁGENES

(http://www.cicancer.org/en/eventos/235/nuevas-herramientas-en-los-laboratorios-de-patologia-digitalizacion-y-cuantificacion-de-imagenes)

Date: 16/07/2017

Place: Centro de Investigación del Cáncer de Salamanca. Salón de Actos, Campus Miguel de Unamuno s/n. Salamanca

Organizers: María del Carmen García Macías / Manel Roldán, Director Comercial / Iván González. Especialista de producto ZEISS

Summary: The digitalization of histological preparations offers numerous benefits to the Laboratories dedicated to Comparative Pathology, Histopathology, Pathological Anatomy and Biobanks, since it provides these preparations with capacities that make them permanent and immutable, providing images of a high quality and configuring them with a traceability that is completely reproducible, adapting them to the requirements of ISO regulations.

The Comparative Molecular Pathology Service and the Coordinating Node of the BEOCyL, of the CIC in collaboration with the Zeiss Microscopy Company, are pleased to invite you to the introductory presentation of the Axioscan.Z1 port scanner.

The Axioscan.Z1 manages to automatically obtain high-resolution virtual slides for complete samples in brightfield, polarization and fluorescence. Its great flexibility and that of its software offers great possibilities for viewing and the possibility of sharing images as well as their subsequent analysis.

8 • LA PATENTABILIDAD DE LAS INVENCIONES EN EL ÁMBITO DE LA BIOTECNOLOGÍA

(https://transferencia.usal.es/jornada-la-patentabilidad-de-las-invenciones-en-el-ambito-de-la-biotecnologia/; http://www.cicancer.org/es/eventos/263/la-patentabilidad-de-las-invenciones-en-el-ambito-de-la-biotecnologia)

Date: 23/11/2017

Place: Centro de Investigación del Cáncer de Salamanca. Salón de Actos, Campus Miguel de Unamuno s/n. Salamanca

Organizer: Oficina de Transferencia de Resultados de Investigación (OTRI)

Collaborate : Fundación General de la USAL, FICUS y OEPM

Speaker: Gabriel González Limas. Head of the Area of Chemical Patents Department of Patents and Information Technology, Spanish Patent and Trademark Office)

Summary: Organized by the Office of Transfer of Research Results within the framework of the TCUE Program (Knowledge Transfer University Business of the Junta de Castilla y León), in collaboration with the General Foundation of the University of Salamanca, the Cancer Research Foundation of the University of Salamanca and the Spanish Patent and Trademark Office.

The talk, eminently practical, will be given by Gabriel González Limas (Head of the Area of Chemical Patents Department of Patents and Information Technology, Spanish Patent and Trademark Office), and will have a maximum duration of 2 hours, in which attendees can ask questions to the rapporteur on specific aspects of the patentability of this type of inventions.

9 • CÁNCER Y PREVENCIÓN DE RIESGOS LABORALES: SITUACIÓN ACTUAL Y CAPACIDADES I+D+I DE LOS CENTROS DE LA UNIVERSIDAD DE SALAMANCA

(http://www.cicancer.org/es/eventos/264/cancer-y-prevencion-de-riesgos-laborales-situacion-actual-y-capacidades-idi-de-los-centros-de-la-universidad-de-salamanca

Date: 29/11/2017

Place: Centro de Investigación del Cáncer de Salamanca. Salón de Actos, Campus Miguel de Unamuno s/n. Salamanca

Objectives:
- Promote knowledge of regulations and practice aimed at the evaluation and prevention of risks related to occupational exposure to carcinogens or mutagens.
- Promote the use of the I+D+i capabilities of the University of Salamanca in the field covered by the seminar.

Program:
1. Presentation. Enrique Cabero Morán. University of Salamanca.
2. Cancer and prevention of occupational risks: brief introduction to the European and national regulatory framework. Julio Cordero González. University of Salamanca.
3. Prevention of occupational risks and Cancer. Jerónimo Maqueda Blasco. National Institute of Safety, Health and Welfare at Work (Ministry of Employment and Social Security). Specialist in Occupational Medicine. Researcher and teacher. He has been director of the National School of Occupational Medicine (Carlos III Health Institute).
4. Colloquium: PRL, Cancer and I+D+i of the centers of the University of Salamanca. Fernando Gutiérrez Hernández will participate in the colloquium. Industrial hygienist with more than twenty years of professional experience. Quirón prevention.

SCIENTIFIC SEMINAR PROGRAM

DATE	TITLE	SPEAKER	AFFILIATION
14/01/2016	**Tackling Janus Kinases for the Treatment of Hematologic Malignancies**	Thomas Radimerski	Novartis Institutes for Biomedical Research [Basel, Switzerland]
21/01/2016	**Regulation of human kinase VRK1 by the reprogramming transcriptional factor Sox2 during cell proliferation and differentiation**	David S. Moura	CIC-IBMCC (CSIC-USAL) Lab. 4
27/01/2016	**Oncogenic signaling pathways and mechanisms of resistance in acute lymphoblastic leukemia**	Adolfo Álvarez Ferrando	Herbert Irving Comprehensive Cancer Center at Columbia University [New York. USA]
11/02/2016	**Precision Medicine in Lung Cancer: what´s in the horizon?**	Luis Paz-Ares	Hospital 12 de Octubre [Madrid, Spain]
18/02/2016	**Definición del pronóstico del carcinoma epidermoide cutáneo mediante la combinación de factores clínico-patológicos, marcadores proteicos y expresión de miRNAs**	Javier Cañueto	CIC-IBMCC (CSIC-USAL) Lab. 7 and Servicio de Dermatología (HUS, Salamanca).
03/03/2016	**Orderly progression through S-phase requires dynamic ubiquitylation and deubiquitylation of PCNA**	Vanesa Álvarez Álvarez	CIC-IBMCC (CSIC-USAL) Lab. 5
17/03/2016	**Functional analysis of Securin in mouse spermatogenesis**	Laura Gómez Hernández	CIC-IBMCC (CSIC-USAL) Lab. 9

DATE	TITLE	SPEAKER	AFFILIATION
31/03/2016	**Novel insights into how oncogenic mutants of the stem cell factor receptor/KIT signal: similarities and differences to normal, wild-type KIT**	Lars Rönnstrand	Lund Stem Cell Center-Lund University [Lund, Sweden]
21/04/2016	**The making-up of the human DNA Damage Response: a computational exploration**	Ana Rojas Mendoza	Instituto de Biomedicina de Sevilla [Sevilla, Spain]
27/04/2016	**Microscopía avanzada de super-resolución**	Gery Sexton	Especialista en Microscopía confocal, Super-resolución y Lightsheet.
28/04/2016	**NGF (next generation flow) para detectar EMR en MM y células plasmáticas tumorales circulantes en Gammapatias monoclonales**	Luzalba Sanoja-Flores	CIC-IBMCC (CSIC-USAL) Lab. 11
05/05/2016	**Chromatin dynamics in cell transformation**	Sandra Peiró	Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) [Barcelona, Spain]
12/05/2016	**The p53 response reveals tumor suppressor and oncogenic lncRNAs**	Maite Huarte	Centro de Investigación Médica Aplicada (CIMA) [Pamplona, Spain]
26/05/2016	**Networks of alternative splicing regulation in cancer**	Juan Valcárcel	Centro de Regulación Genómica (CRG) [Barcelona, Spain]
02/06/2016	**Regulación post-transcripcional en el mieloma múltiple**	Irena Misiewicz-Krzeminska	CIC-IBMCC (CSIC-USAL) Lab. 12
16/06/2016	**Living on the edge: Novel mechanisms of regulation and functions of myosin II in migrating cells**	Miguel Vicente-Manzanares	Universidad Autónoma de Madrid [Madrid, Spain]
23/06/2016	**Exploring the role of RAS signalling through PI3-Kinase in lung cancer**	Esther Castellano Sánchez	Barts Cancer Institute, [London, UK]
30/06/2016	**Understanding RNA-¬mediated genome instability**	Andrés Aguilera	Centro Andaluz de Biología Molecular y Medicina Regenerativa, (CABIMER) [Sevilla, Spain]
07/07/2016	**Nuevas aproximaciones terapéuticas basadas en la autofagia en glioblastoma**	Elena Bueno	CIC-IBMCC (CSIC-USAL) Lab. 14
14/07/2016	**Mecanismos de resistencia a Trastuzumab-emtansina en cáncer de mama HER2 positivo**	Carla Ríos Luci	CIC-IBMCC (CSIC-USAL) Lab. 15
21/07/2016	**Cracking the code of mitosis**	Helder Maiato	Instituto de Biologia Molecular e Celular Universidade do Porto [Oporto, Portugal]
06/10/2016	**Cohesin ubiquitylation and mobilization facilitate sister chromatid entrapment and promote stalled fork re-start.**	Rodrigo Bermejo Moreno	Centro de Investigaciones Biológicas (CIB) [Madrid, Spain]
13/10/2016	**Contribution of the RAP-GEF C3G to signaling pathways in platelets**	Sara Gutiérrez Herrero	CIC-IBMCC (CSIC-USAL) Lab. 17
17/10/2016	**Molecular Basis of the KEAP1-NRF2 Antioxidant Gene Regulatory System**	Prof. Yamamoto	Tohoku University
20/10/2016	**Senescencia y reprogramación en regeneración tisular y patologías crónicas**	Manuel Serrano	Centro Nacional de Investigaciones Oncológicas (CNIO) [Madrid, Spain]
27/10/2016	**LMO2 expression in HSCs causes thymus-dependent T-ALL**	Idoia García Ramírez	CIC-IBMCC (CSIC-USAL) Lab. 13
03/11/2016	**Structure determination of genomes and genomic domains by satisfaction of spatial restraints**	Marc Marti Renom	Centro de Regulación Genómica (CRG) [Barcelona, Spain]
10/11/2016	**Unconventional autophagy mediated by the WD40 domain of ATG16L1 is derailed by the T300A Crohn's disease risk polymorphism**	Inmaculada Serramito Gómez	CIC-IBMCC (CSIC-USAL) Lab. 18
24/11/2016	**GRF2 regulation of nuclear trafficking**	David Jimeno García	CIC-IBMCC (CSIC-USAL) Lab. 1

DATE	TITLE	SPEAKER	AFFILIATION
01/12/2016	**Survival analysis of cancer patients and risk prediction based in genes signatures: methods and application to breast cancer subtypes**	Santiago Bueno Fortes	CIC-IBMCC (CSIC-USAL) Lab. 19
15/12/2016	**A network biology approach to novel therapeutic strategies**	Patrick Aloy	Instituto de Investigación Biomédica (IRB) [Barcelona, Spain]
12/01/2017	**Dual inhibition of mTOR Combined with Phenformin in the Management of Hepatocellular Carcinoma**	Sara Kozma	Bellvitge Biomedical Research Institute (IDIBELL) [Barcelona, Spain]
19/01/2017	**Rewiring the posttranscriptional networks of the host**	Alfredo Castello	University of Oxford [Oxford, UK]
26/01/2017	**Nucleosome positioning in the genome driven by the DNA sequence**	Francisco Antequera	Instituto de Biología Funcional y Genómica (IBFG) [Salamanca, Spain]
02/02/2017	**Vav2 oncogene: a gear in the squamous-lineage proliferation and differentiation balances**	L. Francisco Lorenzo Martín	CIC-IBMCC (CSIC-USAL) Lab. 2
09/02/2017	**Notch and Wnt in normal and leukemic hematopoiesis**	Anna Bigas	Instituto Hospital del Mar de Investigaciones Médicas (IMIM) [Barcelona, Spain]
16/02/2017	**The formation of ribosomes in proliferating cells. Alterations in cancer and ribosomopathies**	Blanca Nieto Bernáldez	CIC-IBMCC (CSIC-USAL) Lab. 3
23/02/2017	**Evolution of regulatory landscapes**	José Luis Gómez-Skarmeta	Centro Andaluz de Biología del Desarrollo (CABD) [Sevilla, Spain]
02/03/2017	**Specific inhibition of chromatin remodelers and its connection with defects in DNA repair after inducing DNA damage**	Ignacio Campillo	CIC-IBMCC (CSIC-USAL) Lab. 4
09/03/2017	**Rho GTPase signalling in cancer cell migration and invasion**	Anne Ridley	King´s Collegue London [London, UK]
16/03/2017	**Hematopoiesis and inflammatory signals. New emergency exit for bone marrow-residing inflammatory progenitors.**	Juana Serrano López	Hospital Reina Sofía [Córdoba, Spain]
23/03/2017	**Phenotypic plasticity in melanoma**	Berta López Sánchez-Laorden	Instituto de Neurociencias, CSIC-UMH [Alicante, Spain]
30/03/2017	**Tolerance to DNA damage is down-regulated at replication forks through PCNA deubiquitylation.**	Avelino Bueno	CIC-IBMCC (CSIC-USAL) Lab. 5
06/04/2017	**A life for Oct4 outside embryonic stem cells**	Moises Mallo	Instituto Gulbenkian de Ciência [Lisboa, Portugal]
20/04/2017	**Phenotypic evolution in a GE mouse model exposes a role for the ERBB network in KRAS-driven lung cancer**	Daniel Murphy	Beatson Institute-Cancer Research UK / University of Glasgow [Glasgow, UK]
27/04/2017	**LOXL2 and LOXL3: New players in tumourigenesis and metastasis**	Amparo Cano	Instituto de Investigaciones Biomedicas «Alberto Sols» (CSIC-UAM) [Madrid, Spain]
04/05/2017	**Loss of Pax5 confers the metabolic shift essential for the development of pB-ALL as a result of BCR-ABLp190 susceptibility**	Alberto Martín-Lorenzo	CIC-IBMCC (CSIC-USAL) Lab. 13
11/05/2017	**Novel cell-cell communication networks in organotropic metastasis**	Bruno Costa-Silva	Champalimaud Centre for the Unknown [Lisboa, Portugal]
25/05/2017	**The mechanism(s) of Ras activation: Where? How?... and how long?**	Ignacio Rubio	University of Jena [Jena, Germany]
29/05/2017	**Cancer cytogenetic in the era of next –generation-sequencing**	Paola Dal Cin	Harvard Medical School Cytogeneticist Brigham and Women's Hospital Department of Pathology, CAMD [Boston, MA, USA]

DATE	TITLE	SPEAKER	AFFILIATION
30/05/2017	**Separación magnética e inmunología**	Miguel A. Tam	BioLegend [San Diego, CA USA]
01/06/2017	**Models of cell signaling activity reveal mechanisms of disease and drug action and predict cancer outcome**	Joaquin Dopazo	Fundacion Progreso y Salud de Sevilla [Savilla, Spain]
08/06/2017	**From integrative OMICS to predictive, mechanistic models**	Lars Kaderali	Institute for Bioinformatics / University Medicine Greifswald [Greifswald, Germany]
15/06/2017	**Progresión de linfocitosis B monoclonal a leucemia linfática crónica: papel de la interacción entre el tumor y el medioambiente**	Ignacio Criado	CIC-IBMCC (CSIC-USAL) Lab. 11
22/06/2017	**Role of post-lactational involution in the protective effect against breast cancer induced by early pregnancy.**	Adrián Blanco Gómez	CIC-IBMCC (CSIC-USAL) Lab. 7
29/06/2017	**Identification and functional characterization of SIX6OS1, a novel central element of the synaptonemal complex associated with genome-wide recombination rate**	Laura Gómez	CIC-IBMCC (CSIC-USAL) Lab. 9
06/07/2017	**Talin coordinating the Actin and microtubule cytoskeletons at the plasma membrane**	Ben Goult	University of Kent [Kent, UK]
13/07/2017	**Unraveling the molecular profile of Waldenström's macroglobulinemia: Diagnostic applications, prognostic value and role in transformation**	Cristina Jiménez Sánchez	CIC-IBMCC (CSIC-USAL) Lab. 12
20/07/2017	**Nuevas aproximaciones en el estudio del carcinoma escamoso de cabeza y cuello**	Javier Fernández Mateos	CIC-IBMCC (CSIC-USAL) Lab. 14
05/09/2017	**Reprogramación epigenética del envejecimiento y sus enfermedades**	Alejandro Ocampo	Gene Expression Laboratory (GEL-B) / Salk Institute for Biological Studies [La Jolla, CA, USA]
07/09/2017	**Evidence Synthesis: Repurposing Data to Inform Practice Change**	Eitan Amir	Princess Margaret Cancer Centre / University of Toronto [Toronto, Canadá]
28/09/2017	**Remodeling of Store Operated Channels in Colon Cancer**	Carlos Villalobos Jorge	Institute of Molecular Biology and Genetics (IBGM) [Valladolid, Spain]
05/10/2017	**Copy number driven dependency genes implicated in core regulatory circuits and cellular states in NB**	Frank Speleman	Center of Genetics Research / University of Ghent [Ghent, Belgium]
19/10/2017	**Histone variants link chromatin architecture and metabolism**	Marcus Bushbeck	Josep Carreras Leukaemia Research Institute (IJC) [Barcelona, Spain]
26/10/2017	**Resistencia a Trastuzumab y Trail**	Elena Díaz	CIC-IBMCC (CSIC-USAL) Lab. 15
02/11/2017	**Fuel and oil of the cancer engine**	Arkaitz Carracedo	Center for Cooperative Research in Biosciences (CIC-bioGUNE) [Bizkaia, España]
09/11/2017	**Papel de C3G en la diferenciación y maduración de megacariocitos**	Sara Ortiz Rivero	CIC-IBMCC (CSIC-USAL) Lab. 17
16/11/2017	**A structural journey to the heart of CAD, an anti-tumoral target leading the synthesis of pyrimidines**	Santiago Ramón-Maiques	Severo Ochoa Molecular Biology Center (CBMSO) [Madrid, Spain]
30/11/2017	**Ovarian Granulosa Cell tumors.**	Reiner Veitia	Institut Jacques Monod (IJM) (CNRS -Université Paris Diderot) [Paris, France]
14/12/2017	**Sensing the matrix: transducing mechanical signals from integrins to the nucleus.**	Pere Roca-Cusachs Soulere	Institute for Bioengineering of Catalonia (IBEC) [Barcelona, España]

8

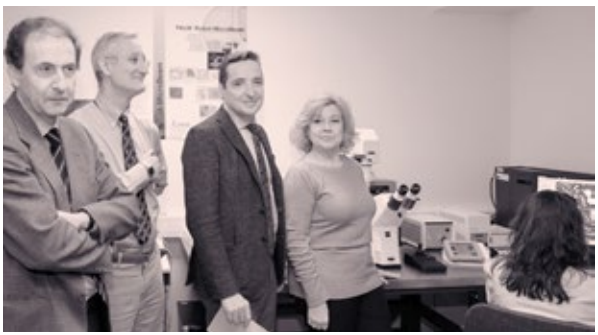
SCIENCE OUTREACH

The FICUS is part of the network of scientific culture and innovation units of the FECYT, for this reason it develops an outstanding activity of the diffusion of the research developed by the CIC researchers and dissemination of the scientific culture.

SCIENCE OUTREACH

THE MOST RELEVANT DISSEMINATION ACTIVITIES 2016-2017 ARE DETAILED BELOW

- **January 28th, 2016.** Delivery of the V National Cancer Research Award «Doctores Diz Pintado».
- **January 29th, 2016.** Delivery at the Casino de Salamanca of the aid to the oncological research of the AECC to the researcher Carmela Gómez.
- **February 7th, 2016.** The AOEX sub-delegation of Malpartida de Plasencia (Cáceres) organized a healthy breakfast at the Pensioner's Home and an informative talk at the Cultural Home, led by the CIC's deputy director, Pandiella.
- **March 1nd, 2016.** Dissemination of the book «Diversity, Versatility and Leukaemia», whose authors are Geoffrey Brown (College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, UK) and Isidro Sánchez-García (of the Center for Cancer Research-IBMCC). http://www.cicancer.org/…/new-book-diversity-versatility-an…
- **April, 2016.** Dissemination of Running for Cancer Research, integrated by a group of runners representing the Cancer Research Center of Salamanca (CIC) in popular races. They participate wearing T-shirts with the CIC logo, they try to raise awareness in society about the importance of cancer research.
- **May 10th, 2016.** Special day of scientific culture. Within the activities of dissemination of scientific culture, a talk followed by a guided visit to the CIC was organized for fifty five-year-old students from the CEIP Santa Catalina.
- **May 16th, 2016.** Orderly progression through S-phase requires dynamic ubiquitylation and deubiquitylation of PCNA.This process represents a window of opportunity for tolerance to DNA damage. http://www.cicancer.org/…/la-progresion-ordenada-de-la-fase…
- **June 8th, 2016.** Identified one of the molecular mechanisms involved in Crohn's disease. http://www.cicancer.org/uploads/archivos/CIC_NP_FXP.pdf
- **June 21th, 2016.** The MEP, Elena Valenciano, visited the Cancer Research Center, accompanied by other national and regional authorities of the PSOE.
- **July 7th, 2016.** Xosé Bustelo receives funding from the Scientific Foundation of the Spanish Association Against Cancer of Stable Coordinated Groups 2016, after the evaluation of the ANEP.
- **September 2nd, 2016.** AECC and the Scientific Foundation visited to the Cancer Research Center. http://www.cicancer.org/…/xose-bustelo-recibe-ayuda-de-la-c…
- **September 23th, 2016.** VI Scientific meeting of young researchers of RTICC 2016.
- **September 24th, 2016.** World Cancer Research Day: CIC has supported and disseminated the World Declaration on Cancer Research. http://worldcancerresearchday.com/
- **September 29th, 2016.** Publication of the bases VI National Cancer Research Award «Doctores Diz Pintado». http://www.cicancer.org/…/bases-vi-premio-nacional-de-inves…
- **October 10th-11th, 2016**. 2nd International IMF-EuroFlow Workshop on Myeloma MRD «Next Generation Flow MRD for Treatment Monitoring in Multiple Myeloma». http://www.cicancer.org/…/Program__2nd_International_IMF-Eu…
- **October 17th, 2016.** The Cancer Research Center glowed pink in honor of Breast Cancer for another year.



- **October 18th, 2016.** Four genes were identified that predict aggressiveness in patients with breast cancer.
- **October 24th, 2016.** The Cancer Research Foundation of the University of Salamanca (FICUS) has been admitted as an accredited member of the Network of Scientific Culture and Innovation Units (UCC + i Network) of the Spanish Foundation for Science and Technology. Membership is valid until December 31th, 2017.
  http://www.cicancer.org/…/la-ficus-forma-parte-de-la-red-de…
- **October 31th, 2016.** Identified new protein that is responsible for the differences in the rate of meiotic recombination between individuals that is essential for fertility.
  http://www.cicancer.org/…/identificada-una-nueva-proteina-r…
- **November 14th-20th, 2016.** The Cancer Research Center has collaborated with the University of Salamanca to celebrate Science Week, specifically organized:
  - Scientific tweets contest.
  - Coordinated visits with the Animal Experimentation GMO (genetically modified organisms) to explain how biomedicine is researched with the support of genetically modified mice.
- **December 1st, 2016.** The AECC grants about 250,000 euros to six research projects.
- **December 7th, 2016.** Xosé R. Bustelo named President Elect of the Spanish Association for Research on Cancer.
- **January 2nd, 2017.** Several genes that are frequently altered in peripheral T cell lymphomas of «unclear origin» have been identified.
  http://www.cicancer.org/es/actualidad/102/identificados-varios-genes-que-estan-alterados-frecuentemente-en-los-linfomas-de-celulas-t-perifericos-de-origen-poco-claro
- **January 13th, 2017.** ArrestAD new research project of the H2020.
  http://www.cicancer.org/es/actualidad/103/arrestad-nuevo-proyecto-de-investigacion-del-h2020
- **January 31th, 2017.** Presentation of the microdissector laser microscope.
  http://www.cicancer.org/es/actualidad/104/presentacion-del-microscopio-laser-microdisector-de-la-universidad-de-salamanca

- **February 23th, 2017.** Biobanks
  http://www.cicancer.org/es/actualidad/106/biobancos
- **February 24th, 2017.** Relationship between glucose and acute B-cell lymphoblastic leukemia.
  http://www.cicancer.org/es/actualidad/107/relacion-entre-glucosa-y-la-leucemia-linfoblastica-aguda-de-celulas-b
- **March 2nd, 2017.** Gene editing allows reverting chronic myeloid leukemia cells to their normal state.
  http://www.dicyt.com/noticias/la-edicion-de-genes-permite-revertir-celulas-de-leucemia-mieloide-cronica-a-su-estado-normal
- **March 20th, 2017.** Crebbp loss cooperates with Bcl2 over-expression to promote lymphoma in mice.
  http://www.cicancer.org/es/actualidad/110/mejora-la-comprension-del-origen-del-linfoma-folicular-y-del-linfoma-difuso-de-celulas-b-grandes
- **April 26th, 2017.** Identification and validation of new biomarkers of osteoarticular diseases.
  http://www.cicancer.org/es/actualidad/111/identificacion-y-validacion-de-nuevos-biomarcadores-de-enfermedades-osteoarticulares
- **May 12th, 2017.** Nanomedicine can destroy leukemic cells in places protected and resistant to conventional therapies.
  http://www.cicancer.org/es/actualidad/112/las-celulas-de-leucemia-resistentes-a-terapias-convencionales-y-que-residen-en-lugares-protegidos-pueden-ser-destruidas-mediante-nanomedicina
- **June 20th, 2017.** Exposure to infection promotes the development of B-cell leukemia.
  http://www.cicancer.org/es/actualidad/115/la-exposicion-a-la-infeccion-promueve-el-desarrollo-de-la-leucemia-infantil-de-celulas-b
- **July 10th, 2017.** Relationship between the use of drugs against an antitumor target and the development of cardiovascular problems.
  http://www.cicancer.org/es/actualidad/117/relacion-entre-el-uso-de-farmacos-contra-una-diana-antitumoral-con-el-desarrollo-de-problemas-cardiovasculares
- **July 10th, 2017.** Multifunctional platform based on efficient iron oxide nanoparticles as antitumor drug carrier.
  http://www.cicancer.org/es/actualidad/116/plataforma-multifuncional-basada-en-nanoparticulas-de-oxido-de-hierro-eficientes-portadoras-de-farmacos-antitumorales
- **October, 18th, 2017.** Revealed a mechanism of resistance to a drug that is used for the treatment of breast cancer.
  http://www.cicancer.org/es/actualidad/126/desvelado-un-mecanismo-de-resistencia-a-un-farmaco-que-se-usa-para-el-tratamiento-del-cancer-de-mama
- **November 14th, 2017.** A Paradoxical Tumor-Suppressor Role for the Rac1 Exchange Factor Vav1 in T Cell Acute Lymphoblastic Leukemia.
  http://www.cicancer.org/es/actualidad/128/identificado-un-nuevo-mecanismo-que-frena-la-formacion-de-cancer-de-celulas-de-la-sangre

SCIENCE OUTREACH

COMMUNICATIONS AND FUNDRAISING:

During 2016 and 2017, FICUS received more than € 263,600 in donations from individuals and associations. In all the events in favor of the CIC, it has helped in the dissemination of the same.

ACTIVITIES TO PROMOTE SCIENTIFIC CULTURE

International Day of Women and Girls in Science

- February 6th, 2017 Exhibition: female milestones in the biomedical sciences.

  http://www.cicancer.org/es/actualidad/105/exposicion-hitos-femeninos-en-las-cienciasbiomedicas

  From March 6th to 27th, 2017, a series of conferences and round tables on Women and Science were held every Monday in the Public Library of the Casa de las Conchas, where several researchers from the Cancer Research Center participated.

  http://www.cicancer.org/uploads/archivos/Mujs_y_Ciencia_3-2017.jpg

  https://bibliotecas.jcyl.es/web/jcyl/BibliotecaSalamanca/es/Plantilla100Detalle/1284353878191/_/1284713122120/Comunicacion

  http://www.cicancer.org/es/actualidad/109/las-mujeres-y-la-ciencia

Promotion of scientific culture - Salamanca City of Knowledge Foundation. January to December 2017:

- Visits of more than 1000 students during 2017 through collaboration with the Salamanca City of Knowledge Foundation The Cancer Research Center has a collaboration agreement with the Salamanca City of Knowledge Foundation, dependent on the Salamanca City Council. Within the Program of scientific culture that is offered as a formative - educational activity for the educational centers of Salamanca, a talk and guided visit to the Cancer Research Center is included to students between 4th of ESO and Bachillerato. The activity is requested by the teachers at the beginning of the academic year.

Other student visits

- Throughout 2017 more than 220 students visited the Cancer Research Center of all educational cycles (children, primary, secondary and university).

Summer camps of the University of Salamanca

- July 4th, 5th and 6th, 2017. Activities are organized to publicize research infrastructures of the University of Salamanca. Children of different ages (6-12 years old) are included in the program. In the CIC, the content of the talk and the visit to the age are adapted. They are shown among other activities how to work with animal models (genetically modified mice).

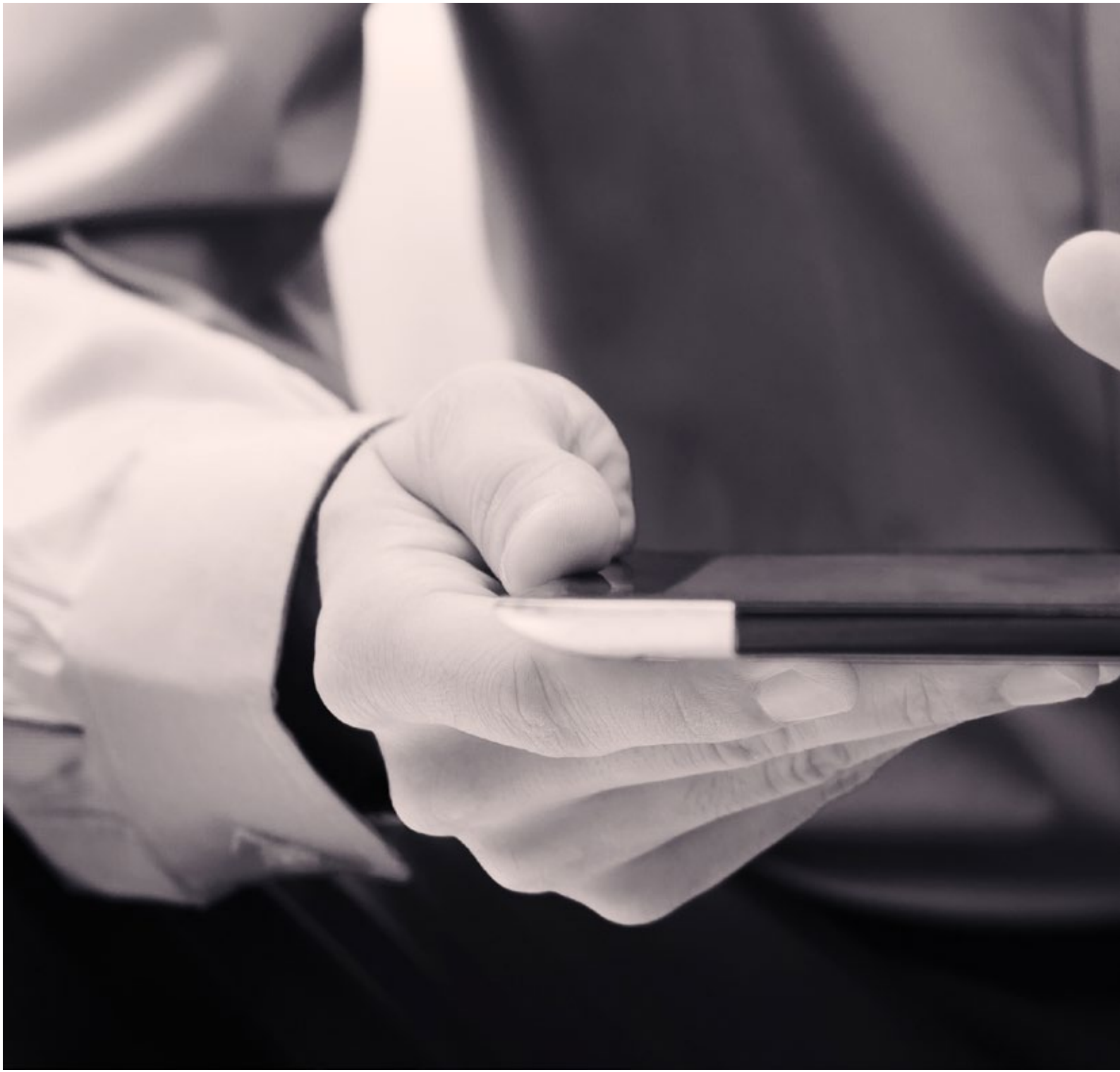
  https://alumni.usal.es/semicolonias-universitarias-verano-2017/

Activities directed to donors

- During 2016 and 2017, activities aimed at donors have continued to explain in detail the work that is being carried out at the Cancer Research Center.

PROFILES OF THE CENTER FOR CANCER RESEARCH IN NETWORKS

The Cancer Research Center has a Twitter, Facebook and LinkedIn account.




9
PRESS
CLIPPINGS

1. **Innovadores.** (octubre)
2. **RTVCL.** (julio)
3. **Diario Sanitario.** (octubre)
4. **La Nueva España.** (diciembre)
5. **Agencia Iberoamericana para la Difusión de la Ciencia y la Tecnología.** (junio)
6. **Diario Sanitario.** (julio)

1

BLOG
OPINIÓN

Cáncer de mama hereditario

ATANASIO PANDIELLA

Con motivo de la dedicación del 19 de octubre al cáncer de mama, he decidido presentar en esta columna algunos aspectos relacionados con el cáncer de mama hereditario. A pesar de que el cáncer de mama es una enfermedad frecuente en mujeres, más de un 80% de las mujeres diagnosticadas con esta enfermedad sobreviven tras 5 años desde su diagnóstico.

Cuando imparto charlas divulgativas sobre el cáncer de mama, es frecuente la pregunta de si el cáncer de mama se hereda. Es importante distinguir entre cáncer hereditario y alteraciones genéticas que causan el cáncer de mama. Respecto a este último aspecto, es importante mencionar que todos los tumores y no sólo aquellos de mama tienen alteraciones de su material genético. Pero esto no quiere decir que los tumores se hayan heredado. De hecho, la mayoría de los tumores no tienen un componente hereditario, o sea no se trasladan de padres a descendientes la predisposición a padecer el tumor. Dicho esto, volvamos al cáncer de mama para decir que la inmensa mayoría de los tumores mamarios no se heredan. Sin embargo, hay un pequeño porcentaje en los cuales existe una predisposición que se transmite de padres a descendientes. Este porcentaje supone alrededor del 5%, y aunque no se conocen todos los factores que influyen en este tipo de cáncer de mama hereditario, se sabe que mutaciones en las proteínas BRCA dan riesgo de padecer cáncer de mama o cáncer de ovario. En el campo de la Oncología Molecular se está trabajando intensamente para encontrar otros factores que contribuyan al desarrollo de cáncer de mama hereditario, y en desarrollar fármacos que puedan impedir o atenuar los cánceres debidos a mutaciones en BRCA.

La pregunta que suele asaltar a mujeres que tienen o han tenido algún antecedente familiar de cáncer de mama, es si ellas tienen predisposición a padecerlo. De momento, la única prueba para determinar predisposición hereditaria a padecer cáncer de mama es un análisis de mutaciones en BRCA. ¿En qué circunstancias se recomienda realizar tal análisis? Según la Sociedad Europea de Oncología Médica (ESMO), es conveniente hacer tales ensayos genéticos si en una familia (1) hay más de 3 casos de cáncer de mama o de ovario de los cuales al menos una de las pacientes tenía menos de 50 años; (2) ha habido dos casos de cáncer de mama en pacientes menores de 40 años; (3) ha habido un caso de cáncer de mama en el varón y un caso de cáncer de ovario o de mama de aparición precoz; (4) cáncer de mama bilateral de comienzo precoz en un mismo paciente; (5) cáncer de mama y ovario en un mismo paciente.

Atanasio Pandiella es vicedirector del Centro de Investigación del Cáncer de Salamanca.

2

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8 SALAMANCA Destacados Noticias Programas Guía TV Webcam

La generosidad permite investigar

La Asociación Española contra el Cáncer se ha convertido en los años de la crisis en el gran soporte de la investigación contra la enfermedad. Este año destinará casi 8 millones de euros a distintos proyectos, un 20% más que el anterior, y uno de los programas más ambiciosos se desarrolla precisamente en Salamanca. El equipo del profesor Bustelo buscará una terapia de bloqueo del cáncer de ovario.

3

"Al cáncer de mama le quedan 20 años"

Publicado por: Redacción en Albacete, Asociaciones, Investigación 14 octubre, 2016

El investigador Atanasio Pandiella, un referente en la lucha contra el cáncer, ha dicho en Albacete que aspira a quedarse en el paro en dos décadas. Y es que los tumores están acorralados. Él no duda de que "al cáncer de mama le quedan 20 años". Así lo ha dicho en el Hospital General Universitario de Albacete, donde, acompañado del oncólogo y también investigador Alberto Ocaña, ha recibido un cheque de 35.000 euros de manos de la asociación albaceteña Acepain.

Equipo. A la izquierda Atanasio Pandiella y a la derecha Alberto Ocaña sostienen el cheque con la nueva donación de Acepain. Fotografía: Acepain

Cada vez hay más y mejores tratamientos, lo que ha dado lugar a que el cáncer vaya avanzando hacia una enfermedad crónica que, aunque despacio, se dirige hacia la curación. Pero, para llegar hasta esa meta, es imprescindible la investigación, de ahí que asociaciones como **Acepain** hayan decidido dirigir todos sus esfuerzos hacia la contratación de investigadores.

En sólo año y medio, Acepain ha reunido **70.000 euros** para que el oncólogo **Alberto Ocaña** pueda mantener tres líneas de investigación encaminadas a mejorar los tratamientos. De hecho, cuando este médico estuvo a las puertas de perder a uno de los especialistas de su equipo, porque dirigir todos sus esfuerzos hacia la contratación de investigadores.

En sólo año y medio, Acepain ha reunido **70.000 euros** para que el oncólogo **Alberto Ocaña** pueda mantener tres líneas de investigación encaminadas a mejorar los tratamientos. De hecho, cuando este médico estuvo a las puertas de perder a uno de los especialistas de su equipo, porque el dinero de la Administración no llegaba, fue Acepain quien asumió las nóminas. Su presidenta, **Juaqui Alarcón** ha subrayado que la asociación se una ahora a la **Fundación Cris** porque persiguen la misma meta. Así, entre ambas organizaciones, sufragan las nóminas de tres investigadores de la Unidad de Investigación del Complejo Hospitalario de Albacete.

Alarcón ha insistido en que la investigación es la medicina de mañana. En su opinión, las administraciones deben asumir que el cáncer es un problema de salud prioritario y que, por tanto, no se debe escatimar en investigación. Asimismo, ha advertido que aún queda mucho por hacer en situaciones como el apoyo psicológico tras el diagnóstico.

4

Álvarez Ferrando, premio nacional por sus investigaciones sobre la leucemia

El hematólogo ovetense, que trabaja en Nueva York en la Universidad de Columbia, destaca los grandes avances de los tres últimos años

Oviedo. Javier Neira | 23.12.2015 | 03:35

El hematólogo ovetense Adolfo Álvarez Ferrando, que desarrolla sus investigaciones en Nueva York, en la Universidad de Columbia, como profesor asociado de Pediatría y Patología, ha sido galardonado con el V Premio Nacional de Investigación en Cáncer "Doctores Diz Pintado" por sus trabajos sobre la leucemia. El galardón, que anualmente promueve la Fundación para la Investigación del Cáncer de la Universidad de Salamanca, está dotado con 15.000 euros. El doctor Álvarez Ferrando indicó ayer que el premio le hacía "mucha ilusión, es una recompensa que viene de la comunidad científica, de un centro de referencia como es el de Salamanca, y que valoro muy especialmente estando fuera de España. Es un honor". En mayo del año pasado, Álvarez Ferrando fue distinguido como "Asturiano del mes", premio que concede LA NUEVA ESPAÑA. Ayer se mostró muy optimista. "Estamos viviendo un momento histórico de avance y progreso en la lucha contra la leucemia, con repercusiones ya clínicas. Es un momento de mucha ilusión y transformación. Lo que ya sabemos de las bases moleculares sobre la leucemia se está trasladando a los fármacos. Después de tres décadas de pocos avances, en los últimos tres años se ha progresado mucho. Y es sólo el comienzo".

Adolfo Álvarez Ferrando, con el galardón de 'Asturiano del mes'. NACHO OREJAS

Fotos de la noticia

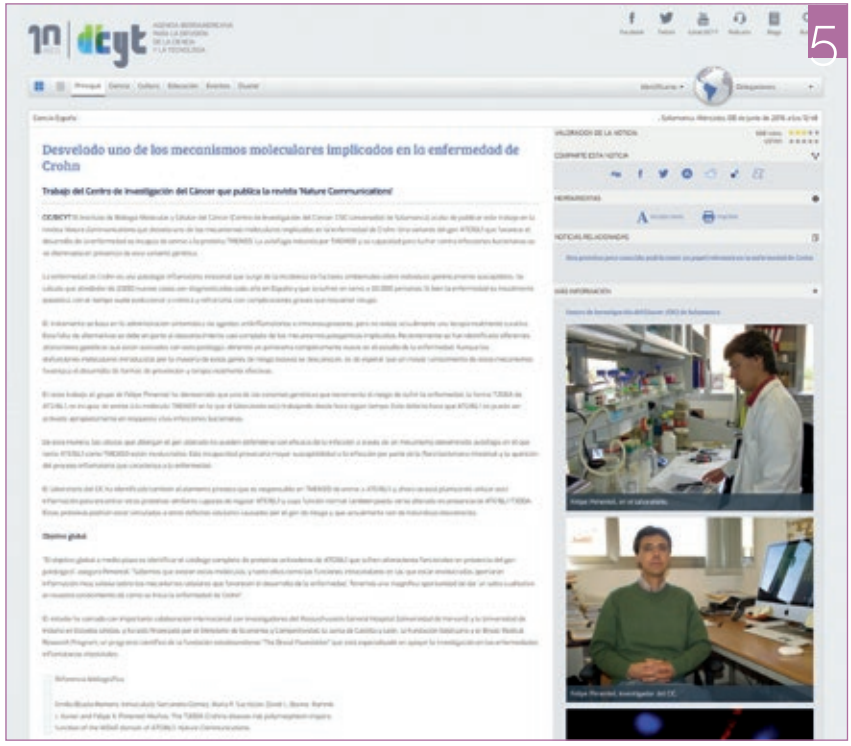
El premio nacional reconoce el esfuerzo y la trayectoria científica en el área de la investigación oncológica del mejor joven investigador español, realizada dentro o fuera de España, y que haya supuesto nuevos conocimientos biológicos y clínicos sobre el cáncer. En su quinta convocatoria, el galardón de Investigación en Cáncer "Doctores Diz Pintado" ha distinguido a Álvarez Ferrando, "que desde hace once años dirige un grupo de investigación especializado en las bases genéticas y moleculares de las leucemias y linfomas de células T. Su trabajo destaca por ser pionero en el desarrollo de estudios genómicos, de biología de sistemas y modelos animales, así como terapias experimentales aplicadas al estudio de la leucemia aguda linfoblástica T (LAL-T) y los linfomas T periféricos".

El programa de investigación dirigido por Álvarez Ferrando se centra en la identificación de nuevos oncogenes y genes supresores de tumores, la caracterización de sus mecanismos de acción y el desarrollo de nuevas terapias dirigidas. Sus resultados han transformado el conocimiento de las bases genéticas y moleculares de estas enfermedades, han identificado nuevos marcadores moleculares de diagnóstico, pronóstico y resistencia, han establecido nuevas dianas de tratamiento y han definido nuevas combinaciones terapéuticas altamente eficaces, actualmente en desarrollo clínico, según las fuentes.

El galardón es uno de los más prestigiosos en España en el ámbito de la oncología, está convocado por la Fundación de Investigación del Cáncer de la Universidad de Salamanca (FICUS), en memoria de los doctores Manuel y Alfonso Diz Pintado. En anteriores convocatorias, los premiados fueron Manel Esteller, Óscar Fernández Capetillo, Eduard Batlle y Joan Seoane.

"En diez años, el tratamiento de la leucemia será totalmente distinto al actual", añadió ayer el doctor Álvarez Ferrando, que tuvo, asimismo, un recuerdo al premio "Asturiano del mes", que recogió ahora hace un año, "que entendí como de LA NUEVA ESPAÑA pero también de todos los asturianos".

5



Desvelado uno de los mecanismos moleculares implicados en la enfermedad de Crohn

Trabajo del Centro de Investigación del Cáncer que publica la revista 'Nature Communications'

6

El equipo del doctor Bustelo, del Centro del Cáncer, recibe 1,2 millones de la AECC

La dotación de apoyo al equipo investigador salmantino supone la continuación de su trabajo, tras los buenos resultados obtenidos en mayo de 2014

REDACCIÓN / WORD

SALAMANCA. El equipo investigador del doctor Xosé Bustelo, que desarrolla su actividad en el Centro de Investigación del Cáncer de Salamanca (CIC-IBMCC), ha recibido 1,2 millones de euros de la Fundación Científica de la Asociación Española Contra el Cáncer (AECC) como apoyo para continuar su trabajo sobre la enfermedad.

La dotación de apoyo al equipo investigador del doctor Bustelo supone un reconocimiento a los buenos resultados obtenidos en mayo de 2014, cuando ya identificó una nueva diana terapéutica contra el cáncer de mama más agresivo.

Con esta nueva adjudicación, se espera poder identificar otras nuevas dianas candidatas para el tratamiento de pacientes mediante un enfoque terapéutico innovador y más eficaz contra las células precursoras del cáncer, resistentes a agentes quimioterapéuticos tanto convencionales como de nueva generación.

Asimismo, se ha identificado un nuevo oncogén, denominado RRAS2, que parece actuar como «interruptor autónomo del desarrollo de una amplia variedad de tumores, así como que la eliminación de la proteína R-RAS2 evita el crecimiento del cáncer y la formación de metástasis en tumores epidemiológicamente relevantes como los de [illegible] y células hematopoyéticas.

Sus objetivos generales [illegible] tran en identificar y entender el comportamiento de este gen en diferentes tipos de tumores, pudiendo establecer su relevancia clínica, y así poder diseñar estrategias terapéuticas eficientes, mediante ensayos clínicos, que permitan un mejor tratamiento de los tumores con la mutación de este gen.

Bustelo, en el centro, con miembros de su equipo, en una imagen de archivo.

Ayudas de la AECC

Estas ayudas que concede la AECC, por medio de su fundación, cuentan con una cuantía total de 7,9 millones de euros para este año, un 1,8 por ciento más que el año pasado. Una dotación proveniente de donaciones de personas de toda España que «depositan su confianza en la AECC para impulsar la investigación contra el cáncer», según explican desde la asociación en un comunicado.

Cabe recordar que, estas líneas de investigación financiadas por la AECC cubren todas las fases del cáncer, desde la prevención hasta la metástasis.

Dentro de los 22 proyectos sufragados gracias a estas ayudas. De ellos, cuatro, dotados con 1,2 millones cada uno, se dedican a la investigación de tumores de gran impacto social, entre estos grupos coordinados estables se encuentra el equipo que desarrolla su actividad en el centro salmantino o el coordinado por los doctores, Mariano Barbacid y Alfredo Carracedo, del departamento de Oncología del Hospital Ramón y Cajal de Madrid.

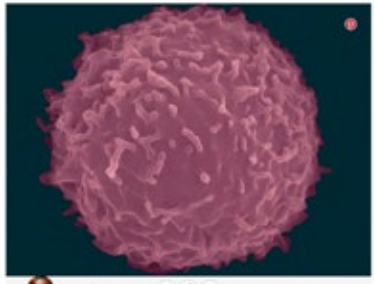
PRESS CLIPPINGS

2017

1 **Muy Interesante.** (enero)
2 **Salud A Diario.** (febrero)
3 **La Sexta.** (noviembre)
4 **Europa Press Castilla y León.** (mayo)
5 **Agencia SINC.** (enero)
6 **Cuatro.** (enero)
7 **Antena 3.** (noviembre)
8 **ABC.** (noviembre)

1

Identifican las mutaciones genéticas que causan los linfomas de células T per...



Los linfocitos T como el de la foto son **los perros de presa del sistema inmune**. Estas células de la sangre destruyen las células malignas que genera nuestro organismo y también las que han sido infectadas por virus y otros patógenos. Además, regulan la actividad defensiva de **otras células del sistema inmune** sin las que estaríamos muertos en poco tiempo. Pero, como los perros agresivos, a veces se descontrolan y **pueden llegar a hacernos mucho daño.**

En algunos casos, los linfocitos T sufren alteraciones genéticas que los transforman de agentes protectores en causantes de **tumores,** entre ellos **los tenidos linfomas de células T periféricos, con una tasa de supervivencia de solo el 30 % y muy difíciles de diagnosticar.**

Ahora, un equipo internacional en el que figura el laboratorio del doctor Xosé Bustelo, del Centro de Investigación del Cáncer (CIC-IBMCC), un organismo mixto del CSIC y la Universidad de Salamanca, ha identificado varios **genes que están alterados frecuentemente** en los linfomas de células T periféricos 'de origen poco claro', que suponen un tercio de los casos.

El hallazgo es importante porque descubrir las alteraciones genéticas que causan estos cánceres **ayudará a mejorar su diagnóstico y a desarrollar medicamentos más potentes para tratarlos.** Los linfomas de células T periféricos presentan una alta incidencia (del 10 al 15 % de los tumores que se originan en las células de la sangre) y se caracterizan por su malignidad y agresividad. Son muy resistentes a las terapias convencionales, y cuando sucumben a estas, **la posibilidad de que se reproduzcan es muy alta.**

Este trabajo, publicado en la revista científica *PNAS*, destaca **la importancia de las mutaciones del proto-oncogén VAV1 en el surgimiento de la dolencia.** El doctor Javier Robles, miembro del equipo del doctor Bustelo, explica que "dado que la oncoproteína VAV1 tiene una actividad biológica que podría inhibirse con medicamentos, estos hallazgos establecen una posible diana para el desarrollo de tratamientos farmacológicos más efectivos contra esta enfermedad a largo plazo".

Los investigadores señalan que **estos tumores presentan alteraciones genéticas numerosas y heterogéneas.** Por eso, "según el tipo de mutaciones que albergues, habrá personas con comportamientos clínicos diferentes tanto en su evolución como en la respuesta a tratamientos". Esta complejidad implica que el estudio deberá extenderse a un gran número de pacientes para poder asignar a cada uno un tratamiento específico.

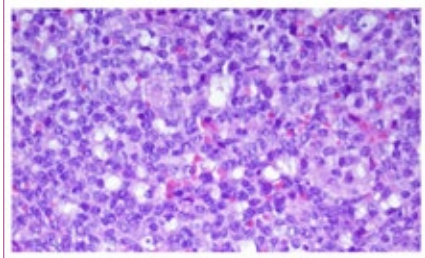
2

AVANCE

Un grupo de científicos identifica la relación entre glucosa y la leucemia linfoblástica aguda de células B

Los resultados han sido publicados en el artículo Metabolic gatekeeper function of B-lymphoid transcription factors, en Nature

Vote este artículo ★ ★ ★ ★ ★ (1 voto) Imprimir Email 0 Comentarios



Los resultados además ofrecen una explicación para el hallazgo empírico que los glucocorticoides son efectivos en el tratamiento de linfoide B, pero no para enfermedad mieloide. Del mismo modo, se demuestra que la función de los factores de transcripción de linaje linfoide B como control metabólico, por limitar la cantidad de ATP a niveles insuficientes para la transformación maligna.

Los factores de transcripción como PAX5 y 3KZF1 son críticos para el desarrollo temprano de células B, además las lesiones de los genes que codifican esa transcripción suceden más del 80% de leucemia linfoblástica aguda de células B. Este artículo actiera el papel de estas lesiones en la leucemia linfoblástica aguda, que hasta ahora no son muy conocidas.

El artículo expone que los científicos han identificado un nuevo programa linfoide B para supresión de glucosa y suministro de energía. Sin dicho control de glucosa, se favorece la transformación maligna de las células. El análisis revela que PAX5 y 3KZF1 fuerza la privación crónica de energía, siendo esencial para la activación de AMPK. AMPK es un sensor de energía celular que contribuye a regular el balance energético y participa en la regulación de la glucólisis. La glucólisis es la vía metabólica que permite obtener energía para la célula.

Las mutaciones de PAX5 e 3KZF1 sin embargo, mitigan esta glucosa y la restricción de energía. En modelo de ratón de leucemia linfoblástica aguda de células pre-B afectado por la mutación de PAX5 aumenta la absorción de glucosa y los niveles de ATP. Si se modifica PAX5 e 3KZF1 en muestras humanas con leucemia linfoblástica aguda de células pre-B, restaura la no tolerancia e induce la crisis energética que genera muerte celular.

3

Descubren un mecanismo para frenar un infantiles más comunes

Un estudio liderado por el Centro de Investigación del **Cáncer** de la Universidad de **Sala** parar la leucemia linfoblástica a través de un gen. La supervivencia a este tumor ronda

Presentan nuevos avances en cánceres infantiles | Agencias

El Centro de Investigación Biomédica en Red de Cáncer (CIBERONC) ha descubierto que el gen VAV1, habitualmente implicado en la formación de una amplia gama de tumores, puede también ejercer papeles implicados en la supresión de algunos tipos específicos de leucemia linfoblástica aguda de linfocitos T, que es el cáncer pediátrico más frecuente.

Así lo han señalado las entidades promotoras de la investigación **publicada en la revista científica Cancer Cell** y que hace referencia a un tipo de leucemia que "todavía hoy tiene muchos retos para un diagnóstico y tratamiento adecuados".

Este tumor es el más frecuente en niños en España y **también afecta a un número significativo de adultos**. Sobre los porcentajes de curación de esta enfermedad, han mejorado a lo largo de estos últimos años, aunque "todavía presenta importantes retos como es el tratamiento de pacientes que son resistentes a las terapias actuales o que recaen tras la aplicación de las mismas.

Debido a ello, la supervivencia de los pacientes con estos tumores -58 por ciento de los casos- es "todavía hoy muy mejorable" desde el punto de vista clínico, han apuntado los entidades promotoras del proyecto.

Según han explicado los responsables del proyecto, los linfocitos T son células del sistema inmune que tienen por función el reconocimiento y **destrucción de células de nuestros órganos** que se han convertido en cancerosas o que han sido infectadas por virus u otros patógenos.

4

Nanomedicina para reducir efectos secundarios en leucemias

EN DIRECTO... Rueda de prensa de Pedro Sánchez tras registrar la moción de censura contra Rajoy

Actualizado 12/05/2017 18:24:18 CET

SALAMANCA, 12 May. (EUROPA PRESS) -

Los investigadores Isidro Sánchez y Alberto Martín-Lorenzo del Centro de Investigación del Cáncer (IBMCC) han participado en un estudio sobre nanomedicina que "ofrece un enfoque prometedor para reducir los efectos secundarios de los tratamientos convencionales de la leucemia aguda promielocítica y mejora el acceso del tratamiento a las células de leucemia resistentes".

Este trabajo ha sido publicado en Natura Comunicationes, en el artículo titulado 'Prolonged intracellular accumulation of light-inducible nanoparticles in leukemia cells allows their remote activation'.

Según el Centro de Investigación del Cáncer de Salamanca, la aplicación de nanotecnología puede reducir los efectos secundarios de los fármacos y, "de hecho, está siendo empleada para diseñar nuevos tratamientos en diversos tipos de cáncer".

En ese sentido, ha continuado, "la diferenciación de células de leucemia es una estrategia terapéutica empleada con frecuencia en la clínica para erradicar el cáncer de la sangre" y "la concentración del agente utilizado para inducir la diferenciación de la célula de la leucemia es una variable importante para el éxito de este enfoque terapéutico". "También es importante controlar una segunda variable el control espacio-temporal de su aplicación", ha añadido.

La inducción de la diferenciación de células de leucemia por ácido retinoico es una estrategia terapéutica que ha tenido "gran éxito" en el tratamiento de leucemia aguda promielocítica. Pero, a pesar de su eficacia terapéutica, aproximadamente el 25 por ciento de los pacientes sufre recidiva con complicaciones.

Ante esta situación, la ciencia está investigando para evitar efectos secundarios, a lo que se suma, además, que las células de leucemia resistentes residen en nichos que son "difíciles para acceder" mediante las intervenciones terapéuticas.

"Por todo ello, es necesario avanzar en estas estrategias que solventen estas dificultades", ha explicado el Centro de Investigación del Cáncer en la información remitida a Europa Press.

Ahora, el trabajo presentado parte de la hipótesis que las nanopartículas cargadas con ácido retinoico poliméricos inducibles por la luz "puede ser una estrategia más efectiva para diferenciar células de leucemia", ha valorado.

Asimismo, ha destacado que en el trabajo publicado "se describe como dichas nanopartículas son capaces de acumularse en el citoplasma de las células de la leucemia durante varios días, y se desensamblan dentro de las células después de la activación de la luz". Además, esta investigación permitirá avanzar para diferenciar las células tumorales ubicadas en los nichos protegidos.

Por ello, con este resultado, la investigación "ofrece una estrategia prometedora tanto para controlar las poblaciones de células distintas como para modular remotamente dichos nichos leucémicos", ha concluido.

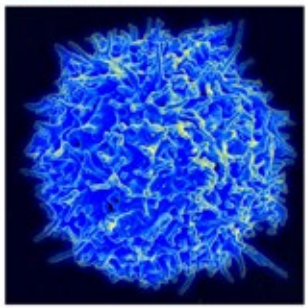
5

Identifican mutaciones que causan los linfomas periféricos de células T

Un equipo internacional con participación española ha logrado identificar las mutaciones en las células que causan los linfomas T de origen poco claro, uno de los tumores con mayor tasa de mortalidad. Los autores del estudio creen que este avance contribuirá a desarrollar fármacos más efectivos para su tratamiento.

Más información sobre: células T · cáncer · linfomas · tumor

SINC | Seguir a @agencia_sinc | 02 enero 2017 21:00



Micrografía de una célula T sana del sistema inmune / Wikipedia Commons

Los linfocitos T son células de la sangre cuya misión es destruir las células malignas que afectan a nuestro organismo. Luchan contra las células enfermas que en ocasiones se originan en los órganos o las que han sido infectadas por virus. Sin embargo, cuando sufren determinadas alteraciones genéticas pueden causar tumores como los linfomas de células T periféricas, que tienen una tasa de mortalidad muy elevada.

Además de su agresividad, otra de las razones que dificultan su tratamiento es que no son fáciles de identificar. Normalmente un 30% se diagnostican como linfomas T de origen poco claro.

Esta semana, un grupo internacional de científicos, en el que participa el Centro de Investigación del Cáncer (CIC,un centro mixto de la Universidad de Salamanca y el CSIC), ha publicado en la revista *PNAS* los resultados de un estudio en el que se logran identificar varios de estos genes alterados en los linfomas de células T de origen poco claro.

Los linfomas de células T se encuentran entre los tumores con una tasa de mortalidad más elevada

Uno de ellos es el proto-oncogén VAV1, que habitualmente se encuentra con alteraciones genéticas en un 12% de los pacientes analizados. El mismo gen aparece en frecuencias más bajas (entre el 3% y el 7% de los casos) en otro tumor con propiedades malignas similares, el linfoma de células T angioinmunoblástico.

Estos hallazgos establecen una posible diana para el desarrollo de tratamientos farmacológicos más efectivos, según los autores

"Lo interesante no es solo el hecho de haber encontrado mutaciones con alta frecuencia en el gen VAV1 en estos tumores, sino también que muchas de estas originan moléculas hiperactivas que probablemente contribuyan al desarrollo de este tipo de tumores" explica Xosé R. Bustelo, científico del CIC y uno de los autores del trabajo.

Además, el avance puede ayudar al tratamiento de este linfoma con fármacos. "Dado que la oncoproteína VAV1 tiene una actividad biológica potencialmente factible de poder ser inhibida por fármacos, estos hallazgos establecen también una posible diana para el desarrollo de tratamientos farmacológicos más efectivos", asegura Javier Robles, investigador del equipo de Bustelo.

Numerosas alteraciones genéticas

En cualquier caso, una de las dificultades que habrá que afrontar es que estos tumores son muy heterogéneos y presentan numerosas alteraciones genéticas. "Dependiendo del tipo de mutaciones que alberguen, habrá pacientes que exhibirán comportamientos clínicos diferentes tanto en su evolución clínica como en la respuesta a tratamientos", indican los autores.

La complejidad que describen implica que aún deben seguir investigando para extender el estudio a un gran número de pacientes, de forma que puedan asignar a cada firma molecular un comportamiento clínico específico.

El trabajo está coordinado por los españoles Teresa Palomero y Adolfo Ferrando, cuyos grupos de investigación se encuentran en el Institute for Cancer Genetics de la Universidad de Columbia, en Nueva York. También participan centros como el Instituto de Investigaciones Biomédicas Pi i Sunyer de Barcelona y el Instituto de Investigación Sanitaria de Valdecilla de Santander, entre otros.

6

El proyecto europeo 'ArrestAD' comienza su andadura para encontrar un diagnóstico del Alzheimer en sangre

EUROPA PRESS • 13/01/2017 - 11:40 h.

El proyecto europeo 'ArrestAD', en el que participa el grupo de Bioinformática y Genómica Funcional del Centro de Investigación del Cáncer (CICIBMCC), va a comenzar su andadura para encontrar un diagnóstico del Alzheimer en sangre, así como una nueva línea terapéutica.

Para ello, se va a partir de un nuevo marcador identificado en muestras de pacientes con enfermedad de Alzheimer en 2016, el heparán sulfato, el cual se estudiará en detalle a través de análisis genómicos y proteómicos en muestras humanas, tanto de población sana como en pacientes diagnosticados bien controlados.

El proyecto, que tendrá una duración de cuatro años, cuenta con la financiación de casi 4 millones de euros de la Unión Europea, y forma parte de la convocatoria 'FET-Open', en la que se persigue el desarrollo de proyectos que abran nuevas líneas de investigación que tengan un enfoque radicalmente novedoso, y con potencial transferencia de resultados de investigación, que

7

Identifican un mecanismo que frena el cáncer pediátrico más frecuente

Gracias a la identificación de un gen clave, se ha conseguido parar el crecimiento eventualmente se mueran.

El 75% de los casos de cáncer infantil en España son curables | Agencias

Un grupo de investigación liderado por Xosé Bustelo, perteneciente al Centro de Investigación del Cáncer (CIC) de Salamanca, ha descubierto un gen que actúa como supresor de la formación del tumor pediátrico más frecuente, un subtipo de leucemia linfoblástica aguda de linfocitos T.

Según ha explicado el CIC a través de un comunicado, este trabajo ha revelado que el gen, dependiendo del tipo de cáncer, puede actuar como promotor o supresor de la formación de tumores y, en este caso concreto, se ha demostrado que actúa como supresor de la formación del citado subtipo de leucemia linfoblástica aguda.

De esta manera, el estudio **permitirá diseñar fármacos a medida** que, en función del tipo de tumor, sirvan para inactivar o activar las funciones protumorales y antitumorales ejercidas por este gen. El trabajo ha sido realizado por el Centro de Investigación Biomédica en Red de Cáncer (Ciberonc), a través del grupo de investigación liderado por Xosé Bustelo, perteneciente al Centro de Investigación del Cáncer de Salamanca, y ha sido publicado por la revista científica Cancer Cell.

Los linfocitos T sufren en algunos casos alteraciones genéticas que los hacen pasar de agentes protectores a células malignas causantes de tumores, siendo el más frecuente la leucemia linfoblástica aguda de linfocitos T, **el tumor más frecuente en niños españoles y también afecta a un número significativo de adultos**. A través de este trabajo, se ha identificado un gen que actúa como un freno clave en la formación de la LLA-T, la leucemia linfoblástica aguda de linfocitos T.

Como ha señalado el doctor Xosé Bustelo a través de la nota de prensa, este trabajo "ha demostrado que VAVs, a través de la formación de un complejo multiproteico con la proteína CBL-B, corre literalmente al acelerador ICN1 **haciendo que éste desaparezca** de las células tumorales. Esto hace que se pare el crecimiento de las mismas y que eventualmente se mueran". El trabajo también ha identificado la estrategia que las células tumorales desarrollan para eliminar este freno, el cual se basa la generación de alteraciones genéticas que provocan la activación espuria de unas proteínas denominadas TLX.

"Pese a ello hemos podido demostrar que si reactivamos VAV1 podemos volver a parar el crecimiento de estas **células alteradas genéticamente e inducir su muerte de forma muy rápida**. Esto sugiere que, a largo plazo, podría ser factible el diseño de vías terapéuticas que pudiesen reproducir el mismo efecto en pacientes", ha agregado el doctor Bustelo.

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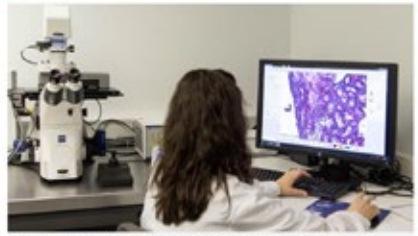
Identifican un gen que ayuda a fre cánceres pediátricos más frecuentes

El estudio del Centro de Investigación del Cáncer de Salamanca permitirá diseñar f



El estudio ha sido llevado a cabo por el Centro de Investigación del Cáncer de Salamanca - ICAL

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NOTICIAS RELACIONADAS

El CIC de Salamanca destaca el aumento significativo de la supervivencia de los pacientes

Relacionan los nuevos fármacos contra el cáncer con problemas cardiovasculares

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