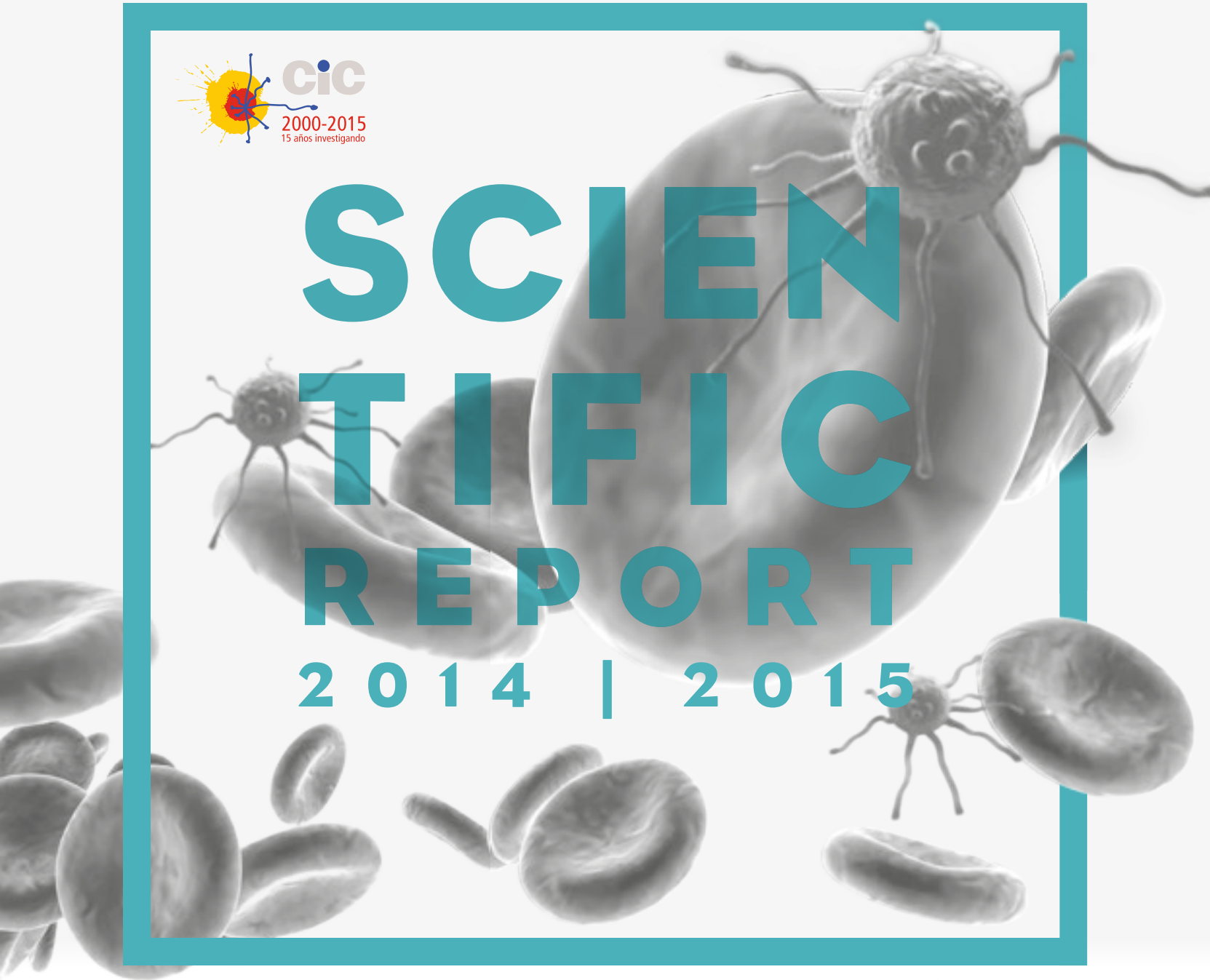

2000-2015
15 años investigando

SCIENTIFIC REPORT

2014 | 2015

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

SCIENTIFIC REPORT

2014 | 2015

CiC
Centro de Investigación del Cáncer

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

Centro de Investigación del Cáncer
Instituto de Biología Molecular y Celular del Cáncer
CIC-IBMCC (USAL-CSIC)
Campus Miguel de Unamuno s/n
37007 Salamanca (Spain)

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E-mail: cicancer@usal.es

http://www.cicancer.org/es/memoria-cientifica-2014-2015

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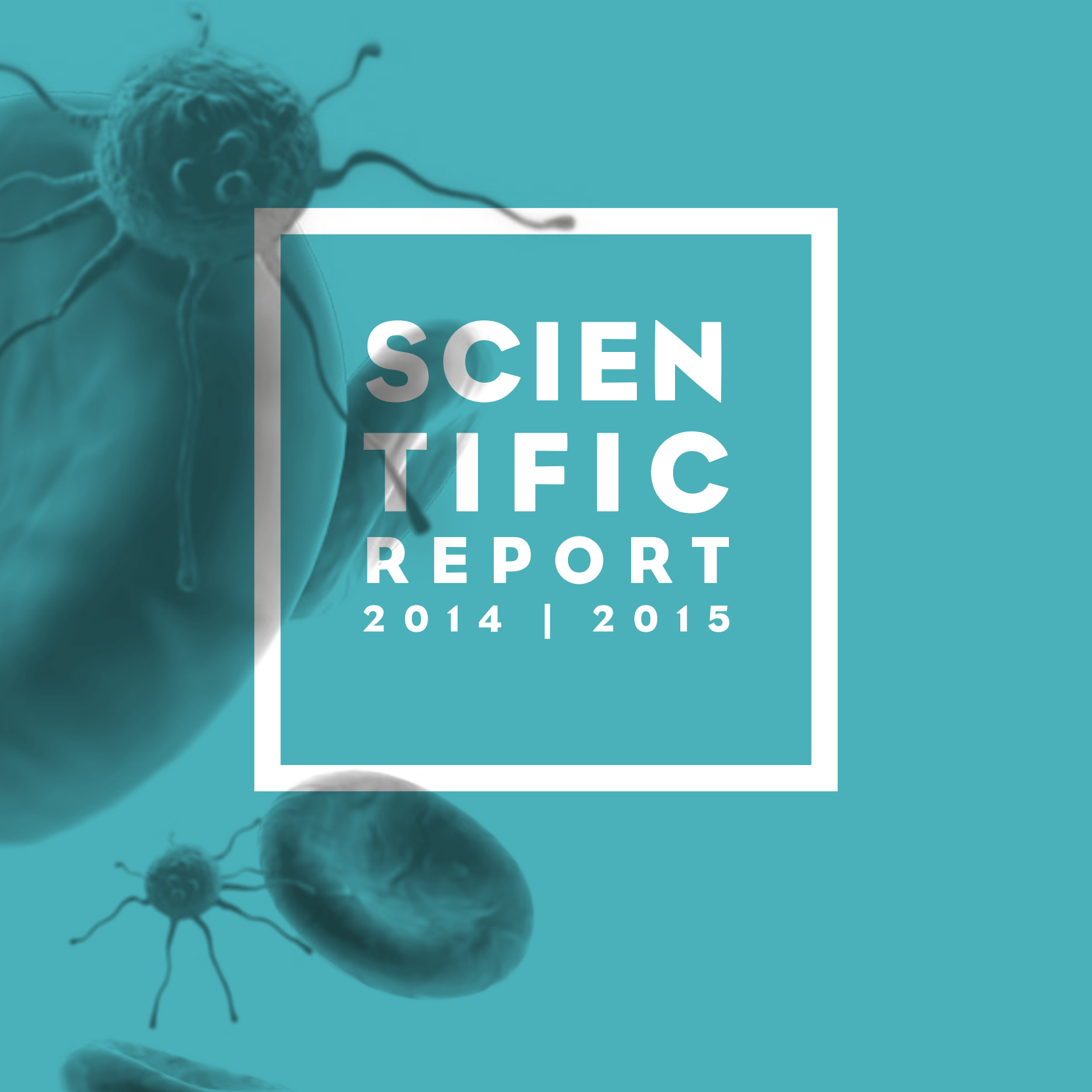
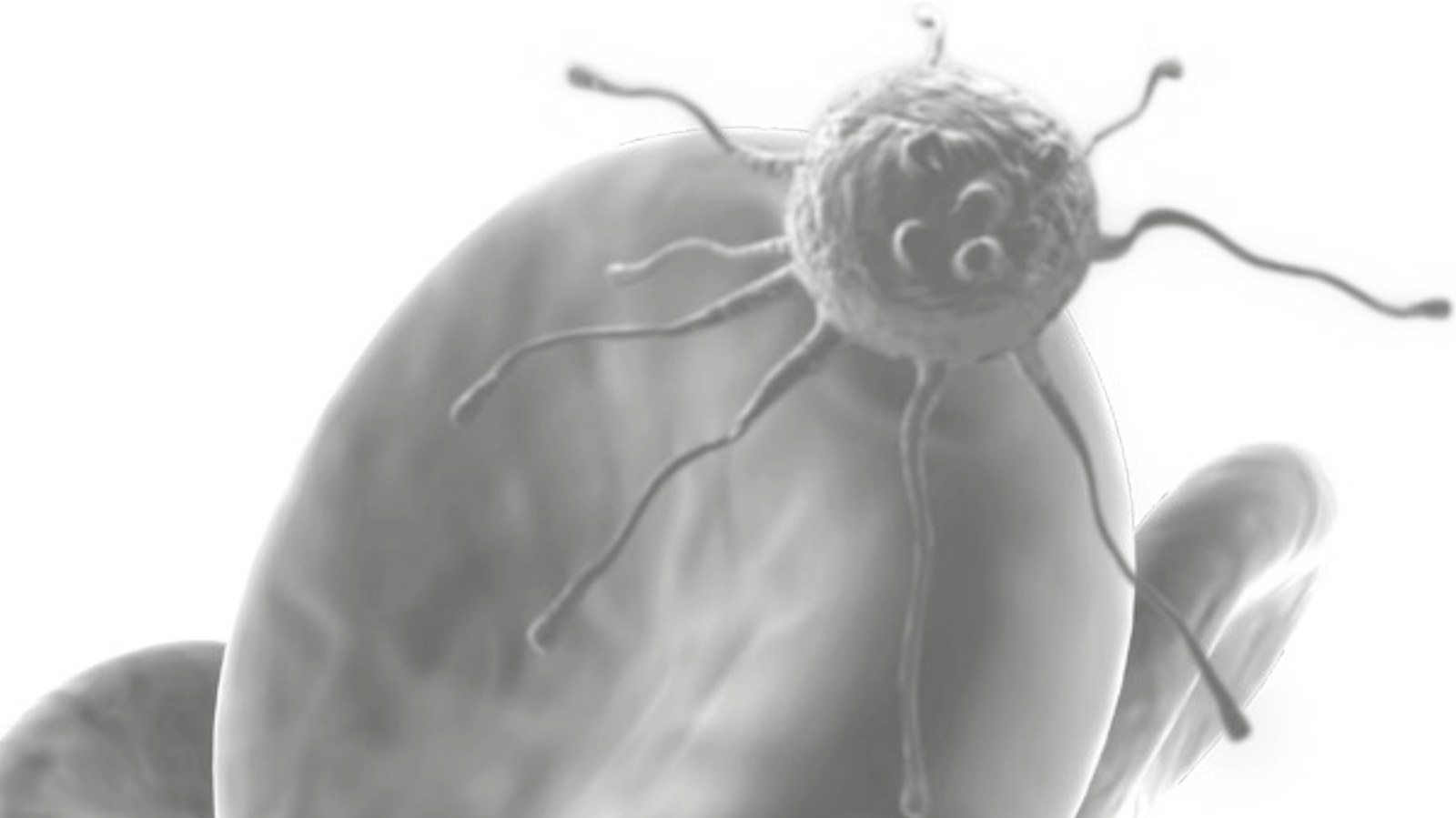
a.f. diseño y comunicación / www.afgrafico.com



SCIENTIFIC REPORT

2014 | 2015



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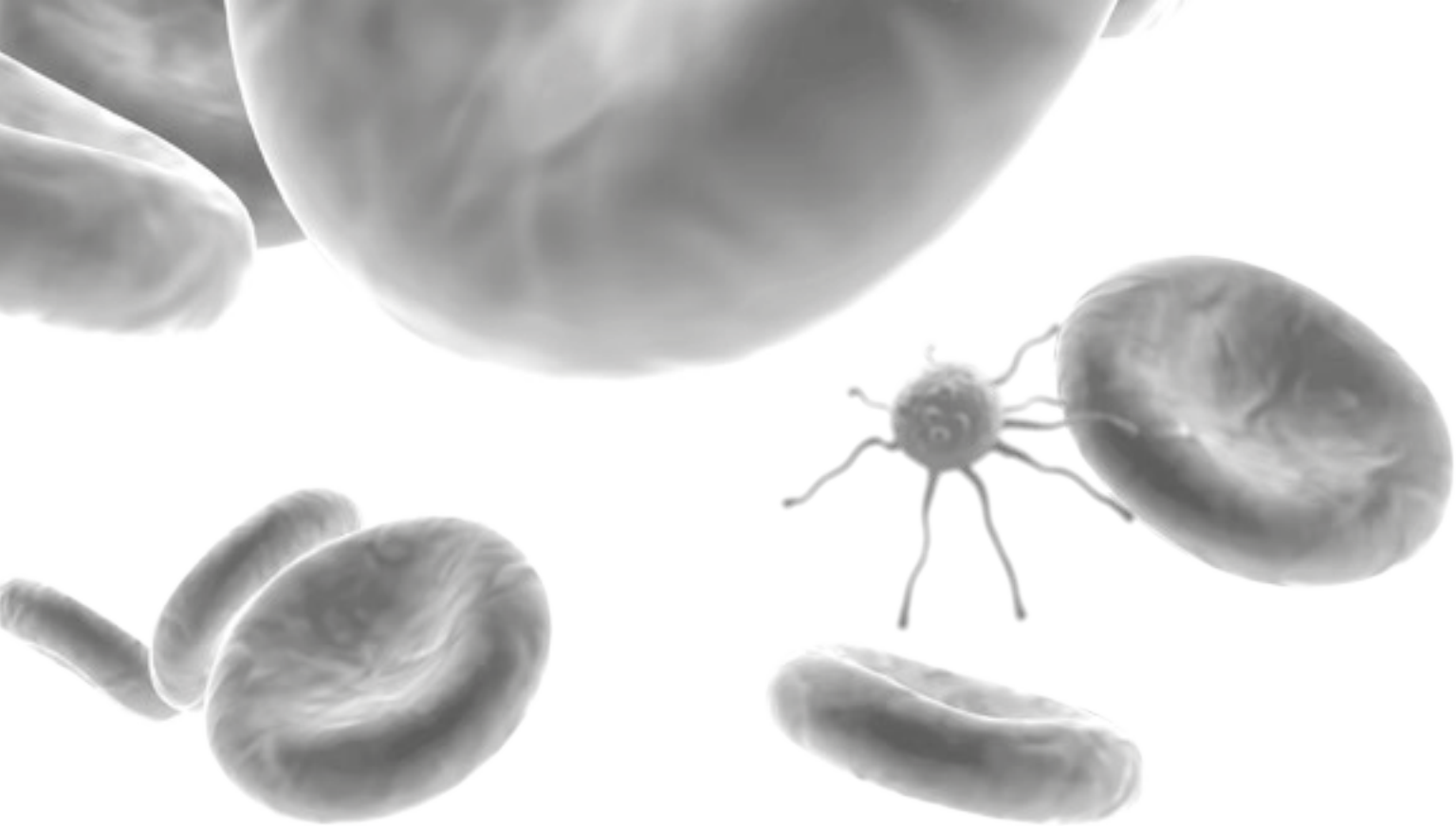



CENTRO
DE INVESTIGACION
DEL CANCER

1 FOREWORD

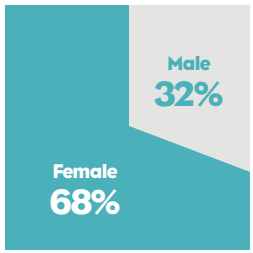
A very remarkable and pleasant highlight for the period covered by this report was the celebration, during year 2015, of the **XV Anniversary** of our CIC-IBMCC. It seems like only yesterday, but a lot of good things have happened in cancer research in our Center since the at that time presidents of USAL (Ignacio Berdugo) and CSIC (César Nombela) inaugurated our new building on **27 January 2000**. For the past 15 years our Center has focused on carrying out internationally competitive, high quality basic, clinical and translational cancer research applying a multidisciplinary approach reminiscent of the US Comprehensive Cancer Centers in an effort to achieve a quick and efficient transfer of our laboratory results to society and the patients. Indeed, our Center continues today to represent the biggest and best concentration of qualified human resources and infrastructures dedicated to cancer research in Castilla y León, with a clear call to being also a national and international reference in this endeavor.

A **scientific conference** was held on October 1st to celebrate this anniversary with the participation of some of most renowned Spanish scientists in the field of cancer research, including Joan Massagué (Memorial Sloan Kettering Institute, New York), Carlos López-Otín (IUOPA, Oviedo University), María Blasco, Marisol Soengas and Óscar Fernández Capetillo (CNIO, Madrid), Manel Esteller (IDIBELL, Barcelona), Eduard Batlle (IRB, Barcelona) and Joan Seoane (VHIO, Barcelona). Notably, the last four speakers were also the winners of the National Prize for Cancer Research "Doctores Diz Pintado" awarded each of the previous four years by our Center to the most relevant young cancer investigators in our country. We want to express our deepest gratitude to all the speakers and participants for their support and generous contribution to the success of our Center anniversary.

During the period 2014-2015, the work at the CIC-IBMCC was carried out by 16 independent **Research Units** led by senior PIs, 7 Research Units led by junior PIs, 9 **Scientific Sociosanitary Service Units** and 8 **Technical Support Units**. Unfortunately, continuing the trend of recent past years, as of December 2015 the count of senior PIs was further reduced in our Center due to the transfer of Dr. **Faustino Mollinedo** to the CSIC "Centro de Investigaciones Biológicas"

(CIB) in Madrid. During his tenure with us (00-15) Dr. Mollinedo was a signified leader and reference at the CIC-IBMCC in research areas related to cellular death and cancer therapy approaches. On behalf of everyone in our Center I want to convey our deepest gratitude and recognition to Faustino for his work and dedication to the CIC-IBMCC over the years, and wish him professional and personal success in his new position. The present report contains in-depth descriptions of the composition and function of each of our Research and Support Units during 2014 and 2015.

As our Center is jointly sponsored (Instituto Mixto) by the University of Salamanca (**USAL**) and the Spanish Research Council (**CSIC**), about 52% of our **personnel** were formally affiliated with either USAL or CSIC. On the other hand, the remaining 48% of our staff were supported by work contracts (102 contracts in 2014 and 95 contracts in 2015) underwritten by our supporting **FICUS** Foundation (Fundación de Investigación del Cáncer de la Universidad de Salamanca),



Average Distribution by Gender 2014-2015

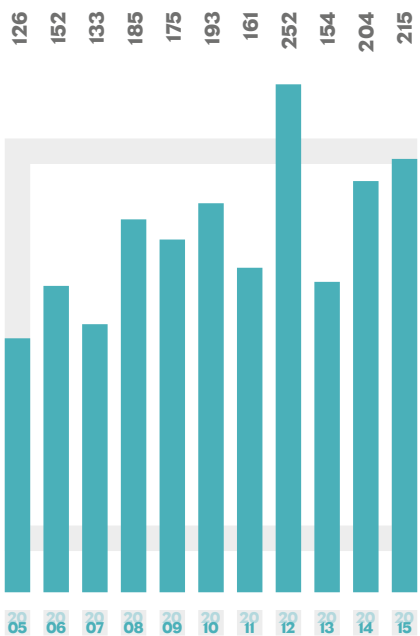
Staff Research Units vs Service Units 2014-2015

whose Board of Directors includes members representing USAL, CSIC, Carlos III National Health Institute (ISCIII) and the regional Ministries of Health and Education of the Castile and Leon Government.

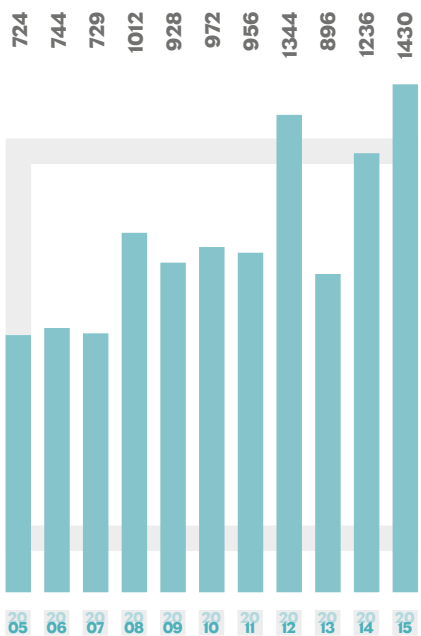
Within the 2014-2015 period, the CIC-IBMCC researchers published a total of **419 original articles** dealing with various aspects of basic, translational or clinical cancer research. Our publications appeared in 174 different, indexed journals, involving a total Impact Index of 2666. Most of these articles (64%) were published in scientific journals ranked within the first quartile (Q1) of its area and the **average impact factor** per paper was **6.33**. These parameters represent an improvement over the previous biennium 2012-2013 regarding total number of published scientific articles (4% higher), total overall impact factor (19% higher) or average impact per individual publication (15% higher). The detailed list of these publications can be found in the corresponding sections of this report for each individual Research or Service group.

During this two-year period our PIs also earned **competitive grant awards** amounting to 4.2 million euros to carry out 51 separate research projects. These figures represent a reduction in comparison to previous periods and reflect the major,

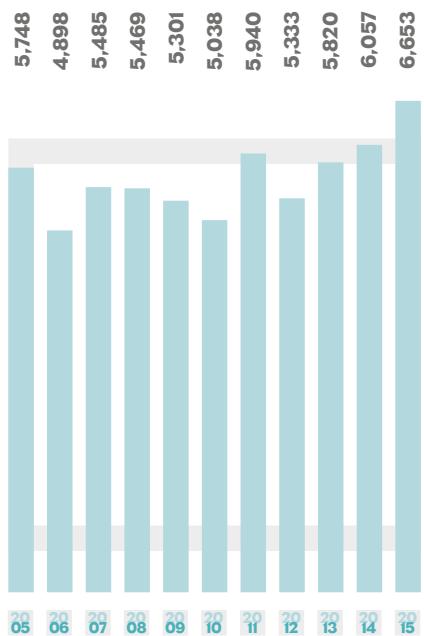
CIC-IBMCC Publications 2005-2015



CIC-IBMCC Impact Factor 2005-2015



CIC-IBMCC IF/paper 2005-2015



sustained recent cuts in research money available from Spanish granting Agencies. Nevertheless, despite the significant cuts in the R+D Spanish research budget, the CIC-IBMCC scientists kept generating intellectual property during this period and registered 6 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 the Spanish Cancer Research Network (Red Temática de Investigación Cooperativa en Cáncer, **RTICC**) sponsored by the Carlos III National Health Institute (ISCIII) and coordinated by Dr E. Santos.

The scientific work of the CIC-IBMCC has also been recognized with various **awards** during 2014-2015. The CIC IBMCC received in 2014 the "Premio Sociedad Civil" awarded by Consejo Social of USAL and the "Premio ECO" awarded by Fundación para la Excelencia y la Calidad de la Oncología (ECO). Significant individual scientific contributions made by different PIs of the CIC IBMCC were also recognized

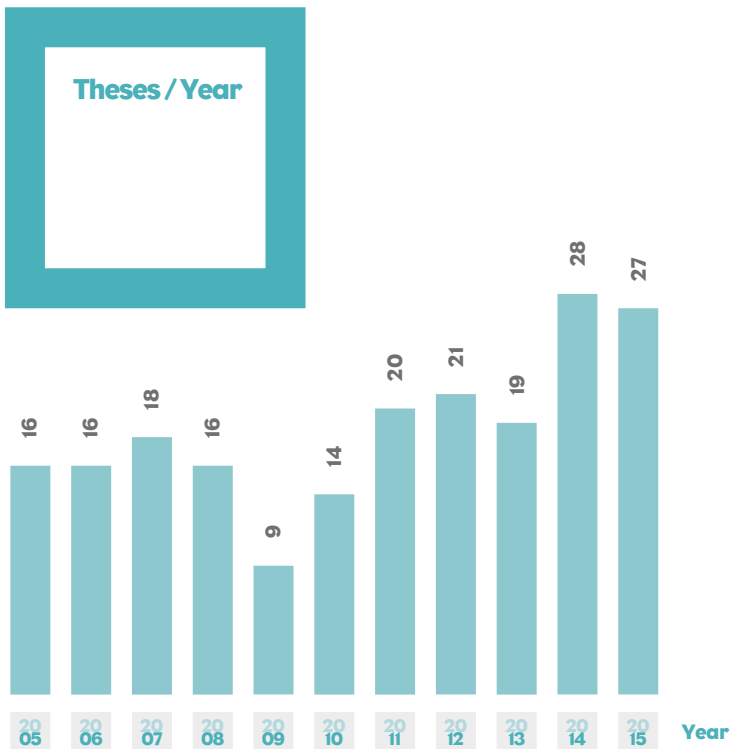
CIC-IBMCC Nº Projects and Funding 2005-2015

Year	Nº Projects	Euros
2005	46	4.257.228,00
2006	37	2.587.504,00
2007	51	9.441.651,37
2008	59	5.237.078,64
2009	52	6.111.893,89
2010	33	3.795.406,71
2011	22	4.260.226,00
2012	25	3.214.851,00
2013	21	2.609.474,00
2014	23	2.110.857,20
2015	28	2.032.020,00

nationally or internationally during this period. In particular, Alberto Orfao received the "Premio en Biomedicina Aplicada Valdés-Salas" from the University of Oviedo; Isidro Sánchez-García received the "Proyecto de Investigación en Oncología Infantil" from Fundacion Inocente Inocente; Eugenio Santos received the ICAL 2014 prize; Xosé R. Bustelo received the "Alberto Sols" Conference award from the Argentinian Society of Biochemistry and Molecular Biology; Marcos González Díaz received the "Maria de Maeztu" award to Scientific Excellence from the University of Salamanca. It is also worth mentioning that during this period 12 research groups led by PIs from the CIC-IBMCC were recognized, in a competitive call from the Junta de Castilla y León, as "Consolidated Research Units (**UIC**)" on the basis of their excellence and scientific career during recent years.

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 during this period to award the "**Doctores Diz Pintado Award**" in order to recognize each year the excellence of the most outstanding Spanish cancer researcher **younger than 45**. The awardees in 2014 and 2015 were, respectively, **Dr. Joan Seoane** (VHIO, Barcelona) and **Dr. Adolfo A. Ferrando** (Columbia University, NY), two of the most relevant and recognized young cancer scientists at the current Spanish and international cancer scene.

As an Accredited University 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 Clinics of Cancer" from which **41 students** have graduated in the last two academic years, and a **PhD program** entitled "Bioscience: Biology and Clinic of Cancer and Translational Medicine" sponsored by the CIC-IBMCC in collaboration with the USAL departments of Microbiology& Genetics (School of Biology) and Medicine (School of Medicine) with **227 students** enrolled in it. During 2014-2015, a total **55 Doctoral Theses** (PhD) directed by CIC-IBMC scientists were presented



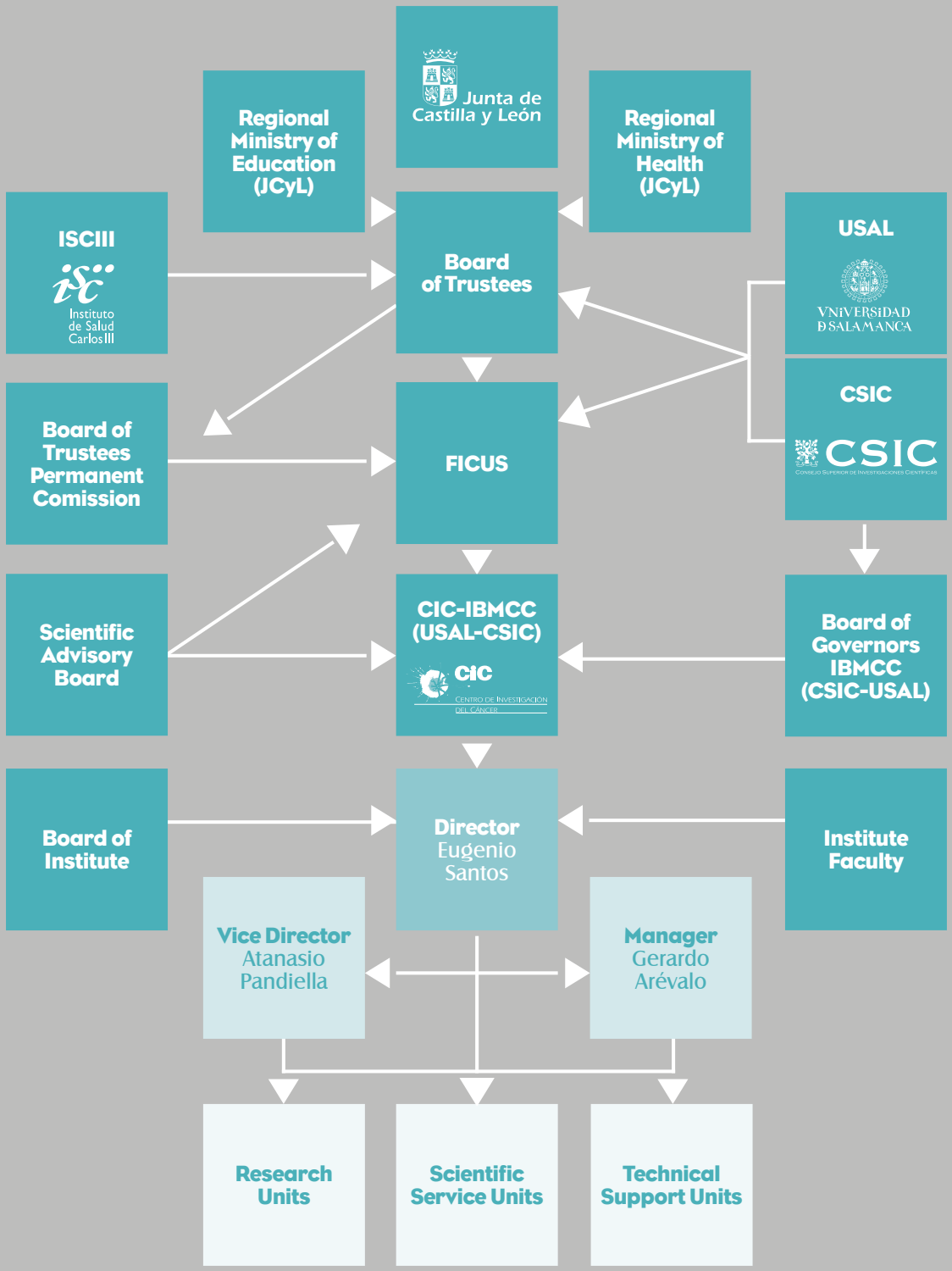
and successfully defended. Other activities included the continuation of our open **Cancer Seminar Series** program, which involved 70 different national and international speakers and the celebration of **8 specialized congresses/ symposia/courses** also organized by our institution that involved the participation of more than 70 different speakers and the attendance of more than 750 participants.

As an integral cancer research center, our main goal at the CIC-IBMCC must be to maintain and improve on a yearly basis our 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**. Unlike other competitor research centers, most of those costs are covered at the CIC-IBMCC by deducting funds from the competitive grant monies earned by the PIs in its scientific staff. It is obvious that such a situation deeply compromises our competitiveness and long-term viability as well as our ability to **keep first-rate scientists** in our staff or to **attract new, young talented researchers** to our cancer center in Salamanca. Under these circumstances, a pressing, major task facing the directive teams of CIC-IBMCC and FICUS for the immediate future will be to continually remind our **sponsoring institutions (USAL, CSIC, ISCIII, Junta de Castilla y León)** to fulfill their supporting role by covering with **structural, institutional funds** at least 50% of the regular operational costs of our Center. Unfortunately, our success with this request has been rather limited so far.

I want to conclude this foreword by expressing the most sincere **gratitude and recognition to all the scientific, technical and support staff personnel** of our Center, whose 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 past 15 years. Our deep gratitude is also due to the members of our External **Scientific Advisory Board**, who always provided the scientific guidance and steering needed to proceed adequately with our research work. Thanks also to the outside **sponsors and anonymous donors** who helped our center during this 15 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


Junta de Castilla y León
Regional Ministry of Education (JCyL)
Regional Ministry of Health (JCyL)
ISCIII
Instituto de Salud Carlos III
Board of Trustees
USAL
VNiVERSiDAD D SALAMANCA
Board of Trustees Permanent Comission
FICUS
CSIC
CSIC
Scientific Advisory Board
CIC-IBMCC (USAL-CSIC)
CIC
CENTRO DE INVESTIGACIÓN DEL CÁNCER
Board of Governors IBMCC (CSIC-USAL)
Board of Institute
Director Eugenio Santos
Institute Faculty
Vice Director Atanasio Pandiella
Manager 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.

ORGANIZATION

Board of Trustees of the Cancer Research Foundation of the University of Salamanca (FICUS)

President

Excmo. Sr.

D. Daniel Hernández Ruipérez

Rector of the Salamanca University (USAL)

Vice president

Excmo. Sr.

D. Emilio Lora-Tamayo D'Ocon

President of the Spanish National Research Council (CSIC)

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D. Antonio María Sáez Aguado

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D. Fernando Rey Martínez

Education Counsellor of Castilla y León Government

D. Juan Manuel Corchado Rodríguez

Vice-Chancellor of Research and Knowledge Transfer

D. Ricardo López Fernández

Vice-Chancellor of Economic Affairs

D. Jesús Fernández Crespo

Director of the Health Institute Carlos III

D. Eugenio Santos

Director of Institute of Molecular Biology and Cancer (IBMCC)

D. José Ignacio Sánchez Galán

President of Social Council of Salamanca University

Secretary

D. Gerardo Arévalo Vicente

Head of Economic Affairs of the University of Salamanca

ORGANIZATION

Scientific Advisory Board

Chairman

Dr. Elías Campo
Hospital Clínic, Barcelona

Members

Dr. Eduardo Díaz Rubio
University Hospital "San Carlos", Madrid

Dr. Juan Bernal Carrasco
"Alberto Sols" Biomedical Research Institute, Madrid

Dr. Carlos López Otín
University of Oviedo, Oviedo

Dr. Francisco Sánchez Madrid
University Hospital "La Princesa", Madrid

Dr. Julio Rodríguez Villanueva
Honorary Deputy Chairman, Scientific Council of the Ramón Areces Foundation, Madrid

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

ORGANIZATION

Research Units

Basic Research

GTPases and cancer. Ras mediated signalling
Eugenio Santos

Role of oncogenic molecules and cytoskeletal regulators in cancer and other high-incidence diseases
Xosé R. Bustelo

Kinases in oncology and neurodegeneration. Signalling 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

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

Animal models in cancer. 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

Immunology and cancer
José Alberto Orfao de Matos Correia e Vale

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

Cell death and cancer. Atypical cell death pathways
Felipe X. Pimentel-Muiños

Bioinformatics and functional genomics of cancer
Javier De las Rivas

Clinical Research

Oncohematology
Marcos González Díaz

Hereditary cancer
Rogelio González Sarmiento

Clinical and molecular analysis of solid tumors
Juan Jesús Cruz Hernández

ORGANIZATION

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**

Molecular & Cellular Diagnostics
Scientific Coordinators: **José Alberto Orfao de Matos Correia e Vale / Jesús María Hernández Rivas / Marcos González Díaz**

Comparative Molecular Pathology
Scientific Coordinator: **Carmen García Macías**

Hereditary Cancer & Genetic Counselling
Scientific Coordinators: **Rogelio González Sarmiento / Juan Jesús Cruz Hernández**

Structural Biology
Scientific Coordinator: **José María de Pereda Vega**

Microscopy
Scientific Coordinators: **Atanasio Pandiella / Alberto Martín Pendás**

ORGANIZATION

Technical Support Units

Manager

Secretary

Administration

Communication & Marketing

Equipment & Building Maintenance

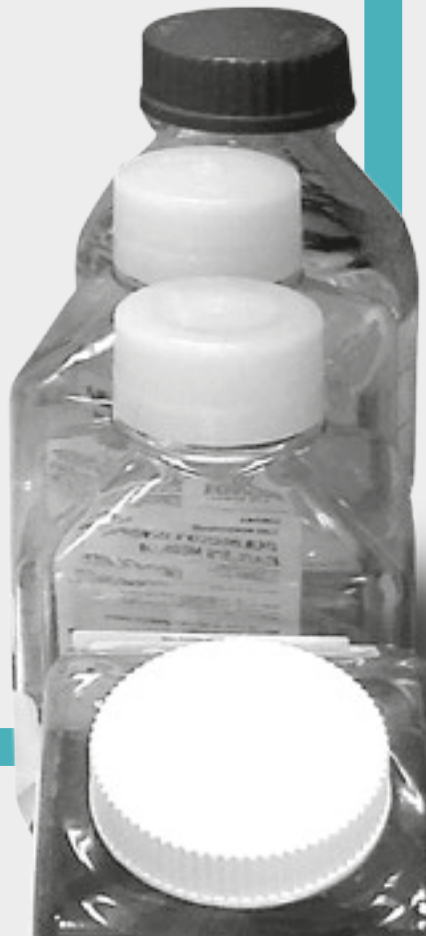
Quality Control & Risk Prevention

Information Technologies Service

Central Warehouse & Radiological Protection

Glassware Cleaning, Media / Solutions Preparation & Sterilization

3 RESEARCH UNITS



Fotografía: Sergio R. Manzano

LABORATORY 1

GTPases and cancer. Ras mediated signalling

Team Leader

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Research Team

Senior Researcher

Alberto Fernández Medarde

Postdoctoral

Fernando Calvo Baltanás

Carmela Gómez Rodríguez

David Jimeno García

Begoña Anta Rodríguez

Rósula García Navas

Predoctoral

Alicia Ginel Picardo

Mª Pilar Liceras Boillos

Technician

Nuria Calzada Nieto

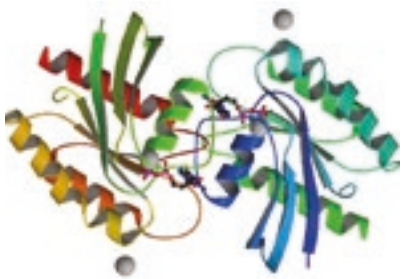
Ximena Marcela Bonilla Fore

María Luz Hernández Mulas

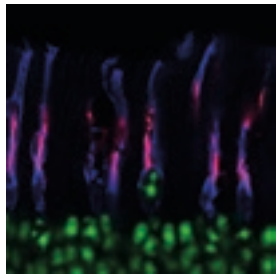
María Santos Jiménez Rodríguez

Master Student

Rocío Fuentes Mateos



3D Structure of K-Ras protein dimers.



"Ectopic" nuclei of retinal cone photoreceptors in RasGRF2-KO mice

During this period we focused our research on genomic/ proteomic and functional analyses of knockout mice strains lacking RAS or GEF genes (H-ras, N-ras, K-ras, RasGrf1, RasGrf2, Sos1, Sos2) individually or in combination. Research work was specifically aimed at determining the functional specificity -or redundancy- of different Ras and RasGEF isoforms in various physiological or pathological contexts. The bulk of the experimental evidence generated so far supports the hypothesis of functional specificity for the different Ras and RasGEF isoforms analyzed.

Regarding the functional specificity of members of the Ras family, our work has demonstrated that different Ras isoforms play distinct cellular roles, with a critical functional involvement of N-RAS in immune modulation/host defense and apoptotic responses, and of K-RAS in control of progression through the G1/S phase of the cell cycle. In collaborative studies we also showed differential involvement of H-RAS and K-RAS in downstream signaling as well as the specific functional contribution of R-RAS2 to mammary gland development and of H-RAS to renal physiology and control of peripheral vascular pressure.

The study of our single or double RasGrf1/ RasGrf2 knockout mice has also documented their differential functionality demonstrating that RasGRF1 plays specific roles in control of pancreatic beta cells and neurosensory processes including visual photoreception, and that RasGRF2 cooperates with VAV proteins in T cell signaling and lymphomagenesis. Our work participating in international consortiums performing GWAS studies supports a role of RasGRF1 in predisposition to myopia and refractive errors of vision, and of RasGRF2 in predisposition to addictive substance (alcohol) abuse. 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.

The functional role of the SOS1 and SOS2 RasGEF proteins has also been analyzed in adult mice using a conditional, tamoxifen-inducible, Sos1-KO model generated in this laboratory. We showed that Sos1/2-DKO (double-knockout) animals die precipitously whereas individual, adult Sos1-KO and Sos2-KO mice are perfectly viable, thus demonstrating 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 oxidative stress and demonstrated functional prevalence of SOS1 over SOS2 with regards to cellular proliferation and viability.

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E-mail: afm@usal.es

SENIOR RESEARCHER

Role for Ras Guanine Nucleotide Exchange Factors RasGrf1 and RasGrf2 in Central Nervous System

Role of Ras GEFs RasGrf1 and RasGrf2 in the Central Nervous System. Characterization of the proteins involved in physiological processes regulated by these GEFs: sensory perception and memory generation.

Strategic objectives

(i) Involvement of RasGrfs in adult neurogenesis.
(ii) Role for RasGrf1 and RasGrf2 in odor detection.
(iii) Analysis of the mechanisms underlying the photoreceptor problems in RasGrf1 KO mice.
(iv) A role for RasGrf1 in lens morphogenesis and myopia.

Main lines of research

(1) RasGrf1 KO mice phenotype.
(2) RasGrf2 KO mice phenotype.
(3) Role of RasGrf1 and RasGrf2 in sensory detection.
(4) Role of RasGrf1 and RasGrf2 en neuronal differentiation and adult neurogenesis.

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.
- Disclosing the role of RasGrf2 in binge drinking and alcohol preference.

Future goals

(a) RasGrf1 and RasGrf2 and odor detection.
(b) Mechanisms underlying the changes in the lens of the RasGrf1 KO animals.
(c) Analysis of RasGrf2 role in addiction to alcohol and drugs.
(d) Implication of RasGrf1 and RasGrf2 in neuronal differentiation and adult neurogenesis.

Publications

1 **Rasgrf2 controls noradrenergic involvement in the acute and subchronic effects of alcohol in the brain.** Easton AC, Rotter A, Lourdusamy A, Desrivières S, Fernández-Medarde A, Biermann T, Fernandes C, Santos E, Kornhuber J, Schumann G, Müller CP. **Psychopharmacology (Berl). 2014 Oct;231(21):4199-209. doi: 10.1007/s00213-014-3562-x. Epub 2014 Apr 16.** PMID: 24737505 **IF: 3,875 / Q1**

2 **Dimerization opens new avenues into Ras signaling research.** Santos E. **Sci Signal. 2014 May 6;7(324):pe12. doi: 10.1126/scisignal.2005318.** PMID: 24803535 **IF: 6,279 / Q1**

3 **Transcriptional profiling reveals functional links between RasGrf1 and Pttg1 in pancreatic beta cells.** Manyes L, Arribas M, Gómez C, Calzada N, Fernández-Medarde A, Santos E. **BMC Genomics. 2014 Nov 25;15:1019. doi: 10.1186/1471-2164-15-1019.** PMID: 25421944 **IF: 3,986 / Q1**

4 **Rasgrf2 controls dopaminergic adaptations to alcohol in mice.** Easton AC, Rotter A, Lourdusamy A, Desrivières S, Fernández-Medarde A, Biermann T, Fernandes C, Santos E, Kornhuber J, Schumann G, Müller CP. **Brain Res Bull. 2014 Oct; 109:143-50. doi: 10.1016/j.brainresbull.2014.10.008. Epub 2014 Oct 22.** PMID: 25454123 **IF: 2,718 / Q3**

5 **Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy.** Pérez-Herrero E, Fernández-Medarde A. **Eur J Pharm Biopharm. 2015 Jun;93:52-79. doi: 10.1016/j.ejpb.2015.03.018. Epub 2015 Mar 23. Review.** PMID: 25813885 **IF: 3,850 / Q1**

6 **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, Martínot JL, Nees F, Paus T, Pausova Z, Rietschel M, Rotter A, Santos E, Smolka M, Sommer W, Mameli M, Spanagel R, Girault JA, Mueller C, Schumann G; IMAGEN consortium. **J Psychiatry Neurosci. 2015 Dec 11;41(2):150138. doi: 10.1503/jpn.150138.** PMID: 26679926 **IF: 5,861 / Q1**

7 **RasGRF2 controls nuclear migration in postnatal retinal cone photoreceptors.** David Jimeno, Carmela Gómez, Nuria Calzada, Pedro de la Villa, Concepción Lillo, Eugenio Santos. **J Cell Sci. 2015. doi:10.1242/jcs.180919 In press. IF: 5,432 / Q1**

Grants for research in progress

Project	IP	Grant	Time	Funding
Los ratones KNOCKOUT para RASGRF1 y RASGRF2 como modelos de degeneración retiniana	Eugenio Santos	Fundación Lucha Contra La Ceguera	2013-2014	24,000.00 €
Red Temática de Investigación Cooperativa en Cáncer (RD12/0036/0001)	Eugenio Santos (national coordinator)	Instituto de Salud Carlos III	2013-2016	442,343.65 €
Activadores Ras-GEF de las familias Sos y Grf como marcadores y dianas en procesos de desarrollo normal y tumoral	Eugenio Santos	Consejería de Educación Junta de Castilla y León	2013-2014	35,000.00 €
Activación de oncopreotínas Ras por GEFs de las familias Sos y Grf y su implicación en procesos fisiológicos y tumorales. Validación como biomarcadoresy/o dianas terapéuticas	Eugenio Santos	Ministerio de Sanidad y Consumo	2014-2016	195,415.00 €
Las proteínas Sos como dianas terapéuticas en leucemia mieloide crónica	Alberto Fernández Medarde	Junta de Castilla y León - Consejería de Sanidad	2014	25,110.00 €

Other activities & relevant facts

- During this period the IP of this group has continued his activities as director of the CIC IBMCC, national coordinator of the Spanish Cancer Research Network (RTICC, ISCIII) and member of various scientific advisory bodies including, among others, the Scientific Foundation of the AECC, the Cancer Strategy of the SNS or the European Academy of Cancer Sciences.

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Rodrigo Hernando Llorente

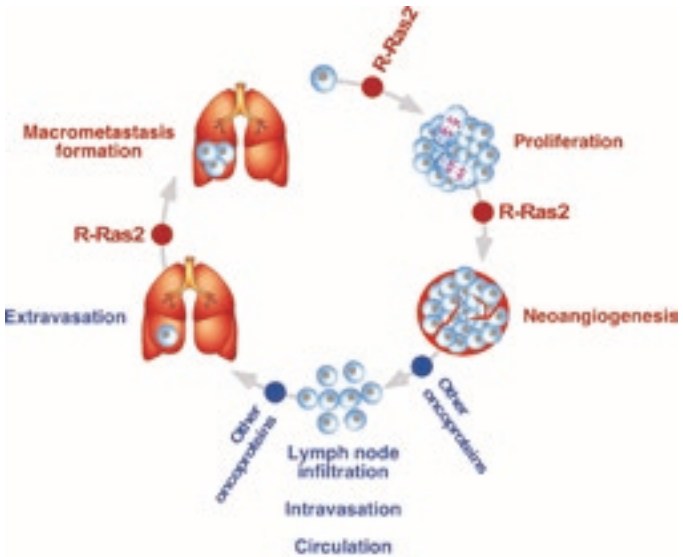
Alba Vicente Blázquez

LABORATORY 2

Role of oncogenic molecules and cytoskeletal regulators in cancer and other high-incidence diseases

3.2 — LABORATORY 2

Role of oncogenic molecules and cytoskeletal regulators in cancer and other high-incidence diseases



Our research is focused on the functional characterization of signal transduction molecules with oncogenic potential and, particularly, on the functional analysis of oncoproteins specialized in connecting the stimulation of membrane receptors with signaling routes that lead to both cytoskeletal change and mitogenic processes.

Within this general goal, the current research of our laboratory is aimed at solving the following biological issues:

(1) Functional characterization of the Vav oncoprotein family, a group of signal transduction molecules that work as phosphorylation-dependent GDP/GTP exchange factors for the GTPases of the Rho/Rac family.

(2) Functional analysis of specific members of Rho/Rac family of GTPases.

(3) Characterization of the role of these signaling routes in cancer, paying attention to both intrinsic (proliferation, survival, metastasis) and extrinsic (angiogenesis, inflammatory response) pathways that affect the final fitness of tumors in vivo.

(4) Characterization of the role of these signal transduction pathways in other high incidence health problems such as cardiovascular disease and metabolic syndrome.

(5) Development of new therapeutic avenues and gene signatures to treat and diagnose the foregoing diseases from those signaling routes.

To achieve these aims, our laboratory utilizes a quite diverse collection of experimental tools, including biochemical, cell biology, cell signaling, genome-wide high-throughput and in silico tools as well as genetically modified animal models.

Fotografía: Sergio R. Manzano

SENIOR RESEARCHER

Ribosome synthesis and cell growth

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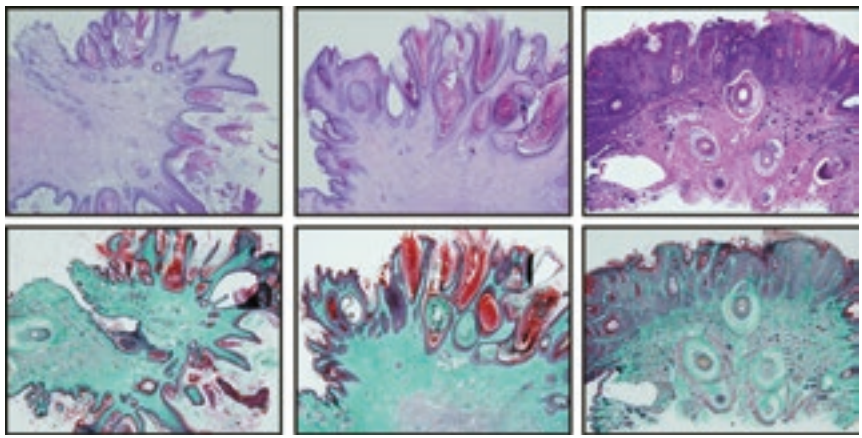
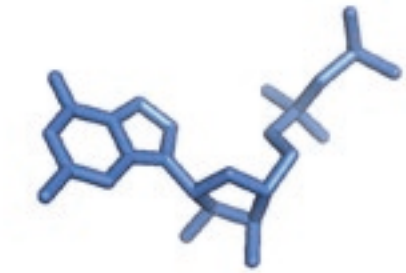
Our group is interested on the characterization of the assembly and regulatory mechanisms that mediate the biosynthesis of ribosomes. In addition to its housekeeping roles, it is now known that alterations in this biological process can lead to human diseases. In this context, we have three main short-term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

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

To this end, our lab used a number of biochemical, proteomic, and genetic studies using both yeast and high eukaryotic cells as models.





Publications

1 **The C-terminal SH3 domain contributes to the intramolecular inhibition of Vav family proteins.** Barreira M, Fabbiano S, Couceiro JR, Torreira E, Martínez-Torrecuadrada JL, Montoya G, Llorca O, Bustelo XR. **Sci Signal. 2014 Apr 15;7(321):ra35. doi: 10.1126/scisignal.2004993.** PMID: 24736456 **IF: 6,279 / Q1**

2 **Contribution of the R-Ras2 GTP-binding protein to primary breast tumorigenesis and late-stage metastatic disease.** Larive RM, Moriggi G, Menacho-Márquez M, Cañamero M, de Álava E, Alarcón B, Dosil M, Bustelo XR. **Nat Commun. 2014 May 14;5:3881. doi: 10.1038/ncomms4881.** PMID: 24826867 **IF: 11,470 / D1**

3 **VAV3 mediates resistance to breast cancer endocrine therapy.** Aguilar H, Urruticoechea A, Halonen P, Kiyotani K, Mushiroda T, Barril X, Serra-Musach J, Islam A, Caizzi L, Di Croce L, Nevedomskaya E, Zwart W, Bostner J, Karlsson E, Pérez Tenorio G, Fornander T, Sgroi DC, García-Mata R, Jansen MP, García N, Bonifaci N, Climent F, Soler MT, Rodríguez-Vida A, Gil M, Brunet J, Martrat G, Gómez-Baldó L, Extremera AI, Figueras A, Balart J, Clarke R, Burnstein KL, Carlson KE, Katzenellenbogen JA, Vizoso M, Esteller M, Villanueva A, Rodríguez-Peña AB, Bustelo XR, Nakamura Y, Zembutsu H, Stål O, Beijersbergen RL, Pujana MA. **Breast Cancer Res. 2014 May 28;16(3):R53. doi: 10.1186/bcr3664.** PMID: 24886537 **IF: 5,490 / Q1**

4 **Coronin1 proteins dictate rac1 intracellular dynamics and cytoskeletal output.** Ojeda V, Castro-Castro A, Bustelo XR. **Mol Cell Biol. 2014 Sep 15;34(18):3388-406. doi: 10.1128/MCB.00347-14. Epub 2014 Jun 30.** PMID: 24980436 **IF 4,777 / Q1**

5 **Genetic dissection of the vav2-rac1 signaling axis in vascular smooth muscle cells.** Fabbiano S, Menacho-Márquez M, Sevilla MA, Albarrán-Juárez J, Zheng Y, Offermanns S, Montero MJ, Bustelo XR. **Mol Cell Biol. 2014 Dec;34(24):4404-19. doi: 10.1128/MCB.01066-14. Epub 2014 Oct 6.** PMID: 25288640 **IF: 4,777 / Q1**

6 **K-RasV14I recapitulates Noonan syndrome in mice.** Hernández-Porras I, Fabbiano S, Schuhmacher AJ, Aicher A, Cañamero M, Cámara JA, Cussó L, Desco M, Heeschen C, Mulero F, Bustelo XR, Guerra C, Barbacid M. **Proc Natl Acad Sci U S A. 2014 Nov 18;111(46):16395-400. doi: 10.1073/pnas.1418126111. Epub 2014 Oct 30.** PMID: 25359213 **IF: 9,674 / D1**

7 **Rrp12 and the Exportin Crm1 participate in late assembly events in the nucleolus during 40S ribosomal subunit biogenesis.** Moriggi G, Nieto B, Dosil M. **PLoS Genet. 2014 Dec 4;10(12):e1004836. doi: 10.1371/journal.pgen.1004836. eCollection 2014 Dec.** PMID: 25474739 **IF: 7,528 / D1**

8 **Vav family exchange factors: an integrated regulatory and functional view.** Bustelo XR. **Small GTPases. 2014;5(2):9. doi: 10.4161/21541248.2014.973757. Review.** PMID: 25483299 **IF: NI**

9 **New avenue to inhibit Ras signaling.** Bustelo XR. **Chem Biol. 2014 Dec 18;21(12):1599-600. doi: 10.1016/j.chembiol.2014.12.001.** PMID: 25525987 **IF: 6,645 / Q1**

10 **The disease-linked Glu-26-Lys mutant version of coronin 1a exhibits pleiotropic and pathway-specific signaling defects.** Ojeda V, Robles-Valero J, Barreira M, Bustelo XR. **Mol Biol Cell. 2015 Jun 24. pii: mbc.E15-01-0052.** PMID: 26108624 **IF: 4,466 / Q2**

11 **Identification of a Vav2-dependent mechanism for GDNF/Ret control of mesolimbic DAT trafficking.** Zhu S, Zhao C, Wu Y, Yang Q, Shao A, Wang T, Wu J, Yin Y, Li Y, Hou J, Zhang X, Zhou G, Gu X, Wang X, Bustelo XR, Zhou J. **Nat Neurosci. 2015 Aug;18(8):1084-93. doi: 10.1038/nn.4060. Epub 2015 Jul 6.** PMID: 26147533 **IF: 16,095 / D1**

12 **Immunosuppression-independent role of regulatory t cells against hypertension-driven renal dysfunctions.** Fabbiano S, Menacho-Márquez M, Robles-Valero J, Pericacho M, Matesanz-Marín A, García-Macías C, Sevilla MA, Montero MJ, Alarcón B, López-Novoa JM, Martín P, Bustelo XR. **Mol Cell Biol. 2015 Aug 3. pii: MCB.00518-15.** PMID: 26240279 **IF: 4,777 / Q1**

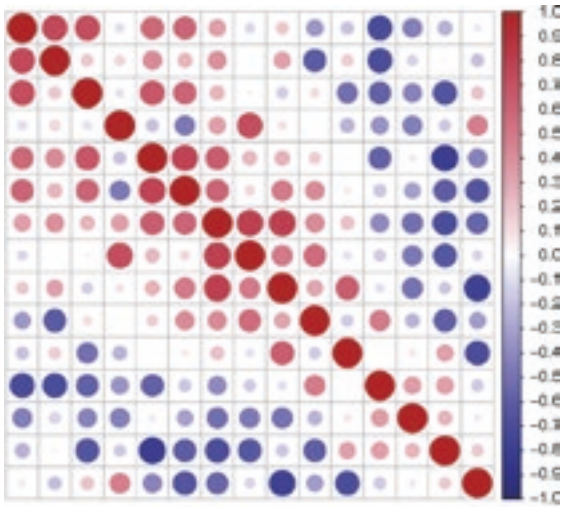
Other publications & book chapters

1 **Rho/Rac GTPases.** Bustelo, X.R. (2014). **In Encyclopedia of Medical Immunology (Vol. 1: Autoimmune diseases). I. Mackay and N. R. Rose (Editors). Springer.** ISBN 978-0-387-84827-3

Grants for research in progress

Project	IP	Grant	Time	Funding
Role of the oncogenic TC21 GTPase in tumorigenic processes	Xosé R. Bustelo	Spanish Association against Cancer	2009-2014	1,200,000.00 €
Role of the oncogenic GTPase TC21 in breast cancer (CSI101U13)	Xosé R. Bustelo	Castilla & León Education Ministry	2013-2014	35,000.00 €
Vav family oncoproteins: new inroads about their regulation, effector routes and potential value as therapeutic targets for high-incidence diseases (SAF2012-31371)	Xosé R. Bustelo	Spanish Ministry of Economy and Competitiveness	2013 - 2015	468,000.00 €
Spanish Cancer Cooperative Network (RD12/0036/0002)	Xosé R. Bustelo	Carlos III Health Institute	2013 - 2016	322,000.00 €
Role of the oncogenic TC21 GTPase in lung cancer (CSI101U13)	Xosé R. Bustelo	Castilla & León Education Ministry	2013-2014	35,000.00 €
Vav proteins: catalytic role in skin tumorigenesis and tumor fate reprogramming	Xosé R. Bustelo	Worldwide Cancer Research	2014-2017	232,000.00 €
Role of the RRAS2 oncogene in lung tumorigenesis (BIO/SA01/15)	Xosé R. Bustelo	Castilla & León Health Ministry	2015	53,800.00 €
Análisis fármaco-mimético del valor terapéutico de rutas metabólicas Vav-dependientes en cáncer de mama	Xosé R. Bustelo	Ramón Areces Foundation	2015-2018	128,000.00 €
Molecular functions of ribosomal biogénesis factors (BFU2011-23668)	Mercedes Dosil	Spanish Ministry of Science and Innovation	2012-2014	113,740.00 €
Molecular mechanisms that integrate the distinct steps of the ribosomal biosynthetic pathways	Mercedes Dosil	Spanish Ministry of Economy and Competitiveness	2015-2017	169,400.00 €

Other activities & relevant facts



Scientific appointments

- 2013–Present — Coordinator. Molecular Mechanisms Program of the 3rd Spanish Cancer Cooperative Network
- 2013–Present — Member of the Executive Committee. 3rd Spanish Cancer Cooperative Network
- 2014–Present — Vice-Director. Centro de Investigación del Cáncer/Cancer Research Center, CSIC-University of Salamanca, Salamanca, Spain

Editorial Boards

- Front. Immunol. (since 2010)
- Small GTPases (since 2011)
- Encyclopedia of Signaling Molecules (since 2012)
- Front. Cell Develop Biol (since 2015)

Membership in Scientific Committees

- External Scientific Committee. Oncology Program, Santiago University Hospital (Santiago of Compostela, Spain, 2006-Present)
- External Scientific Committee. Galician Colon Cancer Network (Galicia, Spain, 2012-Present)
- 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)
- External Scientific Committee. La Princesa Hospital Health Research Institute (Madrid, Spain, 2009-Present)
- Scientific Committee. Biotech Annual Congress (Salamanca, Spain, 2014-2015)

Fotografía: Sergio R. Manzano

LABORATORY 4

Kinases in oncology and neurodegeneration. Signalling by nuclear serine-threonine kinases

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Kinases in oncology and neurodegeneration. Signalling by nuclear serine-threonine kinases

There is a unique and isolated family of Ser-Thr kinases in the human kinome known as VRK (vaccinia-related kinases). A family formed by three members that appeared very late in evolution and coordinate multiple functions in higher eukaryotes. Most of the intracellular signals are transmitted by Ser-Thr kinases. 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 role human VRK family and we are studying 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 chromatin structure.

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 cell response to genetic damage either natural (oxidative stress, UV) or induced (tobacco, radiation, chemotherapy).

5 Characterize and integrate VRK pathways in the context chromatin remodeling and its association to DNA response pathways, neurodegenerative diseases and stem cells.

6 Characterize the mechanism by which mutations of VRK1 contribute to neurological diseases such as spinal muscular atrophy (SMA) or amyotrophic lateral sclerosis (ALS).

Publications

1 Gene amplification of the histone methyltransferase SETDB1 contributes to human lung tumorigenesis. Rodríguez-Paredes M, Martínez de Paz A, Simó-Riudalbas L, Sayols S, Moutinho C, Morán S, Villanueva A, Vázquez-Cedeira M, Lazo PA, Carneiro F, Moura CS, Vieira J, Teixeira MR, Esteller M. **Oncogene. 2014 May 22;33(21):2807-13. doi: 10.1038/onc.2013.239. Epub 2013 Jun 17.** PMID: 23770855 **IF: 8,459 / D1**

2 VRK1 interacts with p53 forming a basal complex that is activated by UV-induced DNA damage. López-Sánchez I, Valbuena A, Vázquez-Cedeira M, Khadake J, Sanz-García M, Carrillo-Jiménez A, Lazo PA. **FEBS Lett. 2014 Mar 3;588(5):692-700. doi: 10.1016/j.febslet.2014.01.040. Epub 2014 Jan 31.** PMID: 24492002 **IF: 3,169 / Q2**

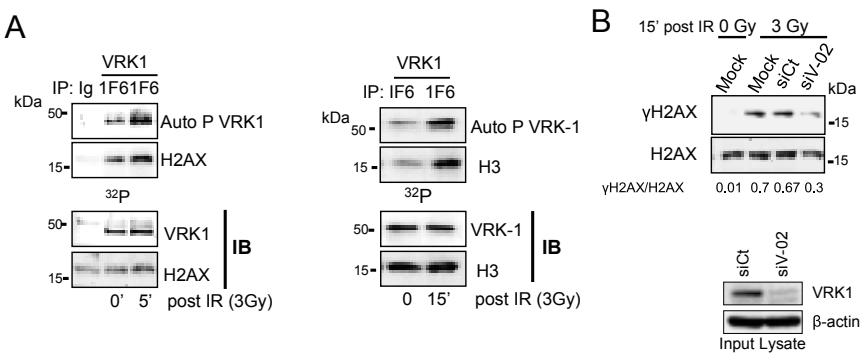
3 Vaccinia-related kinase 1 (VRK1) confers resistance to DNA-damaging agents in human breast cancer by affecting DNA damage response. Salzano M, Vázquez-Cedeira M, Sanz-García M, Valbuena A, Blanco S, Fernández IF, Lazo PA. **Oncotarget. 2014 Apr 15;5(7):1770-8.** PMID: 24731990 **IF: 6,359 / D1**

4 The spinal muscular atrophy with pontocerebellar hypoplasia gene VRK1 regulates neuronal migration through an amyloid-ß precursor protein-dependent mechanism. Vinograd-Byk H, Sapir T, Cantarero L, Lazo PA, Zeligson S, Lev D, Lerman-Sagie T, Renbaum P, Reiner O, Levy-Lahad E. **J Neurosci. 2015 Jan 21;35(3):936-42. doi: 10.1523/JNEUROSCI.1998-14.2015.** PMID: 25609612 **IF: 6,344 / Q1**

5 VRK1 chromatin kinase phosphorylates H2AX and is required for foci formation induced by DNA damage. Salzano M, Sanz-García M, Monsalve DM, Moura DS, Lazo PA. **Epigenetics. 2015;10(5):373-83. doi: 10.1080/15592294.2015.1028708. Epub 2015 Apr 29.** PMID: 25923214 **IF: 4,780 / Q1**

6 VRK1 regulates Cajal body dynamics and protects coilin from proteasomal degradation in cell cycle. Cantarero L, Sanz-García M, Vinograd-Byk H, Renbaum P, Levy-Lahad E, Lazo PA. **Sci Rep. 2015 Jun 12;5:10543. doi: 10.1038/srep10543.** PMID: 26068304 **IF: 5,578 / D1**

7 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, de Pouplana LR, Esteller M. **Oncogene. 2015 Dec 7. doi: 10.1038/onc.2015.469.** PMID:26640150 **IF: 8,459 / D1**



Effect of ionizing radiation on histone phosphorylation. (**A**). Endogenous VRK1 activated by IR phosphorylates H2AX (left panel) and H3 (right panel). Endogenous VRK1 was immunoprecipitated from A549 or MCF-7 cells. A control immunoprecipitation with αAU5 antibody. The immunoprecipitated VRK1 was used in an in vitro kinase assay using as substrate recombinant H2AX (left) or H3 (right). (**B**). Specifity of H2AX phosphorylation by VRK1 induced by IR. A549 cells were transfected with siRNA control (siCt) or siRNA for VRK1 (siV1-02).VRK1 was immunoprecipitated and used in a kinase assay. Expression of VRK1 is shown at the bottom and γH2AX phosphorylation was evaluated by immunoblots after histone acidic extraction with a phospho-specific antibody.

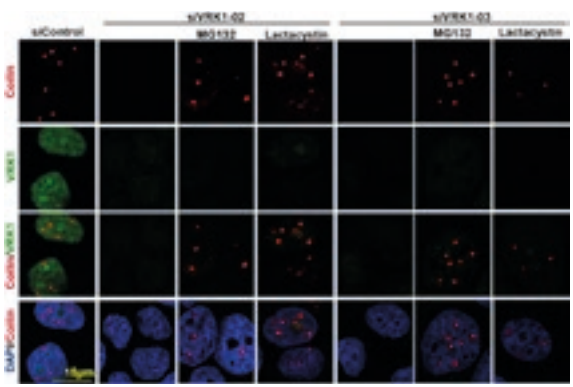
Grants for research in progress

Project	IP	Grant	Time	Funding
Cancer Biology (Biología del Cáncer) (SAF2014-577DC-REDC)	Pedro A. Lazo-Zbikowski Taracena	Red Consolider-Ministerio de Economía y Competitividad	2015-2016	45,000.00 €
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 €
Caracterización molecular de los efectos causados por mutaciones de VRK1 causante de hipoplasia pontocerebelar con atrofia muscular y ataxia (CSI002U14)	Pedro A. Lazo-Zbikowski Taracena	Junta de Castilla y León, Consejería de Educación	2014-2015	29,000.00 €

Other activities & relevant facts

Scientific appointments

- Member of the Advisory Council of EACR (European Association for Cancer Research) (2013-2016)
- President of ASEICA (Spanish Society for Cancer Research (2015-2016)



Proteasomal inhibitors protect CBs from VRK1 knock-down and serum deprivation. MCF7 cells were transfected with two different siRNA for VRK1: siVRK1-02 or siVRK1-03. Cells were incubated with MG132 (35 μM) for six hours, or with lactacystin (5 μM) for ten hours, before cells were lysed at seventy-two hours post knock-down. Cells were processed for immunofluorescence. Colin was detected with Pdelta monoclonal antibody and VRK1 with a polyclonal antibody. Sci. Rep 5:10543 (2015).

LABORATORY 5

Reversible processes in cell cycle control: Phosphorylation by CDK in mitosis and ubiquitylation of PCNA

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Patricia Ayala de la Roca

Vanesa Álvarez Álvarez

Technician

Sonia Andrés Recio

Master Students

Laura Ahumada Arranz

Amalia Muñiz Carrillo

Ana Pariente Delgado

Saúl Martín Sánchez

Janine Wörthmüller Rodríguez

Reversible processes in cell cycle control: Phosphorylation by CDK in mitosis and ubiquitylation of PCNA

Many cellular processes in eukaryotes are controlled by reversible events. Among them, protein phosphorylation or ubiquitylation are two different reversible processes key in the regulation of the cell cycle. These post-translational modifications of proteins depend on the activity of specific enzymes that target their substrates to regulate their activity, localization or (network) interactions. Mitosis is one of the cell cycle stages regulated by reversible phosphorylation events that coordinate in time and space diff erent processes such as chromosomal condensation and segregation. The cyclin-dependent protein kinase 1 (Cdk1), a conserved master kinase, plays a crucial role in the regulation of mitosis and is also regulated by a complex network of reversible phosphorylations. Entry into mitosis is promoted by high Cdk1 activity, which drive mitotic progression as far as metaphase. Then, Cdk1 must be inactivated at the end of mitosis, and dephosphorylation of Cdk1 substrates is required to reverse its eff ects and allow the cell exiting mitosis. In this regard, phosphatases are major effectors in the exit from mitosis. However, protein phosphatases also have regulatory roles before and during mitosis. In the budding yeast, the Cdc14 phosphatase is essential to promote the exit from mitosis. Cdc14 is a highly conserved dual specificity phosphatase, whose functions in higher eukaryotes remain poorly characterized. On the other hand, the identity of the phosphatases involved in opposing Cdk1 effects during mitosis is also poorly known in mammalian cells. Our group studies the role of human Cdc14 phosphatases in regulating Cdk1 activity, and the progression through mitosis by dephosphorylation of Cdk1 mitotic substrates. Our work is focused on the identification of in vivo Cdc14 substrates and the study of the regulatory mechanisms of human Cdc14 phosphatases. Our group is interested in studying the functions of Cdc14 proteins and to contribute with it to the knowledge of the cellular proliferation mechanisms.

A different reversible process in cell cycle progression is PCNA ubiquitylation. In this post-translational modification underlies the mechanism of tolerance to DNA damage in eukaryotes, one of the three major pathways that cells evolved to maintain genome integrity. It has been shown that PCNA is monoubiquitylated at Lys 164 by the ubiquitin ligase complex Rad6/Rad18 when the replication fork encounters damaged DNA. Damaged nucleotides in DNA prevent replicative polymerases synthesis and, thus, they have to be replaced by translesion synthesis DNA polymerases (TLS) in order to replicate over the damaged DNA. Based on the high-affinity that monoubiquitylated PCNA has for TLS polymerases, the current understanding is that cells ubiquitylate PCNA to allow the change from a replicative DNA polymerase to a TLS polymerase. Although the evolutionary conserved mechanism of PCNA ubiquitylation is well understood, the deubiquitylation of ubPCNA remains poorly characterized. Our research group is interested in understanding the role of the reversible PCNA ubiquitylation in the process of DNA polymerase switching during S phase.

These two aims, the analysis of dephosphorylation events in the control mitosis and PCNA deubiquitylation during S phase, perfectly match the general interest of our research team regarding the study of the mechanisms that regulate cell cycle progression in eukaryotes.

SENIOR RESEARCHER

Reversible phosphory-lation processes in the DNA damage response

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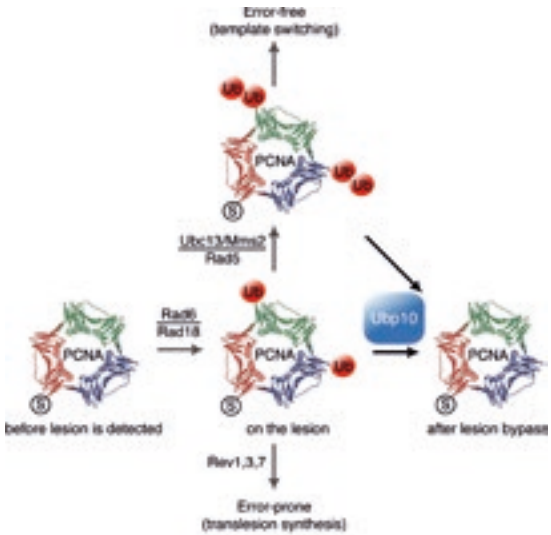
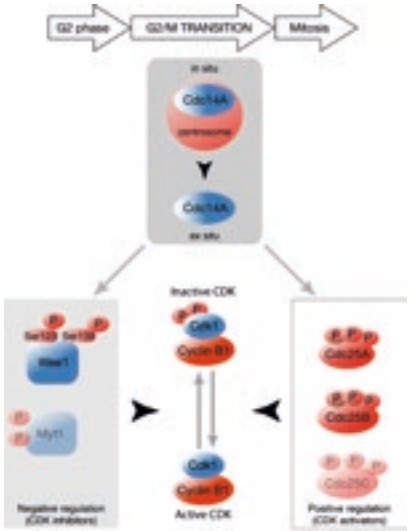
DNA damage is a major source of genome instability and cancer in living cells. To deal with DNA damage, cells have evolved the DNA damage response (DDR), a complex network of pathways that protect the integrity of the genome after genotoxic insults, which is essential to safeguarding cell and organism fitness. We are focused on deciphering the mechanisms by which DDR is regulated.

In the DDR are implicated cellular events such as cell cycle arrest, DNA repair, apoptosis and senescence, in which protein phosphorylation processes plays a major role. Moreover, in recent years, it has become increasingly clear that phosphatases regulate the DDR not only by counteracting the function of kinases, but also by initiation of specific DDR processes.

Cdc14 is an evolutinary conserved family of phosphatases with crucial roles in cell cycle control. Moreover, Cdc14 has been involved in cell cycle arrest upon replication stress in yeast. Over the last few years, we have used yeast and human culture cells in order to understand the relevance of these proteins in the control of cell division and proliferation. Our current work is focused on the analysis of human Cdc14 phosphatases in the control of the checkpoint response to DNA damage and/or its role in DNA repair mechanisms.



Working model for PCNA deubiquitylation at replication forks.



Human Cdc14A modulates Cdk1 activity at the G2/M transition of the cell cycle.

Other publications & book chapters

1 Bases moleculares del ciclo de división celular en organismos eucariotas. **(Bioquímica Básica)** Sacristán M.P., Vázquez-Novelle, M.D., y Bueno,A. **(2014) Capítulo 35 pp.: 489-501, Herrera-Castillón, E., Ramos-Álvarez, M.P., Roca-Salom, P., y Viana-Arribas, M.M., eds. Editorial Elsevier.** ISBN (edición impresa) 978-84-8086-898-3 ISBN (edición electrónica) 978-84-9022-388-8

Grants for research in progress

Project	IP	Grant	Time	Funding
Estudio de procesos reversibles en el control del ciclo celular: Fosforilación por CDK en mitosis y ubiquitinación de PCNA (BFU2012-30787)	Avelino Bueno	Ministerio de Economía y Competitividad	2013-2015	196,560.00 €
Fosfatasas en el mantenimiento de la estabilidad genómica: el papel de Cdc14B en la respuesta celular frente a daño en el DNA	María P. Sacristán	Fundación Samuel Solórzano Barroso	2015	2,808.00 €

LABORATORY 6

Cell death and cancer therapy

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Gláucia Fernanda Rocha D'Epiro

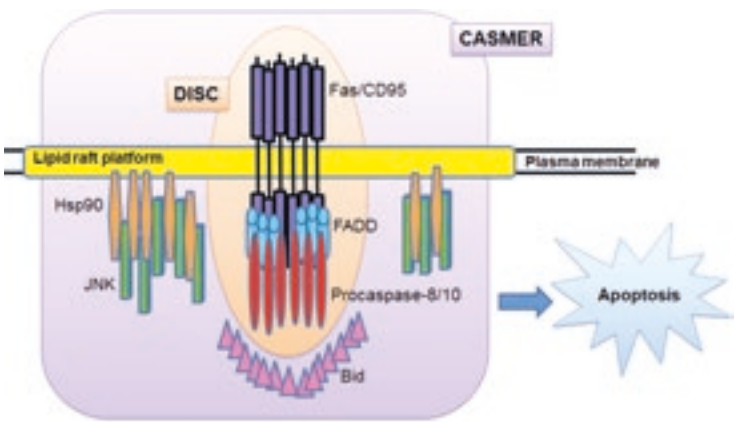
One of the major hallmarks of cancer cells is a deficient ability to undergo cell death, particularly apoptosis. A deficient apoptosis response in cancer cells increases their malignancy, favoring accumulation of mutations and rendering tumor cells resistant to therapy. This implies that a therapeutic potential for cancer treatment may lie in potentiating apoptosis. Thus, apoptosis-targeted therapy can be a new and effective way to kill tumor cells. In this regard, we have found that death receptors as well as downstream signaling molecules are recruited into lipid raft membrane domains upon addition of some anticancer drugs, thus acting as the linchpin from which a potent apoptotic response is launched, and linking lipid rafts and cancer chemotherapy. Co-clustering of death receptors and membrane rafts regulates apoptosis and constitutes a novel anticancer target. In addition, lipid rafts act as scaffolds for additional proteins involved in dictating cell fate, leading to apoptosis or survival. Translocation of Fas/CD95 death receptor into membrane rafts can be rendered independently of Fas/CD95 ligand, thus opening new prospects for pharmacological intervention. Furthermore, additional subcellular structures, particularly mitochondria and endoplasmic reticulum, play a major role in regulating cell death, and thereby can also be targets in cancer therapy. The antitumor compounds collectively known as alkylphospholipid analogs (APLs) are the first lipid raft-targeted drugs that promote apoptosis in a number of cancer cells both in vitro and in vivo. The antitumor ether lipid edelfosine, considered as the prototypic APL molecule, induces apoptosis through a raft-mediated process in several hematological cancers as well as through an endoplasmic reticulum stress response in solid tumor cells. Both signaling routes involve mitochondria as a critical organelle in the cell death outcome. In addition, we are interested in understanding the role of inflammation in cancer, and how arginase, highly abundant in neutrophils, affects cancer development.

Objectives

- Characterization and role of membrane rafts in apoptosis induction and cancer chemotherapy.
- Functional relationship between membrane rafts and subcellular structures affecting cell fate.
- Lipid metabolism in cancer cell development and therapy.
- Search for novel anticancer drugs targeting cell death in tumor cells.
- Mechanism of action of antitumor ether lipids (also known as alkylphospholipid analogs, APLs) as pro-cell death agents against cancer cells. Identification of distinct types of cell death induced by APLs.
- Analysis of cell death in cancer stem cells and cancer stem cell targeting in cancer therapy.
- Role and mechanisms of action of antitumor APLs as drugs for additional biomedical applications (inflammatory diseases, leishmaniasis).
- Use of additional biological systems (yeast, *Caenorhabditis elegans*) to uncover new signaling routes regulating cell death and to study the mechanisms of action of APLs and additional anticancer drugs.
- Inflammation and cancer relationship.
- Role of neutrophils and arginase in cancer.
- Neutrophils as a model system for the search of new therapeutic targets in cancer.
- Targeting of cancer stem cells.

Main Lines of Research

We first reported the recruitment of Fas/CD95 receptor in lipid rafts as a new way to regulate apoptosis in cancer cells, thus identifying lipid rafts as a novel therapeutic target. This finding opened a new therapeutic approach in cancer treatment, and we are devoted to uncover the role of lipid rafts in regulating cell death and survival. We have coined the term CASMER, as an acronym for «cluster of apoptotic signaling molecule-enriched rafts», to refer to the recruitment of death receptors together with downstream apoptotic signaling molecules in aggregated rafts, thus leading to a raft-based supramolecular entity playing a major role in apoptosis regulation. We are mainly involved in the study of the mechanism of action of APLs as anticancer drugs against both hematological and solid tumors, especially the ether phospholipid edelfosine, considered as the first lipid raft-targeted drug. Furthermore, major interests in our lab also include the search for new drugs and therapeutic targets in pancreatic cancer, as well as the elucidation of the role of cancer stem cells in pancreatic cancer, and other additional gastrointestinal cancers, as a major target in cancer therapy. In addition, we are studying neutrophil development to understand how a proapoptotic phenotype is generated. We are also analyzing new pro-cell death routes in additional biological systems, including yeast and *C. elegans*, which in turn are being used as model organisms to uncover the mechanism of action of APLs. Overall, our major focus is the identification of novel targets, and the design of new therapeutic agents and approaches, to eventually induce the onset of cell death in tumor cells as an apoptosis- or cell death-targeted therapy in cancer. Particular emphasis is placed on the role of subcellular structures, including lipid raft membrane domains, endoplasmic reticulum and mitochondria, as major targets for cancer therapy and in the mechanism of action of APLs. In addition, we are analyzing how APLs can promote distinct types of cell death in different cancer cells, and trying to understand the triggers and signaling cross-talk controlling cell death commitment. As a result of the ability of edelfosine to promote cell death in different biological systems, we are also studying the underlying mechanisms involved in the antiparasitic action of this ether lipid.



The concept of CASMER (cluster of apoptotic signaling molecule-enriched rafts). A number of apoptotic signaling molecules, including CD95, FADD and procaspase-8 or -10, forming the DISC (death-inducing signaling complex), and additional apoptotic signaling molecules are recruited and brought together in close proximity in large lipid raft platforms, either through direct interaction with the membrane or through intermediate proteins, to generate the CASMER supramolecular entity.

Publications

1 Arginase as a new concern in blood transfusion. Mollinedo F, Palomero-Rodríguez MA, Sánchez-Conde P, García-Navas R, Laporta-Báez Y, de Vicente-Sánchez J, Suárez-Gonzalo L. **Blood Transfus. 2014 Jan;12 Suppl 1:s165-6. doi: 10.2450/2013.0237-12. Epub 2013 May 29.** PMID: 23736936 **IF: 2,372 / Q3**

2 The HSP90 inhibitor 17-AAG potentiates the antileishmanial activity of the ether lipid edelfosine. Varela-M RE, Mollinedo-Gajate C, Muro A, Mollinedo F. **Acta Trop. 2014 Mar;131:32-6. doi: 10.1016/j.actatropica.2013.11.018. Epub 2013 Dec 1.** PMID: 24299925 **IF: 2,270 / Q2**

3 Synthesis and biological activity of polyalthenol and pentacyclindole analogues. Marcos IS, Moro RF, Costales I, Basabe P, Díez D, Gil A, Mollinedo F, Pérez-de la Rosa F, Pérez-Roth E, Padrón JM. **Eur J Med Chem. 2014 Feb 12;73:265-79. doi: 10.1016/j.ejmech.2013.12.012. Epub 2013 Dec 25.** PMID: 24412720 **IF: 1,466 / Q4**

4 Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusion. Palomero-Rodríguez MA, Laporta-Báez Y, Sánchez-Conde MP, Mollinedo F. **Br J Anaesth. 2014 Mar;112(3):576-7. doi: 10.1093/bja/aeu024.** PMID: 24535508 **IF: 4,8563 / D1**

5 Editorial: Antitumor alkylphospholipid analogs: a promising and growing family of synthetic cell membrane-targeting molecules for cancer treatment. Mollinedo F. **Anticancer Agents Med Chem. 2014 May;14(4):495-8.** PMID: 24628231 **IF: 2,469 / Q2**

6 Lipid rafts, endoplasmic reticulum and mitochondria in the antitumor action of the alkylphospholipid analog edelfosine. Gajate C, Mollinedo F. **Anticancer Agents Med Chem. 2014 May;14(4):509-27. Review.** PMID: 24628241 **IF: 2,469 / Q2**

7 In vitro and in vivo anti-schistosomal activity of the alkylphospholipid analog edelfosine. Yepes E, Varela-M RE, López-Abán J, Dakir el H, Mollinedo F, Muro A. **PLoS One. 2014 Oct 10;9(10):e109431. doi: 10.1371/journal.pone.0109431. eCollection 2014. Erratum in: PLoS One. 2015;10(4):e0123149. Dakir, E L Habib [corrected to Dakir, El Habib].** PMID: 25302497 **IF: 3,234 / Q1**

8 Lipid rafts as major platforms for signaling regulation in cancer. Mollinedo F, Gajate C. **Adv Biol Regul. 2015 Jan;57:130-46. doi: 10.1016/j.jbior.2014.10.003. Epub 2014 Oct 27.** PMID: 25465296 **IF: NI**

9 Caenorhabditis elegans as a platform to study the mechanism of action of synthetic antitumor lipids. Sánchez-Blanco A, Rodríguez-Matellán AG, Reis-Sobreiro M, Sáenz-Narciso B, Cabello J, Mohler WA, Mollinedo F. **Cell Cycle. 2014;13(21):3375-89. doi: 10.4161/15384101.2014.952183.** PMID: 25485582 **IF: 4,565 / Q2**

10 Triggers and signaling cross-talk controlling cell death commitment. Melo-Lima S, Gajate C, Mollinedo F. **Cell Cycle. 2015;14(4):465-6. doi: 10.1080/15384101.2015.1006540.** PMID: 25590143 **IF: 4,565 / Q2**

11 Necroptosis is associated with low procaspase-8 and active RIPK1 and -3 in human glioma cells. Melo-Lima S, Celeste Lopes M, Mollinedo F. **Oncoscience. 2014 Oct 22;1(10):649-64. eCollection 2014.** PMID: 25593994 **IF: NI**

12 Lipid rafts and raft-mediated supramolecular entities in the regulation of CD95 death receptor apoptotic signaling. Gajate C, Mollinedo F. **Apoptosis. 2015 May;20(5):584-606. doi: 10.1007/s10495-015-1104-6.** PMID: 25702154 **IF: 3,685 / Q2**

13 Arginase activity and CD3ζ expression after major surgery. Palomero Rodríguez MÁ, García Navas R, Laporta Báez Y, de Vicente Sánchez J, Moyano Maza JC, Rodríguez López JM, Sánchez Conde MP, Mollinedo F. **Intensive Care Med. 2015 May;41(5):939-40. doi: 10.1007/s00134-015-3714-4. Epub 2015 Mar 5.** PMID: 25739821 **IF: 7,214 / Q1**

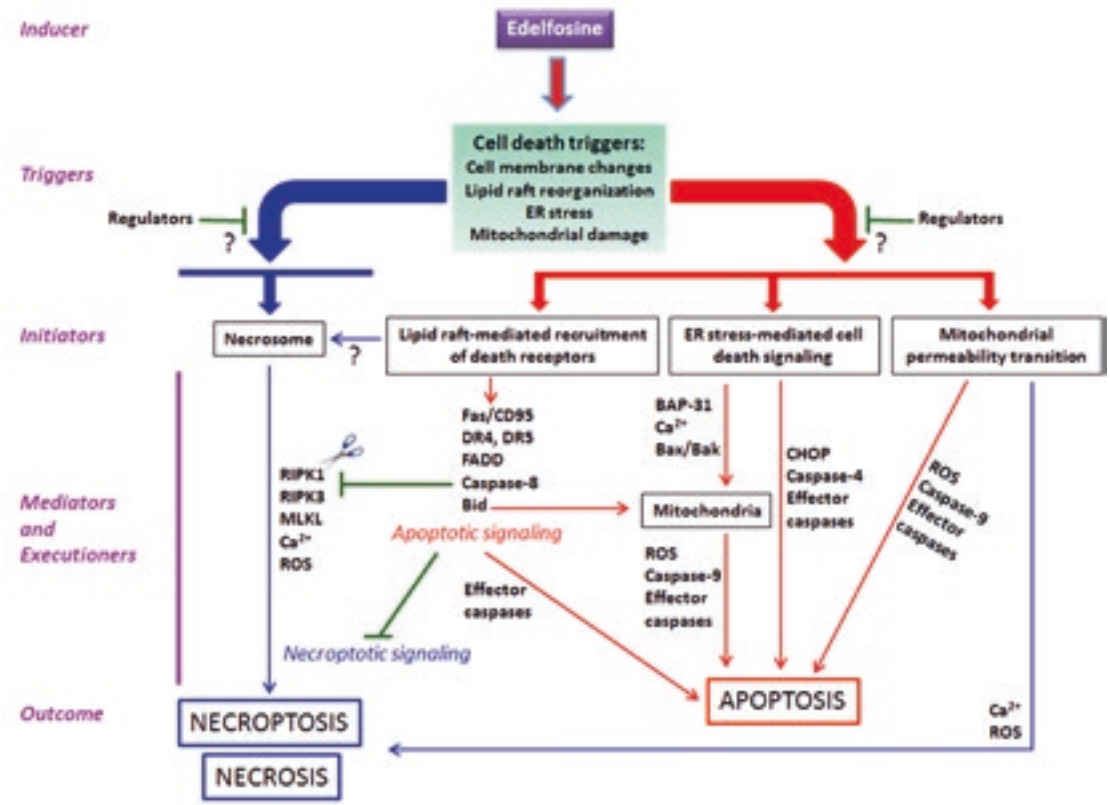
14 ERK1/2 acts as a switch between necrotic and apoptotic cell death in ether phospholipid edelfosine-treated glioblastoma cells. Melo-Lima S, Lopes MC, Mollinedo F. **Pharmacol Res. 2015 May-Jun;95-96:2-11. doi: 10.1016/j.phrs.2015.02.007. Epub 2015 Mar 6.** PMID: 25749008 **IF: 4,408 / Q1**

15 Endoplasmic reticulum targeting in Ewing's sarcoma by the alkylphospholipid analog edelfosine. Bonilla X, Dakir el-H, Mollinedo F, Gajate C. **Oncotarget. 2015 Jun 10;6(16):14596-613.** PMID: 25999349 **IF: 6,359 / D1**

16 Inhibition of Granulomatous Inflammation and Prophylactic Treatment of Schistosomiasis with a Combination of Edelfosine and Praziquantel. Yepes E, Varela-M RE, López-Abán J, Rojas-Caraballo J, Muro A, Mollinedo F. **PLoS Negl Trop Dis. 2015 Jul 20;9(7):e0003893. doi: 10.1371/journal.pntd.0003893. eCollection 2015 Jul.** PMID: 26191954 **IF: 6,359 / D1**

17 Lipid raft-mediated Fas/CD95 apoptotic signaling in leukemic cells and normal leukocytes and therapeutic implications. Gajate C, Mollinedo F. **J Leukoc Biol. 2015 Nov;98(5):739-59. doi: 10.1189/jlb.2MR0215-055R. Epub 2015 Aug 5. Review.** PMID: 26246489 **IF: 4,289 / Q1**

18 Synthesis of Bioconjugate Sesterterpenoids with Phospholipids and Polyunsaturated Fatty Acids. Gil-Mesón A, Roncero AM, Tobal IE, Basabe P, Díez D, Mollinedo F, Marcos IS. **Molecules. 2015 Dec 30;21(1). pii: E47. doi: 10.3390/molecules21010047.** PMID: 26729084 **IF: 2,416 / Q2**



Schematic view of the putative phases involved in edelfosine-induced cell death in distinct cancer cell types.

Other publications & book chapters

1 Alkylphospholipids and Leishmaniasis. Mollinedo, F. **In «Leishmaniasis –Trends in Epidemiology, Diagnosis and Treatment». (David M. Claborn, ed.), chapter 19, pp. 441-463, InTech Publishing, Rijeka, Croatia (2014).** ISBN: 978-953-51-1232-7 **DOI: 10.5772/58318**

Grants for research in progress

Project	IP	Grant	Time	Funding
Integrating chemical approaches to treat pancreatic cancer: making new leads for a cure (HEALTH-F2-2011-256986, PANACREAS)	Faustino Mollinedo	European Union	2011-2016	365.250,00 €
Estructuras subcelulares, regulación de apoptosis, y microentorno tumoral como dianas de agentes antitumorales: análogos alquil-lisofosfolípidos (SAF2011-30518)	Faustino Mollinedo	Ministerio de Ciencia e Innovación	2012-2014	338.800,00 €
Red Temática en Investigación Cooperativa en Cáncer (RD12/0036/0065)	Faustino Mollinedo	Instituto de Salud Carlos III	2013-2016	155.961,00 €
Lipid rafts, cancer stem cells y microentorno tumoral inflamatorio en la terapia del cáncer: análogos alquilfosfolipidos como agentes líder en terapias dirigidas a lipid rafts (SAF2014-59716-R)	Faustino Mollinedo	Ministerio de Economía y Competitividad	2015-2017	338.800,00 €

Other activities & relevant facts

Editorial Board

- «World Journal of Biological Chemistry» (WJBC) (2009-present).
- «Recent Patents on Anti-Cancer Drug Discovery» (2010-present).
- «Anti-Cancer Drugs» (2011-present).
- «World Journal of Pharmacology» (WJP) (2012-present).
- «International Journal of Biochemistry and Molecular Biology» (2011-present)
- «World Journal of Translational Medicine» (2012-present)

Fotografía: Sergio R. Manzano

LABORATORY 7

Molecular and genetic determinants of cancer susceptibility, evolution and treatment response

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Roberto Corchado Cobos

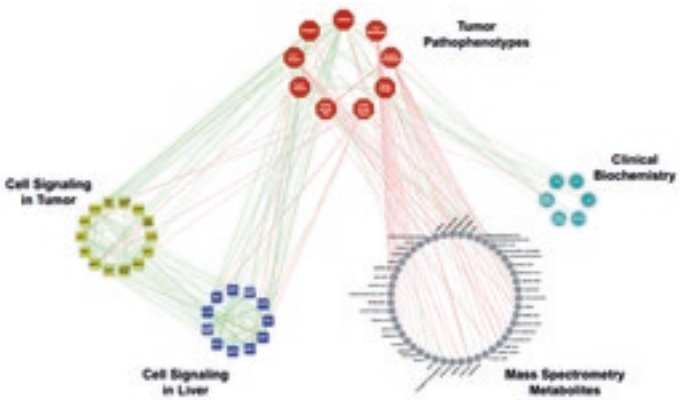
Laura Díaz Gil

Ana Krotenberg García

Facundo Nehuen Ramos Ochoa

3.6 — 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 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.

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.

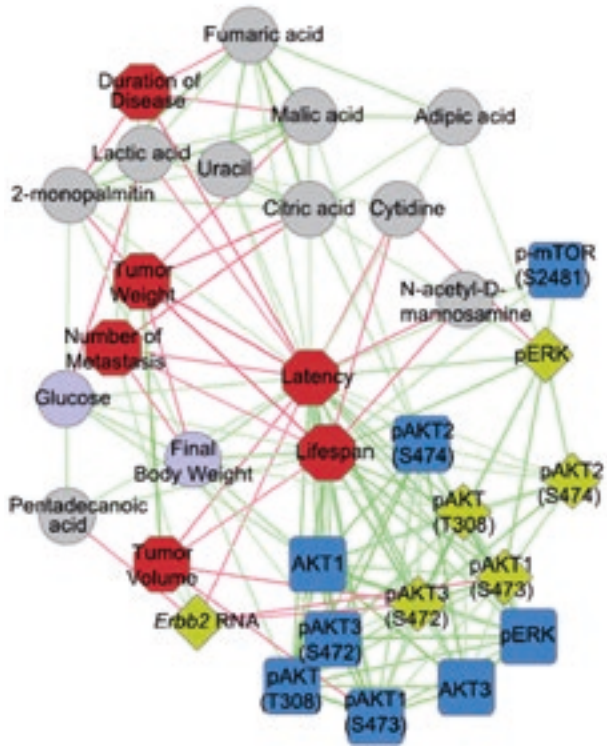
Publications

1 **Identifying phenotypes involved in susceptibility to Schistosoma mansoni infection in F1B6CBA mice.** Pérez del Villar L, Vicente B, Blanco-Gómez A, Castellanos A, Pérez-Losada J, Muro A. **Acta Parasitol. 2014 Sep;59(3):529-39. doi: 10.2478/s11686-014-0277-4. Epub 2014 Aug 15.** PMID: 25119369 **IF: 0,905 / Q4**

2 **Unraveling heterogeneous susceptibility and the evolution of breast cancer using a systems biology approach.** Castellanos-Martín A, Castillo-Lluva S, Sáez-Freire Mdel M, Blanco-Gómez A, Hontecillas-Prieto L, Patino-Alonso C, Galindo-Villardón P, Pérez Del Villar L, Martín-Seisdedos C, Isidoro-García M, Abad-Hernández M del M, Cruz-Hernández JJ, Rodríguez-Sánchez CA, González-Sarmiento R, Alonso-López D, De Las Rivas J, García-Cenador B, García-Criado J, Lee do Y, Bowen B, Reindl W, Northen T, Mao JH, Pérez-Losada J. **Genome Biol. 2015 Feb 21;16:40. doi: 10.1186/s13059-015-0599-z.** PMID: 25853295 **IF: 10,810 / D1**

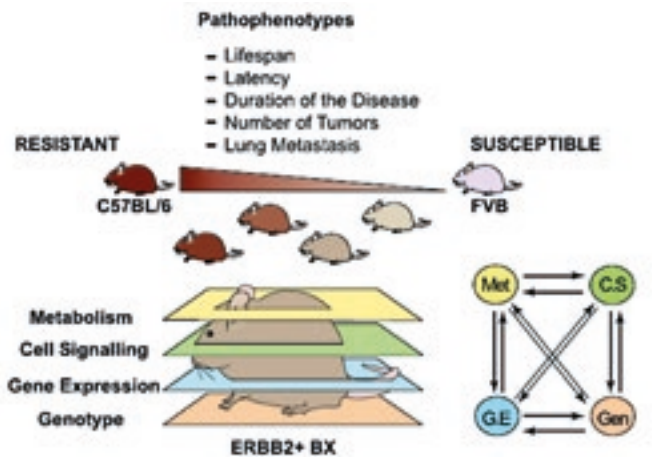
3 **Cyr61 as mediator of Src signaling in triple negative breast cancer cells.** Sánchez-Bailón MP, Calcabrini A, Mayoral-Varo V, Molinari A, Wagner KU, Losada JP, Ciordia S, Albar JP, Martín-Pérez J. **Oncotarget. 2015 May 30;6(15):13520-38.** PMID: 25980494 **IF: 6,359 / D1**

4 **A new role of SNAI2 in postlactational involution of the mammary gland links it to luminal breast cancer development.** Castillo-Lluva S, Hontecillas-Prieto L, Blanco-Gómez A, Del Mar Sáez-Freire M, García-Cenador B, García-Criado J, Pérez-Andrés M, Orfao A, Cañamero M, Mao JH, Gridley T, Castellanos-Martín A, Pérez-Losada J. **Oncogene. 2015 Jun 22. doi: 10.1038/onc.2015.224.** PMID: 26096931 **IF: 8,459 / D1**



Grants for research in progress

Project	IP	Grant	Time	Funding
Development of a technology to produce microcapsules, based on the formation of drops from viscous non-Newtonian liquids sprayed through fan-jet nozzles, to use in cancer therapy	Eva Martín del Valle (Collaborator: Jesús Pérez Losada)	Unión Europea (ERC-2010-StG_20091028; Project Number: 258984)	2011-2016	1,500,000.00 €
Papel de la Inmunoglobulina Intravenosa en el tratamiento del Cáncer-2	Isidro Sánchez-García (Collaborator: Jesús Pérez Losada)	Instituto Grifols S.A.	2012-2014	370,800.00 €
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 €)
Identificación de determinantes genéticos y moleculares comunes a la susceptibilidad de cáncer de mama y envejecimiento mediante una estrategia de Biología de Sistemas	Jesús Pérez Losada	Ministerio de Economía y Competitividad	2015-2017	120,000.00 €
Prevención del cáncer de mama mediante modificación de la involución postlactancia	Jesús Pérez Losada	Junta de Castilla y León. Biomedicina	2015	71,760.00 €



LABORATORY 9

Animal models in cancer. Chromosome segregation and human disease

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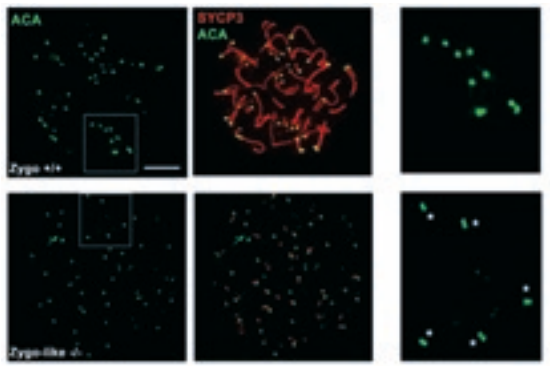
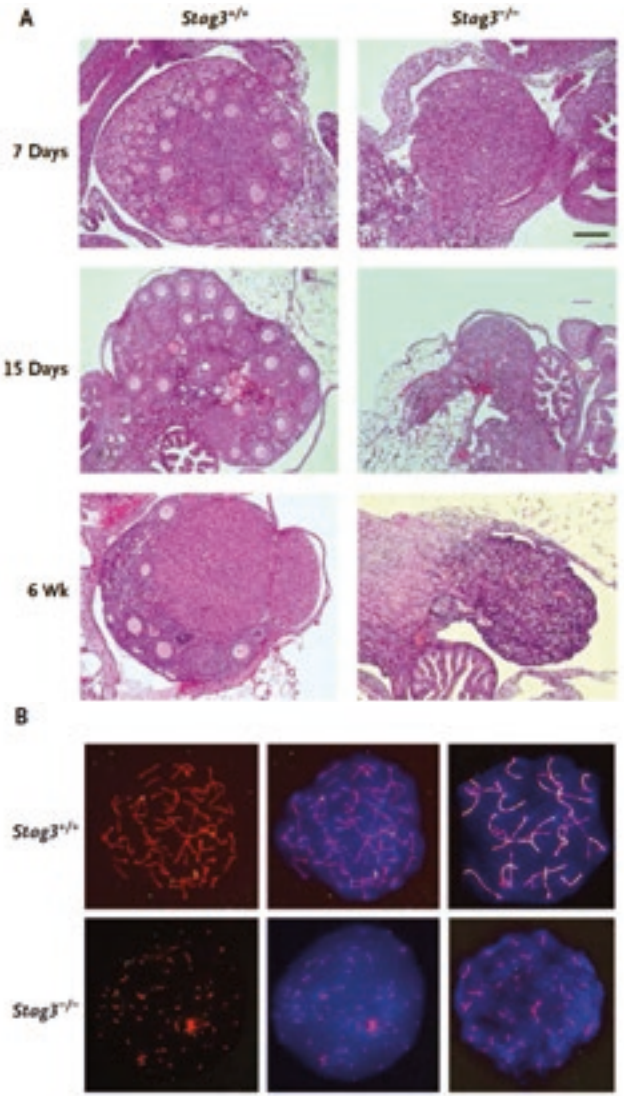


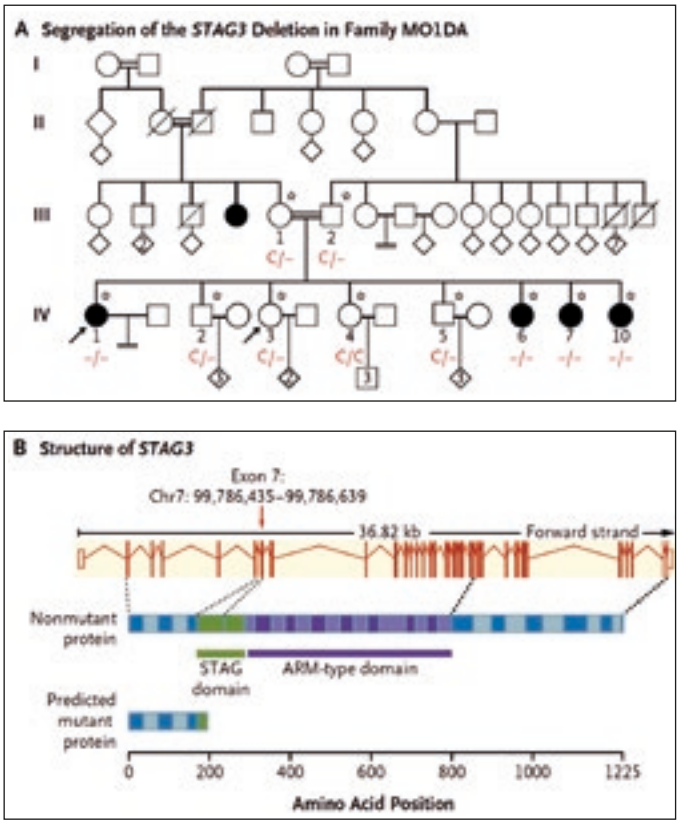
STAG3 deficiency leads to premature loss of cohesion. Double Immunofluorescence of SYCP3 (red) and ACA (green).
Llano et al., Hum Mol Genet 2014

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 (UCLA) 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 cohesin subunit STAG3 on chromosome 7. The pathogenicity of the STAG3 mutations was functionally validated with a 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.



Premature Ovarian Failure in Stag3-/- Mice.
Caburet et al., NEJM 2014



Identification of a Mutation in the Coding Sequence of STAG3 in a Consanguineous Family with Premature Ovarian Failure.
Caburet et al., NEJM 2014

Publications

1 Cohesin removal precedes topoisomerase IIα-dependent decatenation at centromeres in male mammalian meiosis II. Gómez R, Viera A, Berenguer I, Llano E, Pendás AM, Barbero JL, Kikuchi A, Suja JA. **Chromosoma. 2014 Mar;123(1-2):129-46. doi: 10.1007/s00412-013-0434-9. Epub 2013 Sep 8.** PMID: 24013524 **IF: 4,602 / Q1**

2 Mutant cohesin in premature ovarian failure. Caburet S, Arboleda VA, Llano E, Overbeek PA, Barbero JL, Oka K, Harrison W, Vaiman D, Ben-Neriah Z, García-Tuñón I, Fellous M, Pendás AM, Veitia RA, Vilain E. **N Engl J Med. 2014 Mar 6;370(10):943-9. doi: 10.1056/NEJMoa1309635.** PMID: 24597867 **IF: 55,873 / D1**

3 STAG3 is a strong candidate gene for male infertility. Llano E, Gómez-H L, García-Tuñón I, Sánchez-Martín M, Caburet S, Barbero JL, Schimenti JC, Veitia RA, Pendás AM. **Hum Mol Genet. 2014 Jul 1;23(13):3421-31. doi: 10.1093/hmg/ddu051. Epub 2014 Mar 7.** PMID: 24608227 **IF: 6,393 / Q1**

4 Meikin is a conserved regulator of meiosis-I-specific kinetochore function. Kim J, Ishiguro K, Nambu A, Akiyoshi B, Yokobayashi S, Kagami A, Ishiguro T, Pendás AM, Takeda N, Sakakibara Y, Kitajima TS, Tanno Y, Sakuno T, Watanabe Y. **Nature. 2015 Jan 22;517(7535):466-71. doi: 10.1038/nature14097. Epub 2014 Dec 24.** PMID: 25533956 **IF: 41,456 / D1**

Grants for research in progress

Project	IP	Grant	Time	Funding
Análisis funcional de la red de cohesinas en mamíferos	Alberto Martín Pendás	MINECO BFU2014-59307-R	2015-2017	340,000.00 €
Biología funcional de la red meiótica	Alberto Martín Pendás	MINECO BFU2015-71786-REDT	2015-2016	47,000.00 €
Identificación de los genes causantes de una enfermedad rara reproductiva, la azoospermia y el POF por bloqueo meiótico	Alberto Martín Pendás	Junta de Castilla y León	2014-2015	34,000.00 €

LABORATORY 11

Immunology and cancer

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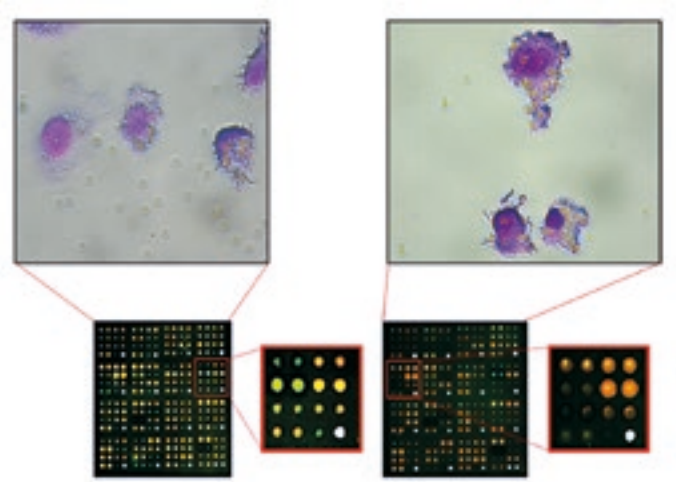
Immunology and cancer



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.

Objectives

The general aim of this program is based on the fact that the oncogenic events that induce deregulation of cellular processes in haematological 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 haematological malignancies. In the same line, understanding of the role of the immune system on different malignancies/clonal disorders, through the analysis of the interactions between tumour cells and the immune microenvironment, could constitute the basis for novel immunotherapeutic strategies in the near future.

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SENIOR RESEARCHER

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 to predict the severity and evolution of SM. 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. Results: 1) D816V *KIT* mutation is a hallmark of SM, present in almost 100% patients (Blood. 2006; 108: 2366-72. IF: 10.432; 227 citations). 2) Extensive affectation of D816V *KIT* mutation in hematopoiesis is the main risk factor to predict disease (SM) progression (J Allergy Clin Immunol. 2009; 124:514-21. IF: 9.773; 104 citations). 3) Mast cells from different molecular and prognostic subtypes of SM display distinct immunophenotypes (J Allergy Clin Immunol. 2010; 125:719-26. IF: 9.773; 64 citations). 4) An immature immunophenotype of bone marrow MC predicts for multilineage D816V *KIT* mutation in SM (Leukemia 2012; 26(5):951-958. IF: 10.164; 28 citations). 5) Pathological MC from SM patients present a characteristic, common, genetic expression pattern with some molecular pathways differentially expressed in ASM vs ISM (J Allergy Clin Immunol. 2013; 131:1213-e4. IF: 11.248; 10 citations). 6) Detection of the D816V *KIT* mutation in peripheral blood is an useful tool for diagnostic and prognostic of SM patients (Modern Pathology 2015; 28:1138-49. IF: 6.187). 7) Increased IL6 plasma levels in ISM patients are associated with high risk of disease progression (Leukemia 2015; [in press]. IF: 10.431). 8) Acquisition of the D816V *KIT* mutation in a common pluripotent progenitor cell, prior to differentiation into bone marrow mesenchymal stem cells and hematopoietic precursor cells, confers a significantly greater risk for disease progression and a poorer outcome. (Blood 2015; [in press]. IF: 10.452). Future research: To identify a molecular signature for SM patients that can be applied in any clinical laboratory for the diagnosis and prediction of progression of SM.

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SENIOR RESEARCHER

Chronic lymphoid neoplasms: from the origin to the establishment/ progression of the disease

"Immunology and Cancer" applied to the field of hematological malignancies (Leukemias and lymphomas,particularly those 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 lines: 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 and 3) translation to diagnosis, classification and treatment monitoring; 4) biological characterization of their normal (immune) cell counterparts. She is also involved in 5) research lines focused on the analysis of the role/alterations and monitoring of immune cells in several pathologic (i.e. haematological malignancies and autoimmune diseases), infectious (HIV) and toxic (chronic alcoholims) conditions.

Results referred from January 1st 2014 to December 31st 2015: LINE 1: Circulating clonotypic B-cells in Multiple Myeloma and Monoclonal Gammopathy of Undetermined Significance (Thiago et al, Haematologica 2014; Q1; IF: 5.814); HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/25252186" Subjects with chronic lymphocytic leukaemia-like B-cell clones with stereotyped B-cell receptors frequently show MDS-associated phenotypes on myeloid cells (Rodríguez-Caballero et al, Br. J. Haematol 2015; Q1; IF: 4.711 -IF 2014-. LINE 2: Molecular and cytogenetic characterization of expanded B-cell clones from multiclonal vs. monoclonal B-cell chronic lymphoproliferative disorders (Henriques et al, Haematologica 2014; Q1; FI: 5.814); Classification and clinical behavior of blastic plasmacytoid dendritic cell neoplasm according to their maturation-associated immunophenotypic profile (Martín-Martín et al, OncoTarget 2015; Q1; IF: 6.359 –IF 2014-); Phenotypic profile of expanded NK cells in chronic lymphoproliferative disorders: a surrogate marker for NK-cell clonality (Bárcena et al, OncoTarget 2015; Q1; IF: 6.359 –IF 2014-); Contribution of cerebrospinal fluid sCD19 levels to the detection of CNS lymphoma and its impact on disease outcome (Muñiz et al; Blood 2014; Q1; IF: 10.452); Introduction to the diagnosis and classification of monocytic-lineage leukemias by flow cytometry (Matarraz et al, Cytometry B Clin Cytometry 2015; IF: 2.398 –IF 2014-). LINE 5: Altered distribution of peripheral blood maturation-associated B-cell subsets in chronic alcoholism (Almeida et al, ACER 2015; Q1; IF: 3.205 –IF 2014-); Effect of mTORC1/mTORC2 inhibition on T cell function: potential role in graft-versus-host disease control (Herrero et al, Br. J. Haematol 2015; Q1; IF: 4.711 –IF 2014-).

In the last 6 years, her scientific activity has translated into around 66 publications in SCI journals (H-factor: 34; >3,000 citing articles). She is currently a member of the executive board of the Iberian Society of Cytometry (1999-act.).

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SENIOR RESEARCHER

Immunotechnology, nanotechnolgy, and proteomics approaches for biomarker and drug discovery in cancer and immunopathologies

The successful future of medicine will depend on ensuring that patients are managed with treatments that are appropriate for each individual, a concept referred to as personalized medicine.

Personalized medicine rests on two broad and equally important pillars. First, novel therapeutics that are tailored to treat the specific molecular causes of each individual disease. Second, diagnostic tests are needed to quickly identify the specific disease individual has and which treatment would be most appropriate.

The two approaches are mutually dependent. A specific therapy only makes sense if there is a test to tell patients if they will benefit from it.

Broadly, our laboratory is interested in using a multidisciplinary approach (molecular biology, proteomics, nanotechnology, immunotechnology) to discovering new tools that will help advance the cause of personalized medicine. The completion of the human genome project signaled the start of a dramatic acceleration in the pace of biological research. One of the most compelling next steps has been learning the functional roles for all proteins; then in 2010 the Human Proteome Project has been launched. We base our work in the high throughput study of proteins, a next generation field called «Functional Proteomics». Proteins provide the verbs to biology; they are its engines and its bricks. Most human disease is the result of protein dysfunction and nearly all drugs either act through proteins or are themselves proteins.

We initiated a project to create a sequence-verified collection of full-length cDNAs representing all coding regions for the human and several model organisms in a vector system that is protein expression-ready. In addition, we have designed, developed and implemented protein microarrays platforms in combination with nanoapproaches (i.e. label-free detection methods such as magnetic nanoparticles, nanoparticles conjugation,...) and immunotechnology strategies (such as tailor-made synthesis of immunogens, phage display libraries, recombinant proteins production,...) in order to identify biomarkers panels useful in diagnostics and therapeutics in immune disorders or tumoral diseases.

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SENIOR RESEARCHER

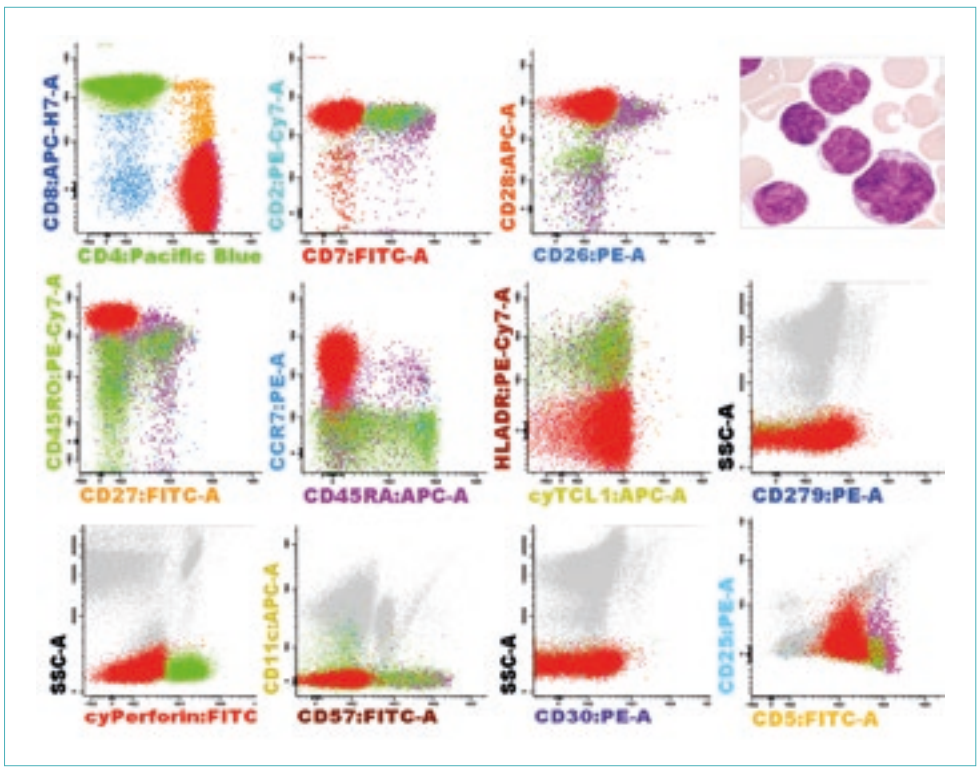
Integrated miRNA and mRNA signatures associated with metastatic sporadic colorectal cancer

Occurrence of distant metastases is the main cause of death sporadic colorectal cancer (sCRC), and the liver is the most common site for metastatic spread of primary tumor. Metastasis is a complex multi-step process leading to the accumulation of genomic alterations that occur at the single cell level over the lifetime of a tumor, from benign to invasive and metastatic states leading to patient death. The genomic abnormalities, which are potentially characteristic of such advanced stages of the disease, are complex and so far, poorly described and partially understood. This relates to the fact that most genomic studies in colorectal cancer have focused on primary tumors, particularly in the stage II disease at diagnosis; whereas few studies have compared the deregulated transcripts of primary versus paired metastatic samples. Despite this, multiple mRNAs and miRNAS found in primary tumors have been associated with metastatic colorectal carcinoma. Among others, these mainly include PTEN/PI3K, EGFR, TGF*ß*, and TP53, as well as the metastatic CRC-associated miRNAs, miR-31, miR-503 and miR-133.

Microarray analysis allows the exploration of several thousands of cancer-related or cancer-specific genes. The potential of expression profiling using microarray analysis as a tool to predict the prognosis and treatment for different types of cancer has been realized, including CRC. Data obtained from microarray analysis can provide significant insight into biological differences between patients with good and poor prognoses and can be used as a screening tool to find individual molecules for individualization of therapy. In this regard, several gene expression profiles for predicting outcomes in patients with stage II colon cancer have been identified, such as Oncotype DX® Colon Cancer test (Genomic Health, Inc., Redwood City, CA) and Coloprint® (Agendia, Inc., Irvine, CA). However, the molecular mechanisms underlying the association of such genomic profiles with metastatic colorectal carcinoma remain largely unknown.

Here we evaluate the molecular heterogeneity of CRC tumors based on simultaneous assessment of the overall GEP of both coding mRNA and non-coding RNA genes -including miRNA, small nucleolar and large intergenic RNAs– in primary tumor and their paired liver metastases from 23 consecutive CRC patients vs. non-tumoral tissue (n=10). Overall, our results define a common GEP for all metastatic CRC, at the same time they confirm some observations from previous studies and revealed new specific mRNA and miRNA signatures as potential biomarkers for distant-disease free.

Future research: To define differential gene expression profile between metastatic and non-metastatic tumors, for a better understanding of the genetics of the metastatic process in colorectal tumors.


CD8:APC-H7-A
CD4:Pacific Blue
CD2:PE-Cy7-A
CD7:FITC-A
CD28:APC-A
CD26:PE-A
CD45RO:PE-Cy7-A
CD27:FITC-A
CCR7:PE-A
CD45RA:APC-A
HLADR:PE-Cy7-A
cyTCL1:APC-A
SSC-A
CD279:PE-A
SSC-A
cyPerforin:FITC
CD11c:APC-A
CD57:FITC-A
SSC-A
CD30:PE-A
CD25:PE-A
CD5:FITC-A

Publications

1 **Circulating clonotypic B cells in multiple myeloma and monoclonal gammopathy of undetermined significance.** Thiago LS, Pérez-Andrés M, Balanzategui A, Sarasquete ME, Paiva B, Jara-Acevedo M, Bárcena P, Sánchez ML, Almeida J, González M, San Miguel JF, García-Sanz R, Orfao A. **Haematologica. 2014 Jan;99(1):155-62. doi: 10.3324/haematol.2013.092817. Epub 2013 Jul 19.** PMID: 23872308 **IF: 5,814 / D1**

2 **Nonaggressive systemic mastocytosis (SM) without skin lesions associated with insect-induced anaphylaxis shows unique features versus other indolent SM.** Álvarez-Twose I, Zanotti R, González-de-Olano D, Bonadonna P, Vega A, Matito A, Sánchez-Muñoz L, Morgado JM, Perbellini O, García-Montero A, De Matteis G, Teodósio C, Rossini M, Jara-Acevedo M, Schena D, Mayado A, Zamò A, Mollejo M, Sánchez-López P, Cabañes N, Orfao A, Escribano L; Spanish Network on Mastocytosis (REMA); Italian Network on Mastocytosis (RIMA). **J Allergy Clin Immunol. 2014 Feb;133(2):520-8. doi: 10.1016/j.jaci.2013.06.020. Epub 2013 Aug 6.** PMID: 23921094 **IF: 11,476 / D1**

3 **Testosterone replacement therapy in hypogonadal men is associated with increased expression of LAMP-2 (CD107b) by circulating monocytes and dendritic cells.** Corrales JJ, Almeida M, Martín-Martín L, Miralles JM, Orfao A. **Clin Endocrinol (Oxf). 2014 Apr;80(4):577-84. doi: 10.1111/cen.12338. Epub 2013 Oct 23.** PMID: 24111582 **IF: 3,457 / Q2**

4 **Surfing transcriptomic landscapes. A step beyond the annotation of chromosome 16 proteome.** Segura V, Medina-Aunon JA, Mora MI, Martínez-Bartolomé S, Abian J, Aloria K, Antúnez O, Arizmendi JM, Azkargorta M, Barceló-Batllori S, Beaskoetxea J, Bech-Serra JJ, Blanco F, Monteiro MB, Cáceres D, Canals F, Carrascal M, Casal JI, Clemente F, Colomé N, Dasilva N, Díaz P, Elortza F, Fernández-Puente P, Fuentes M, Gallardo O, Gharbi SI, Gil C, González-Tejedo C, Hernáez ML, Lombardía M, López-Lucendo M, Marcilla M, Mato JM, Mendes M, Oliveira E, Orera I, Pascual-Montano A, Prieto G, Ruiz-Romero C, Sánchez del Pino MM, Tabas-Madrid D, Valero ML, Vialas V, Villanueva J, Albar JP, Corrales FJ. **J Proteome Res. 2014 Jan 3;13(1):158-72. doi: 10.1021/pr400721r. Epub 2013 Nov 5.** PMID: 24138474 **IF: 4,245 / Q1**

5 **Enhanced cytotoxic activity of bile acid cisplatin derivatives by conjugation with gold nanoparticles.** Sánchez-Paradinas S, Pérez-Andrés M, Almendral-Parra MJ, Rodríguez-Fernández E, Millán A, Palacio F, Orfao A, Criado JJ, Fuentes M. **J Inorg Biochem. 2014 Feb;131:8-11. doi: 10.1016/j.jinorgbio.2013.10.021. Epub 2013 Oct 31.** PMID: 24239907 **IF: 3,444 / Q1**

6 **Distinction between asymptomatic monoclonal B-cell lymphocytosis with cyclin D1 overexpression and mantle cell lymphoma: from molecular profiling to flow cytometry.** Espinet B, Ferrer A, Bellosillo B, Nonell L, Salar A, Fernández-Rodríguez C, Puigdecanet E, Gimeno J, García-García M, Vela MC, Luño E, Collado R, Navarro JT, de la Banda E, Abrisqueta P, Arenillas L, Serrano C, Lloreta J, Miñana B, Cerutti A, Florensa L, Orfao A, Sanz F, Solé F, Dominguez-Sola D, Serrano S. **Clin Cancer Res. 2014 Feb 15;20(4):1007-19. doi: 10.1158/1078-0432.CCR-13-1077. Epub 2013 Dec 18.** PMID: 24352646 **IF: 8,722 / D1**

7 **Evaluation of homo– and hetero–functionally activated glass surfaces for optimized antibody arrays.** González-González M, Bartolomé R, Jara-Acevedo R, Casado-Vela J, Dasilva N, Matarraz S, García J, Alcázar JA, Sayagués JM, Orfao A, Fuentes M. **Anal Biochem. 2014 Apr 1;450:37-45. doi: 10.1016/j.ab.2014.01.002. Epub 2014 Jan 15.** PMID: 24440232 **IF: 2,219 / Q2**

8 **Relevance of Nck-CD3 epsilon interaction for T cell activation in vivo.** Borroto A, Arellano I, Blanco R, Fuentes M, Orfao A, Dopfer EP, Prouza M, Suchánek M, Schamel WW, Alarcón B. **J Immunol. 2014 Mar 1;192(5):2042-53. doi: 10.4049/jimmunol.1203414. Epub 2014 Jan 27.** PMID: 24470497 **IF: 4,922 / Q1**

9 **Molecular and cytogenetic characterization of expanded B-cell clones from multiclonal versus monoclonal B-cell chronic lymphoproliferative disorders.** Henriques A, Rodríguez-Caballero A, Criado I, Langerak AW, Nieto WG, Lécrevisse Q, González M, Cortesão E, Paiva A, Almeida J, Orfao A. **Haematologica. 2014 May;99(5):897-907. doi: 10.3324/haematol.2013.098913. Epub 2014 Jan 31.** PMID: 24488564 **IF: 5,814 / D1**

10 **Contribution of cerebrospinal fluid sCD19 levels to the detection of CNS lymphoma and its impact on disease outcome.** Muñiz C, Martín-Martín L, López A, Sánchez-González B, Salar A, Almeida J, Sancho JM, Ribera JM, Heras C, Peñalver FJ, Gómez M, González-Barca E, Alonso N, Navarro B, Olave T, Sala F, Conde E, Márquez JA, Cabezudo E, Cladera A, García-Malo M, Caballero MD, Orfao A; Spanish Group for the Study of Central Nervous System Disease in Non-Hodgkin Lymphoma. **Blood. 2014 Mar 20;123(12):1864-9. doi: 10.1182/blood-2013-11-537993. Epub 2014 Feb 5.** PMID: 24501214 **IF: 10,452 / D1**

11 **Proposal for a new risk stratification classification for meningioma based on patient age, WHO tumor grade, size, localization, and karyotype.** Domingues PH, Sousa P, Otero Á, Gonçalves JM, Ruiz L, de Oliveira C, Lopes MC, Orfao A, Tabernero MD. **Neuro Oncol. 2014 May;16(5):735-47. doi: 10.1093/neuonc/not325. Epub 2014 Feb 16.** PMID: 24536048 **IF:6,776 / Q1**

12 **Persistent polyclonal B-cell lymphocytosis: extensively proliferated CD27+IgM+IgD+ memory B cells with a distinctive immunophenotype.** Berkowska MA, Grosserichter-Wagener C, Adriaansen HJ, de Ridder D, Mirani-Oostdijk KP, Agteresch HJ, Böttcher S, Orfao A, van Dongen JJ, van Zelm MC. **Leukemia. 2014 Jul;28(7):1560-4. doi: 10.1038/leu.2014.77. Epub 2014 Feb 19.** PMID: 24549258 **IF: 10,431 / D1**

13 **The protein expression profile of meningioma cells is associated with distinct cytogenetic tumour subgroups.** Domingues PH, Teodósio C, Otero Á, Sousa P, Gonçalves JM, Nieto AB, Lopes MC, de Oliveira C, Orfao A, Tabernero MD. **Neuropathol Appl Neurobiol. 2015 Apr;41(3):319-32. doi: 10.1111/nan.12127.** PMID: 24612434 **IF: 3,927 / Q1**

14 **Immunophenotypic alterations of bone marrow myeloid cell compartments in multiple myeloma patients predict for myelodysplasia-associated cytogenetic alterations.** Matarraz S, Paiva B, Díez-Campelo M, Bárrena S, Jara-Acevedo M, Gutiérrez ML, Sayagués JM, Sánchez ML, Bárcena P, Garrastazul MP, Berruezo MJ, Durán JM, Cerveró C, García-Erce JA, Florensa L, Méndez GD, Gutiérrez O, Del Cañizo MC, van Dongen JJ, San Miguel JF, Orfao A. **Leukemia. 2014 Aug;28(8):1747-50. doi: 10.1038/leu.2014.103. Epub 2014 Mar 14.** PMID: 24625552 **IF: 10,431 / D1**

15 **Identification of a characteristic copy number alteration profile by high-resolution single nucleotide polymorphism arrays associated with metastatic sporadic colorectal cancer.** González-González M, Fontanillo C, Abad MM, Gutiérrez ML, Mota I, Bengoechea O, Santos-Briz Á, Blanco O, Fonseca E, Ciudad J, Fuentes M, De Las Rivas J, Alcázar JA, García J, Muñoz-Bellvis L, Orfao A, Sayagués JM. **Cancer. 2014 Jul 1;120(13):1948-59. doi: 10.1002/cncr.28681. Epub 2014 Mar 25.** PMID: 24668684 **IF: 5,068 / Q1**

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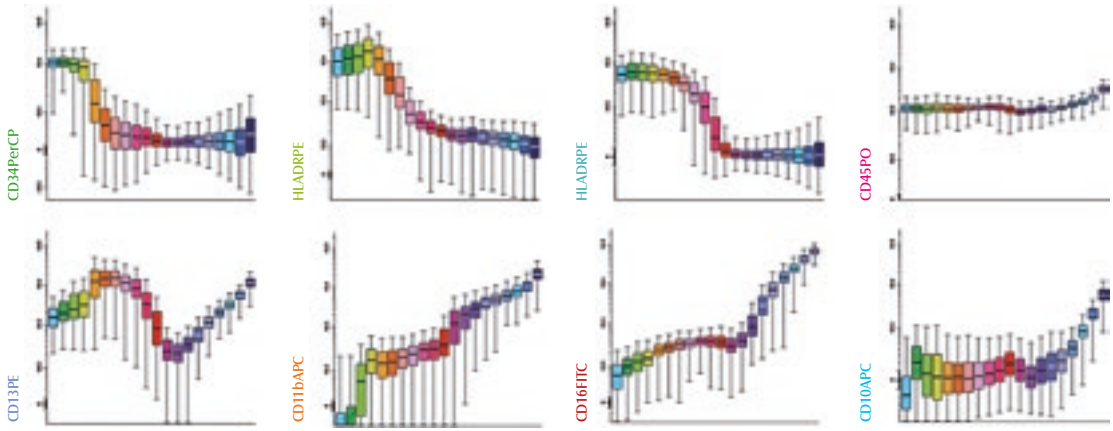
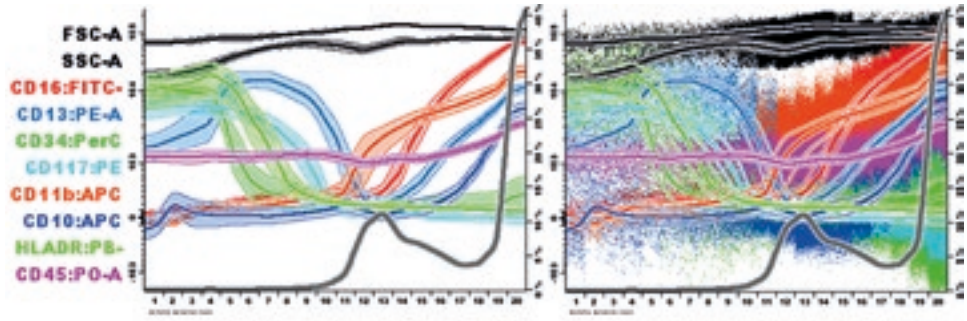


Neutrophil maturation stages in normal BM



Neutrophil maturation stages

Neutrophil maturation stages

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Other publications & book chapters

1 Metal ions in the context of nanoparticles toward biological applications. C Carrillo-Carrión; M Nazarenus; S Sánchez Paradinas; S Carregal-Romero; MJ Almendral; M Fuentes; B Pelaz; P del Pino; I Hussain; M Clift; B Rothen-Rutishauser; X-J Liang; WJ Parak. **Chemical Engineering. 4, pp. 88 - 96. 05/03/2014.**

2 Guía clínica de HPN: Consenso español para diagnóstico y tratamiento de hemoglobinuria paroxística nocturna Arrizabalaga B, Colado E, Gaya A, González A, Jarque I, Núñez R, Ojeda E, Orfao A, Ribera Jm, Urbano A, Vicente V, Villegas A. **Guía Clínica editada por el Grupo de trabajo de HPN de la Sociedad Española de hematología y Hemoterapia. BcnScience SL, Barcelona; 2014.**

3 EuroFlow quality assurance program: proposal for structure and implementation. En: «3rd ESLHO Symposium on New developments in the ESLHO Networks» Kalina T, Flores-Montero J, Lecrevisse Q, Pedreira C, Van Der Velden VHJ, Novakova M, Mejstrikova E, Hrusak O, Bottcher S, Karsh D, Sedek L, Trinquand A, Boeckx N, Caetano J, Asnafi V, Lucio P, Lima M, Santos Ah, Bonaccorso P, Van Der Sluijs-Gelling A, Langerak Aw, Martín-Ayuso M, Szczepanski T, Van Dongen Jjm, Orfao A:. **European Scientific Foundation for Laboratory Hemato-Oncology (eds). Erasmus Medical Center, Rotterdam (The Netherlands)** ISBN 978-94-91811-00-5: 35-38, **2014.**

4 Dissection of the peripheral blood B-cell compartment and immunoglobulin subclass subsetting. En: «3rd ESLHO Symposium on New developments in the ESLHO Networks» Pérez-Andrés M, Blanco E, de Arriba S, López-Granados E, Torres-Cañizales J, Van Der Burg M, Kalina T, Kienzler AK, Vlkova M, Sobral E, Chapel H, Lorente F, Van Zelm Mc, Van Dongen JJM, Orfao A. **European Scientific Foundation for Laboratory Hemato-Oncology (eds). Erasmus Medical Center, Rotterdam (The Netherlands)** ISBN 978-94-91811-00-5: 41-49, **2014.**

5 EuroFlow databases per screening tube and per classification tube set. En: «3rd ESLHO Symposium on New developments in the ESLHO Networks». Orfao A, Lecrevisse Q, Pedreira CE, Mejstrikova E, Van Der Velden VHJ, Bottcher S, Flores-Montero J, Matarraz S, Langeral Aw, Almeida J, Trinquand A, Martín-Martín L, Van Der Sluijs-Gelling AJ, Karsch D, Sedek L, Lima M, Gomes Da Silva M, Costa ES, Gaipa G, Roussel M, Campos-Goyat L, Paiva B, Villamor-Casas N, Fluxa R, Verde J, Grigore G, Van Dongen JJM: **European Scientific Foundation for Laboratory Hemato-Oncology (eds). Erasmus Medical Center, Rotterdam (The Netherlands)** ISBN 978-94-91811-00-5: 51-63, **2014.**

6 Serum profiling by targeted proteomics for biomarker discovery. En: «Proteomics: targeted technology, innovations and applications» Díez P, González-González M, Dasilva N, Jara-Acevedo M, Orfao A, Fuentes M. Fuentes M, Labaer J (Eds.). **Caister Academic Press, Norfolk (United Kingdom); pp: 19-34, 2015.**

Patents

Patent reference	Title	Inventors	Priority Date
US 62/072,498	Reagents, methods and kits for diagnosing primary immunodeficiencies	JJM van Dongen, JA Orfao de Matos Correia e Vale, M. Van der Burg, M. Pérez-Andrés, MC van Zelm, T Kalina, M Vlkova, E López-Granados, E Blanco, AK Kienzler	10/10/2014

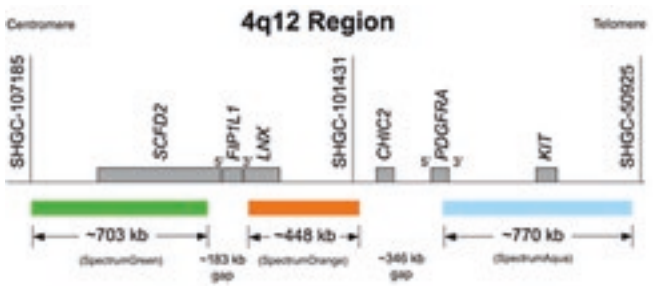
Grants for research in progress

Project	IP	Grant	Time	Funding
Diseño de un método de análisis de severidad en Mastocitosis Sistémica (PI11/02399)	Andrés García Montero	Instituto de Salud Carlos III	2012-2014	42,360.89 €
Identificación de factores genéticos predictivos de progresión clonal en Mastocitosis Sistémica (CIVP16A1806)	Andrés García Montero	Fundación Ramón Areces	2012-2015	76.440,00 €
Importance of oncogenic GTPase TC21 in tumorigenic processes	Alberto Orfao	Fundación Científica de la Asociación Española Contra el Cáncer	2009-2014	1.200.000,00 €
Molecular Oncology: identification of novel targets in signal transduction pathways for the development of therapeutic approaches in the management of oncology diseases	Alberto Orfao	National Development Agency of Hungary: New Science Plan	2012-2015	
RD-CONNECT: an integrated platform connecting registries, biobanks and clinical bioinformatics for rare disease research. (FP7-HEALTH 2012-INNIVATION-1, Proposal nº 305444-2 from European Union)	Alberto Orfao (one participating group)	European Union	2013-015	53,800.00 €
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	Proyectos Intrasalud. Instituto de Salud Carlos III, Ministerio de Economía y Competitividad	2013-2016	389,620.00 €
Caracterización fenotípica y funcional de los macrófagos tisulares circulantes: nueva estrategia de diagnóstico precoz y de monitorización de enfermedades. (PI13/014)	Julia Almeida Parra	Instituto de Salud Carlos III. Ministerio de Economía y Competitividad	2014-2016	79,355.00 €
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	Junta de Castilla y León	2014-2016	28,750.00 €
Estudio multiparamétrico de la heterogeneidad celular tumoral mediante citometría de flujo en pacientes con carcinoma colorrectal esporádico: implicaciones clínicas. (BIO/SA02/13)	José María Sayagués Manzano	Junta de Castilla y León	2013-2014	19,300.00 €
Regulación de la expresión génica en cáncer ductal de páncreas (GRS861/A/13)	José María Sayagués Manzano	Junta de Castilla y León	2014	19,300.00 €
Identificación y validación de microARNS como nuevos biomarcadores en cáncer ductal de páncreas.	José María Sayagués Manzano	Fundación Samuel Solórzano Barroso	2014	4,000.00 €

Project	IP	Grant	Time	Funding
Pronóstico de las anomalías genéticas en cáncer colorrectal esporádico mediante técnicas de alto rendimiento (PI12/02053)	José María Sayagués Manzano	Instituto de Salud Carlos III. Ministerio de Economía y Competitividad	2012-2015	75.020,00 €
Regulación de la expresión génica del proceso metastásico en el cáncer colorrectal esporádico (BIO/SA55/14)	José María Sayagués Manzano	Junta de Castilla y León	2014-2015	27,031.00 €
Identificación de biomarcadores en cáncer colorrectal Esporádico mediante técnicas proteómicas de alto rendimiento (GRS1040/A/14)	José María Sayagués Manzano; Luis Muñoz Bellvis	Junta de Castilla y León	2014-2016	15,700.00 €
Development of a protein microarray for biomarker discovery in osteoarthritis	Cristina Ruiz Romero; Manuel Fuentes García	Conselleria de Sanidad, Xunta de Galicia	2011-2014	120,000.00 €
Profund II: Interactomics of the Centrosome	Juan Pablo Albar	Consejería de Educación. Comunidad de Madrid	2012-2014	662,400.00 €
TC21 rol in solid tumors. New therapeutic target	Alberto Orfao; Manuel Fuentes	Fundacion Científica Asociación Española Contra el Cáncer	2010-2015	1,200,000.00 €
Nanoproteomics methodologies for biomarker discovery in hematological diseases by using as model B-Chronic Lymphocytic Leukemia	Manuel Fuentes García	Consejería de Educación. Castilla y León	2012-2015	27,774.00 €
Design and development of nanoproteomics methodologies for biomarker discovery in hematological diseases	Manuel Fuentes García	Instituto de Salud Carlos III	2012-2015	98,241.11 €
Recursos Biomoleculares y Bioinformáticos (PRB2-ISCIII; PT13/0001/0003)	Manuel Fuentes García	Instituto de Salud Carlos III	2014-2018	12,500,000.00 € (90,000.00 €)
Diseño y desarrollo de estrategias nanoproteómicas para la caracterización de biomarcadores en enfermedad leptomeningea, empleando linfoma non-Hodgkin como modelo	Manuel Fuentes García	Instituto de Salud Carlos III	2014-2017	120,000.00 €
«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	Manuel Fuentes García	Instituto de Salud Carlos III	2015-2016	8,678.00 €

Other activities & relevant facts

PDGFRα TC Rearragement probe (4q12)



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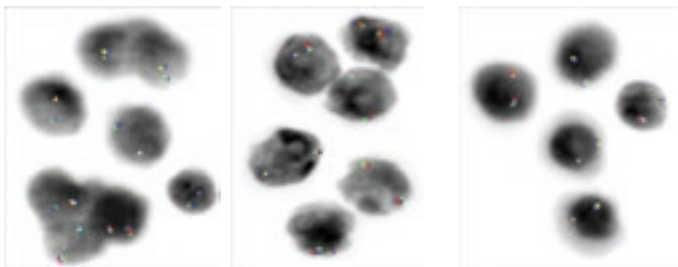

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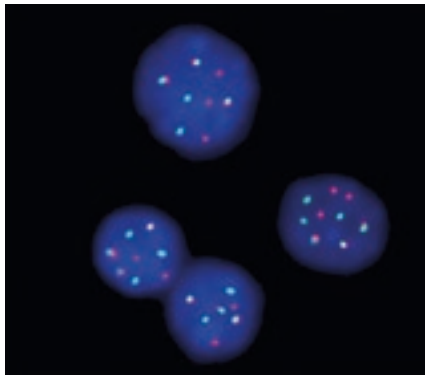
- 1994-Present. Evaluator of research projects of the Interministerial Commission of Science and Technology, Ministry of Education and Science It includes the evaluation of projects of the National Plan for Research in Biomedicine and Physiology, Special Actions, Infrastructure and the Foundation La Caixa, Foundation Sandra Ibarra and Asociación Española Contra el Cáncer (AECC).
- 2012-Present . External Scientific Committee. Biobanco VIH Gregorio Marañon Hospital (Madrid, Spain).
- 2014-Present. Honorary Member of the Romanian Society of Cytometry. Bucharest (Romania).
- May 2014. Coordinator of the workshop «IMF (International Myeloma Foundation) workshop on Automated -EuroFlow, Highly-sensitive flow cytometry standardized method for detection of minimal residual disease in multiple myeloma». Cancer Research Center, University of Salamanca. Salamanca.
- May 2014. Presentation «Proyecto de estudio de enfermedad oculta en LCR en LAL del adulto». PETHEMA Group Meeting 2014. Gijón.



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LABORATORY 12

Oncohematology

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The main characteristic of Prof. González's group is the translational research, resulting from the interaction between lab 12 in 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 To evaluate potential antitumoral targets in order to design novel therapeutic strategies in the preclinical setting that could be quickly translated into the clinics.

Main lines of research

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

1 Onco-Haematologic 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 ethiopathogenesis and prognosis.
- Study of antigenic receptors for B & T lymphocytes: applications in the diagnosis and ethiopathogenesis 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.
- Mechanisms of Resistance: Role of the marrow microenvironment and identification of the stem cell.
- Phase I/II/III clinical trials with experimental agents.

Achieved goals

Among the main achieved goals in the last years we can highlight: a) Our group has described the prognostic value of several cytogenetic abnormalities in MM, MDS or CLL, and we have also significantly contributed to the whole sequentiation of the genome of CLL. b) Establishment of the prognostic impact of minimal residual disease 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 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.
- To identify and characterize the tumoral stem cells and to gain further insights into the role of the tumor microenvironment.
- To analyze the mechanisms responsible for the development of drug-resistance.
- To activate novel clinical trials based on our preclinical studies.

SENIOR RESEARCHER

Genetics in Oncohematology

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This group is focused in the cytogenetics 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 of hematological malignancies.
B) The genomic and epigenomic studies on solid tumors.
C) Pharmacogenomics of new drugs used in cancer therapy.

The challenges of the group will be integration of data obtained on the different research lines in order to provide a personalized medicine in cancer therapy. In addition, implementation of these new tools, including next generation sequencing, and the translation to the clinical setting is a main goal of the group.

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SENIOR RESEARCHER

Bone marrow micro-environment 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 (50-100nm 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 putative contribution of these cells of the microenvironment in the onset of symptomatic myeloma, myeloma progression and or 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 evaluate the potential contribution of stromal cells from different origins to myeloma tumor engraftment, myeloma growth and development of osteolytic lesions in a murine model of human myeloma with bone lesions.
4. To elucidate the role of exosomes as paracrine signaling mediators in myeloma bone marrow microenvironment.
5. 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 the mechanisms by which the bone marrow microenvironment mediates therapeutic resistance and survival to myeloma cells in minimal residual disease.
- To characterize the effects of current anti-myeloma agents used in the clinic on the bone marrow mesenchymal stromal cells.
- To explore the potential biomarker value of circulating exosomal microRNAs from myeloma patients.

Publications

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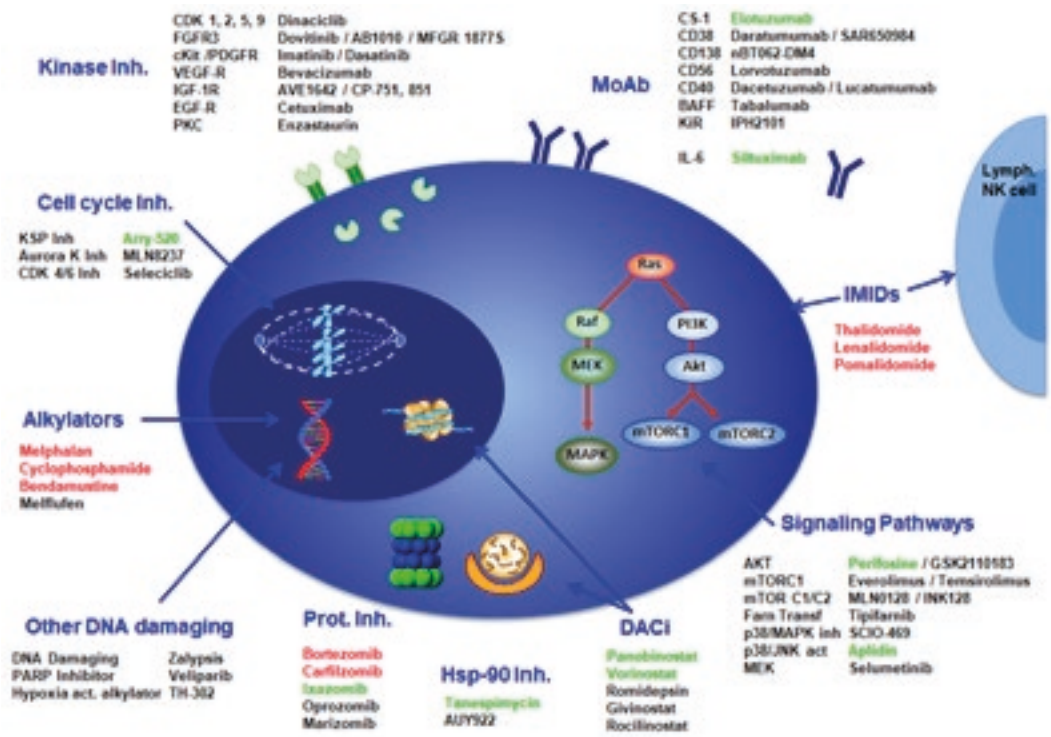

Schematic representation of the main targets in MM plasma cells and the drugs tested against them.
Approved drugs are presented in red and drugs that have reached phase III development are presented in green (from Ocio EM et al., Leukemia 2014;28:525-42)

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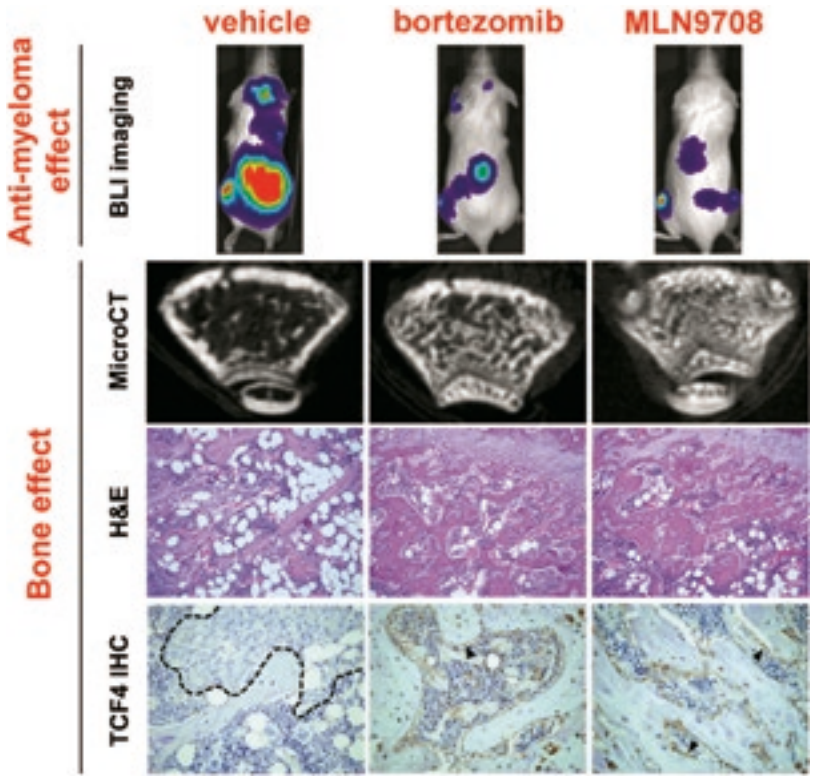

Similarly to its precesor bortezomib, the second-generation proteasome inhibitor ixazomib (MLN9708) has been shown to control tumor burden and to have a beneficial effect against osteolytic lesions in a bone marrow disseminated myeloma model.
Orally administered ixazomib has an anti-myeloma effect as observed by bioluminescence (BLI) imaging of tumor cells. Mice also and show global bone anabolic activity as revealed by the higher density and number of trabeculae at metaphyses of femurs -microcomputed tomography (microCT) studies and hematoxilin eosin (H&E) staining-, as well as the active appearance of osteoblasts lining the trabeculae, here immunostained for transcription factor TCF4. Dotted line delimits infiltrating myeloma cells and host tissue [modified from García-Gómez et al. Clin Cancer Res (2014) 20:1542-54].

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3 **Guía práctica clínica para el tratamiento de pacientes con linfoma de Hodgkin.** Ferrer S, García-Sanz R, Jarque I, Martínez C, Moraleda JM, Rámila E, Rubio A, Rueda A, Sánchez B, Sureda A, Xicoy B. **Grupo de Trabajo de Linfoma de Hodgkin del Grupo Español de Linfomas/ Trasplante Autólogo de Médula Ósea (GEL/TAMO). 2015.**

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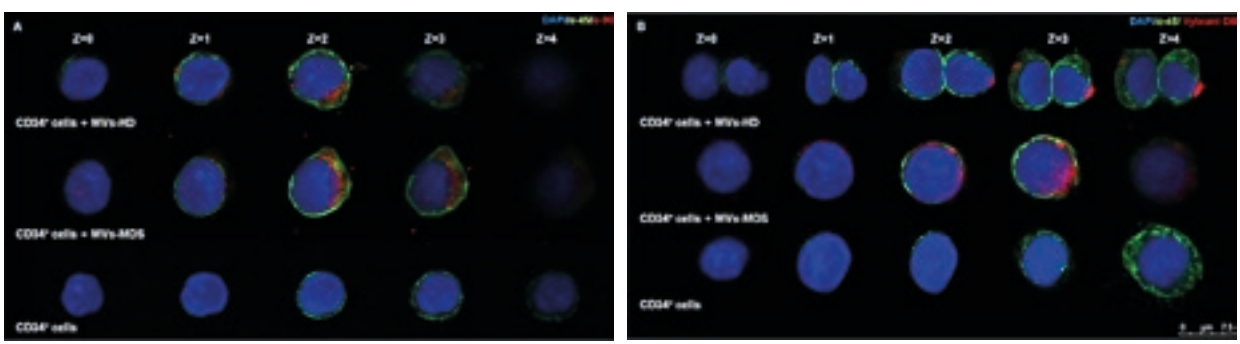
Patents

Patent reference	Title	Inventors	Priority Date
WO/2015/181157 / PCT/EP2015/061572	Combination comprising a glucocorticoid and EDO-S101	Mehrling TJ, Ocio EM	12/03/2015
WO/2015/181156 / PCT/EP2015/061571	Pharmaceutical combinations for treating cancer	Mehrling TJ, Ocio EM	12/03/2015



Incorporation of microvesicles (MV) from mesenchymal stem cells of myelodisplastic syndrome patients (MSC-MDS) and of healthy donors (MSC-HD) into CD34+ cells. (A) Representative images of incorporation of MVs by CD34+ cells stained with anti-CD90 Ab (red) and anti-CD45 Ab (green). **(B)** Representative images of MVs previously labeled with Vybrant-Dil cell-labeling solution (red) that were incorporated into CD34+ cells and stained with anti-CD45 Ab (green). **(A-B)** Images in the top row are from CD34+ cells that incorporated the MVs released from MSC-HD. Images on the middle row show the incorporation of MVs released from MSC-MDS. In the lower row, images of the CD34+ cells (without incorporation) are shown. Nuclei were counterstained with DAPI (blue). Scale bar, 7.5µm. Images obtained by confocal microscopy and acquired in layers (z-Stacks) of 1µm.

Grants for research in progress

Project	IP	Grant	Time	Funding
Red Temática de Investigación Cooperativa en Cáncer (RD12/0036/0069)	Marcos González Díaz	Instituto de Salud Carlos III	2012-2016	92,575.00 €/año
Utilidad clínica de la secuenciación masiva de paneles de genes y perfiles de expresión génica en el diagnóstico y pronóstico de la leucemia mieloblástica aguda (HUS327U14)	Marcos González Díaz	Consejería de Educación de la Junta de Castilla y León	2015	29,000.00 €
Valor diagnóstico y pronóstico del perfil de expresión génica, mutaciones somáticas y nivel de enfermedad mínima residual en la leucemia mieloblástica aguda (LMA) (PI12/02321)	Marcos González Díaz	FIS-ISCIII	2013-2015	105,270.00 €
Mecanismos moleculares responsables de la transformación histológica del linfoma folicular. Implicaciones pronósticas (GRS 1180/A/15)	Marcos González Díaz	Gerencia Regional de Salud de la Junta de Castilla y León	2015-2016	20,000.00€
Mieloma múltiple: Grupos de riesgo basados en nuevos biomarcadores y evaluación de intervenciones terapéuticas con intención curativa con técnicas para EMR de alta sensibilidad (PI12/02311)	Ramón García Sanz	FIS-ISCIII	2013-2015	129,470.00 €
Análisis de marcadores de resistencia en mieloma múltiple y desarrollo de alternativas terapéuticas para superarla: proyecto basado en dos ensayos nacionales	Ramón García Sanz y Juan José Lahuerta Palacios	AECC GCB120981SAN	2012-2017	418,837.00 €
Aplicación clínica de la secuenciación masiva de paneles de genes en el diagnóstico, pronóstico y seguimiento de los pacientes con leucemia mieloblástica aguda (BIO/SA44/14)	Carmen Chillón Santos	Consejería de Sanidad de la Junta de Castilla y León	2014	38,782.00 €
Factores genéticos implicados en la evolución del trasplante alogénico de progenitores hematopoyéticos emparentado HLA idéntico con acondicionamiento de intensidad reducida (PI12/02361)	Mª Dolores Caballero Barrigón	FIS-ISCIII	2013-2015	61,105.00 €
Resistencia adquirida a nuevos fármacos frente al mieloma múltiple. Estudio de sus características, mecanismos responsables y reversibilidad (PI11/01465)	Enrique M. Ocio San Miguel	FIS-ISCIII	2012-2015	113,000,00 €
Evaluación del efecto sinérgico del inhibidor de «Kinesin Spindle Protein» Filanesib (ARRY-520) en combinacion con fármacos inmunomoduladores en modelos preclínicos de mieloma múltiple (GRS 1029/A/14)	Enrique M. Ocio San Miguel	Gerencia Regional de Salud de Castilla y León	2014-2015	14,900,00 €
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 de Castilla y León	2015-2016	19,000.00 €
Interacciones entre las células de mieloma y estroma de la médula ósea: papel en la progresión de las gammapatías asintomáticas, fisiopatología y lesiones osteolíticas del mieloma múltiple (PI12/02591)	Mercedes Garayoa Berrueta	FIS-ISCIII	2013-2015	110,715.00 €
Genómica funcional de Células Stem Mesenquimales (MSC) de individuos normales y pacientes con mieloma múltiple (FIC335U14)	Mercedes Garayoa Berrueta	Consejería de Educación de la Junta de Castilla y León	2014-2017	29,000.00 €

Project	IP	Grant	Time	Funding
Caracterización del perfil de miRNAs de exosomas en plasma de médula ósea y sangre periférica de pacientes con mieloma del ensayo CLARIDEX (RV-CL-MM-PETHEMA-004594) (BIO/SA74/15)	Mercedes Garayoa Berrueta	Consejería de Sanidad de la Junta de Castilla y León	2015-2016	31,350.00 €
Nuevas rutas de supervivencia y quimiorresistencia en Mieloma múltiple: estudio del papel de la kinasa Pim-2 (BIO/SA05/14)	Teresa Paíno Gómez	Consejería de Sanidad de la Junta de Castilla y León	2014	25,217.00 €
Investigación del splicing del RNA y de su regulación en el mieloma múltiple (FIS13/00111)	Norma C Gutiérrez Gutiérrez	FIS-ISCIII	2014-2016	67,155.00 €
Investigación de la regulación del splicing del RNA en mieloma múltiple (BIO/SA57/13)	Norma C Gutiérrez Gutiérrez	Consejería de Sanidad de la Junta de Castilla y León	2013-2014	45,791.00 €
Optimización y validación de un método de «western» automatizado para cuantificar proteínas esenciales en la patogenia del mieloma múltiple (BIO/SA35/14)	Norma C Gutiérrez Gutiérrez	Consejería de Sanidad de la Junta de Castilla y León	2014-2015	21,792.00 €
Evaluación de la actividad antitumoral de la amilorida en modelos pre-clínicos de mieloma múltiple (BIO/SA22/15)	Irena Misiewicz-Krzeminska	Consejería de Sanidad de la Junta de Castilla y León	2015-2016	30,667.00 €
Providing the right care to the right patient with MyeloDysplastic Syndrome at the right time (Ref. MDS-RIGHT)	Mª Consuelo del Cañizo Fernández Roldán (Investigadora coordinadora)	EU	2015-2020	35,145.00 €
Ensayo clínico multicéntrico, aleatorizado, comparativo y Add-on, en dos grupos paralelos para evaluar la eficacia y seguridad de las células madre autólogas derivadas del tejido adiposo, para el tratamiento de la patología perianal compleja en pacientes sin enfermedad inflamatoria intestinal (EC11-394)	Mª Consuelo del Cañizo Fernández Roldán	Ministerio de Sanidad, Ayudas Investigación Clínica Independiente	2012-2015	159,160.00 €
Nodo 13 perteneciente a la «Red Nacional de Terapia Celular-TerCel» (RD12/0017/0019)	Mª Consuelo del Cañizo Fernández Roldán	FIS-ISCIII	2013-2016	331,200.00 €
Estudio molecular y funcional de los exosomas procedentes de células mesenquimales de médula ósea y de su papel en el injerto hematopoyético postrasplante (PI12/01775)	Mª Consuelo del Cañizo Fernández Roldán	FIS-ISCIII	2013-2015	105,000.00 €
Análisis de la capacidad de las células mesenquimales de pacientes con neoplasias proliferativas Philadelfia negativas para favorecer la hematopoyesis leucémica in vivo (BIO/SA28/14)	Mª Consuelo del Cañizo Fernández Roldán	Consejería de Sanidad de la Junta de Castilla y León	2014	16,702.00 €
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 de Castilla y León	2015-2016	18,960.00 €
Nodo 16 del Consorcio RETHRIM (Restoring tissue regeneration in patients with visceral graft versus host disease; proposal number 643580)	Fermín M. Sánchez-Guijo	H2020-PHC-2014-single-stage_RTD, actividad PCH-15-2014	2015-2019	314,850.00 €
Análisis del nicho hematopoyético en las neoplasias mieloproliferativas crónicas: estudio de las células mesenquimales y de sus microvesículas extracelulares (GRS 1034/A/14)	Fermín M. Sánchez-Guijo	Consejería de Sanidad de la Junta de Castilla y León	2014-2015	16,000.00 €

Project	IP	Grant	Time	Funding
Next Generation Sequencing-Personalized therapy in Leukemia (NGS-PTL) (FP7-HEALTH-2012-INNOVATION-1, 306242-2)	Jesús Mª Hernández Rivas	EU	2013-2015	399,682.00 €
IRON-III (Interlaboratory robustness of Next generation Sequencing)	Haferlach T (MLL, Munich): Coordinador // Jesús Mª Hernández Rivas: IP Grupo Español	Roche IVS	2014-2015	
Estudio genómico de la leucemia linfática crónica con pérdida de 13q (PI12/00281)	Jesús Mª Hernández Rivas	FIS-ISCIII	2013-2015	139,150.00 €
Estudio de la leucemia aguda linfoblástica B mediante microarrays y secuenciación de última generación (HUS272U13)	Jesús Mª Hernández Rivas	Consejería Educación de la Junta Castilla y León	2013-2015	35,000.00 €
Estudio mediante secuenciación masiva de las mutaciones de los genes implicados en mielofibrosis (GRS 994/A/14)	Jesús Mª Hernández Rivas	Gerencia Regional de Salud de Castilla y León	2014-2015	16,140.00 €
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 de Castilla y León	2015-2016	19,700.00 €
Análisis integrado de las alteraciones génicas detectadas por secuenciación masiva, MLPA y CGH-arrays en la Leucemia Aguda Linfoblástica B (BIO/SA10/14)	Rocío Benito Sánchez	Consejería de Sanidad, Junta Castilla y León	2014-2015	25,369.00 €
Estudio de las mutaciones presentes en las células progenitoras hematopoyéticas en los Síndromes Mielodisplásicos mediante Secuenciación masiva (BI0/SA52/14)	Mónica del Rey González	Consejería de Sanidad, Junta Castilla y León	2014-2015	37,740.00 €

Other activities & relevant facts

Scientific appointments

- 2014–Present – Marcos González Díaz, Coordinator. Hematological Tumors Program of the 3rd Spanish Cancer Cooperative Network (RTICC).
- 2014–Present – Marcos González Díaz, Member of the Executive Committee. 3rd Spanish Cancer Cooperative Network (RTICC).
- 2014-2015 – Marcos González Díaz, Director Excellence group GREX 33. Regional Ministry of Education of Castilla and Leon.

Others

- Marcos González Díaz, Coordinator of symposium «VI Jornadas de Gammapatías Monoclonales» (Salamanca, Spain, 7-8 March 2014).
- Marcos González Díaz, Coordinator of several courses titled «Advanced Courses on Multiple Myeloma and Related Disorders» (Salamanca, Spain, 2014 and 2015).

LABORATORY 13

Stem cells, cancer stem cells and cancer biology

Team Leader

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Research Team

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Master Students

Esther Arnaiz González

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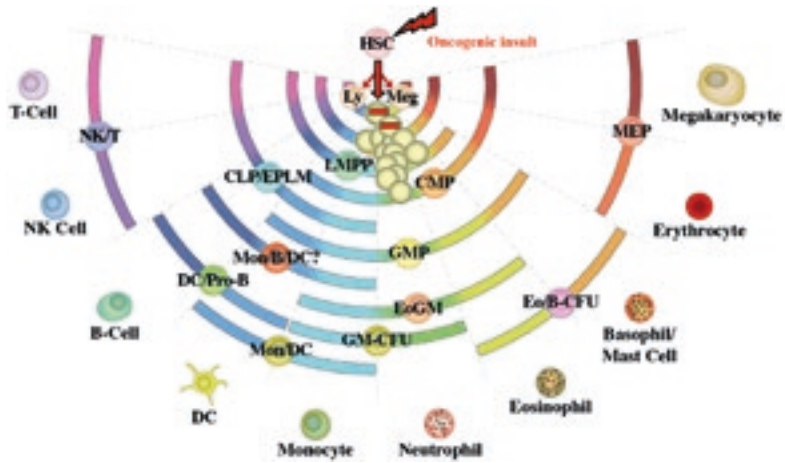
Zuzanna Urban

Franziska Auer



Tumoral Reprogramming-Leukemia Stem Cells are reprogrammed by an oncogenic insult to an invariant cell lineage.

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. A few years ago, we initiated an ambitious hypothesis-driven research program to study the function of oncogenes within the cancer stem cells (CSC). Using as a model the BCR-ABL oncogene responsible for the development of chronic myeloid leukemia (CML), we demonstrated that cancer development can be established in mice by limiting oncogene expression to tumor-initiating stem cells. We further showed that CSC survival was BCR-ABL kinase independent, suggesting that curative approaches must focus on kinase-independent mechanisms of resistance (Pérez-Caro et al., EMBO J., 2009). These studies showed that CSCs are not oncogene addicted (in contrast to the oncogene addition showed by tumor differentiated cells) and represented the first demonstration of development of CSC as a result of a reprogramming-like mechanism. These findings challenge the current accepted/working model of the role of oncogenes in cancer. Moreover, these observations, beyond their impact on the current theories of the genesis of cancer, have also clinical implications. In fact, these results derived from our Sca1-BCRABL CML mice have been translated to human patients (Corbin et al., 2011; Chomel et al. 2011; Chu et al. 2011; Hamilton et al., 2011; Kumari A et al. 2012), being the first time that a preclinical model anticipates the human CSC-therapeutic response. The challenge is now to find a way to identify the molecular mechanisms that govern the development of CSCs as a result of a reprogramming-like mechanism. 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 CSC 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 **Identification of cancer initiating cells in K-Ras driven lung adenocarcinoma.** Mainardi S, Mijimolle N, Francoz S, Vicente-Dueñas C, Sánchez-García I, Barbacid M. **Proc Natl Acad Sci U S A. 2014 Jan 7;111(1):255-60. doi: 10.1073/pnas.1320383110. Epub 2013 Dec 23.** PMID: 24367082 **IF: 9,674 / D1**

2 **Tumoral stem cell reprogramming as a driver of cancer: Theory, biological models, implications in cancer therapy.** Vicente-Dueñas C, Hauer J, Ruiz-Roca L, Ingenhag D, Rodríguez-Meira A, Auer F, Borkhardt A, Sánchez-García I. **Semin Cancer Biol. 2015 Jun;32:3-9. doi: 10.1016/j.semcancer.2014.02.001. Epub 2014 Feb 12. Review.** PMID: 24530939 **IF: 9,330 / D1**

3 **Lineage-specific function of Engrailed-2 in the progression of chronic myelogenous leukemia to T-cell blast crisis.** Abollo-Jiménez F, Campos-Sánchez E, Toboso-Navasa A, Vicente-Dueñas C, González-Herrero I, Alonso-Escudero E, González M, Segura V, Blanco O, Martínez-Climent JA, Sánchez-García I, Cobaleda C. **Cell Cycle. 2014;13(11):1717-26. doi: 10.4161/cc.28629. Epub 2014 Mar 25.** PMID: 24675889 **IF: 4,565 / Q2**

4 **Hit-and-run lymphomagenesis by the Bcl6 oncogene.** Green MR, Vicente-Dueñas C, Alizadeh AA, Sánchez-García I. **Cell Cycle. 2014;13(12):1831-2. doi: 10.4161/cc.29326. Epub 2014 May 27.** PMID: 24867153 **IF: 4,565 / Q2**

5 **Transient expression of Bcl6 is sufficient for oncogenic function and induction of mature B-cell lymphoma.** Green MR, Vicente-Dueñas C, Romero-Camarero I, Long Liu C, Dai B, González-Herrero I, García-Ramírez I, Alonso-Escudero E, Iqbal J, Chan WC, Campos-Sánchez E, Orfao A, Pintado B, Flores T, Blanco O, Jiménez R, Martínez-Climent JA, Criado FJ, Cenador MB, Zhao S, Natkunam Y, Lossos IS, Majeti R, Melnick A, Cobaleda C, Alizadeh AA, Sánchez-García I. **Nat Commun. 2014 Jun 2;5:3904. doi: 10.1038/ncomms4904.** PMID: 24887457 **IF: 11,470 / D1**

6 **Early epigenetic cancer decisions.** Martín-Lorenzo A, González-Herrero I, Rodríguez-Hernández G, García-Ramírez I, Vicente-Dueñas C, Sánchez-García I. **Biol Chem. 2014 Nov 1;395(11):1315-20. doi: 10.1515/hsz-2014-0185. Review.** PMID: 25205718 **IF: 3,268 / Q2**

7 **Genetically engineered mouse models of human B-cell precursor leukemias.** Hauer J, Borkhardt A, Sánchez-García I, Cobaleda C. **Cell Cycle. 2014;13(18):2836-46. doi: 10.4161/15384101.2014.949137.** PMID: 25486471 **IF: 4,565 / Q2**

8 **Mutations in early follicular lymphoma progenitors are associated with suppressed antigen presentation.** Green MR, Kihira S, Liu CL, Nair RV, Salari R, Gentles AJ, Irish J, Stehr H, Vicente-Dueñas C, Romero-Camarero I, Sánchez-García I, Plevritis SK, Arber DA, Batzoglou S, Levy R, Alizadeh AA. **Proc Natl Acad Sci U S A. 2015 Mar 10;112(10):E1116-25. doi: 10.1073/pnas.1501199112. Epub 2015 Feb 23.** PMID: 25713363 **IF: 9,674 / D1**

9 **Sustained proliferation in cancer: Mechanisms and novel therapeutic targets.** Feitelson MA, Arzumanyan A, Kulathinal RJ, Blain SW, Holcombe RF, Mahajna J, Marino M, Martínez-Chantar ML, Nawroth R, Sánchez-García I, Sharma D, Saxena NK, Singh N, Vlachostergios PJ, Guo S, Honoki K, Fujii H, Georgakilas AG, Bilsland A, Amedei A, Niccolai E, Amin A, Ashraf SS, Boosani CS, Guha G, Ciriolo MR, Aquilano K, Chen S, Mohammed SI, Azmi AS, Bhakta D, Halicka D, Keith WN, Nowsheen S. **Semin Cancer Biol. 2015 Apr 17. pii: S1044-579X(15)00014-0. doi: 10.1016/j.semcancer.2015.02.006. Review.** PMID: 25892662 **IF: 9,330 / D1**

10 **How tumour cell identity is established?** Sánchez-García I. **Semin Cancer Biol. 2015 Jun;32:1-2. doi: 10.1016/j.semcancer.2015.04.004. Epub 2015 Apr 28.** PMID: 25931389 **IF: 9,330 / D1**

11 **Post-transcriptional Modifications Contribute to the Upregulation of Cyclin D2 in Multiple Myeloma.** Misiewicz-Krzeminska I, Sarasquete ME, Vicente-Dueñas C, Krzeminski P, Wiktorska K, Corchete LA, Quwaider D, Rojas EA, Corral R, Martín AA, Escalante F, Bárez A, García JL, Sánchez-García I, García-Sanz R, San Miguel JF, Gutiérrez NC. **Clin Cancer Res. 2015 Sep 4.** PMID: 26341922 **IF: 8,722 / D1**

12 **Infection Exposure Is a Causal Factor in B-cell Precursor Acute Lymphoblastic Leukemia as a Result of Pax5-Inherited Susceptibility.** Martín-Lorenzo A, Hauer J, Vicente-Dueñas C, Auer F, González-Herrero I, García-Ramírez I, Ginzel S, Thiele R, Constantinescu SN, Bartenhagen C, Dugas M, Gombert M, Schäfer D, Blanco O, Mayado A, Orfao A, Alonso-López D, Rivas Jde L, Cobaleda C, García-Cenador MB, García-Criado FJ, Sánchez-García I*, Borkhardt A*. **Cancer Discov. 2015 Dec;5(12):1328-43. doi: 10.1158/2159-8290.CD-15-0892. Epub 2015 Sep 25.** PMID: 26408659. *Should be considered as equal senior authors **IF: 19, 453 / D1**

13 **Infection causes childhood leukemia.** Hauer J, Martín-Lorenzo A, Sánchez-García I. **Aging (Albany NY). 2015 Sep;7(9):607-8.** PMID: 26412458 **IF: 6,432 / Q1**

14 **Is lineage decision-making restricted during tumoral reprograming of haematopoietic stem cells?** Brown G, Sánchez-García I. **Oncotarget. 2015 Oct 19. doi: 10.18632/oncotarget.6145.** PMID: 26498146 **IF: 6,359 / D1**

15 **Designing a broad-spectrum integrative approach for cancer prevention and treatment.** Block KI, Gyllenhaal C, Lowe L, Amedei A, Amin AR, Amin A, Aquilano K, Arbiser J, Arreola A, Arzumanyan A, Ashraf SS, Azmi AS, Benencia F, Bhakta D, Bilsland A, Bishayee A, Blain SW, Block PB, Boosani CS, Carey TE, Carnero A, Carotenuto M, Casey SC, Chakrabarti M, Chaturvedi R, Chen GZ, Chen H, Chen S, Chen YC, Choi BK, Ciriolo MR, Coley HM, Collins AR, Connell M, Crawford S, Curran CS, Dabrosin C, Damia G, Dasgupta S, DeBerardinis RJ, Decker WK, Dhawan P, Diehl AM, Dong JT, Dou QP, Drew JE, Elkord E, El-Rayes B, Feitelson MA, Felsher DW, Ferguson LR, Fimognari C, Firestone GL, Frezza C, Fujii H, Fuster MM, Generali D, Georgakilas AG, Gieseler F, Gilbertson M, Green MF, Grue B, Guha G, Halicka D, Helferich WG, Heneberg P, Hentosh P, Hirschey MD, Hofseth LJ, Holcombe RF, Honoki K, Hsu HY, Huang GS, Jensen LD, Jiang WG, Jones LW, Karpowicz PA, Keith WN, Kerkar SP, Khan GN, Khatami M, Ko YH, Kucuk O, Kulathinal RJ, Kumar NB, Kwon BS, Le A, Lea MA, Lee HY, Lichtor T, Lin LT, Locasale JW, Lokeshwar BL, Longo

VD, Lyssiotis CA, MacKenzie KL, Malhotra M, Marino M, Martínez-Chantar ML, Matheu A, Maxwell C, McDonnell E, Meeker AK, Mehrmohamadi M, Mehta K, Michelotti GA, Mohammad RM, Mohammed SI, Morre DJ, Muralidhar V, Muqbil I, Murphy MP, Nagaraju GP, Nahta R, Niccolai E, Nowsheen S, Panis C, Pantano F, Parslow VR, Pawelec G, Pedersen PL, Poore B, Poudyal D, Prakash S, Prince M, Raffaghello L, Rathmell JC, Rathmell WK, Ray SK, Reichrath J, Rezazadeh S, Ribatti D, Ricciardiello L, Robey RB, Rodier F, Rupasinghe HP, Russo GL, Ryan EP, Samadi AK, Sánchez-García I, Sanders AJ, Santini D, Sarkar M, Sasada T, Saxena NK, Shackelford RE, Shantha Kumara HM, Sharma D, Shin DM, Sidransky D, Siegelin MD, Signori E, Singh N, Sivanand S, Sliva D, Smythe C, Spagnuolo C, Stafforini DM, Stagg J, Subbarayan PR, Sundin T, Talib WH, Thompson SK, Tran PT, Ungefroren H, Vander Heiden MG, Venkateswaran V, Vinay DS, Vlachostergios PJ, Wang Z, Wellen KE, Whelan RL, Yang ES, Yang H, Yang X, Yaswen P, Yedjou C, Yin X, Zhu J, Zollo M. **Semin Cancer Biol. 2015 Dec;35 Suppl:S276-304. doi: 10.1016/j.semcancer.2015.09.007. Review.** PMID: 26590477 **IF: 9,330 / D1**

16 **GEMMs addressing Pax5 loss-of-function in childhood pB-ALL.** Auer F, Ingenhag D, Bhatia S, Enczmann J, Cobaleda C, Sánchez-García I, Borkhardt A, Hauer J. **Eur J Med Genet. 2015 Nov 25. pii: S1769-7212(15)30047-1. doi: 10.1016/j.ejmg.2015.11.009. Review.** PMID: 26626503 **IF: 1,466 / Q4**

Other publications & book chapters

1 **Stem cell reprogramming as a driver of cancer.** I. Sánchez-García **Guest Editor for a special issue of Seminars in Cancer Biology. Volume 32, June 2015,** ISSN 1044-579X

2 **Diversity, Versatility, and Leukaemia.** Dr. Geoffrey Brown and Dr. Isidro Sánchez-García. **SoftCover. Invited by Nova Science Publishers, Inc., New York,** NY 11788-3619, **USA before May 2016.**

3 **Cancer Stem Cells: changing the way we treat cancer.** Isidro Sánchez-García. **Digital e-book 2014 (http://www.adjacentgovernment.co.uk/ebooks-archive/page/2/)**

4 **Closing down cancer.** Isidro Sánchez-García. **May 2014, International Innovation (www.researchmedia.eu).**

5 **A focus on Stem Cells and Cancer.** Isidro Sánchez-García. Spanish Research Council (CSIC). **http://www.adjacentgovernment.co.uk/stakeholders/spanish-research-council-csic-a-focus-on-stem-cells-and-cancer/**

6 **MAFB (v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog B).** Vicente-Dueñas C, González-Herrero I, García-Ramírez I, Sánchez-García I. **Atlas Genet Cytogenet Oncol Haematol. September 2014 URL : http://AtlasGeneticsOncology.org/Genes/MAFBID41236ch20q11.html**

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).

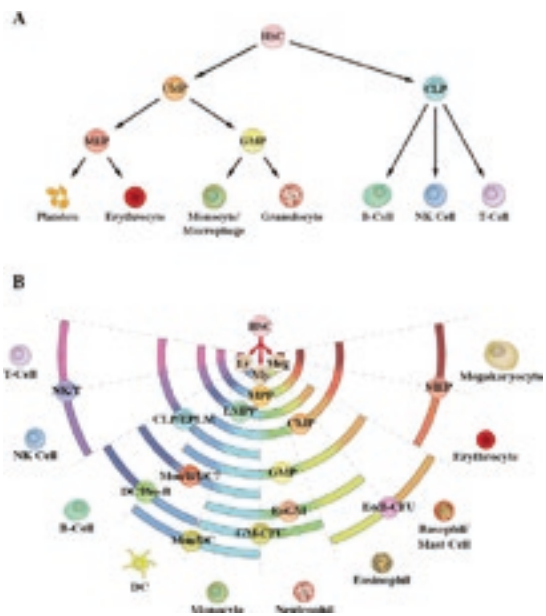
Grants for research in progress

Project	IP	Grant	Time	Funding
El papel de la inmunoglobulina intravenosa (IGIV) en el tratamiento de cáncer-2	Isidro Sánchez García	Instituto Grifols, S.A (50108120001)	2012-2014	267,624.00 €
Mecanismos moleculares que gobiernan en el desarrollo de las células madre cancerígenas como resultado del proceso de reprogramación: implicaciones en el desarrollo y tratamiento	Isidro Sánchez García	Ministerio de Economía y Competitividad (SAF2012-32810)	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	
Papel de la Células Stem Cancerígenas en la biología del linfoma difuso de células grandes (BIO/SA32/14)	Isidro Sánchez García	Consejería de Sanidad–Junta de Castilla y León	2014	34,114.00 €
Significance and Function of HGAL in Lymphoma (2R01 CA109335-04A1)	Isidro Sánchez García	NIH	2009-2014	250,000.00 €
El ciclo celular y los microRNAs en la autorenovación y diferenciación de las células progenitoras (P2010/BMD-2502 (ONCOCYCLE))	Isidro Sánchez García (investigador asociado)	Consejería de Educación de la Comunidad de Madrid	2011-2015	
Estudio del desarrollo de las leucemias linfoblásticas agudas infantiles TEL-AML1 con el fin de establecer nuevas bases terapéuticas y profilácticas (CSI001U14)	Isidro Sánchez García	Consejería de Educación–Junta de Castilla y León	2014-2015	29,000.00 €
Advanced Research on Interaction Mechanisms of electroMagnetic exposures with organisms for RisK (282891 (ARIMMORA))	Isidro Sánchez García	European Union (FP7-ENV-2011 (ENV.2011.1.2.2)	2011-2015	366,000.00 €
Advanced Research on Interaction Mechanisms of electroMagnetic exposures with organisms for risk	Isidro Sánchez García	Unión Europea (C-ENVIR/1165)	2011-2014	333,856.00 €
Biología del cáncer (SAF2014-57791-REDC)	Isidro Sánchez García	Acciones de dinamización «Redes de Excelencia», del Programa Estatal de Fomento de la Investigación Científica y Técnica de Excelencia, Subprograma Estatal de Generación de Conocimiento, en el marco del Plan Estatal de Investigación Científica y Técnica y de Innovación 2013-2016 Tipo de red: Consolider	2015-2016	45,000,00 €
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 €

Project	IP	Grant	Time	Funding
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 €
Chemotherapy cardiotoxicity in the elderly: a translational and personnel approach. CARTIER (CARdioToxicity In the Elderly progRamme) (PIE 14/00066)	Isidro Sánchez García	ISCIII- Proyectos Integrados de Excelencia en los IIS acreditados	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	Telefónica Móviles España S.A.	2014	15,000.00 €
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	Telefónica Móviles España S.A.	2015	15,000.00 €

Other activities & relevant facts

- 2012-present. Director IBSAL CANC-15 group - Institute for Biomedical Research (IBSAL). Salamanca.
- Member of the 2014 Life Sciences Judging panel for 2014 Life Sciences Category for the Undergraduate Award (This is a collection of world-renowned academics in the expansive field of Life Sciences to judge some of the best undergraduate work from around the globe). The Undergraduate Awards. Patron: Michael D. Higgins, President of Ireland <http://www.undergraduateawards.com/>



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.

LABORATORY 14

Hereditary cancer

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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 CFH (rs1410996), HTRA1 (rs112000638) and ARMS2 (rs10490923) gene polymorphisms are associated with AMD risk in Spanish patients. Cruz-González F, Cieza-Borrella C, López Valverde G, Lorenzo-Pérez R, Hernández-Galilea E, González-Sarmiento R. **Ophthalmic Genet. 2014 Jun;35(2):68-73. doi: 10.3109/13816810.2013.781193. Epub 2013 Mar 27.** PMID: 23534868 **IF: 1,455 / Q3**

2 Role of XRCC3, XRCC1 and XPD single-nucleotide polymorphisms in survival outcomes following adjuvant chemotherapy in early stage breast cancer patients. Castro E, Olmos D, García A, Cruz JJ, González-Sarmiento R. **Clin Transl Oncol. 2014 Feb;16(2):158-65. doi: 10.1007/s12094-013-1055-8013-1055-8. Epub 2013 Jun 6.** PMID: 23740134 **IF: 2,077 / Q3**

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8 Novel mutation p.A64D in the Serpina7 gene as a cause of partial thyroxine-binding globulin deficiency associated with increases affinity in transthyretin by a known p.A109T mutation in the TTR gene. Sklate RT, Olcese MC, Maccallini GC, Sarmiento RG, Targovnik HM, Rivolta CM. **Horm Metab Res. 2014 Feb;46(2):100-8. doi: 10.1055/s-0033-1358741. Epub 2013 Dec 19.** PMID: 24356794 **IF: 2,121 / Q3**

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10 Genetic polymorphisms and lung cancer risk: a case-control study. Jiménez-Massa AE, Alonso-Sardón M, Menacho-Miguel JA, Mirón-Canelo JA, González-Sarmiento R. **Med Clin (Barc). 2014 Aug 4;143(3):97-103. doi: 10.1016/j.medcli.2013.07.034. Epub 2014 Feb 13. Spanish.** PMID: 24529400 **IF: 1,417 / Q2**

11 A genetic variant in the microRNA-146a gene is associated with susceptibility to alcohol use disorders. Novo-Veleiro I, González-Sarmiento R, Cieza-Borrella C, Pastor I, Laso FJ, Marcos M. **Eur Psychiatry. 2014 Jun;29(5):288-92. doi: 10.1016/j.eurpsy.2014.02.002. Epub 2014 Mar 14.** PMID: 24630744 **IF: 3,439 / Q2**

12 Relationship between target organ damage and blood pressure, retinal vessel calibre, oxidative stress and polymorphisms in VAV-2 and VAV-3 genes in patients with hypertension: a case-control study protocol (LOD-Hipertension). Gómez-Marcos MA, González-Sarmiento R, Recio-Rodríguez JI, Agudo-Conde C, Gamella-Pozuelo L, Perretta-Tejedor N, Martínez-Salgado C, García-Ortiz L. **BMJ Open. 2014 Apr 3;4(4):e005112. doi: 10.1136/bmjopen-2014-005112.** PMID: 24699462 **IF: 2,271 / Q2**

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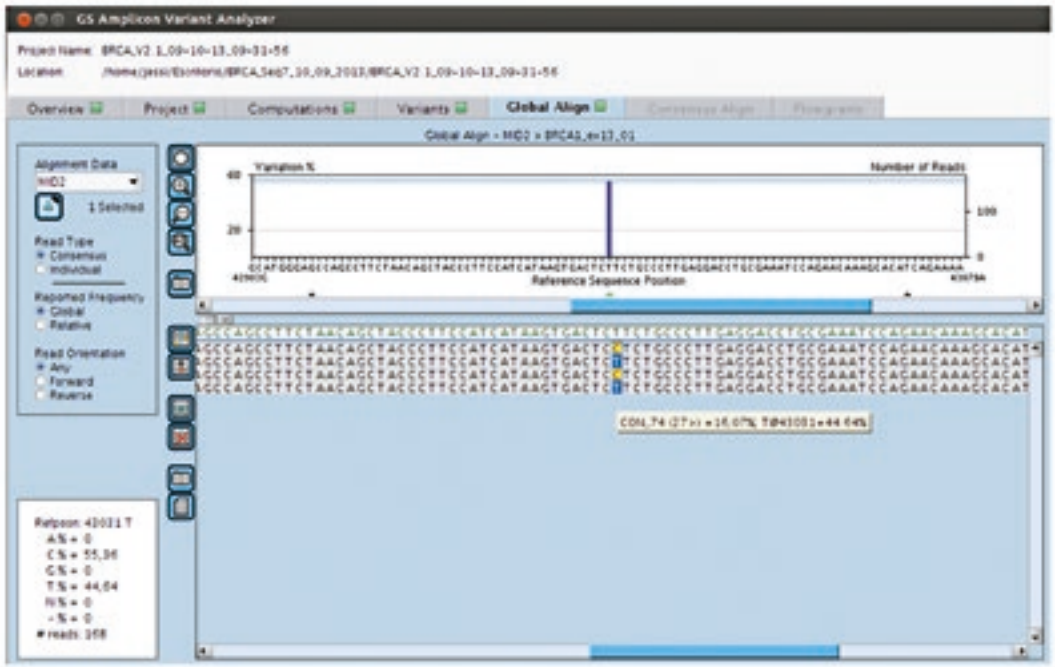

Roche GS-Junior

32 **Exploring the size adaptability of the B ring binding zone of the colchicine site of tubulin with para-nitrogen substituted isocombretastatins.** Jiménez C, Ellahioui Y, Álvarez R, Aramburu L, Riesco A, González M, Vicente A, Dahdouh A, Ibn Mansour A, Jiménez C, Martín D, Sarmiento RG, Medarde M, Caballero E, Peláez R. **Eur J Med Chem. 2015 Jul 15;100:210-22. doi: 10.1016/j.ejmech.2015.05.047. Epub 2015 Jun 4.** PMID: 26092446 **IF: 1,466 / Q4**

33 **Recent advances in congenital ichthyoses.** Hernández-Martín A, González-Sarmiento R. **Curr Opin Pediatr. 2015 Aug;26(4):473-9. doi: 10.1097/MOP.0000000000000239.** PMID: 26164154 **IF: 2,528 / Q1**

34 **Study of the True Clinical Progression of Autosomal Dominant Alport Syndrome in a European Population.** Rosado C, Bueno E, Felipe C, Valverde S, González-Sarmiento R. **Kidney Blood Press Res. 2015;40(4):435-42. doi: 10.1159/000368519. Epub 2015 Jul 31.** PMID: 26277931 **IF: 2,123 / Q2**

35 **Classifying early-onset colorectal cancer according to tumor location: new potential subcategories to explore.** Perea J, Cano JM, Rueda D, García JL, Inglada L, Osorio I, Arriba M, Pérez J, Gaspar M, Fernández-Miguel T, Rodríguez Y, Benítez J, González-Sarmiento R, Urioste M. **Am J Cancer Res. 2015 Jun 15;5(7):2308-13. eCollection 2015.** PMID: 26328262 **IF: 4,165 / Q1**

36 **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, González-Porras JR, González-Sarmiento R, Lozano FS. **Pain Pract. 2015 Sep 26. doi: 10.1111/papr.12343** PMID: 26407542 **IF: 2,361 / Q2**

37 **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. 2015 Dec 9. doi: 10.1111/pde.12740.** PMID: 26646773 **IF: 1,015 / Q3**

Patents

Patent reference	Title	Inventors	Priority Date
ES 201531891	Biomarcador para el diagnóstico, pronóstico y seguimiento de cáncer colorrectal de aparición precoz	José Perea García, Rogelio González Sarmiento, Miguel Urioste Azcorra, Daniel Rueda Fernández, María Arriba Domenech, Juan Luis García Hernández, Jéssica Pérez García	

Grants for research in progress

Project	IP	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	ISCIII	2014-2016	113.740,00 €

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Mª Dolores Rivero Megías

Sandra Moro Villa

Visiting Researchers

Elaine Cristima Kormann

Ana Paula Oliveira Hohne

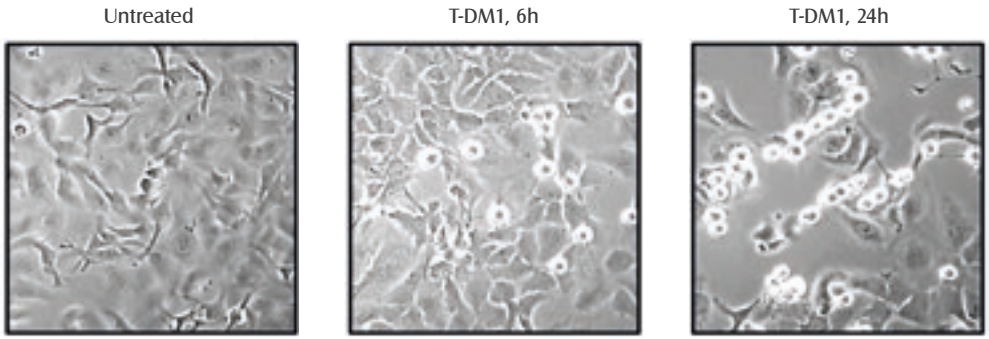
Ana Paula Zen Petisco Fiore

Almahy Mohammed Hassan

LABORATORY 15

Kinases in oncology. Signaling by receptor tyrosine kinases

Kinases in oncology. Signaling by receptor tyrosine kinases



Effect of T-DM1 on HER2-overexpresing ovarian cancer cells. The drug T-DM1 indices rounding of the cells, characteristic of its antitumoral effect by inhibiting tubulin function.

Our research is 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.

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.

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SENIOR RESEARCHER

The ERK5 pathway in cancer

Receptor tyrosine kinases such as EGFR, IGF-1R, HER2, are involved in the genesis/progression of several types of tumors. These receptors act by regulation of various intracellular signaling pathways. One of these pathways, the MEK5/ERK5 signaling route, plays an important role in the pathophysiology of several neoplasias. Therefore, targeting of the components of this route may be of therapeutic relevance. Lung cancer is the most frequently diagnosed tumor and the most common cause of cancer-related mortality worldwide. Genome –Wide Association Studies revealed that MEK5 and ERK5 gene regions are linked to lung cancer. Recently it has been reported that a functional polymorphism in the promoter of ERK5 increases the risk of lung cancer in the Chinese population. Based on these data we are:

Analyzing the relevance of the MEK5/ERK5 pathway in lung cancer by genetic and pharmacological approaches. We are evaluating the potential therapeutic relevance of targeting this route in lung cancer.

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.

Publications

1 Active kinase profiling, genetic and pharmacological data define mTOR as an important common target in triple-negative breast cancer. Montero JC, Esparís-Ogando A, Re-Louhau MF, Seoane S, Abad M, Calero R, Ocaña A, Pandiella A. **Oncogene. 2014 Jan 9;33(2):148-56. doi: 10.1038/onc.2012.572. Epub 2012 Dec 17.** PMID: 23246963 **IF: 8,459 / D1**

2 Biological insights into effective and antagonistic combinations of targeted agents with chemotherapy in solid tumors. Ocaña A, Freedman O, Amir E, Seruga B, Pandiella A. **Cancer Metastasis Rev. 2014 Mar;33(1):295-307. doi: 10.1007/s10555-013-9451-7. Review.** PMID: 24338003 **IF: 7,234 / D1**

3 Genetic and pharmacologic evidence that mTOR targeting outweighs mTORC1 inhibition as an antimyeloma strategy. Chen X, Díaz-Rodríguez E, Ocio EM, Paiva B, Mortensen DS, López-Girona A, Chopra R, Miguel JS, Pandiella A. **Mol Cancer Ther. 2014 Feb;13(2):504-16. doi: 10.1158/1535-7163.MCT-13-0022. Epub 2014 Jan 15.** PMID: 24431075 **IF: 5,683 / Q1**

4 Activation of the PI3K/mTOR/AKT pathway and survival in solid tumors: systematic review and meta-analysis. Ocaña A, Vera-Badillo F, Al-Mubarak M, Templeton AJ, Corrales-Sánchez V, Díez-González L, Cuenca-López MD, Seruga B, Pandiella A, Amir E. **PLoS One. 2014 Apr 28;9(4):e95219. doi: 10.1371/journal.pone.0095219. eCollection 2014. Review.** PMID: 24777052 **IF: 3,234 / Q1**

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6 NADPH oxidases as therapeutic targets in chronic myelogenous leukemia. Sánchez-Sánchez B, Gutiérrez-Herrero S, López-Ruano G, Prieto-Bermejo R, Romo-González M, Llanillo M, Pandiella A, Guerrero C, Miguel JF, Sánchez-Guijo F, Del Cañizo C, Hernández-Hernández A. **Clin Cancer Res. 2014 Aug 1;20(15):4014-25. doi: 10.1158/1078-0432.CCR-13-3044. Epub 2014 May 15.** PMID: 24833663 **IF: 8,722 / D1**

7 In vivo murine model of acquired resistance in myeloma reveals differential mechanisms for lenalidomide and pomalidomide in combination with dexamethasone. Ocio EM, Fernández-Lázaro D, San-Segundo L, López-Corral L, Corchete LA, Gutiérrez NC, Garayoa M, Paíno T, García-Gómez A, Delgado M, Montero JC, Díaz-Rodríguez E, Mateos MV, Pandiella A, Couto S, Wang M, Bjorklund CC, San-Miguel JF. **Leukemia. 2015 Mar;29(3):705-14. doi: 10.1038/leu.2014.238. Epub 2014 Aug 8.** PMID: 25102946 **IF: 10,431 / D1**

8 The mitogen-activated protein kinase ERK5 regulates the development and growth of hepatocellular carcinoma. Rovida E, Di Maira G, Tusa I, Cannito S, Paternostro C, Navari N, Vivoli E, Deng X, Gray NS, Esparís-Ogando A, David E, Pandiella A, Dello Sbarba P, Parola M, Marra F. **Gut. 2015 Sep;64(9):1454-65. doi: 10.1136/gutjnl-2014-306761. Epub 2014 Sep 2.** PMID: 25183205 **IF: 14,660 / D1**

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10 Effect of p95HER2/611CTF on the response to trastuzumab and chemotherapy. Parra-Palau JL, Morancho B, Peg V, Escorihuela M, Scaltriti M, Vicario R, Zacarias-Fluck M, Pedersen K, Pandiella A, Nuciforo P, Serra V, Cortés J, Baselga J, Perou CM, Prat A, Rubio IT, Arribas J. **J Natl Cancer Inst. 2014 Sep 24;106(11). pii: dju291. doi: 10.1093/jnci/dju291. Print 2014 Nov.** PMID: 25253614 **IF: 12,583 / D1**

11 Transcriptomic profile induced in bone marrow mesenchymal stromal cells after interaction with multiple myeloma cells: implications in myeloma progression and myeloma bone disease. García-Gómez A, De Las Rivas J, Ocio EM, Díaz-Rodríguez E, Montero JC, Martín M, Blanco JF, Sánchez-Guijo FM, Pandiella A, San Miguel JF, Garayoa M. **Oncotarget. 2014 Sep 30;5(18):8284-305.** PMID: 25268740 **IF: 6,359 / D1**

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16 Modulation of cereblon levels by anti-myeloma agents. Díaz-Rodríguez E, Pandiella A. **Leuk Lymphoma. 2015 May 12:1-10.** PMID: 25860244 **IF: 2,891 / Q2**

17 Effect of Oncoxin Oral Solution in HER2-Overexpressing Breast Cancer. Hernández-García S, González V, Sanz E, Pandiella A. **Nutr Cancer. 2015 Aug 4:1-11.** PMID: 26241555 **IF: 2,322 / Q3**

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20 **Breast cancer dissemination promoted by a neuregulin-collagenase 3 signalling node.** Seoane S, Montero JC, Ocaña A, Pandiella A. **Oncogene. 2015 Sep 14. doi: 10.1038/onc.2015.337.** PMID: 26364598 **IF: 8,459 / D1**

21 **Phospho-kinase profile of colorectal tumors guides in the selection of multi-kinase inhibitors.** Serrano-Heras G, Cuenca-López MD, Montero JC, Corrales-Sánchez V, Morales JC, Núñez LE, Morís F, Pandiella A, Ocaña A. **Oncotarget. 2015 Oct 13;6(31):31272-83. doi: 10.18632/oncotarget.5211.** PMID: 26418718 **IF: 6,359 / D1**

22 **Antitumoral activity of the mithralog EC-8042 in triple negative breast cancer linked to cell cycle arrest in G2.** Pandiella A, Morís F, Ocaña A, Núñez LE, Montero JC. **Oncotarget. 2015 Oct 20;6(32):32856-67. doi: 10.18632/oncotarget.5942.** PMID: 26439989 **IF: 6,359 / D1**

23 **Influence of companion diagnostics on efficacy and safety of targeted anti-cancer drugs: systematic review and meta-analyses.** Ocaña A, Ethier JL, Díez-González L, Corrales-Sánchez V, Srikanthan A, Gascón-Escribano MJ, Templeton AJ, Vera-Badillo F, Seruga B, Niraula S, Pandiella A, Amir E. **Oncotarget. 2015 Nov 24;6(37):39538-49. doi: 10.18632/oncotarget.5946. Review.** PMID: 26446908 **IF: 6,359 / D1**

24 **Circulating DNA and survival in solid tumors.** Ocaña A, Díez-González L, García-Olmo DC, Templeton AJ, Vera-Badillo F, Gascón-Escribano MJ, Serrano-Heras G, Corrales-Sánchez V, Seruga B, Andrés-Pretel F, Pandiella A, Amir E. **Cancer Epidemiol Biomarkers Prev. 2015 Nov 24. pii: cebp.0893.2015.** PMID: 26604269 **IF: 4,125 / Q1**

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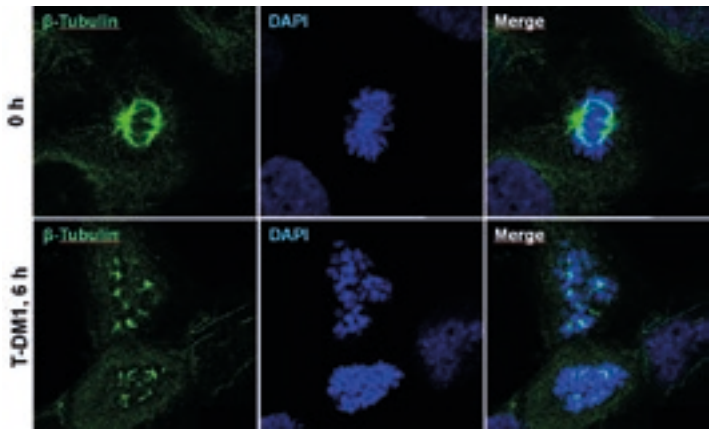
Other publications & book chapters

1 Terapias personalizadas y mecanismos de acción en cáncer. J.C. Montero, A. Esparís-Ogando, y A. Pandiella. Published in: **«Descoberta, desenho e desenvolvimento de novos agentes anticancer no ambito do programa iberoamericano CYTED». Ed. Univali, p465-483. 2014**

Patents

Patent reference	Title	Inventors	Priority Date
ES 15185746.3-1453	Antitumor activity of mithramycin analogues in triple negative breast cancer	Atanasio Pandiella Alonso, Alberto Ocaña Fernández, Francisco Morís Varas	17/09/2015
ES14170596.2-1462	Antitumor activity of multikinase inhibitors in triple negative breast cancer	Atanasio Pandiella Alonso, Alberto Ocaña Fernández, Francisco Morís Varas	30/05/2014



T-DM1 induces the appearance of aberrant mitotic spindles in HER2+ ovarian cancer cells.

Grants for research in progress

Project	IP	Grant	Time	Funding
Red Temática de Investigación Cooperativa en Cáncer. (RD12/0036/0003)	Atanasio Pandiella Alonso	Instituto de Salud Carlos III	2012-2016	92,575.00 €
Nuevas estrategias para tratar el cáncer de mama positivo para HER2.	Atanasio Pandiella Alonso (Coordinated with Joaquín Arribas)	Fundación científica de la AECC	2012-2018	600,000.00 €
Identification of new molecular targets in triple negative breast cancer. (CP12/03073)	Juan Carlos Montero González	Instituto de Salud Carlos III	2013-2015	121,500.00 €
Señalización por receptores ERBB/HER. (BFU2012-39151)	Atanasio Pandiella Alonso	Ministerio de Economía y Competitividad	2013-2015	351,000.00 €
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 €

LABORATORY 17

Structural biology of cell adhesion and signaling

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María José Bueno Montero
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Structural biology of cell adhesion and signaling

Our group is interested in understanding at atomic level the function of proteins involved in tumoral processes. Specifically, one of our main interests focuses on the role in the assembly and regulation of cell adhesion complexes of two types of proteins: the integrin family of cell adhesion receptors and the plakin family of cytolinkers. In addition, we study proteins involved in signaling processes, such as guanine nucleotide exchange factors of small GTPases and protein-phosphatases. By elucidating the atomic 3D structures of these proteins and the macromolecular complexes that they participate in, we aim at understanding their functions. Our results will pave the way to a rational structure-base design of small molecules that may alter the function of these proteins, thus having a potential therapeutic usage.

A key objective in our research is to understand how the α6α4 integrin exhorts its functions in cell adhesion and signal transduction and how it is regulated. In epithelial tissues, α6α4 is an essential component of hemidesmosomes, which are adhesion complexes that mediate the anchoring of cells to the basement membrane. In carcinoma cells, α6α4-mediated signaling favors migration, invasion, and survival. The roles of α6α4 in carcinomas correlate with an inhibition of the assembly of hemidesmosomes. Plectin and the bullous pemphigoid antigen 1 (BPAG1e) are member of the plakin family and connect the integrin α6α4 to the intermediate filaments in the hemidesmosomes. We have elucidated the structural basis of the interaction between α6α4 and plectin. Our results show that missense mutations in the α4 subunit that cause a skin blistering disease, termed epidermolysis bullosa, prevent important intermolecular contacts. Recently, we have recently combined hybrid methods to elucidate the structure of the 3rd and 4th FnIII domains of the integrin α4 subunit, which mediate binding to BPAG1e in hemidesmosomes. In addition we have mapped the mutual binding sites in α6β4 and BPAG1e. On a related objective we are characterizing the structural basis of the role of plakins in cell adhesion. We have elucidated the structure of the plakin domain, which is a region conserved in most plakins. The plakin domain of plectin is built up of nine «spectrin repeats» and a non-canonical SH3 domain. This region is responsible for the sub-cellular localization of plakins, harbors binding sites for other proteins, and potentially contributes to mechanotransduction through the intermediate filament cytoskeleton.

Finally, in collaboration with the group of Dra Carmen Guerrero we are characterizing the structural basis of the regulation of C3G, a guanine nucleotide exchange factor for small GTPases, mainly Rap1 and R-Ras.

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SENIOR RESEARCHER

Role of C3G-p38aMAPK pathway in the pathogenesis of chronic mieloide leukemia using animal models. C3G regulation of platelet function and its impact on coronary syndrome and stroke

Our group is mainly interested in the role of C3G in the development of chronic myeloid leukemia (CML) and platelet function. Studies by the group demonstrated that p87C3G, a truncated C3G isoform abundantly expressed in CML, forms complexes with Bcr-Abl and is phosphorylated by the kinase activity of Bcr-Abl. In addition, C3G participates in apoptosis in CML cells acting through p38a MAPK. C3G is also involved in the regulation of adhesion processes in CML, through modulation of the expression and phosphorylation of focal adhesion proteins, including FAK and paxillin. The relevance of C3G in cell adhesion, together with the known role of its effector Rap1 in platelets, have led us to consider a possible role of C3G in platelet function. In fact, using transgenic models with specific expression of C3G in platelets, we have demonstrated an important role for C3G in platelet homeostasis by regulating the response of different platelet agonists. Specifically, C3G contributes to thrombin-triggered activation of the platelet integrin aIIbß3. This has prompted us to study a possible involvement of C3G in thrombotic disease.

Publications

1 Risk factors for thrombotic microangiopathy in allogeneic hematopoietic stem cell recipients receiving GVHD prophylaxis with tacrolimus plus MTX or sirolimus. Labrador J, López-Corral L, López-Godino O, Vázquez L, Cabrero-Calvo M, Pérez-López R, Díez-Campelo M, Sánchez-Guijo F, Pérez-López E, Guerrero C, Alberca I, Del Cañizo MC, Pérez-Simón JA, González-Porras JR, Caballero D. **Bone Marrow Transplant. 2014 May;49(5):684-90. doi: 10.1038/bmt.2014.17. Epub 2014 Feb 24.** PMID: 24566710 **IF: 3,570 / Q2**

2 NADPH oxidases as therapeutic targets in chronic myelogenous leukemia. Sánchez-Sánchez B, Gutiérrez-Herrero S, López-Ruano G, Prieto-Bermejo R, Romo-González M, Llanillo M, Pandiella A, Guerrero C, Miguel JF, Sánchez-Guijo F, Del Cañizo C, Hernández-Hernández A. **Clin Cancer Res. 2014 Aug 1;20(15):4014-25. doi: 10.1158/1078-0432.CCR-13-3044. Epub 2014 May 15.** PMID: 24833663 **IF: 8,722 / D1**

3 p38 MAPK down-regulates fibulin 3 expression through methylation of gene regulatory sequences: role in migration and invasion. Arechederra M, Priego N, Vázquez-Carballo A, Sequera C, Gutiérrez-Uzquiza Á, Cerezo-Guisado MI, Ortiz-Rivero S, Roncero C, Cuenda A, Guerrero C, Porras A. **J Biol Chem. 2015 Feb 13;290(7):4383-97. doi: 10.1074/jbc.M114.582239. Epub 2014 Dec 29.** PMID: 25548290 **IF: 4,573 / Q1**

4 Incidence and risk factors for life-threatening bleeding after allogeneic stem cell transplant. Labrador J, López-Corral L, Vázquez L, Sánchez-Guijo F, Guerrero C, Sánchez-Barba M, Lozano FS, Alberca I, Del Cañizo MC, Caballero D, González-Porras JR. **Br J Haematol. 2015 Jun;169(5):719-25. doi: 10.1111/bjh.13344. Epub 2015 Mar 26.** PMID: 25817436 **IF: 4,971 / Q1**

5 Combination of X-ray crystallography, SAXS and DEER to obtain the structure of the FnIII-3,4 domains of integrin □6□4. Alonso-García N, García-Rubio I, Manso JA, Buey RM, Urien H, Sonnenberg A, Jeschke G, de Pereda

JM. **Acta Crystallogr D Biol Crystallogr. 2015 Apr;71(Pt 4):969-85. doi: 10.1107/S1399004715002485. Epub 2015 Mar 27.** PMID: 25849406 **IF:2,680 / Q1**

6 The rod domain is not essential for the function of plectin in maintaining tissue integrity. Ketema M, Secades P, Kreft M, Nahidiazar L, Janssen H, Jalink K, de Pereda JM, Sonnenberg A. **Mol Biol Cell. 2015 Jul 1;26(13):2402-17. doi: 10.1091/mbc.E15-01-0043. Epub 2015 May 13.** PMID: 25971800 **IF: 4,466 / Q2**

7 Increased riboflavin production by manipulation of inosine 5'-monophosphate dehydrogenase in Ashbya gossypii. Buey RM, Ledesma-Amaro R, Balsera M, de Pereda JM, Revuelta JL. **Appl Microbiol Biotechnol. 2015 Jul 7.** PMID: 26150243 **IF: 3,337 / Q1**

8 Guanine nucleotide binding to the Bateman domain mediates the allosteric inhibition of eukaryotic IMP dehydrogenases. Buey RM, Ledesma-Amaro R, Velázquez-Campoy A, Balsera M, Chagoyen M, de Pereda JM, Revuelta JL. **Nat Commun. 2015 Nov 12;6:8923. doi: 10.1038/ncomms9923.** PMID: 26558346 **IF: 11,470 / D1**

Grants for research in progress

Project	IP	Grant	Time	Funding
Modulating EB proteína interactions through small molecules (FP7-PEOPLE-2011-CIG-293831)	Rubén Marínez Buey & José María de Pereda Vega	European Union	2011-2014	75,000.00 €
Estudio del papel de C3G y p38γMAPK en la función plaquetaria y el desarrollo de los neutrófilos: implicaciones en la regulación de la leucemia mieloide crónica (SA157A12-1)	Carmen Guerrero Arroyo	Junta de Castilla y León	2012-2014	30,000.00 €
Bases estructurales de la función de plakinas en adhesión celular, implicación en enfermedades (BFU2012-32847)	José María de Pereda Vega	Ministerio de Economía y Competitividad	2013-2015	134,550.00 €
Plakinas en complejos de adhesión: bases estructurales de su función e identificación de compuestos moduladores (CSI181A12)	José María de Pereda Vega	Dirección General de Universidades e Investigación. Junta de Castilla y León	2012-2014	30,000.00 €
Structure of plectin-integrin ß4 complexes in solution and mechanisms of stabilization by small molecule derivatization (BioStructX 3236)	José María de Pereda Vega	European Union. BioStruct-X consortium	2013-2014	
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 €
Función de C3G en el síndrome coronario y el remodelado cardiaco postinfarto: potencial papel como marcador pronóstico y/o diana terapéutica en patología trombótica (GRS 991/A/14)	Francisco Martín Herrero	Consejería de Sanidad. Junta de Castilla y León	2014-2015	14,900.00 €
Structural biology of bacterial conjugation, riboflavin biosynthesis, redox regulation and cell adhesion (BAG Proposal 2014060903)	José María de Pereda Vega	Sincrotrón ALBA	2015	
Structure of macromolecules and interactions involved in gene regulation, infection and metabolism (BioStructX 7687)	Jerónimo Bravo Sicilia	European Union. BioStruct-X consortium	2015	

Fotografía: Sergio R. Manzano

LABORATORY 18

Cell death and cancer. Atypical cell death pathways

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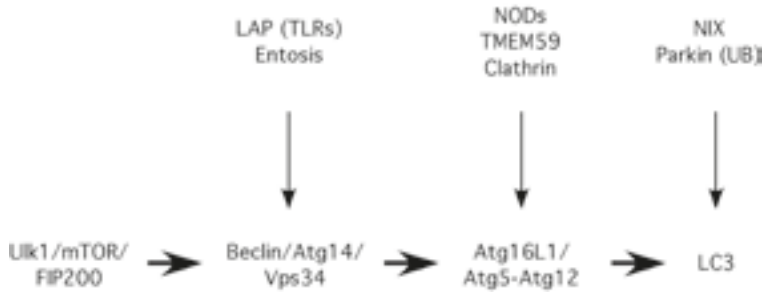
Cell death and cancer. Atypical cell death pathways



Nodes of the canonical autophagic pathway that are specifically engaged in different modalities of unconventional autophagy against membranous compartments.

Our laboratory focuses on the study of novel signaling pathways that activate cell death. In particular, we intend to characterize the apoptotic role of the endoplasmic reticulum and the signaling mechanisms that it utilizes to convey death signals to the mitochondria in unconventional ways. A second focus of the laboratory is the study of autophagy as a cell death mechanism, taking as a model system the transmembrane protein TMEM59 identified in a previous expression-cloning scheme as able to provoke cell death with atypical, autophagic features. A number of other apoptosis and autophagyinducing molecules were cloned before in the laboratory and will be subjected to further characterization.

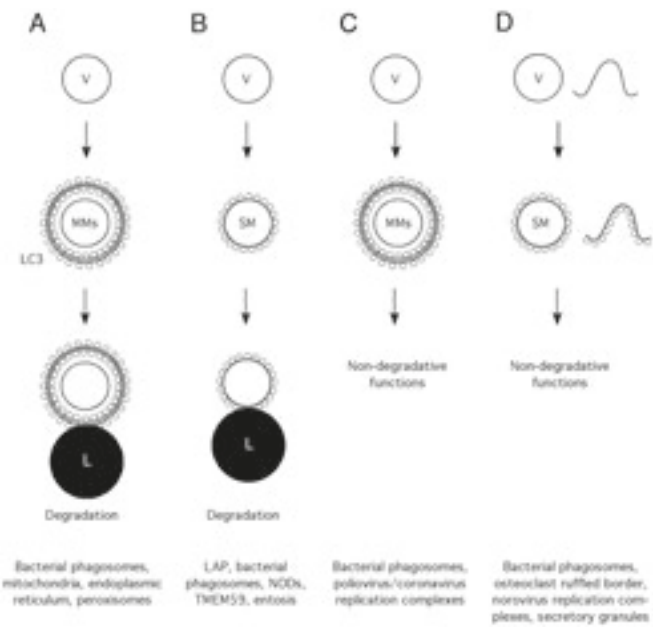
Objectives and Main Research Avenues

- To understand the signaling events governing the apoptotic communication between the endoplasmic reticulum and mitochondria.
- To investigate the mechanisms that mediate cytochrome c release from apoptotic mitochondria in the absence of the conventional Bak and Bax-dependent pathway.
- To identify the signaling mechanisms utilized by TMEM59 to induce autophagy and how they lead to cell death. To characterize the physiological role of TMEM59.
- To functionally characterize a collection of molecules previously identified in the laboratory as capable of inducing cell death upon overexpression, with an emphasis in those able to activate atypical death pathways.

Goals Achieved and Future Challenges

In previous years the laboratory has identified several signaling pathways to cell death that function in non-conventional ways. First, we have discovered that multiple apoptotic inducers function normally in the exclusive presence of the critical apoptotic mediator Bak expressed at the endoplasmic reticulum, thus revealing a novel pathway that works independently of mitochondrial expression of this molecule. In the future, we will try to assess the physiological role of this phenomenon, as well as the molecular mechanisms involved in its regulation. Second, by using a functional screening approach based on genomic systems, we have

discovered a number of molecules able to induce cell death upon overexpression. Through the study of this collection of molecules, we have determined that some of them induce a cell death modality that resembles autophagic death. Interestingly, one of these molecules (TMEM59) induces autophagy through its probable intracellular domain, suggesting the existence of a signaling pathway that excites the autophagic process. We intend to characterize these signaling mechanisms in the hope that they will lead us to novel forms of autophagic regulation as they relate to the induction of cell demise. Since autophagy plays important roles in a variety of physiological and pathological processes, we also hope to improve our knowledge of the molecular mechanisms underlying these phenomena. A number of other identified death-inducing molecules that are able to activate apoptotic or autophagic death programs will also be subjected to detailed functional characterization.



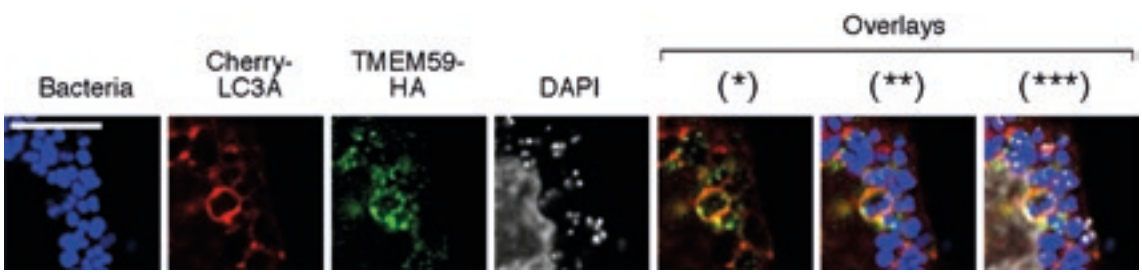
Modalities of autophagy involving membrane compartments and their functional consequences. **(A)** Regular, single-membrane vesicles are targeted by conventional autophagy to produce multi-membrane vacuoles that fuse with lysosomes for degradation of their contents. **(B)** Single-membrane vesicles become directly labeled with LC3-II and fuse with lysosomes for degradation. **(C)** Single-membrane vesicles are targeted by conventional autophagy producing multi-membrane vacuoles with non-degradative functions. **(D)** Regular, single-membrane vesicles or other membranous structures become directly labeled with LC3-II for a variety of non-degradative functions. (V: vesicle; MMs: multiple membranes; SM: single membrane; L: lysosome).

Publications

1 Selective autophagy against membranous compartments: Canonical and unconventional purposes and mechanisms.
Pimentel-Muiños FX, Boada-Romero E.
Autophagy. 2014 Mar;10(3):397-407. doi: 10.4161/auto.27244. Epub 2014 Jan 3. Review. PMID: 24419294 **IF: 11,753 / D1**

Grants for research in progress

Project	IP	Grant	Time	Funding
Caracterización de nuevas proteínas y vías señalizadoras implicadas en la regulación de la autofagia en mamíferos. Implicaciones en patología (SAF2011-23714)	Felipe X. Pimentel Muiños	Ministerio de Ciencia e Innovación	2012-2014	151,250.00 €
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 €
Identification of novel ATG16L1 regulators involved in Crohn´s disease (IBD-0369)	Felipe X. Pimentel Muiños	Broad Medical Research Program	2013-2015	160,000.00 €
Molecular mechanisms involved in inflammatory bowel disease	Felipe X. Pimentel Muiños	Junta de Castilla y León	2015	29,000.00 €



Colocalization between invading bacteria, LC3 and TMEM59 in Hela cells.

LABORATORY 19

Bioinformatics and functional genomics of cancer

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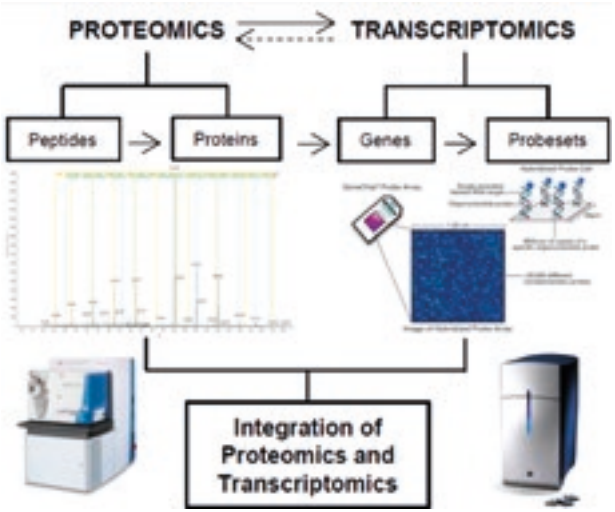
Bioinformatics and functional genomics of cancer



Development of an integrative method for combination of proteomic and transcriptomic data applied to a study on human lymphocytes.

Research framed within the field of Bioinformatics, Functional Genomics and Systems Biology 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 (expression of genes and ncRNAs, splicing, copy-number alteration, methylation, etc.) to achieve statistically robust assignment of signal values to biological entities and to further identify genes groups, gene-profiles and gene-signatures associated to specific biological processes. In particular, focus on cancer-related processes and on the study of leukemia and metastasis in collaboration with experimetal groups.
- Proteomics: Construction and analysis of an integrated biomolecular resource of experimentally determined protein-protein interactions (PPIs) including strategies for quality control and confidence. Use of the PPIs to build a comprehensive human interactome network and derive cancer-related sub-networks.
- Integrative Bioinformatics: Integration of genome-wide expression data with proteomic interaction data to build human biomolecular networks including several relational layers.
- Cancer Computational Biology: Machine Learning (ML) and Reverse Engineering (RE) methods applied to genomic and proteomic cancer data to discover the biomolecular signatures and profiles associated to specific cancer states and cancer survival. Our studies are focused mainly on onco-hematological diseases thanks to our tight collaboration with MDs of HUS-IBSAL.

Publications

1 A gene signature of bone metastatic colonization sensitizes for tumor-induced osteolysis and predicts survival in lung cancer. Luis-Ravelo D, Antón I, Zandueta C, Valencia K, Ormazábal C, Martínez-Canarias S, Guruceaga E, Perurena N, Vicent S, De Las Rivas J, Lecanda F. **Oncogene. 2014 Oct 23;33(43):5090-9. doi: 10.1038/onc.2013.440. Epub 2013 Oct 28.** PMID: 24166494 **IF: 8,459 / D1**

2 RHOB influences lung adenocarcinoma metastasis and resistance in a host-sensitive manner. Luis-Ravelo D, Antón I, Zandueta C, Valencia K, Pajares MJ, Agorreta J, Montuenga L, Vicent S, Wistuba II, De Las Rivas J, Lecanda F. **Mol Oncol. 2014 Mar;8(2):196-206. doi: 10.1016/j.molonc.2013.11.001. Epub 2013 Nov 12.** PMID: 24321314 **IF: 5,331 / Q1**

3 miRNA cargo within exosome-like vesicle transfer influences metastatic bone colonization. Valencia K, Luis-Ravelo D, Bovy N, Antón I, Martínez-Canarias S, Zandueta C, Ormazábal C, Struman I, Tabruyn S, Rebmann V, De Las Rivas J, Guruceaga E, Bandrés E, Lecanda F. **Mol Oncol. 2014 May;8(3):689-703. doi: 10.1016/j.molonc.2014.01.012. Epub 2014 Feb 6.** PMID: 24593875 **IF: 5,331 / Q1**

4 Identification of a characteristic copy number alteration profile by high-resolution single nucleotide polymorphism arrays associated with metastatic sporadic colorectal cancer. González-González M, Fontanillo C, Abad MM, Gutiérrez ML, Mota I, Bengoechea O, Santos-Briz Á, Blanco O, Fonseca E, Ciudad J, Fuentes M, De Las Rivas J, Alcázar JA, García J, Muñoz-Bellvis L, Orfao A, Sayagués JM. **Cancer. 2014 Jul 1;120(13):1948-59. doi: 10.1002/cncr.28681. Epub 2014 Mar 25.** PMID: 24668684 **IF: 5,068 / Q1**

5 TET2 overexpression in chronic lymphocytic leukemia is unrelated to the presence of TET2 variations. Hernández-Sánchez M, Rodríguez AE, Kohlmann A, Benito R, García JL, Risueño A, Fermiñán E, De Las Rivas J, González M, Hernández-Rivas JM. **Biomed Res Int. 2014;2014:814294. doi: 10.1155/2014/814294. Epub 2014 Feb 18.** PMID: 24693539 **IF: 1,579 / Q3**

6 Transcriptomic profile induced in bone marrow mesenchymal stromal cells after interaction with multiple myeloma cells: implications in myeloma progression and myeloma bone disease. García-Gómez A, De Las Rivas J, Ocio EM, Díaz-Rodríguez E, Montero JC, Martín M, Blanco JF, Sánchez-Guijo FM, Pandiella A, San Miguel JF, Garayoa M. **Oncotarget. 2014 Sep 30;5(18):8284-305.** PMID: 25268740 **IF: 6,359 / D1**

7 A robust estimation of exon expression to identify alternative spliced genes applied to human tissues and cancer samples. Risueño A, Rosón-Burgo B, Dolnik A, Hernandez-Rivas JM, Bullinger L, De Las Rivas J. **BMC Genomics. 2014 Oct 8;15:879. doi: 10.1186/1471-2164-15-879.** PMID: 25297679 **IF: 3,986 / Q1**

8 Transcriptomic portrait of human Mesenchymal Stromal/Stem Cells isolated from bone marrow and placenta. Rosón-Burgo B, Sánchez-Guijo F, Del Cañizo C, De Las Rivas J. **BMC Genomics. 2014 Oct 19;15:910. doi: 10.1186/1471-2164-15-910.** PMID: 25326687 **IF: 3,986 / Q1**

9 A proteome-scale map of the human interactome network. Rolland T, Taşan M, Charloteaux B, Pevzner SJ, Zhong Q, Sahni N, Yi S, Lemmens I, Fontanillo C, Mosca R, Kamburov A, Ghiassian SD, Yang X, Ghamsari L, Balcha D, Begg BE, Braun P, Brehme M, Broly MP, Carvunis AR, Convery-Zupan D, Corominas R, Coulombe-Huntington J, Dann E, Dreze M, Dricot A, Fan C, Franzosa E, Gebreab F, Gutiérrez BJ, Hardy MF, Jin M, Kang S, Kiros R, Lin GN, Luck K, MacWilliams A, Menche J, Murray RR, Palagi A, Poulin MM, Rambout X, Rasla J, Reichert P, Romero V, Ruyssinck E, Sahalie JM, Scholz A, Shah AA, Sharma A, Shen Y, Spirohn K, Tam S, Tejeda AO, Trigg SA, Twizere JC, Vega K, Walsh J, Cusick ME, Xia Y, Barabási AL, Iakoucheva LM, Aloy P, De Las Rivas J, Tavernier J, Calderwood MA, Hill DE, Hao T, Roth FP, Vidal M. **Cell. 2014 Nov 20;159(5):1212-26. doi: 10.1016/j.cell.2014.10.050.** PMID: 25416956 **IF: 32,242 / D1**

10 Functional Gene Networks: R/Bioc package to generate and analyse gene networks derived from functional enrichment and clustering. Aibar S, Fontanillo C, Droste C, De Las Rivas J. **Bioinformatics. 2015 May 15;31(10):1686-8. doi: 10.1093/bioinformatics/btu864. Epub 2015 Jan 18.** PMID: 25600944 **IF: 4,981 / D1**

11 ColoLipidGene: signature of lipid metabolism-related genes to predict prognosis in stage-II colon cancer patients. Vargas T, Moreno-Rubio J, Herranz J, Cejas P, Molina S, González-Vallinas M, Mendiola M, Burgos E, Aguayo C, Custodio AB, Machado I, Ramos D, Gironella M, Espinosa-Salinas I, Ramos R, Martín-Hernández R, Risueño A, De Las Rivas J, Reglero G, Yaya R, Fernández-Martos C, Aparicio J, Maurel J, Feliu J, Ramírez de Molina A. **Oncotarget. 2015 Mar 30;6(9):7348-63.** PMID: 25749516 **IF: 6,359 / D1**

12 Unraveling heterogeneous susceptibility and the evolution of breast cancer using a systems biology approach. Castellanos-Martín A, Castillo-Lluva S, Sáez-Freire Mdel M, Blanco-Gómez A, Hontecillas-Prieto L, Patino-Alonso C, Galindo-Villardón P, Pérez Del Villar L, Martín-Seisdedos C, Isidoro-García M, Abad-Hernández Mdel M, Cruz-Hernández JJ, Rodríguez-Sánchez CA, González-Sarmiento R, Alonso-López D, De Las Rivas J, García-Cenador B, García-Criado J, Lee do Y, Bowen B, Reindl W, Northen T, Mao JH, Pérez-Losada J. **Genome Biol. 2015 Feb 21;16:40. doi: 10.1186/s13059-015-0599-z.** PMID: 25853295 **IF: 10,810 / D1**

13 GOBLET: the Global Organisation for Bioinformatics Learning, Education and Training. Attwood TK, Bongcam-Rudloff E, Brazas ME, Corpas M, Gaudet P, Lewitter F, Mulder N, Palagi PM, Schneider MV, van Gelder CW; GOBLET Consortium. **PLoS Comput Biol. 2015 Apr 9;11(4):e1004143. doi: 10.1371/journal.pcbi.1004143. eCollection 2015 Apr. Erratum in: PLoS Comput Biol. 2015 May;11(5):e1004281. Atwood, Teresa K [corrected to Attwood, Teresa K].** PMID: 25856076 **IF: 4,620 / D1**

14 Deregulation of genes related to iron and mitochondrial metabolism in refractory anemia with ring sideroblasts. del Rey

M, Benito R, Fontanillo C, Campos-Laborie FJ, Janusz K, Velasco-Hernández T, Abáigar M, Hernández M, Cuello R, Borrego D, Martín-Zanca D, De Las Rivas J, Mills KI, Hernández-Rivas JM. **PLoS One. 2015 May 8;10(5):e0126555. doi: 10.1371/journal.pone.0126555. eCollection 2015.** PMID: 25955609 **IF: 3,234 / Q1**

15 Analyse multiple disease subtypes and build associated gene networks using genome-wide expression profiles. Aibar S, Fontanillo C, Droste C, Rosón-Burgo B, Campos-Laborie FJ, Hernandez-Rivas JM, De Las Rivas J. **BMC Genomics. 2015;16 Suppl 5:S3. doi: 10.1186/1471-2164-16-S5-S3. Epub 2015 May 26.** PMID: 26040557 **IF: 3,986 / Q1**

16 In Vitro Transcription/Translation System: A Versatile Tool in the Search for Missing Proteins. Horvatovich P, Végvári Á, Saul J, Park JG, Qiu J, Syring M, Pirrotte P, Petritis K, Tegeler TJ, Aziz M, Fuentes M, Díez P, González-González M, Ibarrola N, Droste C, De Las Rivas J, Gil C, Clemente F, Hernaez ML, Corrales FJ, Nilsson CL, Berven FS, Bischoff R, Fehniger TE, LaBaer J, Marko-Varga G. **J Proteome Res. 2015 Jul 28.** PMID: 26155874 **IF: 4,245 / Q1**

17 Integration of Proteomics and Transcriptomics Data Sets for the Analysis of a Lymphoma B-Cell Line in the Context of the Chromosome-Centric Human Proteome Project. Díez P, Droste C, Dégano RM, González-Muñoz M, Ibarrola N, Pérez-Andrés M, Garin-Muga A, Segura V, Marko-Varga G, LaBaer J, Orfao A, Corrales FJ, De Las Rivas J, Fuentes M. **J Proteome Res. 2015 Aug 5.** PMID: 26216070 **IF: 4,245 / Q1**

18 Cystatin D Locates in the Nucleus at Sites of Active Transcription and Modulates Gene and Protein Expression. Ferrer-Mayorga G, Álvarez-Díaz S, Valle N, De Las Rivas J, Mendes M, Barderas R, Canals F, Tapia O, Casal JI, Lafarga M, Muñoz A. **J Biol Chem. 2015 Oct 30;290(44):26533-48. doi: 10.1074/jbc.M115.660175. Epub 2015 Sep 13.** PMID: 26364852 **IF: 4,573 / Q1**

Grants for research in progress

Project	IP	Grant	Time	Funding
PROTEIN INTERACTOME: Construction a new human protein interactome Reference Set (hsRS-PPI) combining proteomic and bioinformatic work; steps to build a more comprehensive human interaction network (i-LING0398)	Javier De Las Rivas	Ministerio de Economía y Competitividad	2011-2014	16,285.00 €
Biología molecular integrativa de hemopatías malignas: análisis bioinformáticos de datos transcriptómicos y proteómicos para identificar genes marcadores, genes causales y redes reguladoras asociadas a subclases patológicas de dos síndromes proliferativos específicos (PI12/00624)	Javier De Las Rivas	Ministerio de Sanidad y Consumo- ISCIII	2013-2015	122,815.00 €
Data Representations and Similarity Measures for High-Throughput Clinical Sample Profiles (CELGENE-FICUS sponsored Research Agreement)	Javier De Las Rivas	Celgene Institute for Translational Research Europe (CITRE)	2013-2015	121,000.00 €
Transcriptómica y epigenómica de Células Stem Mesenquimales (MSC) normales y alteradas en hemopatías malignas (BIO/SA68/13)	Javier De Las Rivas	Junta de Castilla y León - Consejería Sanidad	2013-2014	23,500.00 €
Análisis genómico integrativo y búsqueda de marcadores específicos de Células Stem Mesenquimales (MSC) normales y alteradas en hemopatías malignas (BIO/SA08/14)	Javier De Las Rivas	Junta de Castilla y León - Consejería Sanidad	2014-2015	14,304.00 €
Fly-SMALS: Common RNA-dependent pathways for motor neuron degeneration in spinocerebellar muscular atrophy and amyotrophic lateral sclerosis. (AC14/00024)	Javier De Las Rivas	EU Joint Programme - Neurodegenerative Disease Research (JPND) & Ministerio de Sanidad y Consumo- ISCIII	2015-2018	49,610.00 €

Team Leader

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LABORATORY 20

Clinical and molecular analysis of solid tumors

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Predoctoral

Javier Fernández Mateos

Assays Clinical Unit Coordinator

Juan Carlos Adansa

Data Manager

Adriana Armellini

Administrative Staff

Felicidad Alisente Frías

Clinical and molecular analysis of solid tumors

The group has extensive experience in the treatment of solid tumors, with a sustained role in the development clinical trials with new therapies, particularly related to breast cancer, lung cancer, head and neck tumors, gastrointestinal cancer, gynecologic cancer, bone tumors and testicular tumors. In these years 80 new trials have been started.

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) or GECP (Spanish Group for Lung Cancer) among others. Also our group particia in several projects related with paliative treatment as ALGOS (cancer pain) or ASTHENOS (study and treatment of fatigue in cancer patients).

About research in hereditary cancer, this group developed their works at the University and the Hospital, where he has a genetic counseling consultation and in the Cancer Research Center, which provides all the infrastructure and personnel necessary instrumental for molecular diagnosis of mutations in the BRCA1, BRCA2, APC, MYH, MLH1, MSH2 and MSH6.

Also carried research programs in cooperation with Dr. Isidro Sánchez lab in the study of cancer stem cells, and Dr. Atanasio Pandiella lab in the study Tyrosine Kinase receptor in tumors of head and neck at the Cancer Research Center. Finally highlight the multicenter study of molecular epidemiology for susceptibility and response to treatment in head and neck tumors in collaboration with research groups led by Dr. Pandiella y de Álava and several national hospitals.

Publications

1 **Role of XRCC3, XRCC1 and XPD single-nucleotide polymorphisms in survival outcomes following adjuvant chemotherapy in early stage breast cancer patients.** Castro E, Olmos D, García A, Cruz JJ, González-Sarmiento R. **Clin Transl Oncol. 2014 Feb;16(2):158-65. doi: 10.1007/s12094-013-1055-8. Epub 2013 Jun 6.** PMID: 23740134 **IF: 2,077 / Q3**

2 **Integrated analysis of mismatch repair system in malignant astrocytomas.** Rodríguez-Hernández I, García JL, Santos-Briz A, Hernández-Laín A, González-Valero JM, Gómez-Moreta JA, Toldos-González O, Cruz JJ, Martín-Vallejo J, González-Sarmiento R. **PLoS One. 2013 Sep 20;8(9):e76401. doi: 10.1371/journal.pone.0076401. eCollection 2013.** PMID: 24073290 **IF: 3,234 / Q1**

3 **A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer.** Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, Sastre J, Martínez-Trufero J, Brandariz Castelo JA, Verger E, Cruz-Hernández JJ; Spanish Head and Neck Cancer Cooperative Group (TTCC). **Ann Oncol. 2014 Jan;25(1):216-25. doi: 10.1093/annonc/mdt461. Epub 2013 Nov 19.** PMID: 24256848 **IF: 7,040 / D1**

4 **Analysis of DNA repair gene polymorphisms in glioblastoma.** Rodríguez-Hernandez I, Perdomo S, Santos-Briz A, García JL, Gómez-Moreta JA, Cruz JJ, González-Sarmiento R. **Gene. 2014 Feb 15;536(1):79-83. doi: 10.1016/j.gene.2013.11.077. Epub 2013 Dec 8.** PMID: 24325908 **IF: 2,138 / Q3**

5 **The current and future role of the medical oncologist in the professional care for cancer patients: a position paper by the European Society for Medical Oncology (ESMO).** Popescu RA, Schäfer R, Califano R, Eckert R, Coleman R, Douillard JY, Cervantes A, Casali PG, Sessa C, Van Cutsem E, de Vries E, Pavlidis N, Fumasoli K, Wörmann B, Samonigg H, Cascinu S, Cruz Hernández JJ, Howard AJ, Ciardiello F, Stahel RA, Piccart M. **Ann Oncol. 2014 Jan;25(1):9-15. doi: 10.1093/annonc/mdt522. Epub 2013 Dec 13. Erratum in: Ann Oncol. 2014 Apr;25(4):916.** PMID: 24335854 **IF: 7,040 / D1**

6 **Social value of a quality-adjusted life year (QALY) in Spain: the point of view of oncologists.** Camps-Herrero C, Paz-Ares L, Codes M, López-López R, Antón-Torres A, Gascón-Vilaplana P, Guillem-Porta V, Carrato A, Cruz-Hernández JJ, Caballero-Díaz C, Blasco-Cordellat A, Moreno-Nogueira JA, Díaz-Rubio E. **Clin Transl Oncol. 2014 Oct;16(10):914-20. doi: 10.1007/s12094-014-1170-1. Epub 2014 Jun 13.** PMID: 24924625 **IF:2,077 / Q3**

7 **Limited family structure and triple-negative breast cancer (TNBC) subtype as predictors of BRCA mutations in a genetic counseling cohort of early-onset sporadic breast cancers.** Zugazagoitia J, Pérez-Segura P, Manzano A, Blanco I, Vega A, Custodio A, Teulé A, Fachal L, Martínez B, González-Sarmiento R, Cruz-Hernández JJ, Chirivella

I, Garcés V, Garre P, Romero A, Caldés T, Díaz-Rubio E, de la Hoya M. **Breast Cancer Res Treat. 2014 Nov;148(2):415-21. doi: 10.1007/s10549-014-3167-4. Epub 2014 Oct 24.** PMID: 25342642 **IF:3,940 / Q2**

8 **Unraveling heterogeneous susceptibility and the evolution of breast cancer using a systems biology approach.** Castellanos-Martín A, Castillo-Lluva S, Sáez-Freire Mdel M, Blanco-Gómez A, Hontecillas-Prieto L, Patino-Alonso C, Galindo-Villardón P, Pérez Del Villar L, Martín-Seisdedos C, Isidoro-García M, Abad-Hernández Mdel M, Cruz-Hernández JJ, Rodríguez-Sánchez CA, González-Sarmiento R, Alonso-López D, De Las Rivas J, García-Cenador B, García-Criado J, Lee do Y, Bowen B, Reindl W, Northen T, Mao JH, Pérez-Losada J. **Genome Biol. 2015 Feb 21;16:40. doi: 10.1186/s13059-015-0599-z.** PMID: 25853295 **IF: 10,810 / D1**

9 **Epidemiology and characteristics of febrile neutropenia in oncology patients from Spanish tertiary care hospitals: PINNACLE study.** de Castro Carpeño J, Gascón-Vilaplana P, Tejerina AM, Antón-Torres A, López-López R, Barnadas-Molins A, Cruz-Hernández JJ, Massuti-Sureda B, Camps-Herrero C, Aranda-Aguilar E, Laserna FJ. **Mol Clin Oncol. 2015 May;3(3):725-729. Epub 2015 Mar 5.** PMID: 26137294 **IF: NI**

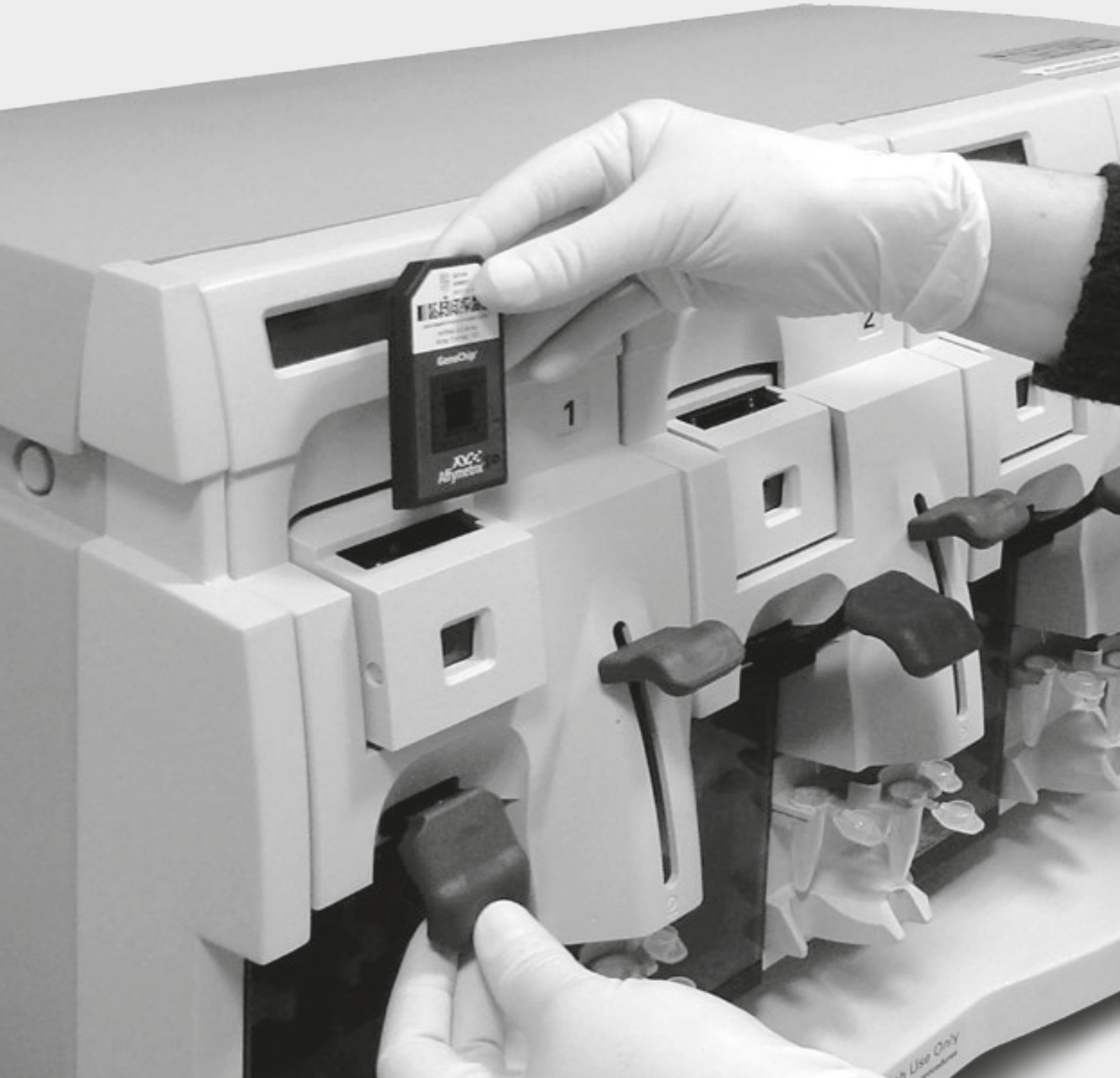
10 **Outcomes of Estrogen Receptor Negative and Progesterone Receptor Positive Breast Cancer.** Chan M, Chang MC, González R, Lategan B, del Barco E, Vera-Badillo F, Quesada P, Goldstein R, Cruz I, Ocaña A, Cruz JJ, Amir E. **PLoS One. 2015 Jul 10;10(7):e0132449. doi: 10.1371/journal.pone.0132449. eCollection 2015.** PMID: 26161666 **IF: 3,234 / Q1**

11 **Management of Infection and Febrile Neutropenia in Patients with Solid Cancer.** Aguado JM, Cruz JJ, Virizuela JA, Aguilar M, Carmona A, Cassinello J, Gudiol C, Jiménez Fonseca P, Lizasoain M, Marco F, Ruiz I, Ruiz M, Salavert M, Vicente D, Carratalà J. **Enferm Infecc Microbiol Clin. 2015 Aug 13. pii: S0213-005X(15)00262-1. doi: 10.1016/j.eimc.2015.06.005.** PMID: 26279208 **IF: 2,172 / Q3**

12 **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. 2015 Nov 17.** PMID: 26577106 **IF: 2,077 / Q3**

13 **A Phase 2 Open Label, Single-arm Trial to Evaluate the Combination of Cetuximab Plus Taxotere, Cisplatin, and 5-Flurouracil as an Induction Regimen in Patients With Unresectable Squamous Cell Carcinoma of the Head and Neck.** Mesía R, Vázquez S, Grau JJ, García-Sáenz JA, Lozano A, García C, Carles J, Irigoyen A, Mañós M, García-Paredes B, Del Barco E, Taberna M, Escobar Y, Cruz JJ; Spanish Head and Neck Cancer Cooperative Group (TTCC). **Int J Radiat Oncol Biol Phys. 2015 Oct 22. pii: S0360-3016(15)26584-4. doi: 10.1016/j.ijrobp.2015.10.019.** PMID: 26675064 **IF: 4,258 / Q1**

14 **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: 1,676 / Q2**


GeneChip
Affymetrix
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4 SCIENTIFIC SERVICE UNITS

SCIENTIFIC SERVICE UNITS

Genomics

Scientific Coordinator

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Genomics Unit

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This core facility provides indoor and outdoor services related to: a) Genome-wide expression profiling and characterization using Affymetrix array technologies. b) Printing and processing of homemade chips. c) DNA sequencing. d) Other genomics-related techniques, such as PCR, qRT-PCR, array hybridization, high-throughput purification of DNAs, etc. (see further information below).

The philosophy of this Unit is to provide full services. Once the customer provides the sample, the facility will run all the subsequent steps (quality control of samples, microarray analysis, and a standard bioinformatics analysis). In addition, it can also provide advice regarding the best experimental approach to be carried out in order to get the desired results (type of experimental conditions, number of replicas, best options to purify nucleic acids, etc.).

Both the Facility and its experimental protocols have been certified by ISO9001. Its Occupational Health and Safety Management System also has been certified by the OHSAS18001 system.

Examples of services provided

- Characterization of DNA sequences, single nucleotide polymorphisms, and genotypes using an ABI-3130 xl sequencer (Applied Biosystems) equipment.
- Affymetrix-based microarray analyses for patients and key experimental organisms using the following platforms:
  - Gene Chip Human Genome U133 Plus 2.0.
  - Gene Chip Human Exon 1.0 and 2.0 ST Array.
  - Prime View Human Genome.
  - Gene Chip Human Gene 1.0 and 2.0 ST Array.
  - Gene Chip Mouse Gene 1.0 and 2.0ST Array.

  - Gene Chip Mouse Genome 430 2.0.
  - Gene Chip Mouse Exon 1.0 and 2.0 ST Array.
  - Gene Chip Rat Gene 1.0 and 2.0 ST Array.
  - Gene Chip Rat Exon 1.0 and 2.0 ST Array.
  - Gene Chip Rat Genome 230 2.0 Array.
  - Gene Chip Drosophila Genome 2.0 Array.
  - Gene Chip Yeast Genome 2.0 Array.
  - Gene Chip Arabidopsis ATH1 Genome Array.
- Identification of regulatory promoter sites by ChIP-on-chip and studies alike requiring complete genome examination. Main Affymetrix array platforms used are in this service are:
  - Gene Chip Human Tiling 1.0 R Array.
  - Gene Chip S. pombe Tiling 1.0 FR Array.
  - Gene Chip S. cerevisiae Tiling 1.0 FR Array.
- Analysis of single nucleotide polymorphisms and gene copy number determinations using the following arrays:
  - Gene Chip Human Mapping 250K NspI/StyI Arrays.
  - Genome-Wide Human SNP Array 6.0.
  - CytoScan 750K Array.
  - CytoScan HD Array.
- Genome-wide analysis of expression of microRNAs and main biosynthetic precursors using the Affymetrix Gene Chip miRNA 2.0, 3.0 and 4.0 Array
- Printing and processing of home-made chips using the MGII Arrayer (Biorobotics). The samples are provided by the user (oligonucleotides, cDNAs, DNA cloned in BACs, antibodies, purified proteins or cellular lysates). Upon generation of chips, these microarrays can be hybridized using the automatized system hs4800pro (Tecan) and finally signals scanned using a GenePix4000 system (Axon).

All results from the foregoing services are provided to the customer using files compatible with most common bioinformatics tools. Functional annotation and more sophisticated in silico analysis can be done if requested at extra cost.

Equipment

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

SCIENTIFIC SERVICE UNITS

Proteomics

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Proteomics Unit

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Rosa Mª Dégano Blázquez

In post-genome era having sequence the human genome, one of the most important pursuits is to understand the function of gene-expressed proteins. The overwhelming size and complexity of human proteome requires very high-throughput techniques for rapid analysis. Hence, Proteomics technologies allow the simultaneous multiplex analysis of complex biological samples.

The goal of the Proteomics Unit at CIC is to provide proteomics services to internal and external users, and to further develop functional and quantitative techniques (based on protein microarrays and mass spectrometry); so that proteomics becomes a set of robust, sensitive, accurate and precise methods that enable not only the generation of novel biological hypothesis but also their subsequent validation in complex biological systems. In addition, our Unit actively participates in several international and national training courses.

The Unit is involved in several international collaborations with several individual researchers and consortia (ie. Human Proteome Project (HYPERLINK "http://www.hupo.org" www.hupo.org). Moreover, the Proteomics Unit is also part of the "Plataforma de Recursos Biomoleculares y BioInformaticos" (HYPERLINK "http://www.prb2.org" www.prb2.org) and "ProteoRed" (HYPERLINK "http://www.proteored.org" www.proteored.org) of the Instituto de Salud Carlos III (as part of the National Health System).

Services

- Protein separation by electrofocusing in IPG strips.
- Protein separation by SDS-PAGE and by 2D-electrophoresis.
- Gel staining with Coomassie or Silver.
- Protein or peptide fractionation by in solution IEF.
- Protein or peptide fractionation by HPLC.

- Enrichment of phosphopeptides by IMAC or TiO2.
- In gel protein digestion.
- In solution protein digestion.
- Desalting and concentration of peptide digests by C18.
- Peptide Mass Fingerprinting analysis by MALDI-TOF MS.
- Protein analysis by LC-MS/MS of low, medium or high complexity protein sample (LTQ-OrbiTrap Velos).
- 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 and sequence-validated.

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.

SCIENTIFIC SERVICE UNITS

Traslational Oncopharmacology

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The traslational oncopharmacology laboratory was created in 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, mainly in 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 to assess drug activity on DNA synthesis in tumoral cells.
- Bioluminescence Assay of cell proliferation (effect of the microenvironment on cell proliferation/survival). Two types of protocols are usually performed. One is based on the incubation of the agent of interest in the presence of bone marrow (BM) cells. In this case, BM cells from patients or the HS-5 cell line are used. The latter is preferred 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.
- 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://cicwebserver.dep.usal.es/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 clinic of new 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 was 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.

SCIENTIFIC SERVICE UNITS

Bioinformatics

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Personnel

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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. The Unit has major expertise in the analysis of either genome-wide DNA-associated data or RNA-associated data obtained with different types of platforms, with a major incidence in the use of Affymetrix platforms data since the CIC-IBMCC is national leader in the use and application of this technology.

The Bioinformatics Unit was launched to provide services in June 2008 and in the last 2 years has performed more than 2000 analyses on about 980 samples coming from different labs and research centers in Spain.

For further information see: http://ubioinfo.cicancer.org/

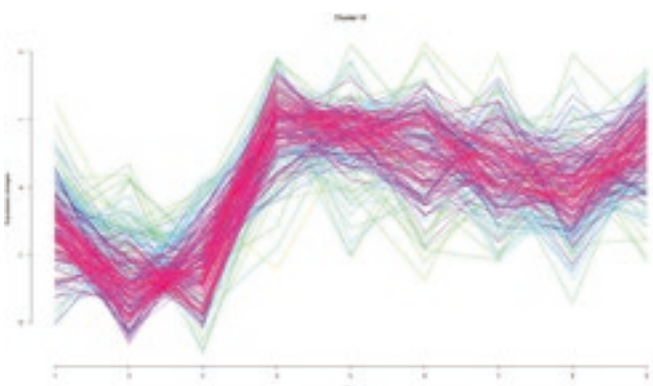
Services

- Multiple comparative analyses of two states. Analysis for search and identification of statistically significant genes -or other biomolecular entities such as miRNAs, etc- that are obtained through differential contrasts of two states (Normal versus Altered) with a minimum of 2 biological replicates for each studied state.
- Expression profiles of specific genes across multiple states / conditions / individuals. Integrated analysis of data for the identification of gene expression profiles with the production of clusters and classification using different machine learning methods.
- Gene set enrichment and functional analysis. Annotation and biological functional assignment of gene / protein lists based on statistical enrichment studies. This type of analysis can be very broad and vary greatly depending on the objectives of each study.
- Software tools. The unit facilitates the use of various bioinformatics tools:
  - Open Access software: Tools and databases provided to the scientific community by other research groups.

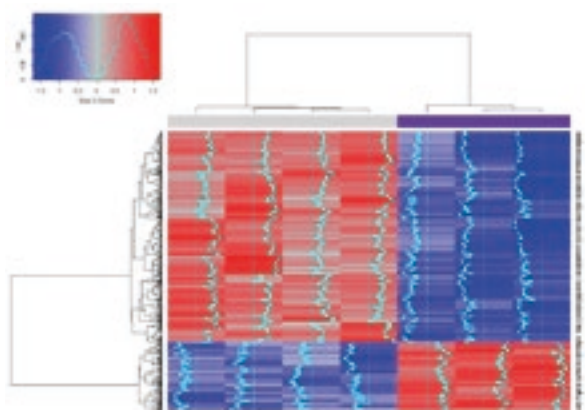
- Commercial software: Tools licensed by CIC-IBMCC and managed by the Unit, such as Ingenuity Pathways Analysis.
- Software developed by the unit: The unit and the research group of Dr. Javier De Las Rivas develop bioinformatics tools that are available to researchers. Some of them are: GATExplorer, APID, APIDConnector, GeneTerm-Linker and FGNet. Most of these tools are developed in R statistical programming language.

- Custom Analysis. The unit also offers custom analysis for data sets of non-standard platforms, and also the reanalysis of data sets that have been produced and analyzed before but need a deeper investigation.
- Advice and assistance. Frequently, regardless of invoiced studies, the unit performs numerous works of advice and assistance to the scientists and researchers of the CIC-IBMCC and the University of Salamanca demanding concrete assistance in Bioinformatics.

Gene co-expression pattern from a time course experiment.



Hierarchical clustering of gene expression data.



SCIENTIFIC SERVICE UNITS

Molecular & Cellular Diagnostics

Cytometry Service

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Cytometry Service

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Miriam Santos
Paloma Bárcena Carrasco
Mª Luz Sánchez García

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 asscoaited 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 suspected mature T-cell lymphoid neoplasms in peripheral blood, cerebrospinal fluid, bone marrow, lymph node or other tissues.
- Immunophenotypic characterization of mature B-cell lymphoid neoplasms and Waldenstrom's macroglobulinemia.
- Screening of clonality of mature alpha/beta TCR+ T cell and gamma/delta TCR+ T cell neoplasms by flow cytometry.
- Immunophenotypic characterization of mature T and NK-cell neoplasms.
- Screening of acute leukemias.
- Immunophenotypic characterization of acute myeloid leukemias and myelodysplastic syndromes.
- Screening and immunophenotypic characterization of B-precursor lymphoblastic leukemia and T-cell lineage acute lymphoblastic leukemia.
- Immunophenotypic characterization of chronic myeloid leukemia.
- Detection of minimal residual disease in acute and chronic leukemias and lymphomas.
- Screening of mastocytosis.
- Immunophenotypic screening of histiocytosis and detection Reed Stenberg cells.
- Screening of primary immunodeficiencies and paroxymal nocturnal hemoglobinuria.
- Immunophenotypic characterization of platelets.
- Detection of antiplatelet autoantibodies in platelets and plasma.
- Quantitation of CD34+ cells.
- Control of leucodepletion.
- Antigenic quantitation.
- Lymphoclonal.
- DNA quantitation in mature and immature B cell, plasma cells and epithelial cells.
- Evaluation of Zap70.
- Evaluation of cell proliferation by DRAQ5 or Dye Cycle.
- DNA quantitation with phenotype and DRAQ5 or Dye Cycle in myeloid leukemia or myelodysplastic syndromes.
- Evaluation of each individual antigen markers.
- 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 individual or multiple genetic abnormalities by in situ hybridization.
- Sample purification for molecular biology techniques.
- Evaluation of KIT mutations by molecular biology.
- Humara PCR test for purified cell populations.
- Sorting of cell populations.
- Flow cytometer data acquisition and analysis in the flow cytometer.
- Immunobead protein assays.

Equipment

- Cytometer Analyzer FACScanto II (BDB) flow cytometer for 8 color analyses.
- 2 Cell sorting flow cytometers FACAria (BDB) for 8 color analyses.
- 2 FACScalibur (BDB) flow cytometers for 4 color analyses.
- 1 Fortessa (BDB) flow cytometers for 16 color analyses.
- Termocyclers.
- Fluorescence microscopes.
- Additional equipment: centrifuges, refrigerators, freezers, baths, ...

Molecular Cytogenetic Service

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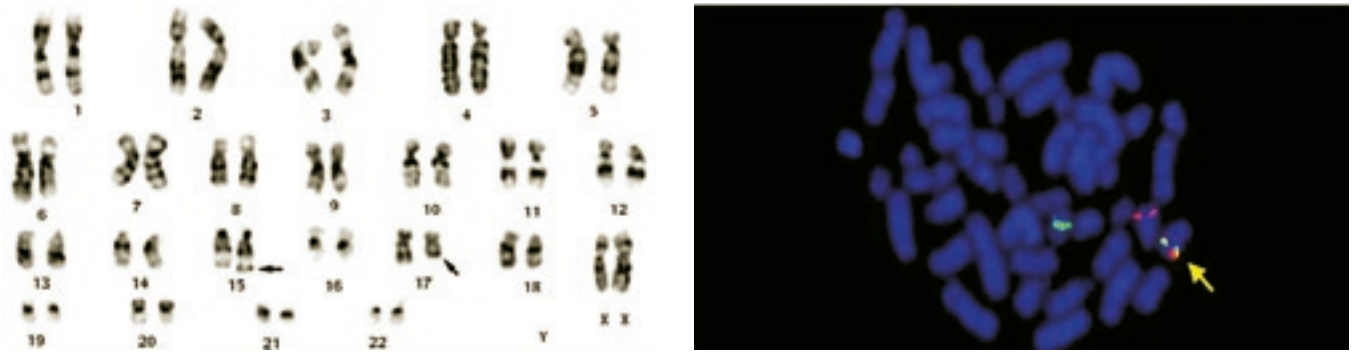
Sandra Santos Minguez

Molecular Cytogenetics Unit (MCU) is a facility devoted to the karyotypic analysis, fluorescence "in situ" hybridization, comparative genomic hybridization, microarrays and next generation sequencing of cancer patients. Most than 100 hospitals in



Conventional cytogenetics and Fluorescence In Situ Hybridization (FISH) on metaphase cell shows PML-RAR translocation in acute promyelocytic leukemia.

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 the 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), and next generation sequencing (IRON, ELAN, NGS-PTL).

Services

- Bone Marrow Cytogenetics: leukemia, lymphoma and myeloma.
- Peripheral blood cytogenetics: leukemia, lymphoma and myeloma.
- Lymph node and spleen cytogenetics: lymphoma.
- Solid tumour cytogenetics.
- Centromeric 'in situ' hybridization: FISH performerd 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.
- MultiFISH.
- Genomic microarrays.
- Farmacogenetic microarrays.
- Next generation sequencing.

Services

- 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.
- Pirosequencer.

Molecular Biology Service

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Molecular Biology Service
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Alicia Antón
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Rebeca Maldonado

The Molecular Biology Unit (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 2014 and 2015 were 12856 and 13519, 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. Sanger and Next-Generation Sequencing technologies.
- Gene expression: RT-PCR for diagnosis, prognosis and MRD detection.
- Genetic polymorphisms (single nucleotide polymorphisms [SNP], short tandem repeats [STR]) analysis: SNP array, Next generation sequencing, 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.

Equipment

- Real-time quantitative (4): One7900HT, two StepOnePlus (Applied Biosystems) and one LightCycler (Roche Diagnostics).
- Automatic sequencer (2): ABI3130 (4-capillary) and ABI3500 XL (16-capillary, Applied Biosystems).
- NGS sequencer (1): MiSeqDx (Illumina).
- Fluoroanalyzer (1): Luminex XYP (Luminex Corp.).
- Thermocyclers (8).
- Automatic nucleic acid extractor (2): MagnaPure (Roche Diagnostics) y Maxwell16 (Promega).
- Microbeads-based system for cellular isolation (Miltenyi-Biotec).

SCIENTIFIC SERVICE UNITS

Comparative Molecular Pathology

Scientific Coordinator

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Comparative Molecular Pathology Unit

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Jairo Nieto Castro
Telmo Rodrigues Teixeira
Sonia Andrés Recio

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 Leon, 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.

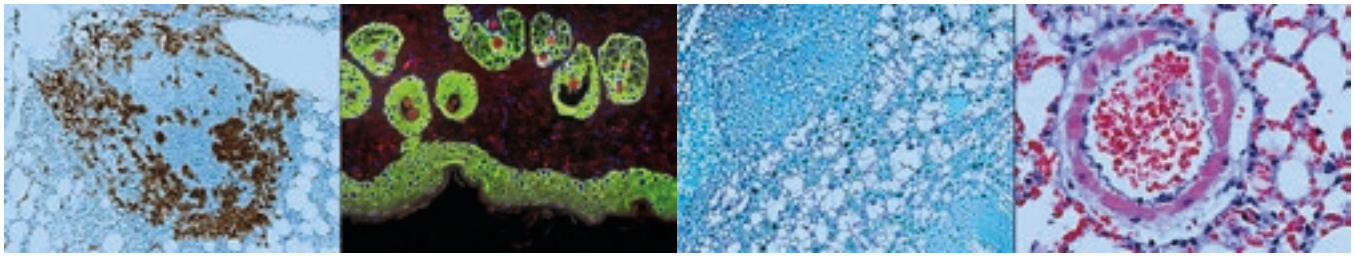
2 It serves all Centers in the Campus as a Comparative Pathology Service, analyzing samples from transgenic animal models offering a full range of histological, immunohistochemical and molecular analysis designed and adapted on request. About 5.319 samples are processed a year, from 510 job applications.

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.

- 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 biases.
- 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 "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

Scientific Coordinator
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Structural Biology Unit
Centro de Investigación del Cáncer (CSIC-USAL). Campus Universitario Miguel de Unamuno s/n, 37007 Salamanca, Spain

The mission of the Structural Biology Unit is to provide the research groups with access to x-ray crystallography methods aim at elucidating the 3D atomic structure of macromolecules of biological relevance, with a main focus on molecules involved in tumoral processes. The scientific director of the Unit is Dr José M de Pereda.

Services

Crystallization: the Structural Biology Unit offers dedicated space for setting up and for storage of crystallization experiments, as well as stereo microscopes for visualization and manipulation of crystals.

Data collection and analysis: the Unit provides access to equipment for X-ray data collection and analysis from macromolecular crystals. It also provides consultations and assistance on optimization of crystallization, data collection and processing, and structure solution.

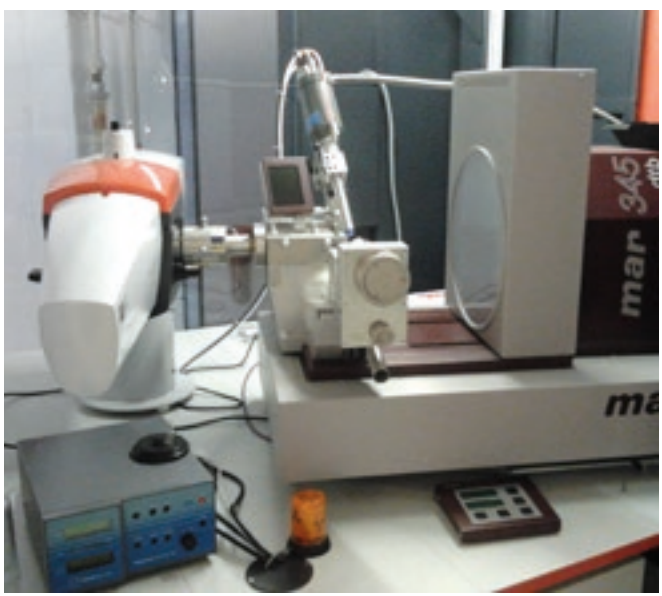
Since 2015 the Unit also provides a setup for remote data collection at syncrhotron facilities.

Equipment

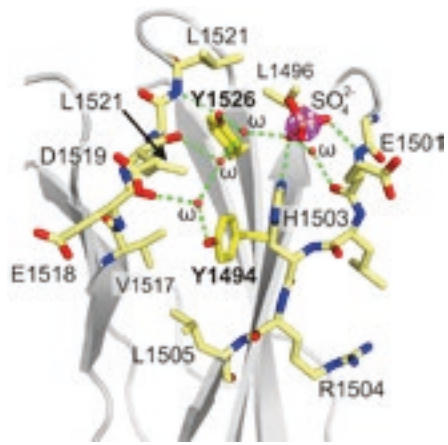
The Unit has an X-ray diffraction system suitable for macromolecular crystallography, which consists of:

- Microstar (Bruker AXS) rotating anode micro-focus x-ray generator.
- Helios high-brightness multilayer X-ray optics (Bruker AXS).
- Mardtb goniostat (Marresearch) that integrates automated collimator, goniometer and detector mount.
- Large-area Image plate detector mar345 (Marresearch).
- Cryostream 700 low temperature system (Oxford Cryosystems).
- Linux workstation for control of data collection, data storage and analysis.

The configuration of this equipment makes it ideal for the data collection from crystals of biological macromolecules. It allows for the measurement of data to a maximum resolution of ~1.4 Å. In addition to the collection of data from native crystals, this system has been routinely used to measure data from crystals derivatized with heavy atoms aimed at obtaining phases by experimental methods. The wavelength produced by the generator, Cu-Kα, allows for the collection of anomalous signal from mercurial derivatives and its application to the phasing of structures by single isomorphous replacement with anomalous scattering (SIRAS). The quality of the data that can be obtained from native crystals in this system allows for the identification of atoms that show anomalous signal, such as sulfurs.



X-ray diffractometer at the Structural Biology Unit.



Detail of the structure of the third FnIII domain of integrin β4 (PDB code 4WTW) solved with data collected at the Structural Biology Unit. The structural environment of two potentially phosphorylatable residues, Tyr1494 and Tyr1526, is shown. The structure contains a sulfate ion next to Tyr1526. An electron density map calculated with the anomalous signal of the native crystal and the phases of the atomic model is shown in magenta contoured at 3σ level.

SCIENTIFIC SERVICE UNITS

Microscopy

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Personnel
Ángel Luis Prieto Martín
María Nistal Chimeno

Due to the acquisition of two new flow cytometry systems the IBMCC Microscopy Unit has drastically improved since 2014. Consequently, the service provided by the facility has been increased and upgraded.

The IBMCC Microscopy Unit provides the following services:

1 Confocal microscopy (Leica SP5 and Zeiss LSM510), both 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.

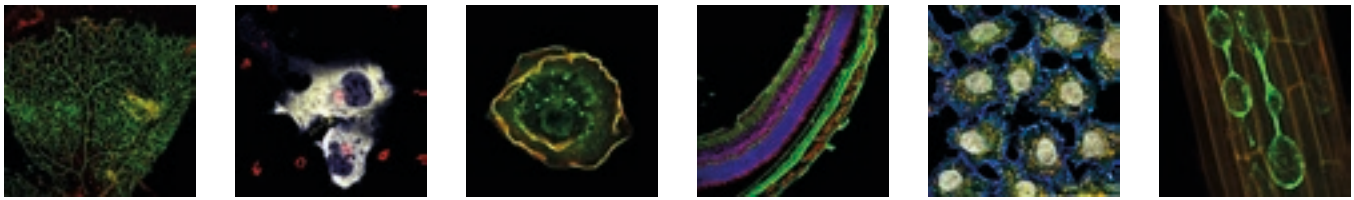
3 Preventative and corrective maintenance of Accuri-C6 flow cytometer. Training and advising about Accuri-C6 use to the researchers so they can reach full autonomy. In addition, the Unit personnel prepare and refill the sheath solution and cleaning solutions when needed in order to keep the system in 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 Cancer Research Center with its variety of equipments offers a high range of possibilities. There are six 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.

SCIENTIFIC SERVICE UNITS

Hereditary Cancer & Genetic Counseling

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Personnel
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Eva María Sánchez Tapia
Jéssica Pérez García
Rosario Vidal Tocino

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 tumor 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 "Dirección General de Salud Pública" of 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 test taking characteristics of the family into account and 3) Collecting biological samples necessary to carry out one or more different genetic studies. At this moment the genetic test is performed by Next generation Sequencing that allow us to reduce the cost of the analysis and reduce the time of the result's communication. 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.


YES
YES
YES

5 TECHNICAL SUPPORT UNITS

TECHNICAL SUPPORT UNITS

Manager

Personnel

Gerardo Arévalo Vicente

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.

TECHNICAL SUPPORT UNITS

Secretary

Personnel

Nuria Morán Aguirre

- Secretarial support and assistance to the Institute Direction.
- Administrative and logistic assistance to the personnel and visitors (travels, meetings, events, bookings...).
- Administrative processing of doctoral thesis and training program for university students.
- Preparation of semiannual activities reports of the Center.

TECHNICAL SUPPORT UNITS

Administration

Personnel

Javier Beltrán Lurueña
Antonio Mata Domínguez
Cristina Santos Gallego
Álvaro Menéndez Sánchez
Margarita Villamor Carba
Miguel Ángel Moreno Valle
María Manuela Calvo González
Isabel Guerra Álvarez

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.

TECHNICAL SUPPORT UNITS

Communication & Marketing

Personnel

Almudena Timón Sánchez

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.
- Attention to the consults and managements of the donations to the CIC through its foundation (FICUS).
- Attention to the media.

TECHNICAL SUPPORT UNITS

Equipment & Building Maintenance

Personnel

Celso Collazo López

Carlos Miguel de los Dolores Redondo

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, CO2 cell culture incubators, spectrophotometer etc.) and steam checkout
- Verification/calibration of balances, pipettes, dry heat incubators, refrigerators, thermoblocks, etc.
- Request of an intervention, overseeing of the work of outside contractors and management of repairs made by external companies

TECHNICAL SUPPORT UNITS

Quality Control & Risk Prevention

Personnel

María José Campo Beneitez

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.

TECHNICAL SUPPORT UNITS

Information Technologies Services (IT)

Personnel

Sonia Pedraza Flores
Pablo González Delgado

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

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

TECHNICAL SUPPORT UNITS

Central Warehouse & Radiological Protection

Personnel

María Sonia Pérez Díez
Mª Eugenia Fernández de la Torre

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.

TECHNICAL SUPPORT UNITS

Glassware Cleaning, Media/Solutions Preparation & Sterilization

Personnel

Ana Brufau Redondo
Mª del Rosario García Rubia
Gloria González Holgado

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

SCIENTIFIC ACTIVITIES

List of journals

This list reflects all the journal in which the investigators of the CIC-IBMCC have published original articles during 2014-2015. The publications with an impact factor over 10 points are highlighted.

Journal	Nº Items	IF	Total IF	Quartile
Acta Crystallographica Section D-Biological Crystallography	1	2,680	2,680	Q1
Acta Oncologica	1	2,997	2,997	Q2
Acta Ophthalmologica	1	2,844	2,844	Q1
Acta Parasitologica	1	0,905	0,905	Q4
Acta Tropica	1	2,270	2,270	Q2
Advances in Biological Regulation	1	NI	NI	NI
Advances in Protein Chemistry and Structural Biology	1	3,036	3,036	Q2
Aging-US	1	6,432	6,432	Q1
Alcoholism-Clinical and Experimental Research	1	3,205	3,205	Q2
Alimentary Pharmacology & Therapeutics	2	5,727	11,454	D1
Allergy	1	6,028	6,028	D1
American Journal of Cancer Research	1	4,165	4,165	Q1
American Journal of Cardiology	1	3,276	3,276	Q2
American Journal of Clinical Pathology	1	2,214	2,214	Q2
American Journal of Hematology	4	3,798	15,192	Q2
American Journal of Pathology	1	4,591	4,591	Q1
Analytical Biochemistry	1	2,219	2,219	Q2
Annals of Allergy Asthma & Immunology	1	2,599	2,599	Q2
Annals of General Psychiatry	1	1,400	1,400	Q3
Annals of Hematology	4	2,634	10,536	Q2

Journal	Nº Items	IF	Total IF	Quartile
Annals of Oncology	4	7,040	28,160	D1
Annals of the Rheumatic Diseases	**1**	**10,377**	**10,377**	**D1**
Anti-Cancer Agents in Medicinal Chemistry	2	2,469	4,938	Q2
Apoptosis	1	3,685	3,685	Q2
Applied Immunohistochemistry & Molecular Morphology	1	2,012	2,012	Q2
Applied Microbiology And Biotechnology	1	3,337	3,337	Q1
Autophagy	**1**	**11,753**	**11,753**	**D1**
Biochimica et Biophysica Acta-Molecular and Cell Biology of Lipids	2	5,162	10,324	D1
Bioinformatics	1	4,981	4,981	D1
Biological Chemistry	1	3,268	3,268	Q2
Biology of Blood and Marrow Transplantation	4	3,404	13,616	Q2
Biomarker Research	1	NI	NI	NI
Biomed Research International	3	1,579	4,737	Q3
Blood	**24**	**10,452**	**250,848**	**D1**
Blood Reviews	1	5,565	5,565	Q1
Blood Transfusion	1	2,372	2,372	Q3
BMC Cancer	2	3,362	6,724	Q2
BMC Genomics	7	3,986	27,902	Q1
BMJ Open	1	2,271	2,271	Q2
Bone Marrow Transplantation	9	3,570	32,130	Q2
Brain Behavior and Immunity	1	5,889	5,889	Q1
Brain Research Bulletin	1	2,718	2,718	Q3
Breast Cancer Research	1	5,490	5,490	Q1
Breast Cancer Research and Treatment	2	3,940	7,880	Q2
British Journal of Anaesthesia	1	4,853	4,853	D1
British Journal of Dermatology	1	4,275	4,275	D1
British Journal of Haematology	15	4,971	74,565	Q1
Cancer	4	5,068	20,272	Q1
Cancer and Metastasis Reviews	3	7,234	21,702	D1

Journal	Nº Items	IF	Total IF	Quartile
Cancer Discovery	**2**	**19,453**	**38,906**	**D1**
Cancer Epidemiology Biomarkers & Prevention	2	4,125	8,250	Q1
Cancer Treatment Reviews	2	7,588	15,176	D1
Cell	**1**	**32,242**	**32,242**	**D1**
Cell Cycle	6	4,565	27,390	Q2
Cell Transplantation	1	3,127	3,127	Q2
Chemical Engineering	1	0,330	0,330	Q4
Chemistry & Biology	1	6,645	6,645	Q1
Chromosoma	1	4,602	4,602	Q1
Clinical & Translational Oncology	4	2,077	8,308	Q3
Clinical and Experimental Immunology	1	3,037	3,037	Q2
Clinical Cancer Research	8	8,722	69,776	D1
Clinical Case Reports	1	NI	NI	NI
Clinical Endocrinology	1	3,457	3,457	Q2
Clinical Lymphoma Myeloma & Leukemia	2	2,020	4,040	Q3
Current Allergy and Asthma Reports	1	2,765	2,765	Q2
Current Cancer Drug Targets	1	3,522	3,522	Q2
Current Opinion in Oncology	1	4,466	4,466	Q1
Current Opinion In Pediatrics	1	2,528	2,528	Q1
Cytometry Part A	1	2,928	2,928	Q2
Cytometry Part B-Clinical Cytometry	4	2,398	9,592	Q2
Cytotherapy	1	3,293	3,293	Q2
Endocrine-Related Cancer	1	4,805	4,805	Q1
Enfermedades Infecciosas y Microbiologia Clinica	1	2,172	2,172	Q3
Enzyme and Microbial Technology	1	2,322	2,322	Q2
Epigenetics	1	4,780	4,780	Q1
European Journal of Haematology	3	2,066	6,198	Q3
European Journal of Medical Genetics	4	1,466	5,864	Q4
European Journal of Pharmaceutics and Biopharmaceutics	1	3,850	3,850	Q1
European Psychiatry	1	3,439	3,439	Q2
Expert Review of Hematology	3	2,070	6,210	Q3

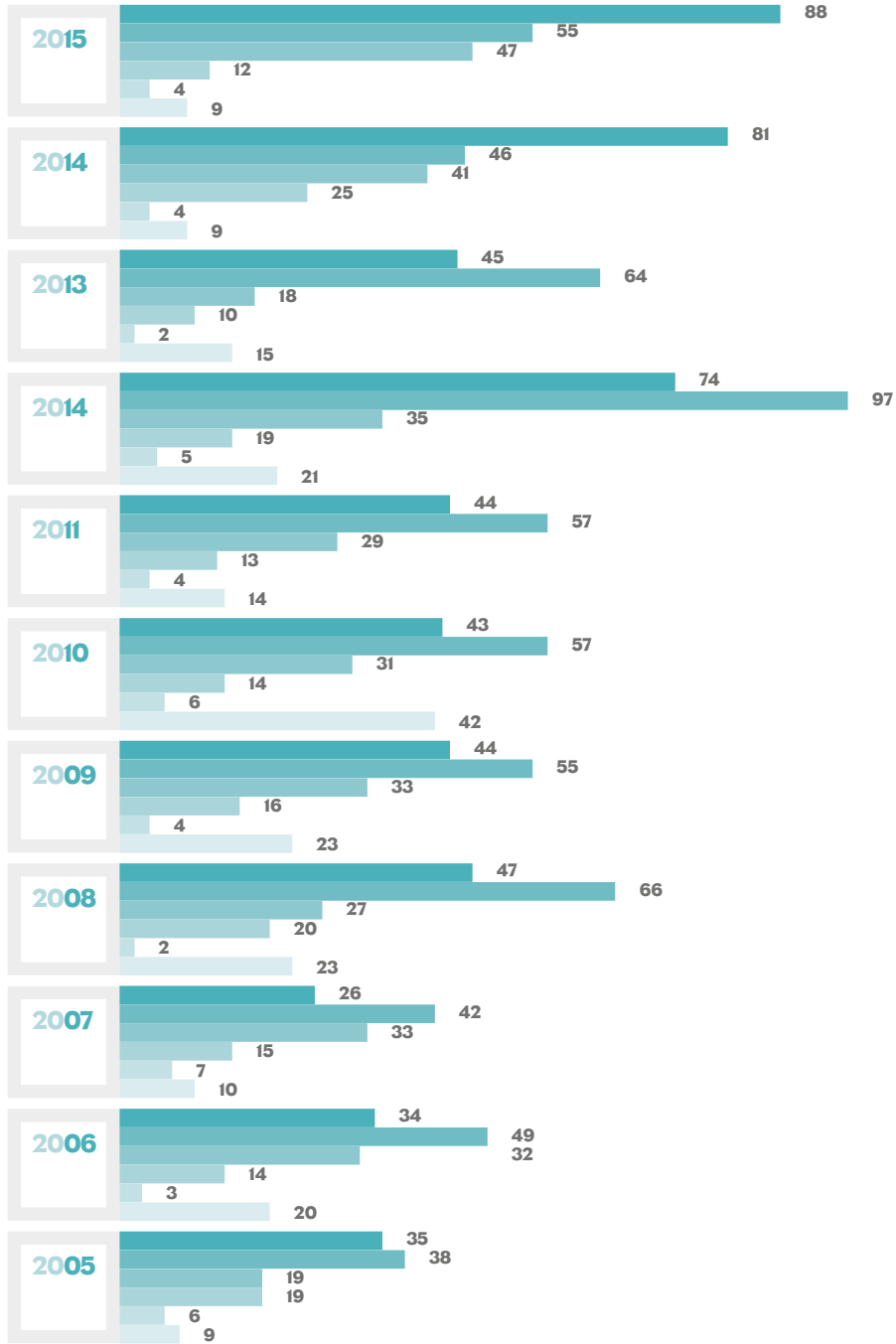
Journal	Nº Items	IF	Total IF	Quartile
FEBS Letters	1	3,169	3,169	Q2
Frontiers in Oncology	1	NI	NI	NI
Gene	2	2,138	4,276	Q3
Genes Chromosomes & Cancer	2	4,041	8,082	Q1
Genome Biology	**5**	**10,810**	**54,050**	**D1**
Genome Research	**1**	**14,630**	**14,630**	**D1**
Graefe's Archive for Clinical and Experimental Ophthalmology	1	1,908	1,908	Q2
Gut	**1**	**14,660**	**14,660**	**D1**
Haematologica	19	5,814	110,466	D1
Hematological Oncology	2	3,084	6,168	Q2
Hematology Reports	1	NI	NI	NI
Hematology-Oncology Clinics of North America	1	2,295	2,295	Q3
Hormone And Metabolic Research	1	2,121	2,121	Q3
Human Molecular Genetics	2	6,393	12,786	Q1
Immunologic Research	1	3,098	3,098	Q2
Immunology	1	3,795	3,795	Q2
Immunology and Allergy Clinics of North America	1	1,818	1,818	Q3
Indian Journal of Dermatology	1	NI	NI	NI
Intensive Care Medicine	1	7,214	7,214	Q1
International Archives of Allergy and Immunology	1	2,673	2,673	Q2
International Immunopharmacology	1	2,472	2,472	Q2
International Journal of Cancer	1	5,085	5,085	Q1
International Journal of Molecular Epidemiology and Genetics	1	NI	NI	NI
International Journal of Radiation Oncology Biology Physics	1	4,258	4,258	Q1
Investigative Ophthalmology & Visual Science	1	3,404	3,404	Q1
Jama Dermatology	1	4,426	4,426	D1
JNCI-Journal of The National Cancer Institute	**1**	**12,583**	**12,583**	**D1**
Journal of Allergy and Clinical Immunology	**4**	**11,476**	**45,904**	**D1**
Journal of Biological Chemistry	2	4,573	9,146	Q1
Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences	1	2,729	2,729	Q2
Journal of Clinical Oncology	**4**	**18,443**	**73,772**	**D1**

Journal	Nº Items	IF	Total IF	Quartile
Journal of Hematology & Oncology	1	4,812	4,812	Q1
Journal of Immunology	1	4,922	4,922	Q1
Journal of Immunology Research	1	NI	NI	NI
Journal of Inorganic Biochemistry	1	3,444	3,444	Q1
Journal of Investigative Medicine	1	1,688	1,688	Q2
Journal of Leukocyte Biology	2	4,289	8,578	Q1
Journal of Molecular Diagnostics	2	4,851	9,702	Q1
Journal of Neuroscience	1	6,344	6,344	Q1
Journal of Proteome Research	8	4,245	33,960	Q1
Journal of Psychiatry & Neuroscience	1	5,861	5,861	Q1
Journal of the European Academy of Dermatology and Venereology	1	2,826	2,826	Q1
Kidney & Blood Pressure Research	1	2,123	2,123	Q2
Lancet Oncology	**2**	**24,690**	**49,380**	**D1**
Langenbecks Archives of Surgery	1	2,191	2,191	Q2
Leukemia	**24**	**10,431**	**250,344**	**D1**
Leukemia & Lymphoma	5	2,891	14,455	Q2
Leukemia Research	9	2,351	21,159	Q3
Leukemia Research Reports	1	NI	NI	NI
Medicina Clinica	1	1,417	1,417	Q2
Medicine	1	5,723	5,723	D1
Methods in Molecular Biology	1	NI	NI	NI
Minerva Cardioangiologica	1	0,530	0,530	Q4
Modern Pathology	1	6,187	6,187	D1
Molecular and Cellular Biology	3	4,777	14,331	Q1
Molecular and Cellular Endocrinology	2	4,405	8,810	Q1
Molecular and Clinical Oncology	1	NI	NI	NI
Molecular Biology of the Cell	2	4,466	8,932	Q2
Molecular Cancer Therapeutics	2	5,683	11,366	Q1
Molecular Carcinogenesis	2	4,808	9,616	Q1
Molecular Oncology	2	5,331	10,662	Q1
Molecules	1	2,416	2,416	Q2

Journal	Nº Items	IF	Total IF	Quartile
Nature	**4**	**41,456**	**165,824**	**D1**
Nature Communications	**5**	**11,470**	**57,350**	**D1**
Nature Neuroscience	**1**	**16,095**	**16,095**	**D1**
Neuro-Oncology	1	6,776	6,776	Q1
Neuropathology and Applied Neurobiology	1	3,927	3,927	Q1
New England Journal of Medicine	**3**	**55,873**	**167,619**	**D1**
Nutrition and Cancer-An International Journal	1	2,322	2,322	Q3
Oncogene	8	8,459	67,672	D1
Oncoscience	2	NI	NI	NI
Oncotarget	19	6,359	120,821	D1
Ophthalmic Genetics	2	1,455	2,910	Q3
Pain Practice	2	2,361	4,722	Q2
Pathobiology	3	2,480	7,440	Q2
Patient Preference and Adherence	1	1,676	1,676	Q2
Pediatric Dermatology	1	1,015	1,015	Q3
Pharmacological Research	1	4,408	4,408	Q1
Plos Computational Biology	1	4,620	4,620	D1
Plos Genetics	1	7,528	7,528	D1
Plos Neglected Tropical Diseases	1	4,446	4,446	D1
Plos One	12	3,234	38,808	Q1
Proceedings of the National Academy of Sciences of the United States of America	3	9,674	29,022	D1
Psychopharmacology	1	3,875	3,875	Q1
Revista Médica de Chile	1	0,304	0,304	Q4
Science Signaling	2	6,279	12,558	Q1
Scientific Reports	1	5,578	5,578	D1
Seminars in Cancer Biology	4	9,330	37,320	D1
Small Gtpases	1	NI	NI	NI
Stem Cell Research & Therapy	2	3,368	6,736	Q2
The Journal of Pathology	1	7,429	7,429	Q1
The Lancet Haematology	1	NI	NI	NI
World Journal of Stem Cells	1	NI	NI	NI

SCIENTIFIC ACTIVITIES

CIC-IBMCC Publications by Quartile 2005-2015



SCIENTIFIC ACTIVITIES

National and International Collaborations

National Collaborations		
Center	**Province**	**Researchers**
Hospital 12 de Octubre	Madrid	A. Sureda / N. Gutiérrez / Juan José Lahuerta
Hospital Universitario de Albacete	Albacete	Alberto Ocaña
Universidad Complutense de Madrid	Madrid	Almudena Porras
Clínica Universidad de Navarra (CUN)	Pamplona	Ana Patiño; Bruno Paiva; Jesús San Miguel
IMDEA-Food Institute (UAM-CSIC)	Madrid	Ana Ramírez de Molina
Instituto de Biología y Genética Molecular (IBGM)	Valladolid	Andrés Alonso
Instituto de Biomedicina de Salamanca (IBSAL)	Salamanca	Antonio Muro
Universidad de Salamanca	Salamanca	Antonio Muro / José Luis Revuelta / Manuel Medarde / Rafael Peláez / Isidro S. Marcos / Pilar Basabe / Rubén Martínez Buey / José M. López-Novoa / Francisco Javier García-Criado / Rafael Jiménez Fernández
Centro Biología Molecular Severo Ochoa (CBMSO)	Madrid	Balbino Alarcón / María L. Toribio / César Cobaleda
Instituto de Neurociencias de Castilla y León (INCYL)	Salamanca	C. Lillo; Ángel Porteros
CIMUS / Universidad de Santiago de Compostela	Santiago de Compostela	Carlos Diéguez / Rubén Nogueiras
Hospital Lozano Blesa	Zaragoza	D. Carrera
Instituto de Biología Funcional y Genómica (IBFG)	Salamanca	Dionisio Martín-Zanca
Hospital Virgen del Rocío	Sevilla	Enrique de Álava

Center	Province	Researchers
Centro de Investigación Médica Aplicada (CIMA)	Pamplona	Fernando Lecanda / José Ángel Martínez-Climent
Universidad de Sevilla	Sevilla	Inmaculada Robina
Hospital La Fe	Valencia	J. de la Rubia
Hospital General de Castellón	Castellón de la Plana	J. Galende
Hospital del Bierzo	León	J. Hernández
Centro Nacional de Investigaciones Cardiovasculares (CNIC)	Madrid	Javier Herranz
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid	Jesús M. Paramio
Hospital del Mar (IMIM)	Barcelona	Joan Albanell / Anna Bigas / Lluis Espinosa
Hospital Vall de Hebrón	Barcelona	Joaquín Arribas
Universidad Autónoma de Madrid (UAM)	Madrid	José A. Suja
Hospital Marqués de Valdecilla	Santander	José Luis Fernández Luna / Miguel Ángel Piris
Hospital Clinico de Salamanca	Salamanca	José Ramón González Porras / Francisco Martín Herrero / Francisco S. Lozano Sánchez / MB Vidriales / G. Mateo / J.J. Pérez / J. Cervero / M. Montalbán / A. Gracia de la Coca / María Consuelo del Cañizo
Hospital Clinic- Institut d'Investigaciones Biomediques August Pi i Sunyer (IDIBAPS)	Barcelona	Joan Bladé
Instituto de Estudios de Mastocitosis de Castilla La Mancha	Toledo	L. Escribano / I. Alvarz-Twose
Hospital Santa Creu I Sant Pau	Barcelona	L. Montejano
Hospital General de Segovia	Segovia	L. Palomera
Instituto de Investigaciones Biomédicas «Alberto Sols» (IIB-CSIC-UAM)	Madrid	Lisardo Boscá / Jorge Martín Pérez
Centro Nacional de Investigaciones Oncológicas (CNIO)	Madrid	M. Drosten / Mariano Barbacid / Marcos Malumbres
Instituto de Investigación Biomédica de Bellvitge (IDIBELL)	Barcelona	Manel Esteller / Miguel A. Pujana
Universidad de Pamplona	Pamplona	María J. Blanco-Prieto
Celgene Institute of Translational Research Europe (CITRE)	Sevilla	Matthew Trotter
Complejo Hospitalario de León	Leon	MV Mateos
Hospital Clínico Universitario de Valladolid	Valladolid	N. de las Heras
Instituto de Salud Carlos III	Madrid	N. Zarich / José María Rojas
Universidad de Alcalá de Henares	Madrid	P. de la Villa
Universidad de Extremadura	Badajoz	Pedro Fernández Salguero
Instituto de Biomedicina y Biotecnología de Cantabria (CSIC-Univ. Cantabria)	Santander	Piero Crespo

Center	Province	Researchers
Centro Nacional de Investigaciones Cardiovasculares (CNIC)	Madrid	Pilar Martín
Hospital Central de Asturias	Oviedo	R. Martínez
Universidad de Málaga	Málaga	Ramón Muñoz Chápuli
Centro de Investigaciones Biológicas (CIB)	Madrid	Rodrigo Bermejo / José L Barbero / Óscar Llorca

International Collaborations		
Center	**Country**	**Researchers**
King's College London	London / UK	A. Easton / G. Schuman / Bernardo Nadal-Ginard / JH. Jansen
Medical University of Gdansk	Gdansk / Poland	A. Hellmann / M. Niedoszytko
VU University Medical Center	Amsterdam / The Netherlands	A. van de Loosdrecht / C. Alhan / MC. Béné
Institute for Cancer Genetics, Columbia University	New York / USA	Adolfo Ferrando
University of California (UCSF)	San Francisco / USA	Allan Balmain / Markus Muschen
Federal University of Rio de Janeiro	Rio de Janeiro / Brasil	C. Pedreira / E. Sobral da Costa
University of Manchester	Manchester / UK	Cathy Tournier
University of Duesseldorf	Duesseldorf / Germany	Arndt Borkhardt / Julia Hauer
Indiana University School of Medicine	Indiana / USA	David L. Boone
Lawrence Berkeley National Laboratory (LBNL). University of California	Berkeley / USA	Jian Hua Mao / Trent Northen
Max Plank Institute for Heart and Lung Research	Bad Nauheim / Germany	Stefan Offermans
Babraham Institute	Cambridge / UK	Sabine Suire
Neurosciences Institute and Chinese Academy of Sciences	Shangai / China	Jiawei Zhou
The Weizmann Institute	Tel Avit / Israel	Orly Reiner
University of Coimbra	Coimbra / Portugal	Paulo J. Oliveira
University of Tokyo	Tokyo / Japan	Yoshi Watanabe
University Hospital Groningen	Groningen / The Netherlands	J. Van Doormaal / J. Gratama.
Stanford University School of Medicine	Stanford / USA	Arash Ash Alizadeh
Princess Margaret Hospital Toronto	Toronto / Canada	Eitan Amir
Laboratory of Physical Chemistry, ETH	Zürich / Switzerland	Inés García Rubio / Gunnar Jeschke
Massachussets General Hospital /Broad Institute	Boston / USA	Ramnik J. Xavier
Dana-Farber Cancer Institute (DFCI) & Harvard Medical School (HMS)	Boston / USA	Marc Vidal

Center	Country	Researchers
Institute for Medical Informatics and Biometry, Medical School, University of Technology	Dresden / Germany	Lars Kaderalli
Fondazione Istituto FIRC di Oncologia Molecolare (IFOM)	Milan / Italy	G. Scita
University of Copenhagen / NNF Center for Protein Research	Copenhaguen / Dinamarca	Guillermo Montoya
Hebrew University of Jerusalem	Jerusalem / Israel	Ephrat Levy-Lahad
University of Calgary	Calgary / Canada	Vanina Zaremberg
University of Oxford	Oxford / UK	Kim Nasmyth
Vrije Universiteit Brussel	Brussels / Belgium	M. Spacek / RG. Owen
Universitá degli studi di Napoli Federico II	Napoles / Italy	M. Triggiani
University of Miami / Sylvester Comprehensive Cancer Center	Florida / USA	Izidore Lossos
Universitá di Firenze	Firenze / Italy	Elisabetta Rovida
Netherlands Cancer Institute (NKI)	Amsterdam / The Netherlands	Arnoud Sonnenberg
University Hospital Ulm	Ulm / Germany	Lars Bullinger
Maine Medical Center Research Institute	Scarborough / USA	Thomas Gridley
Lab Cell Mol Biol. NCI	Bethesda / USA	Larry Samelson
Children's Hospital Research Foundation	Cincinnati / USA	Yi Zheng
Ecole Polytechnique Federale de Lausanne (EPFL)	Lausanne / Switzerland	Pierre Vogel
Dresen University	Dresen / Germany	Rolf Jessberguer
Oslo University	Oslo / Norway	Fritdjof Lund-Johansen
Bombay Technology Institute	Bombay / India	Sanjeeva Srivastava
Massachusetts General Hospital (MGH), Harvard Medical School	Boston / USA	Hanno Reinhard Hock
University of Lisbon	Lisboa / Portugal	Margarida Gama-Carvalho / J. Pedro Simas
Imperial College London	London / UK	Ingrid Müller / Cristina Lo Celso
Bayreuth University	Bayreuth / Germany	Olaff Stemmann
Freidburg University	Freidburg / Germany	Günter Roth
Sanger Center	Cambridge / UK	Natalie Conte / Allan Bradley
Northwestern University	Evanston / USA	Emilia Leucona / Jacob I. Sznajder
Hospital Pitié Salpêtrière	Paris / France	Rita Raisman-Vozari
University Medical Center	Mainz / Germany	Markus Munder
University of Michigan	Ann Arbor / USA	C. Akin

Center	Country	Researchers
University of Texas	Texas / USA	Carol Nilsson
Lund University	Lund / Sweden	Gyorgy Marko-Varga
University of Nebraska Medical Center (UNMC)	Omaha / USA	Michael Green
Arizona State University (ASU)	Tempe / USA	Joshua LaBaer
University Medical Centre Groningen	Groningen / The Netherlands	H.C. Kluin-Nelemans
University of Schleswig-Holstein	Lübeck / Germany	H.P. Horny
National Heart Lung and Blood Institute, NIH	Bethesda / USA	J. Robyn
Cardiovascular Institute / Magna Graecia University	Catanzaro / Italy	Daniele Torella
Technical University of Munich	Munich / Germany	K. Brockow
Clinic and Polyclinic of Dermatology & Venerology, University of Cologne	Cologne / Germany	K. Hartmann
University of Tübingen	Tübingen / Germany	K. Sotlar
Cornell Institute	New York / USA	Ari Melnick
Virginia Commonwealth University	Richmond / USA	L.B. Schwartz
Federal University of Sao Paulo	Sao Paulo / Brasil	M Yamamoto / A. Sandes
Ecole Normale Supérieure de Cachan	Cachan / France	M. Arock
Brigham and Women's Hospital, Harvard Medical School	Boston / USA	M. Castells
Center of Neurociences, University of Coimbra	Coimbra / Portugal	Maria Celeste Lopes
Leiden University Medical Centre	Leiden / The Netherlands	N.A.T. Hamdy
Université René Descarte- Hôpital Necker	Paris / France	O. Hermine
Université Paris V, Hôpital Necker-Enfants Malades, Service des Maladies Infectieuses	Paris / France	O. Lortholary
St. James University Hospital	Leeds / UK	P. Evans; SJ. Richards
Medical University of Vienna	Vienna / Austria	P. Valent / W.R. Sperr / A.W. Hauswirth / M. Födinger
Karolinska Institute	Stockholm / Sweden	Peter Nilsson
Erasmus MC	Rotterdam /The Netherlands	RA. Broimans / D. Hose / JJM van Dongen
Charles University	Prague / Czech Republic	T Kalina / E. Mejstrkova

SCIENTIFIC ACTIVITIES

Spanish Cancer Network (RTICC)

RETICS (Networks for Cooperative Research in Health) are organizational structures formed through association to the Instituto de Salud Carlos III of a range of multidisciplinary research centers and groups in biomedicine 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.

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 overall objective of RETICS is to promote collaboration among research groups of the National Health System working on related areas while also helping to support the structure of research conducted in such groups. The aim of the Networks is to provide high-level scientific, technical and technological support to R+D+I projects in Health Science and Technology, to promote transversal projects specific to the area of activity, to promote Spanish participation in international programs and platforms as well as to foster innovation in health technologies as an instrument to contribute to the sustainability of the National Health Service.

The Strategic Action in Health 2012 of ISCIII included a new call of RETICS program to finance a new network of cooperation in cancer research, 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.

The Application and Strategic Action Plan submitted jointly by 73 groups, to constitute a new RTICC, structured into the eight programs above mentioned and coordinated by Dr. Eugenio Santos from Cancer Research Center of Salamanca, was evaluated positively, and at present five groups of the CIC, led by **Dr. Eugenio Santos, Dr. Xosé Bustelo, Dr. Faustino Mollinedo, Dr. Alberto Orfao, Dr. Marcos González, and Dr. Atanasio Pandiella** are involved in four of the programs of the RTICC.

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.

SCIENTIFIC ACTIVITIES

Award and Recognitions

In 2014-2015 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.

- ICAL 2014 Castilla & Leon Award to **Eugenio Santos.** Valladolid, March 2014.
- Young Investigator Award of the International Society for Laboratory Hematology to **Alberto Orfao** for the work «Immunophenotypic alterations of bone marrow myeloid cell compartments in multiple myeloma patients predict for myelodysplasia-associated cytogenetic alterations», ISLH 2014, The Hague (Netherlands), May 2014.
- The **Cancer Research Center of Salamanca** is awarded in June 2014 with the «Civil society to the Department» distinction by the Social Council of the University of Salamanca. The award recognizes the results obtained in fifteen years, as well as the relationship with society through multiple outreach activities.
- The Foundation for Excellence and quality of oncology (ECO) rewards in July 2014 to the **Cancer Research Center (CIC- IBMCC)** with the ECO prize.
- "Premio Servir 2013-2014" to the **Cancer Research Center** (CIC- IBMCC) by Rotary Club Salamanca 23rd June 2015.
- "Premio Protagonista del Mañana 2013-2014" to **Juan Carlos Montero González** by Rotary Club Salamanca 23rd June 2015
- Award «Alirio Pfiffer» to **Alberto Orfao** the scientific work «Immune reconstitution in patients with Fanconi anemia after allogeneic bone marrow transplantation», best communication about hypoplasia of the Sociedad Brasileira de Transplante de Médula Ossea (SBTMO). Congresso Anual de la SBMTO, Belo Horizonte (Brasil), August 2014.
- III Prize of Biomedicine of the Fundación Valdes-Salas (University of Oviedo-Principado de Asturias) to the Applied Research to **Alberto Orfao** December 2014.
- Prize «Dr Moraza» to **Noemí Puig Morón** to the Best Doctoral Thesis about cancer y therapy, edition 2014.
- Best Tutor Award, XIII Archimedes University Contest to **Xosé R. Bustelo** (Spanish Ministry of Education, Spain) 2014.
- Archimedes Award in Biological and Biomedical Sciences to **Luis Francisco Lorenzo-Martín** (Spanish Ministry of Education, Spain) 2014.
- Cancer Award to **Luis Francisco Lorenzo-Martín** from the Vencer al Cáncer Foundation (Spain, to L.F. Lorenzo-Martín) 2014.
- Prize to the communication: «Analysis of tumor intrinsic factors contributing to the variability in the response to chemotherapy in a HER2 breast cáncer mouse model» Adrián Blanco Gómez*, María del Mar Sáez Freiré*, Sonia Castillo LLuva, Lourdes Hontecillas Prieto, María Luz Hernández Muías, Begoña García Cenador, Javier García Criado, Jian-Hua Mao, Carmen Patino, Purificación

Galindo Villardón, José Pérez-Fontán, Andrés Castellanos Martín, **Jesús Pérez Losada.** Conference sobre Precisión Medicine for Cancer. EARC. 1st-4th March, 2015, Luxemburg.

- First prize to the communication: «Strategy for the identification of the tumor intrinsic QTL determining the response to treatment of ERBB2 breast cancer». Adrián Blanco Gómez, María del Mar Sáez Freire, Sonia Castillo LLuva, Lourdes Hontecillas Prieto, Isabel Ramos Fernández, María Luz Hernández Mulas, Begoña García Cenador, Javier García Criado, Jian-Hua Mao, Carmen Patino, Purificación Galindo Villardón, José Pérez-Fontán, Andrés Castellanos Martín, **Jesús Pérez Losada.** VII Simposium Bases Biológicas del Cáncer y Terapias Personalizadas, 21st & 22nd May 2015, Salamanca, Spain.
- Second prize to the communication: «Identification of the genetic and phenotypic interactions between breast cancer and ageing using an integrative approach. María del Mar Sáez Freire; Adrián Blanco Gómez; Sonia Castillo Lluva; Lourdes Hontecillas Prieto; Ana Krotenberg García; Facundo Ramos Ochoa; Ana Isabel Galán Hernández; María Eugenia Muñoz Bermejo; Begoña García Cenador; Javier García Criado; Carmen Patino Alonso; Purificación Galindo Villardón; José Pérez Fontán; Andrés Castellanos Martín; **Jesús Pérez Losada.** authors. VI Symposium Biological basis of cancer and personalized therapies. 23rd & 24th May 2014, Salamanca, Spain.
- «Premio en Biomedicina Aplicada Valdés Salas» by the University of Oviedo to **Alberto Orfao.** April 2015.
- ASUS Honorary membership to **Eugenio Santos** University of Salamanca, June 2015.
- UGT Castilla y Leon awards in October 2015 to the **Cancer Research Center of Salamanca** with the "X Pablo Iglesias" distinction in the regional collective category, for its contribution to the health and general wellness of all citizens through their research works.
- "1st ASEICA Cancer Research Award" to **Eugenio Santos** by Spanish Association of Cancer Research (ASEICA) 23rd October 2015.
- Young Investigator Award «ICCS 2015 Janis Giorgi Young Investigator Award» to **Sergio Matarraz** for the work «Basophil differentiation traits of blast cells from acute promyelocytic leukemia is associated to a higher and more severe bleeding diathesis» 30th Annual Clinical Cytomtry Meeting and Course Denver, Colorado (USA). October 2015.
- «Alberto Sols» Conference Award from Argentinian Society of Biochemistry and Molecular Biology to **Xosé R. Bustelo** 2015.
- Award «María de Maeztu» of the University of Salamanca to Scientific Excellence to **Marcos González Díaz,** edition 2015.
- Award "Fundación Inocente Inocente "Project Children's Oncology Research" to **Isidro Sánchez García** 2015.

Groups of CIC-IBMCC recognized as "Unidades de Investigación Consolidada" (UIC) for Castilla-León Autonomous Government 2015		
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
092	Faustino Mollinedo García	Manuel Medarde Agustín / Rafael Peláez Lamamie de Clairac Arroyo / Consuelo Gajate Fraile / Raquel Álvarez Lozano
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
116	María Consuelo del Cañizo Fernández Roldán	Fermín Sánchez-Guijo Martín / María Díez Campelo / Olga López Villar / Sandra Muntión Olave / Belén Blanco Durango / Luis Ignacio Sánchez-Abarca Bernal
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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"FUNNEL FACTORS" EN TUMORES HUMANOS COMO FACTORES CLAVE EN LA TRANSFORMACIÓN CELULAR. 4E-BP1, ESTUDIO CLÍNICO Y BÁSICO.
Resumen
Material y métodos
Resultados

7 TRAINING ACTIVITIES

TRAINING ACTIVITIES

Postgraduate Programme: 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, under the same title, has been providing the IBMCC Institute from 2000 to present.

This new Masters 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 or cellular biology and Cancer Clinic. This is a distinctly Masters Research aimed at the basic training necessary for graduates with an interest in Biology and Cancer Clinic without prior experimental experience in the fields of Molecular and Cell Biology that will 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 ranging from basic research (on the grounds microbiological, biochemical or molecular biology) to clinical research areas related to diagnosis, prognosis and treatment experimental. The orientation of this teaching is therefore essentially Postgraduate research and 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 call cancer as well as introduce the culture of cutting-edge research in the future will cure or these diseases to chronic.

In general, this Master aims to provide 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 clinic. Importantly, this knowledge jump the barriers between traditionally separated various biomedical fields such as Medicine, Pharmacy and Biology. In this sense, the training is to propose an interdisciplinary approach and is of interest to graduate with an academic interest and /or applied in the medical, pharmaceutical, biological, biotechnological or bioinformatics.

The molecular content integration with clinical content in the same Master gives an extremely unique character and training key to future researchers in this field. Bookmark finally that this title is related to the degrees that are taught in the Faculties of Biology (Biology and Biotechnology degrees), Medicine and Pharmacy what may 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.

Students Master Program

2013-2014

Laura Ahumada Arranz
Esther Arnáiz González
Iskander Aurrrekoetxea Rodríguez
Santiago Bueno Fortes
Ignacio Campillo Marcos
Arturo Carabias del Rey
Mª José Conde Dusmán
Ana Clara De Tomaso Portaz
Natalia Felipe Medina
María García Álvarez
Patricia Esther González Sáenz
Jesús Mª Hernández Sánchez
Kamila Janusz
Luis Francisco Lorenzo Martín
Elena Martín Doncel
Víctor Miguel Martín Granado
Diego Martín Sánchez
Julia Mayor Pillado
Cristina Mesa Núñez
Fernando Mesías Recamán
Sandra Moro Villa
Amalia Muñiz Carrillo
Álvaro Murillo Bartolomé
Nohra Arleni Ordóñez Pérez
Silvia Preciado Pérez
Facundo Ramos Ochoa
Ana Rico Sorlí
Sonia Rodríguez Fernández
Guillermo Rodríguez Hernández
Elizabeta de los Ángeles Rojas Ricardo
Luzalba del Carmen Sanoja Flores
Inmaculada Serramito Gómez
Carlos Vicente Gutiérrez

2014-2015

Esperanza Macarena Algarín Pachón
Roberto Arévalo Pérez
María José Capmartín Martínez
Beatriz Castejón Vega
Cristina Egido Turrión
Laura García González
Mar Giner Calabuig
María González Múñoz
Gema Marín Royo
Beatriz Martín Gracia
Monica Stella Ospina Saavedra
Ana Pariente Delgado
Lydia Robinson García
Laura Ruiz Remolina
Adrián Sánchez Fernández
Natalia Sanz Gómez
Alicia Uxia Vázquez Bolado
Elda Graciela Vélez Colmenares
Lucía Villamañán de Santiago

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
David López Martínez
Juan Carlos Marín Payá
Marta Martín Izquierdo
Saúl Martín Sánchez
Alejandro Medina Herrera
Pedro Mogollón Arroyo
Adrián Montaño Brioso
Haidi Jazmin Moreno Rodríguez
Daniel Murciano Trigo
Celia Nieto Jiménez
Rubén Picón Murillo
Miguel Quijada Alamo
Dolores Rivero Megías
Laura Rollán Manso

Master´s Student	Director	Title Master's Thesis	Date
Facundo Nehuén Ramos Ochoa	Jesús Pérez Losada	Estudio preliminar del valor pronóstico del gen DDX39 y su participación en la patogenia del cáncer de mama	jun-14
Esther Arnáiz González	Isidro Sánchez-García	Impact of the BCL10 expression in hematopoietic stem cells	jun-14
Guillermo Rodríguez Hernández	Isidro Sánchez-García	Impact of the BCL10 expression in T-cell development	jun-14
Diego Martín Sánchez	Rogelio González Sarmiento	Análisis de la respuesta de proteínas de autofagia al tratamiento con inhibidores de microtúbulos e inhibidores de histonas desacetilasas en líneas celulares de cáncer de colon	jun-14
Fernando Mesías Recamán	Rogelio González Sarmiento	Estudio de genes reparadores en pacientes con cáncer de colon	jun-14
Iskander Aurrekoetxea Rodríguez	Rogelio González Sarmiento	Análisis molecular de genes de susceptibilidad en varones con cáncer de mama	jun-14
Jesús María Hernández Sánchez	Rogelio González Sarmiento	Estudio de las variaciones en el transcriptoma de los enfermos tratados con ruxolitinib	jun-14
Adrián Sánchez Fernández	Azucena Esparís Ogando	Implicación de la MAPKK MEK5 en cáncer de pulmón	jun-14
Inmaculada Serramito Gómez	Felipe X. Pimentel Muiños	Degradación de agregados proteicos mediada por un péptido pro-autofágico presente en la molécula TMEM59	jun-14
Álvaro Murillo Bartolomé	Felipe X. Pimentel Muiños	TMEM59-263-281, dominio activador de autofagia no convencional en diversos sistemas de membrana	jun-14
María José Conde Dusmán	Felipe X. Pimentel Muiños	Papel de la ubiquitinación en la regulación de la proteína inductora de autofagia TMEM59	jun-14
Cristina Mesa Núñez	Felipe X. Pimentel Muiños	Implicación del dominio 263-281 de TMEM59 en procesos autofágicos no convencionales	jun-14
María García Álvarez	Marcos González Díaz	Influencia de los polimorfismos HLA en el desarrollo y evolución de la linfocitosis B monoclonal y la leucemia linfática crónica	jun-14
Kamila Janusz	Jesús Mª Hernández Rivas	Identificación de nuevas variaciones en genes de "splicing" en SMD con sideroblastos en anillo mediante secuenciación masiva (NGS)	jun-14
Silvia Preciado Pérez	Fermín M. Sánchez-Guijo / Mª Consuelo del Cañizo Fernández Roldán	Desarrollo de un modelo murino intraóseo de hematopoyesis	jun-14
Laura Ahumada Arranz	Andrés Avelino Bueno Núñez	Generación de mutantes en la tirosina 211 de PCNA	jun-14
Arturo Carabias del Rey	José María de Pereda Vega	Analysis of the interaction between the desmosomal proteins plakophilin 1 and desmoplakin	jun-14
Amalia Muñiz Carrillo	María P. Sacristán Martín	Estudio del papel de Cdc14B en la respuesta celular al daño en el DNA	jun-14
Ignacio Campillo Marcos	Pedro Lazo-Zbikowski Taracena	Implicación de la quinasa humana VRK1 en la respuesta al daño génico inducido por estrés oxidativo	jun-14
Ana Clara de Tomaso Portaz	Pedro Lazo-Zbikowski Taracena	La quinasa VRK1 y la Glicil-tRNA sintetasa GARS implicadas en neurodegeneración	jun-14

Master´s Student	Director	Title Master's Thesis	Date
Elena Martín Doncel	Pedro Lazo-Zbikowski Taracena	Efecto de la infección de Newcastle Disease Virus en distintas fases del ciclo celular	jun-14
Sara Puente Marín	Faustino Mollinedo / Consuelo Gajate	Análisis de la acción de nanopartículas lipídicas y férricas de edelfosina en promastigotes de Leishmania in vitro	jun-14
Patricia E. González Sáenz	José María de Pereda Vega	Mapping key residues for the head-tail interaction of the guanine nucleotide exchange factor C3G	jun-14
Luis Francisco Lorenzo Martín	Xosé R. Bustelo	Role of the Vav2 oncogene in the regulation of epidermal stem cells in physiological and tumorigenic processes	jun-14
Víctor Miguel Martín Granado	Carmen Guerrero Arroyo	Role of C3G as regulator of platelet releasate	jun-14
Beatriz Martín Gracia	José María de Pereda Vega /Carmen Guerrero Arroyo / Manuel Adolfo Sánchez Martín	Conformational regulation of guanine nucleotide exchange factor C3G	jun-14
Sonia Rodríguez Fernández	Xosé R. Bustelo	Identification of new regulatory mechanisms for the Vav1 oncoprotein	jun-14
Luzalba del Carmen Santoja Flores	Alberto Orfao / Martín Pérez Andrés	Immunophenotypic characterization of normal plasma cells circulating in tonsil, peripheral blood and bone marrow	jun-14
Nohra Arleni Ordóñez Pérez	Alberto Orfao / Sergio Matarraz	Study of cell proliferation index in hematopoietic compartment of bone marrow of patients with myelodysplastic syndromes during the course of their disease	jun-14
Natalia Sanz Gómez	Consuelo Gajate / Faustino Mollinedo	Inducción de distintos tipos de muerte celular y mecanismos implicados en la acción antitumoral de edelfosina en cáncer gástrico	jun-15
Beatriz Castejón Vega	Jesús Pérez Losada	Efecto de la deficiencia del gen Snai2/Slug sobre la tumorigénesis y el desarrollo pulmonar	jun-15
Laura García González	Alberto Martín Pendás	Desarrollo de un ratón Knock-in de cdc20b mediante el uso de CRISPR/CAS9	jun-15
Lucía Villamañán de Santiago	Isidro Sánchez-García	Estudio de la contribución de las células Sca1+ a la formación de cardiomiocitos	jun-15
Cristina Egido Turrión	Rogelio González Sarmiento	Efecto de fármacos modificadores de la autofagia en la línea celular de cáncer de próstata PC3	jun-15
Lydia Robinson García	Rogelio González Sarmiento	Caracterización de variantes de significado desconocido en pacientes con Cáncer de mama y ovario hereditario en los genes BRCA	jun-15
Esperanza Macarena Algarín Pachón	Mercedes Garayoa Berrueta	Estudio de la actividad biológica de los exosomas en el mieloma múltiple	jun-15
Mª José Capmartí Martínez	Jesús Mª Hernández Rivas	Análisis mutacional en pacientes con leucemia linfática crónica y deleción de 13q mediante secuenciación masiva de amplicones	jun-15
Mar Giner Calabuig	Fermín M. Sánchez-Guijo / Teresa L Ramos	Resistencia a los inhibidores de tirosinkinasa en leucemia mieloide crónica: papel de las células stem mesenquimales	jun-15
Adrián Sánchez Fernández	Azucena Esparís Ogando	Implicación de la MAPKK MEK5 en cáncer de pulmón	jun-15

Master´s Student	Director	Title Master's Thesis	Date
Julia Mayor Pillado	Consuelo Gajate / Faustino Mollinedo	Modificación de la eficacia de la edelfosina para inducir muerte celular en células de cáncer de páncreas empleando nanopartículas	jun-15
Ana Pariente Delgado	María P. Sacristán Martín	Estudio de la regulación de Cdc14A por fosforilación por Cdk1	jun-15
Gema Marín Royo	Pedro Lazo-Zbikowski Taracena	Implicación de la quinasa humana VRK1 y el factor de transcripción SOX2 en la progresión del ciclo celular a través de la inducción de ciclina D1	jun-15
Laura Pérez Hernández	Manuel Fuentes García / Alberto Orfao	Mass identification of proteins in lymphoid cell lines by techniques directed proteomics	jun-15
Elda Graciela Vélez	Julia Almeida Parra	Building a reference database for automated immunophenotypic analysis of chronic lymphoproliferative disorders T and NK	jul-15
Noemí Muñoz García	Julia Almeida Parra / Rocío Rodríguez Macías	Mutations in STAT3 and STAT5b in the expansions of large granular lymphocytes (LGG): useful in the diagnosis of clonality and implications in the pathology of neoplasms LGG	jul-15
Sara Núñez	Manuel Fuentes García	Study of membrane proteins in immune cells by proteomic techniques of mass analysis. Implications for Human Proteome Project	jul-15
María González Muñoz	Manuel Fuentes García	Study of nano -cell interaction by mass analysis proteomic approaches	jul-15
Alba Torres Valle	Rafael Góngora / Martín Pérez Andrés	Analysis of populations of memory B cells and plasma cells and their potential usefulness in the study of primary antibody deficiencies	jul-15
Lucía Pedrosa Pérez	Andrés C. García Montero / María Pérez Caro	Stabilization of nucleic acids and cell membrane to reduce the changes in gene expression of cells purified from peripheral blood	jul-15
Mónica Stella Ospina Saavedra	Alberto Orfao	Analysis of circulating leukocyte populations in patients with primary immune thrombocytopenia, and its association with response to treatment with eltrombopag	jul-15

TRAINING ACTIVITIES

Postgraduate Programme: 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.

Students PhD program

2013-2014

Javier Acevedo Bouzas
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Verónica Alonso Pérez
Mª del Pino Blanco González
Francisco José Campos Laboire
María Campos Terrón
Tatiana Elisabeth Carranco Medina
Ester Chico Bermejo
Ana Alejandra Cordero Vaquero
Pilar Costa Alba
Ivan Cruz Gil
Ana Catarina de Aragao Soares Homem
Rosa Mª Díaz Burillo
Beatriz Escudero Paniagua
Marta Fernández Prieto
María Fernández Regueras
Isora Follana Neira
Sara García Alonso
Aránzazu García Mateo
Catalina Gil Restrepo
Laura Gómez Hernández
Jesús Manuel González Santiago
Yolanda Mª Guillén Pérez
Mª Cecilia Guillén Sacoto
Sara Gutiérrez Herrero
Vanesa Hidalgo Sierra
Yuliana Mónica Jamanca Poma
Conrado Jorge Finnigan
Gustavo Eduardo Kcam García
Luis López Mesonero
Laura Manzanedo Bueno
Elisabeth Martínez Linares
Luis Martínez Roldán
Fátima Méndez Ambel
Alfredo Moreno Montoya
Marta Muñoz Ruiz
Blanca Nieto Bernáldez
Alba Noguerido Castro
Ana Mª Orive Ramos
Daniela Pinto Damasceno
Mª Concepción Piñero Pérez
Andrés Julián Plata Izquierdo
Mª Isabel Prieto Conde
Catia Daniela Quintas Faria
Silvio Ragozzino
Cristina Ramón Barros
Mª Esther Ramos Araque
Vanesa Rivero Gutiérrez
Vanessa Rivero Perdomo
Aline Rodrigues
Oliver Raziel Rua Fernández
Josepa Sebastiá Morant
Juan Francisco Soto Delgado
Alicia Elena Villatoro González

2014-2015

Javier Acevedo Bouzas
Laura Ahumada Arranz
Sara Aibar Santos
Ruslan Al ali
Sara Alonso Álvarez
Josefa Verónica Alonso Pérez
Vanesa Álvarez Álvarez
Iskander Aurrekoetxea Rodríguez
Patricia Ayala de la Roca
Mª Jesús Baldeón Conde
David Barreda Gago
José Mª Bastida Bermejo
Cristina Sofía Baz Villoria
Elena Blanco Álvarez
Adrián Blanco Gómez
Santiago Bueno Fortes
Sergio Cadenas Menéndez
Ignacio Campillo Marcos
Francisco José Campos Laboire
María Campos Terrón
Cristina Cantero Díez
Cristina Cañete Campos
Arturo Carabias del Rey
Ana Mª Carballido Vázquez
Tatiana Elisabeth Carranco Medina
Carlos Fabián Castaño Romero
Diana Esther Castilla Perera
Giselle Castillo Villa
Ariana Centa
Ana Alejandra Cordero Vaquero
Ignacio Criado García
David Da Silva Moura
Noelia Dasilva Freire
Ana Catarina de Aragao Soares Homem
Idania De los Santos Ventura
Paula Díez García
Conrad Friedrich Droste
Cristina Egido Turrión
Natalia Felipe Medina
Javier Fernández Mateos
Marta Fernández Prieto
María Fernández Regueras
Isora Follana Neira
Camilla Frattini
Sara García Alonso
María García Álvarez
Aránzazu García Mateo
Francisco Javier García Palomo
Eva García Piney
Idioa García Ramírez
Mercedes Gazón Martínez
Catalina Gil Restrepo
Laura Gómez Hernández
Verónica González de la Calle
Miguel González Hierro
Jesús Manuel González Santiago
María González-Tablas Pimienta
Yolanda Mª Guillén Pérez
Mª Cecilia Guillén Sacoto
Sara Gutiérrez Herrero
Susana Hernández García

Students PhD program

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María Hernández Sánchez
José Manuel Iglesias Clemente
Yuliana Mónica Jamanca Poma
Kamila Janusz
Cristina Jiménez Sánchez
Conrado Jorge Finnigan
Gustavo Eduardo Kcam García
Mª Pilar Liceras Boillos
Teresa Da Conceiçao Lopes Ramos
Oriana Jimena López Godino
Luis López Mesonero
Miriam López Parra
Luis Francisco Lorenzo Martín
Ronald Macías Casanova
Laura Manzanedo Bueno
Elena Martín Doncel
Víctor Miguel Martín Gracnado
Alberto Martín Lorenzo
Diego Martín Sánchez
Luis Martínez Roldán
Ana Mª Mateos Díaz
Soledad Medina Valdivieso
Fátima Méndez Ambel
Alexis E. Morales Boscán
Javier Ignacio Muñoz González
Blanca Nieto Bernáldez
Alba Noguerido Castro
Ana Mª Orive Ramos
Sara Ortiz Rivero
Irene Palacios Álvarez
Atenea Pascual Rodríguez
Pedro Daniel Perdiguero Martín
Daniela Pinto Damasceno
Mª Concepción Piñero Pérez
Andrés Julián Plata Izquierdo
Silvia Preciado Pérez
Mª Isabel Prieto Conde
Silvio Ragozzino
Cristina Ramón Barros
Mª Esther Ramos Araque
Mª Florencia Re Louhau
José Ignacio Recio Rodríguez
Mª Luisa Rivera Reigada
Vanesa Rivero Gutiérrez
Vanessa Rivero Perdomo
Aline Rodrigues
Sonia Rodríguez Fernández
Guillermo Rodríguez Hernández
Blanca Rodríguez Martín
Oliver Raziel Rua Fernández
Lucía Ruiz Roca
Beatriz Sáenz Narciso
Ana Isabel Sánchez Marcos
Luzalba del Carmen Sanoja Flores
Josepa Sebastiá Morant
Inmaculada Serramito Gómez
Juan Francisco Soto Delgado
Ricardo Usategui Martín
Svetlana Zhilina

2015-2016

Ruslan Al ali
Esperanza Macarena Algarín Pachón
Sara Alonso Álvarez
Alicia Alonso Jiménez
Josefa Verónica Alonso Pérez
Vanesa Álvarez Álvarez
Mª Jesús Baldeón Conde
David Barreda Gago
José Mª Bastida Bermejo
Cristina Sofía Baz Villoria
Yazmine Bejarano Condezo
Lorena Bellido Hernández
Elena Blanco Álvarez
Cristina Blanco Dorado
Adrián Blanco Gómez
Santiago Bueno Fortes
Juan Carlos Caballero Berrcal
Sergio Cadenas Menéndez
Elisa Calvo Jiménez
Ignacio Campillo Marcos
Francisco José Campos Laboire
María Campos Terrón
Mª Teresa Cano Mozo
Cristina Cantero Díez
Cristina Cañete Campos
Arturo Carabias del Rey
Ana Mª Carballido Vázquez
Tatiana Elisabeth Carranco Medina
Carlos Fabián Castaño Romero
Diana Esther Castilla Perera
Ariana Centa
Ana Alejandra Cordero Vaquero
Pilar Costa Alba
Ignacio Criado García
David Da Silva Moura
Noelia Dasilva Freire
Julio Dávila Valls
Idania de los Santos Ventura
Mª de los Ángeles De Pedro Muñoz
Elena Díaz Peláez
Eva Mª Díez Baeza
Paula Díez García
Conrad Friedrich Droste
Cristina Egido Turrión
Natalia Felipe Medina
Alfonso Fernandes de Abreu Alves Chaves
Javier Fernández Mateos
Marta Fernández Prieto
María Fernández Regueras
Isora Follana Neira
Camilla Frattini
Julie Milena Galvis Jiménez
Sara García Alonso
María García Álvarez
Aránzazu García Mateo
Francisco Javier García Palomo
Eva García Piney

Students PhD program

Idioa García Ramírez
Mercedes Gazón Martínez
Laura Gómez Hernández
Verónica González de la Calle
Mª Teresa González Sánchez
Jesús Manuel González Santiago
María González-Tablas Pimienta
Yolanda Mª Guillén Pérez
Mª Cecilia Guillén Sacoto
Sara Gutiérrez Herrero
Susana Hernández García
Jesús Mª Hernández Sánchez
María Hernández Sánchez
José Manuel Iglesias Clemente
Yuliana Mónica Jamanca Poma
Kamila Janusz
Cristina Jiménez Sánchez
Soraya Jodra Sánchez
Conrado Jorge Finnigan
Ester Laso Lucas
Mª Pilar Liceras Boillos
Teresa Da Conceiçao Lopes Ramos
Oriana Jimena López Godino
Ana Alicia López Iglesias
Luis López Mesonero
Miriam López Parra
Marco López Zubizarrtea
Luis Francisco Lorenzo Martín
Ronald Macías Casanova
Laura Manzanedo Bueno
Elena Martín Doncel
Víctor Miguel Martín Granado
Ana África Martín López
Alberto Martín Lorenzo
Diego Martín Sánchez
Luis Martínez Roldán
Ana Mª Mateos Díaz
Mª Amparo Mateos Diego
Soledad Medina Valdivieso
Soraya Merchán Gómez
Fátima Méndez Ambel
Mónica Morais Gomes Ferreira
Alexis E. Morales Boscán
Raquel Moreno Mayordomo
Javier Ignacio Muñoz González
Noemí Muñz García
Juan Luis Muñoz Sánchez
Blanca Nieto Bernáldez
Alba Noguerido Castro
Ana Mª Orive Ramos
Francisco Javier Ortega García
Sara Ortiz Rivero
Irene Palacios Álvarez
Pedro Daniel Perdiguero Martín
Mª Luisa Pérez García
Mª Elena Pérez Losada
Henar Pérez Ramos
Daniela Pinto Damasceno
Mª Concepción Piñero Pérez
Andrés Julián Plata Izquierdo
Silvia Preciado Pérez
Mª Isabel Prieto Conde
Andrea Silvana Prolo Acosta
Alba Quesada Moreno
Silvio Ragozzino
Cristina Ramón Barros
Mª Esther Ramos Araque
Mª Florencia Re Louhau
José Ignacio Recio Rodríguez
Ana Rico Sorlí
Mª Luisa Rivera Reigada
Aline Rodrigues
Eva Mª Rodríguez Beltrán
Sonia Rodríguez Fernández
Guillermo Rodríguez Hernández
Blanca Rodríguez Martín
Elizabeta de los Ángeles Rojas Ricardo
Alejandro Rolo Ramírez
Oliver Raziel Rua Fernández
Laura Ruiz Remolina
Lucía Ruiz Roca
Beatriz Sáenz Narciso
Dalia Salim Quwaider
Natalia Sánchez Aguadero
Adrián Sánchez Fernández
Rebeca Sánchez González
Ana Isabel Sánchez Marcos
Diego Sánchez Nieto
Luzalba del Carmen Sanoja Flores
Josepa Sebastiá Morant
Pablo Segovia Alonso
Inmaculada Serramito Gómez
Juan Francisco Soto Delgado
Ricardo Usategui Martín
Mª Paz Vaquero Herrero
Svetlana Zhilina

TRAINING ACTIVITIES

Doctoral Theses

PhD Student	Director	Title	Date
Rósula Mercedes García Navas	Faustino Mollinedo García	Papel inmunosupresor y citotóxico de la arginasa I y la disponibilidad de L-arginina en el sistema inmune y cáncer	24/01/2014
Rosete Sofia das Dores Pais	José Manuel García Pichel / Carmen Guerrero Arroyo	Función de IGF1 e IGF1R en el desarrollo del pulmón del ratón: mecanismos de acción de IGF1 en el desarrollo prenatal e implicación de IGF1R en la diferenciación del epitelio pulmonar	24/01/2014
Ximena Marcela Bonilla Forero	Faustino Mollinedo García	Mecanismo de acción de edelfosina en sarcoma de Ewing y cáncer de cabeza cuello.	17/02/2014
Diana Marcela Monsalve Carmona	Pedro Lazo-Zbikowski Taracena	Implicación de las quinasas humanas VRK1 y VRK2 en las rutas de respuesta a daño génico y apoptosis	31/03/2014
Maryam Arefi	Jesús Mª Hernández Rivas	Papel de la citogenética y de la genética molecular en la detección de la clonalidad en las eosinofilias	01/04/2014
Janny Alexander Villa Pulgarín	Faustino Mollinedo García	Nuevas estrategias para el tratamiento de la leishmaniasis: mecanismo de acción de lípidos antitumorales, interacción hospedero-parásito, y su posible utilidad terapéutica.	16/05/2014
Alejandra Fernández Pordomingo	Rogelio González Sarmiento / Antonio Rodríguez Pérez	Análisis de polimorfismos genéticos implicados en las vías de apoptosis y autofagia en la enfermedad de Crohn	30/05/2014
Carlos Jiménez Criado	Rogelio González Sarmiento	Análisis de la respuesta de líneas celulares tumorales al tratamiento con fármacos reguladores de la actividad epigenética	06/06/2014
Juan Carlos Rama Merchán	Rogelio González Sarmiento / Ignacio Cruz González	La apoptosis en el infarto agudo de miocardio. Asociación de los polimorfismos Arg72Pro del gen p53 y T309G del gen MDM2 con el tamaño del infarto, la función ventricular izquierda post-infarto y el desarrollo de insuficiencia cardiaca	16/06/2014
Tatiana Rasterio Coelho	Pedro Lazo-Zbikowski Taracena / L Almeida	Assessment of JC polyomavirus in normal colorectal mucosa, hyperplastic polyps and sporadic adenomas and adenocarcinomas in a Portuguese population and its association with cancer	20/06/2014

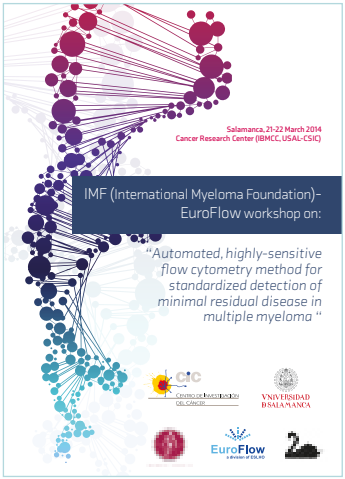
PhD Student	Director	Title	Date
Emilia Pardal de la Mano	Mª Dolores Caballero Barrigón	Impacto pronóstico de la evaluación precoz con tomografía por emisión de positrones (PET) en el tratamiento ajustado al riesgo de los linfomas no Hodgkin B de célula grande	23/06/2014
Alfonso Gallego-Sánchez	Andrés Avelino Bueno Núñez	Caracterización de nuevos reguladores de los mecanismos de tolerancia al daño en el DNA de Saccharomyces cerevisiae.	27/06/2014
Virgina Ojeda Seijas	Xosé Ramón García Bustelo / Josefa Montero Gómez	New roles of coronins in cytoskeletal organization and cell signaling	04/07/2014
José Abelardo Andrés Llamas	Rogelio González Sarmiento / Mercedes Sánchez Barba / Ignacio Cruz González	Implicación de los genes VAV en la insuficiencia cardiaca	11/07/2014
Salvatore Fabbiano	Xosé Ramón García Bustelo / Mauricio Ariel Menacho-Márquez / Mª Ángeles Sevilla Toral	An ontological view of cardiovascular and metabolic disease progression using genetically modified mice	21/07/2014
Maryam Arefi	Jesús María Hernández Rivas / Juan Luis García Hernández	Papel de la citogenética y de la genética molecular en la detección de la clonalidad en las eosinofilias	21/07/2014
Alba María Redondo Guijo	Mª Dolores Caballero Barrigón	Tratamiento de rescate en linfomas agresivos: eficacia del trasplante autólogo de precursores hematopoyéticos y evaluación de nuevos fármacos	21/07/2014
Lucía López- Anglada Fernández	Mª Belén Vidriales Vicente / Marcos González Díaz / Consuelo del Cañizo Fernández-Roldán	Aportación de la citometría de flujo en el estudio de los linfomas no Hodgkin: Análisis de la infiltración de medula ósea y caracterización inmunofenotípica de síndromes linfoproliferativos crónicos con expresión leucémica	24/07/2014
María Gómez Hernández	José María de Pereda Vega / Carmen Guerrero Arroyo	Characterization of the structural organization of guanine nucleotide exchange factor C3G	25/07/2014
Marta García Suquía	Félix Lorente Toledano / María Victoria Rascón Trincado / Isidro Sánchez García	Leucemia aguda infantil: caracterización clínico-biológica e investigación en modelo trasngénico murino Sca 1-TEL-AML1	04/09/2014
Ana Teresa Monteiro Amaral	Enrique de Álava Casado / José Luis Ordoñez García / Alberto Orfao de Matos	The pathogenesis of Ewing Sarcoma implications of mesenchymal stem cells and new therapeutic strategies	18/09/2014
Sara Ovejero Merino	María Paz Sacristán Martín / Andrés Avelino Bueno Núñez	Estudio de la función y regulación de la proteína Cdc14A en el ciclo de división celular	26/09/2014
Noelia Cubino Bóveda	Rogelio González Sarmiento / Carlos Montilla Morales	Análisis de los polimorfismos del gen de PPAR-g, IL-1b e IL-6 en la artritis psoriásica	26/09/2014
Eduardo José Fernández Rodríguez	Juan Jesús Cruz Hernández / María Isabel Rihuete Galve	Estudio abierto aleatorizado de la intervención no farmacológica en el control de la astenia referida por la enfermedad oncológica	06/11/2014
Ana Silvia Puente González	José Ignacio Calvo Arenillas / Juan Jesús Cruz Hernández / Roberto Méndez Sánchez	Influencia de un programa de revitalización geriátrica como actividad física sobre la densidad mineral ósea y el riesgo de caídas en personas con enfermedad de Alzheimer	10/11/2014
Juan Ignacio Rodríguez Melcón	Juan Jesús Cruz Hernández / Luis Alberto Henríquez Hernández	Radioterapia externa en cáncer de próstata localizado: Optimización de la ratio terapéutica	22/11/2014

PhD Student	Director	Title	Date
Isabel Romero Camarero	Isidro Sánchez-García/ Carolina Vicente Dueñas / Francisco Javier García Criado / Rafael Jiménez Fernández	Reprogramación tumoral en neoplasias linfoides	12/12/2014
Víctor Méndez Cenizo	José Ignacio Paz Bouza / Juan Jesús Cruz Hernández	Carcinogénesis pancreática experimental. Papel protector de la niacina en su desarrollo	18/12/2014
Patricia Henriques Domingues	Alberto Orfao de Matos	Patterns of protein expression and cytogenetic alterations in meningiomas: relationship with the clinical and biological features of the disease	09/01/2015
Ana Mª Carballido Vázquez	José María de Pereda Vega	Desmoplakin and plakophilin 1a: structure, subcellular distribution, and interactions	05/02/2015
Patricia Ayala de la Roca	María Paz Sacristán Martín	Estudio de las fosfatasas hCdc14 en el ciclo de división celular y en la respuesta al daño en el DNA	20/02/2015
Fanny Pojero	Alberto Orfao de Matos	MGUS and multiple myeloma: looking for new markers and exploring the interaction with the bone marrow microenvironment	17/03/2015
Emilio Boada-Romero	Felipe X. Pimentel-Muiños	Characterization of the autophagic process induced by the protein TMEM59.	20/03/2015
Giulia Moriggi	Mercedes Dosil	Role of Rrp12 in the formation of ribosomal subunits	27/03/2015
Ana Filipa Parreira Carvalheira dos Santos Henriques	Alberto Orfao de Matos	Immunophenotypic, genetic and molecular characterization of B-cell chronic lymphoproliferative disorders: multiclonal versus monoclonal nature	09/04/2015
Gloria López Valverde	Rogelio González Sarmiento / Fernando Cruz González / Emiliano Hernández Galilea	Estudio genético de la catarata presenil	27/04/2015
María del Carmen Herrero Sánchez	Mª Consuelo del Cañizo Fernández Roldán / Belén Blanco Durango	Inhibidores de la vía PI3K/Akt/mTOR: utilidad en la profilaxis/ tratamiento de la enfermedad injerto contra huésped	04/05/2015
Javier Cañueto Álvarez	Jesús Pérez Losada / Concha Román Curto	Definición del pronóstico del carcinoma epidermoide cutáneo mediante la combinación de factores clínico-patológicos, marcadores proteicos y expresión de miRNAs	05/05/2015
Jaime Ceballos Viro	Rogelio González Sarmiento / Juan Jesús Cruz Hernández	Estudio inmunohistoquímico, clínico y de metilación del promotor de BRCA1 en pacientes diagnosticadas de cáncer de mama triple negativo	13/05/2015
Roberto González Alconada	Fermín M Sánchez-Guijo	Regeneración ósea en un modelo de xenotrasplante de células madre	15/05/2015
Antonio José Velasco Guardado	Mª Dolores Caballero Barrigón	Factores diagnósticos endoscópicos y pronósticos relacionados con el Helicobacter Pylori en la enfermedad de injerto contra huésped tras el rescate alogénico de células hematopoyéticas	22/05/2015
Sara Aibar Santos	Javier De Las Rivas Sanz	Bioinformática aplicada a datos genómicos para la caracterización de subtipos de cáncer: estudios integrativos en hemopatías malignas	25/05/2015

PhD Student	Director	Title	Date
Diego López Fernández	Fermín M Sánchez-Guijo	Hallazgo y caracterización de células stem mesenquimales en núcleo pulposo de disco intervertebral degenerado: comparación con las células obtenidas de médula ósea de los mismos pacientes y resultados previos en la región lumbar	25/06/2015
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	23/07/2015
Edward Yepes Victoria	Faustino Mollinedo García / Antonio Muro Álvarez	Efecto in vitro e in vivo de los alquil-lisofosfolípidos (ALPs) en el desarrollo de nuevos compuestos contra Schistosoma mansoni.	27/07/2015
Josefa Verónica Alonso Pérez	Faustino Mollinedo García	Actividad antitumoral del éter-lípido edelfosina en cáncer de mama.	31/07/2015
Vanesa Rivero Gutiérrez	Rogelio González Sarmiento / Fernando Cruz González / Lourdes Juan Marcos	Estudio de polimorfismos y acortamiento telomérico en pacientes con cataratas	11/09/2015
María Florencia Re Louhau	Atanasio Pandiella Alonso	Identificación de un nuevo intermediario en la vía de señalización NRG-receptores ErbB en cáncer de mama	16/09/2015
María Laura Gutiérrez Troncoso	Luis Muñoz Belvis / José Alberto Orfao de Matos / José María Sayagués Manzano	Análisis de la heterogeneidad genética del adenocarcinoma ductal de páncreas y su relación con las características de la enfermedad	17/09/2015
Ruth Maribel Forero Castro	Jesús M Hernández Rivas	Estudio de las alteraciones genéticas en la leucemia aguda linfoblástica mediante microarrays de alta densidad y secuenciación masiva	02/10/2015
José Ignacio Recio Rodríguez	Luis García Ortiz / Manuel Ángel Gómez Marcos / Mª Carmen Patino Alonso / Rogelio González Sarmiento	Estilos de vida y función vascular. Estudio EVIDENT	09/10/2015
María Abaigar Alvarado	Jesús María Hernández Rivas / María del Rocío Benito Sánchez	Molecular Characterization of Myelodysplastic Syndromes (MDS): Analysis of genomic abnormalities in the development of MDS, progression to Acute Myeloblastic Leukemia and response to treatment with 5-Azacytidine	18/11/2015
Lara Cantarero Abad	Pedro Lazo-Zbikowski Taracena	Implicación de la quinasa humana VRK1 en la formación de los cuerpos de cajal y sus implicaciones patológicas	20/11/2015
Beatriz Rosón Burgo	Javier De Las Rivas Sanz / Fermín Sánchez-Guijo / Consuelo del Cañizo	Transcriptomic characterization of Human Mesenchymal Stromal/ Stem Cells.	16/12/2015
Reyna Alejandra Jiménez Flores	Faustino Mollinedo García	Actividad citotóxica del éter-lípido edelfosina en cáncer de higado.	17/12/2015

TRAINING ACTIVITIES

Conferences, Meetings & Scientific courses



1 — IMF (International Myeloma Foundation)- EuroFlow workshop on: «Automated, highly-sensitive flow cytometry method for standardized detection of minimal residual disease in multiple myeloma»

(http://www.cicancer.org/es/eventos/42/imf-international-myeloma-foundation-euroflow-workshop-on-automated-highly-sensitive-flow-cytometry-method-for-standardized-detection-of-minimal-r)

Date 21/03/214

Summary

During the last eight years, the EuroFlow Consortium has developed novel standardized strategies for the diagnosis and classification of hematological malignancies, using a highly reproducible n-dimensional flow ctyometry. More recently, flow cytometry based minimal residual disease (MRD) assessment has become one of the major projects of the EuroFlow Consortium. Recent advances in multiple myeloma treatment and close collaboration among several EuroFlow laboratories and the IMF have advanced the evolution of MRD detection for this disease.

The International Myeloma Foundation-EuroFlow workshop was specifically organized as an educational activity focused on the «Innovative, automated and high-sensitive flow cytometry method developed for standardized detection of minimal residual disease in myeloma patients», particularly to those laboratories involved in IMF-sponsored/promoted clinical trials.

For this purpose, the complete workflow –from instrument set-up, panel design and optimization of sample preparation to automated data analysis and data interpretation– will be addressed in detailed presentations and roundtable discussions, including «hands-on» sessions. The ultimate goal is to provide full education for translation of the new protocol into routine MRD detection in multiple myeloma.

2 — VI Simposium Bases Biológicas del Cáncer y Terapias personalizadas

(http://www.basesbiologicascancer.com/)

Date 22-23/05/2014

Organizers

Prof. Juan Jesús Cruz Hernández, Hospital Clínico Universitario, Salamanca
Dr. César A. Rodríguez, Hospital Clínico Universitario, Salamanca

3 — IV Encuentro de Jóvenes Investigadores de la Red Temática de Investigación Cooperativa en Cáncer (RTICC)

(http://www.rticc.org/noticia11.php)

Date 23/09/214

Summary

The Executive Committee of the RTICC a proposal of the coordinator of the Training and Mobility RTICC program has agreed to organize the IV Scientific Meeting of Young Researchers from the Spanish Cancer Network (RTICC) 2014.

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-iv-encuentro-jovenes-investigadores-2014.pdf

4 — VII Reunión Anual RTICC

(http://www.rticc.org/noticia12.php)

Date 24/09/214

Program

http://www.rticc.org/docs/noticias/programa-vii-reunion-rticc-2014.pdf

5 — V ProteoRed-ISCIII Protein Microarrays Course

(http://www.cicancer.org/es/eventos/123/v-proteored-isciii-protein-microarrays-course)

Date 15-17/04/2015

Summary

Theoretical and practical course focused on review the current state of knowledge in the field of Protein Microarrays. The course will provide the opportunity for leading scientist to meet for training and discussions on the most recent developments in this area. The main objective of the conference will be to improve the capabilities and competitiveness of Spanish proteomics facilities in the area of protein microarrays. The final objective is to increase the quality and the number of protein microarrays services.

6 — VII Simposium Bases Biológicas del Cáncer y Terapias personalizadas

(http://www.basesbiologicascancer.com/ and http://www.cicancer.org/es/eventos/41/vii-simposium-bases-biologicas-del-cancer-y-terapias-personalizadas)

Date: 21-22/05/2015

Director

Prof. Juan Jesús Cruz Hernández, Hospital Clínico Universitario, Salamanca, Departamento de Medicina, Universidad de Salamanca

Coordinator

Dr. César A. Rodríguez, Hospital Clínico Universitario, Salamanca, Departamento de Medicina, Universidad de Salamanca

Organizer

Asociación para el Desarrollo de la Oncología Médica

Program

http://basesbiologicascancer.com/wp-content/uploads/2015/03/Programa-Salamanca-2015_OK.pdf

7 — Scientific Session commemorating the 15th anniversary of the Cancer Research Center of Salamanca «New developments in the understanding and treatment of cancer»

(http://www.cicancer.org/es/eventos/134/sesion-cientifica)

Date 01/10/2015

Organizers

Drs. X. R. Bustelo, A. Pandiella, and A. Martín-Pendás

Summary

The Centro de Investigación del Cáncer (CIC) commemorates its 15th anniversary this year. Since its opening, the CIC has become a reference point for the cancer community, integrating under the same umbrella a significant group of internationally competitive basic, translational, and clinical scientists. The Center has also strengthened community-oriented services that have resulted in significant numbers of clinical trials and the accessibility to the public and private sector of a variety of high throughput, genome-wide techniques. Through its training activities, it has also contributed to the formation of new generation of scientists currently doing cancer research work elsewhere.

We believe that the 15th anniversary milestone is a good opportunity to celebrate these achievements and use them as a springboard to further expand its activities in the near future. To mark this anniversary, the Center is organizing a one-day meeting in which a selection of the most internationally recognized Spanish cancer scientists will present an update of their research. The talk topics will allow the audience to grasp a good idea about current developments

in the molecular understanding of cancer development and progression, the identification of its main Achilles's heels, and the development of new diagnostic and therapeutic avenues.

In addition to the intrinsic interest of the talks, we plan to create a «casual» environment during the meeting to facilitate the interaction of the invited speakers with the audience, in particular students at the end of the undergrad period, those carrying out Biomedical-oriented masters, and early-stage graduate students

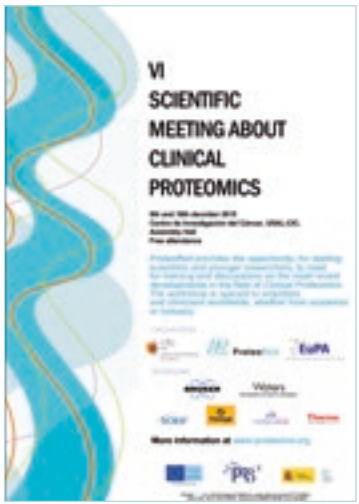
Program

9:00–09:30: Opening Session
Morning Session (Xosé R. Bustelo, chair)
9:30–10:00: «15 years and still going». Eugenio Santos, Centro de Investigación del Cáncer (Salamanca, Spain)
10:00–10:45: «Deconstructing metastasis». Joan Massaguè, Cancer Biology and Genetics Program. Sloan Kettering Institute (New York, USA)
10:45–11:30: «Metastatic stem cells and TGF signaling in colorectal cancer». Eduard Batlle, Coordinator of the Oncology Program. Institute for Research in Biomedicine (Barcelona, Spain)
11:30–12:15 «Imaging and and treating premetastatic niches in melanoma». Marisol Soengas, Department of Molecular Oncology, CNIO
Noon Session (Alberto M. Pendás & Marcos González, chairs)
12:45–13:30: «Cancer Epigenetics: From Knowledge to Applications». Manuel Esteller, Cancer Epigenetics and Biology Program, Bellvitge Biomedical Research Institute (Barcelona, Spain)
13:30–14:15: «Cancer and aging: genomics and degradomics». Carlos López Otín, Cancer Molecular Biology Program. Institute of Oncology, University of Oviedo (Oviedo, Spain)
Afternoon Session (Atanasio Pandiella, chair)
15:30–16:15: «Biological and clinical impact of intratumor heterogeneity» Joan Seoane, Translational Research Program. Vall d'Hebron Institute of Oncology (Barcelona, Spain)
16:15–17:00: «Targeting oncogene-induced DNA damage for cancer therapy». Oscar Fernández Capetillo, Department of Molecular Oncology. CNIO
17:00–17:45 «Telomerase regulation in health and disease». María A. Blasco, Department of Molecular Oncology. CNIO
17:45–18:00 Closing Remarks

8 — VI Scientific Meeting about Clinical Proteomics

(http://www.cicancer.org/es/eventos/160/vi-scientific-meeting-about-clinical-proteomics)

Date 09-10/12/2015



Organizers

Dr. Fernando J. Corrales, ProteoRed General Coordinator Senior Scientist at the Centro de Investigación Médica Aplicada, CIMA
Dr. Francisco J. Blanco, member of the ProteoRed Management Board Scientific Director of the Instituto de Investigación Biomédica A Coruña, INIBIC
Dr. Manuel Fuentes, group leader of the ProteoRed node at Salamanca Junior Scientist at the Centro de Investigación del Cáncer CIC-USAL

Program

http://www.cicancer.org/uploads/archivos/VI_Scientific_Meeting_about_Clinical_Proteomics_programme.pdf

TRAINING ACTIVITIES

Scientific Seminar Program

Date	Title	Speaker	Affiliation
24/01/2014	Análisis de la respuesta de líneas celulares tumorales al tratamiento con fármacos reguladores de la actividad epigenética	Carlos Jiménez Criado	CIC-IBMCC (CSIC-USAL) Lab 14
16/01/2014	Inhibition of insulin signalling by the c-Jun N terminal kinase (JNK) pathway: Output on systemic insulin resistance	Carme Caelles	Facultad de Farmacia; Universidad de Barcelona [Barcelona, Spain]
23/01/2014	From interactomics to cancer cell proliferation: Regulation of MAP kinase ERK5 by oncogenic chaperones	José Miguel Lizcano	Universidad Autónoma de Barcelona [Barcelona, Spain]
30/01/2014	Cancer Genomics and Computational Biology	Alfonso Valencia	Centro Nacional de Investigaciones Oncológicas (CNIO) [Madrid, Spain]
06/02/2014	The never ending story of the origin of Chronic Lymphocytic leukemia	Paolo Ghia	Università Vita-Salute San Raffaele [Milan, Italy]
13/02/2014	Personalised Cancer Medicine: the UK perspective	David Gonzalez de Castro	The Centre for Molecular Pathology; The Royal Marsden NHS Foundation Trust[London, UK]

Date	Title	Speaker	Affiliation
20/02/2014	Targeting signaling molecules and resistance in metastatic breast cancer	Mohamed Bentires-Alj	Friedrich Miescher Institute for Biomedical Research (FMI) [Basel , Switzerland]
27/02/2014	Structural insights into the the TRiC/CCT complex function and mechanism	Guillermo Montoya	University of Copenhagen / Centro Nacional de Investigaciones Oncológicas (CNIO)[Madrid, Spain]
06/03/2014	Unconventional Regulations and Functions of Separase, an essential protease and the universal trigger of eukaryotic anaphase	Olaf Stemmann	University of Bayreuth [Bayreuth, Germany]
13/03/2014	Boosting the biomedical research through Spain-Taiwan collaboration	Wen-Guey Wu	National Science Council of Taiwan [Taipei, Taiwán]
13/03/2014	Caracterización de la interacción entre las proteínas de los hemidesmosomas BPAG1e e integrina 6 4	José Antonio Manso	CIC-IBMCC (CSIC-USAL) Lab 17
20/03/2014	The TET-TDG Axis in Epigenetic Control	Primo Leo Schär	Institute of Biochemistry and Genetics, University of Basel [Basel, Switzerland]
28/03/2014	Pancreatic cancer: EMT, inflammation, and therapeutic opportunities	Francisco X. Real	Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid
03/04/2014	Mecanismos de acción de la vitamina D en cáncer de colon	Alberto Muñoz	Instituto de Investigaciones Biomédicas "Alberto Sols" (IIBM) [Madrid, Spain]
10/04/2014	Bioinformatics approaches to analyse multiple disease subtypes and build associated gene networks using genome-wide expression profiles	Sara Aibar	CIC-IBMCC (CSIC-USAL) Lab 19
24/04/2014	Biología y función de Cereblon, la proteína de unión de IMIDS en mieloma múltiple	Elena Díaz-Rodríguez	CIC-IBMCC (CSIC-USAL) Lab 15
08/05/2014	Parallel approaches to unveil Polycomb functions: from stem cells to cancer	Luciano di Croce	Centro de Regulación Genómica (CRG)[Barcelona, Spain]
15/05/2014	Aneuploidy and tumorigenesis in Drosophila tissues	Marco Milán	Instituto de Investigación Biomédica (IRB) [Barcelona, Spain]
29/05/2014	Role of the new identified Greatwall kinase in the oncogenic process	Anna Castro	Centre de Recherche en Biochimie Macromoléculaire (CRBM-CNRS)[Montpellier, France]
05/06/2014	Interacción entre TMEM59 y ATG16L1 en procesos autofágicos no convencionales	Emilio Boada	CIC-IBMCC (CSIC-USAL) Lab 18
19/06/2014	The multiple facets of Tiam1-Rac signalling in tumourigenesis	Angeliki Malliri	Paterson Cancer Center [Manchester, UK]
26/06/2014	Importancia de Src en cáncer de mama	Jorge Martín Pérez	Instituto de Investigaciones Biomédicas "Alberto Sols" (IIBM) [Madrid, Spain]
03/07/2014	Metástasis óseas del cáncer de pulmón: nuevos mecanismos e implicaciones clínicas	Fernando Lecanda	Centro Investigación Médica Aplicada (CIMA) [Pamplona, Spain]
10/07/2014	Síndrome Cornelia de Lange: Nuevas Perspectivas	Juan Pié Juste	Facultad de Medicina. Universidad de Zaragoza [Zaragoza, Spain]

Date	Title	Speaker	Affiliation
17/07/2014	Recent epidemiological research on environmental causes of cancer	Joachim Schuz	International Agency for Research on Cancer (IARC), Section of Environment and Radiation [Lyon, France]
01/10/2014	Improving resolution through optimizing instrument set-up and minimizing the impact of fluorescence spillover	Maria C. Jaimes	Becton Dickinson Biosciencies [San Jose, USA]
02/10/2014	Proteínas RasGRF: implicación en el movimiento nuclear en los fotorreceptores	David Jimeno	CIC-IBMCC (CSIC-USAL) Lab 1
06/10/2014	Drug resistance and the tumour microenvironment: strategies to improve the clinical benefit from chemotherapy	Ian Tannock	Princess Margaret Cancer Centre and University of Toronto [Toronto, Canada]
06/10/2014	La Bioinformática al servicio de la investigación y la biomedicina	Juan Carlos Triviño	Responsable Dpto. Bioinformática Sistemas Genómicos [Valencia, Spain]
10/10/2014	Cytosine-5 RNA methylation in stem cell differentiation, stress pathways and cancer	Sandra Blanco	Wellcome Trust/Medical Research Council Stem Cell Institute [Cambridge, UK]
16/10/2014	CD39+ regulatory T cells protect against angiotensin-II-dependent cardiorenal fibrosis AND hypertension	Salvatore Fabbiano	CIC-IBMCC (CSIC-USAL) Lab 2
23/10/2014	La quinasa humana VRK1 regula la estabilidad de los Cuerpos de Cajal protegiendo a Coilina de su degradación en el proteasoma	Lara Cantarero Abad	CIC-IBMCC (CSIC-USAL) Lab 4
30/10/2014	Papel de las quinasas activadas por estrés en la tumorigénesis	Ángel Nebreda	Instituto de Investigación Biomédica (IRB) [Barcelona, Spain]
06/11/2014	La desubiquitinación de PCNA como reguladora de las rutas de tolerancia en la respuesta al daño en el DNA.	Alfonso Gallego Sánchez	CIC-IBMCC (CSIC-USAL) Lab 5
13/11/2014	Inactivación de secuencias intergénicas en el genoma de ratón mediante CRISPR-Cas9	Lluís Montoliu	Centro Nacional de Biotecnología (CNB-CSIC) [Madrid, Spain]
20/11/2014	Nuevas herramientas de la citometría de flujo para el análisis multidimensional e interpretación automática de la maduración hematopoyética	Sergio Matarraz Sudón	CIC-IBMCC (CSIC-USAL) Lab 11
27/11/2014	Snai2 participates in luminal breast cancer development	Sonia Castillo-Lluva	CIC-IBMCC (CSIC-USAL) Lab 7
11/12/2014	Separase haploinsuficiency sensitizes to chemically-induced skin cancer in the mouse	Natalia Felipe Medina	CIC-IBMCC (CSIC-USAL) Lab 9
15/01/2015	Nuevas dianas de p38 MAPK	Almudena Porras	Facultad de Farmacia, Universidad Complutense de Madrid [Madrid, Spain]
26/01/2015	Presentación del Servicio de Bioinformática de Nucleus, I+D+i, USAL	Carlos Prieto	Nucleus (USAL) [Salamanca, Spain]
05/02/2015	Repair of Topoisomerase II-blocked DNA double-strand breaks: molecular mechanisms and pathological implications	Felipe Cortés-Ledesma	Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER) [Sevilla, Spain]

Date	Title	Speaker	Affiliation
12/02/2015	Estudio de la célula clonogénica y quimiorresistente en el mieloma múltiple: célula madre tumoral versus modelo de evolución clonal	Teresa Paíno Gómez	CIC-IBMCC (CSIC-USAL) Lab 12
19/02/2015	Lightning the path to metastasis in cancer: applications to gene discovery and drug validation in melanoma	Marisol Soengas	Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid [Madrid, Spain]
26/02/2015	Infection exposure is a causal factor in B-precursor acute lymphoblastic leukemia as a result of Pax5 inherited susceptibility	Alberto Martín Lorenzo	CIC-IBMCC (CSIC-USAL) Lab 13
05/03/2015	G-actin as a signalling molecule	Richard Treisman	Cancer Research UK; Lincoln's Inn Fields Laboratories [London, UK]
19/03/2015	The Influences of Growth Factors and Retinoids on Haematopoiesis	Geoffrey Brown	College of Medical and Dental Sciences, University of Birmingham [Birmingham,UK]
26/03/2015	The end of chromosome replication	Karim Labib	The Sir James Black Centre; University of Dundee [Dundee,UK]
09/04/2015	Therapeutic landscape of cancer drivers	Nuria López-Bigas	Universidad Pompeu Fabra - UPF [Barcelona, Spain]
20/04/2015	Morphologic and Molecular Characteristics of newly described hereditary Renal Cancer.	María José Merino	National Cancer Institute. USA. Head, Translational Surgical Pathology Section [Bethesda, USA]
21/04/2015	Regulación de la desmetilasa de histonas LSD1 durante la diferenciación neuronal y la transición epitelio-mesénquima.	José Carlos Reyes	Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER) [Sevilla, Spain]
07/05/2015	Novel targeted therapies in t-all	Pieter Van Vlierberghe	Center of Medical Genetics, Universidad de Gante, Bélgica [Gent, Belgium]
07/05/2015	TLX1 - NOTCH1 - PHF6: the mystery triangle resolved?	Frank Speleman	Dpto. de Genética, Universidad de Gante [Gent, Belgium]
14/05/2015	microRNAs link the germinal center reaction with mature B cell lymphomagenesis	Almudena Ramiro	Centro Nacional de Investigaciones Cardiovasculares (CNIC) [Madrid, Spain]
04/06/2015	How to target the 'undruggable': inhibiting Myc in cancer	Laura Soucek	Vall d'Hebron Institute of Oncology (VHIO), [Barcelona, Spain]
09/06/2015	How are chromosomes held together?	Kim Nasmyth	University of Oxford [Oxford, UK]
11/06/2015	Identificación de un nuevo intermediario en la vía de señalización por receptores ErbB.	María Florencia Ré Louhau	CIC-IBMCC (CSIC-USAL) Lab 15
18/06/2015	STATegra: Developing new resources for the integrative analysis of multi-omics data	Ana Conesa	Professor Bioinformatics, Microbiology and Cell Science Department, University of Florida, USA / Head of Genomics of Gene Expression Lab, Prince Felipe Research Center [Valencia, Spain]
02/07/2015	Aproximación clínica y molecular al cáncer epidermoide de cabeza y cuello	Raquel Seijas Tamayo	CIC-IBMCC (CSIC-USAL) Lab 14
16/07/2015	Identification of novel mechanisms of mitotic progression	Bill Earnshaw	Wellcome Trust Centre for Cell Biology/ University of Edinburgh [Edinburgh, UK]

Date	Title	Speaker	Affiliation
08/10/2015	Role of the guanine nucleotide exchange factor C3G in platelet function and its implication in ischemic cardiovascular diseases and cancer	Víctor Miguel Martín Granado	CIC-IBMCC (CSIC-USAL) Lab 17
16/10/2015	Understanding the Mechanism of Action to Target Core Binding Factor Leukemia	Lucio Castilla	University of Massachusetts Medical School [Massachusetts, USA]
22/10/2015	Caracterización de una nueva ruta molecular de intercomunicación entre autofagia y apoptosis	Cristina Ramón Barros	CIC-IBMCC (CSIC-USAL) Lab 18
29/10/2015	The MYC/MAX and the SWI/SNF networks: biological understanding and therapeutic applications	Montserrat Sánchez-Céspedes	Hospital Duran i Reynals-Institut d'Investigació Biomèdica de Bellvitge (IDIBELL) Cancer Epigenetics & Biology Program [Barcelona, Spain]
05/11/2015	Molecular genetics in AML: clinical implications	Lars Bullinger	University Hospital of Ulm [Ulm, Germany]
12/11/2015	How to identify biomarkers in heterogeneous patient populations using genomic data	Francisco José Campos Laborie	CIC-IBMCC (CSIC-USAL) Lab 19
19/11/2015	Leucine-rich repeat G protein-coupled receptors and the development of the gastrointestinal system	Gilbert Vassart	Université libre de Bruxelles [Bruxelles, Belgium]
26/11/2015	Sos1 disruption impairs cellular proliferation and viability through an increase in mitochondrial oxidative stress in primary MEFs	Pilar Liceras Boillos	CIC-IBMCC (CSIC-USAL) Lab 01
02/12/2015	From Petri Dish to Human: How to Avoid the Pitfalls of Translational Research	Romuald Menth	LGC Standards [Middlesex, UK]
03/12/2015	L-1 mediated transduction: a new mutational mechanism in cancer	José M.C. Tubío	Wellcome Trust Sanger Institute, [Hinxton, UK]
17/12/2015	Pleiotropic roles of the Vav-1 proto-oncogen in T-cell acute lymphocytic leukemia	Javier Robles Valero	CIC-IBMCC (CSIC-USAL) Lab 02

8 SCIENCE OUTREACH

SCIENCE OUTREACH

The most significant research advances have been disseminated through the following press releases

- March 2014: 10th anniversary of the National DNA Bank. The National DNA Bank has become a biobank with international relevance because of its achievements.
- April 2014: The paper "The C-Terminal SH3 Domain Contributes to the Intramolecular Inhibition of Vav Family Proteins" establishes, for the first time, the complete mechanism of activation of a family of proteins, Vav family, involved in cancer.
- May 2014: Researchers at the CIC have identified a new therapeutic target against breast cancer.
- May 2014: The Association for International Cancer Research (AICR) funds a group at CIC.
- June 2014: A protein is critical to improving treatments for breast cancer. When VRK1 kinase is deleted, tumor cells cannot respond to the damage caused by the therapy.
- June 2014: Researchers advance on the emergence and evolution of diffuse large B-cell lymphoma.
- July 2014: The Foundation for Excellence and quality of oncology (ECO) rewards the Cancer Research Center (CIC- IBMCC) with the ECO prize.
- September 2014: The European Competence Network on mastocytosis appoints Luis Escribano "Researcher 2014".
- October 2014: The Cancer Research Center was illuminated pink in honor of Breast Cancer Awareness Month.
- November 2014: Two young researchers awarded the "XIII Certamen Arquímedes".
- November 2014: New methodology of proteomic techniques to characterize biomarkers for diagnosis of osteoarthrosis.
- November 2014: Researchers present the most advanced map of interactions between human proteins.
- January 2015: Meikin is a conserved regulator of meiosis-I- specific kinetochore function.
- February 2015: Scientists describe pathological mechanism of Follicular Lymphoma.
- September 2015: The development of Acute lymphoblastic leukemia is closely linked to infectious exposure. The research may be relevant in preventive medicine.
- September 2015: Researchers at CIC identified and described unknown proteins.
- September 2015: Nature published the results of the 1000 Genomes Project.
- October 2015: 15th Anniversary of the Cancer Research Center (CIC-IBMCC).
- November 2015: Global task force tackles problem of untreatable cancers and disease relapse: non-toxic chemicals in plants and foods may be key.

SCIENCE OUTREACH

In 2014 and 2015 they have carried out various activities related to fundraising

- National Award in Cancer Research "Drs. Diz Pintado"
  - November 2014: Dissemination of the IV National Award in Cancer Research "Doctores Diz Pintado".
  - December 2014: the IV National Award in Cancer Research "Doctores Diz Pintado" was awarded to Joan Seoane.
  - November 2015: Dissemination of the V National Award in Cancer Research "Doctores Diz Pintado".
  - December 2015: the IV National Award in Cancer Research "Doctores Diz Pintado" was awarded to Adolfo A. Ferrando.
- March 2014-December 2015: Javier Campo and Isabel Vidal have made selfless contributions to the Cancer Research Center (CIC-FICUS) by the Budapest Project.
- 2014-2015: The sale of their book "Tan Alta como un ciprés: nueve mujeres narran su lucha contra el cáncer de mama" has been donated to Cancer Research Center (CIC- FICUS). This association has organized other events with the same purpose.
- 2014-2015: The "Asociación Leonesa de Mujeres Operadas de Cáncer de Mama (ALMOM)" has organized some charity races and donated the amount collected for Cancer Research Center (CIC-FICUS).
- April 2015: Child Orchestra "La Ranita del Tormes and Diego Pisador Youth Orchestra" directed by Sergio Fuentes (professor of violin at the Conservatory of Salamanca) gave a benefit concert for the Center for Cancer Research at the Auditorium of Fonseca.

SCIENCE OUTREACH

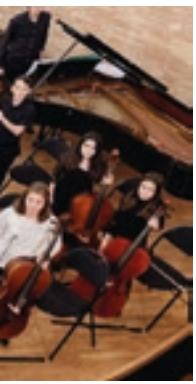
During 2014-15 the area of communication have developed various outreach activities framed within public relations aimed at different sectors of society, of which include

Public relations

- In 2014-2015 they have treated more two thousand five hundred people, among university students, high school students, college and other groups belonging to different associations such as the AECC through guided visits. Most of these visits are part of the program of activities the "Fundación Salamanca Ciudad de Saberes" for the promotion of scientific culture. The purpose of the visits is to supplement the training that students are receiving in the schools and high schools. The CIC is involved in this programming since 2007.
- 2014: Cancer Research Center has participated in the exhibition on crystallography in the exhibition hall of Fonseca. The exhibition has been explained the function of the x-ray generator of the CIC.
- May-2015: Participation in the "I Jornadas de formación de voluntariado de AOEX", of Mérida.

Social networking services

- In 2014-2015, CIC has increased visibility across social networks such as LinkedIn, Twitter and Facebook. This strategy is enabling better communication with the media, with the voluntary sector and other academic and scientific institutions. This communication is strengthening training and support services developed by CIC and its most prominent communications channeled through releases or press conferences.



9
PRESS CLIPPINGS

PRESS CLIPPINGS

2014

1 **El Norte de Castilla** (septiembre)
2 **El Norte de Castilla** (noviembre)
3 **El Mundo / Innovadores** (marzo)
4 **Cadena Ser** (mayo)
5 **La Sexta TV** (mayo)
6 **El Mundo** (mayo)
7 **El Periódico** (diciembre)
8 **El Mundo de Castilla y León** (abril)

1

Investigadores señalan que el fin de la leucemia linfática crónica está más cerca

Un total de 73 grupos pertenecientes a la Red Temática de Investigación Cooperativa en Cáncer ponen en común sus trabajos

SANDRA BAZ / WORD

LOS PROTAGONISTAS

Descubren nuevas metodologías para el diagnóstico de la osteoartrosis

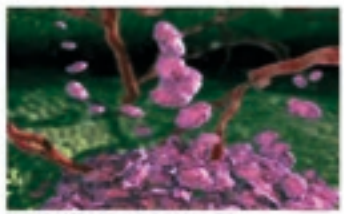
El equipo de Manuel Fuentes, miembro del Centro de Investigación de Cáncer, aborda en su estudio la enfermedad reumática más frecuente

5

Investigadores españoles descubren una proteína que evita que el cáncer de mama se convierta en metástasis

EL MUNDO

Científicos españoles identifican un 'freno' c cáncer de mama



2

3

SALAMANCA

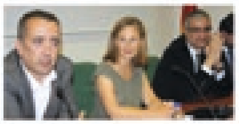
Tras el rastro del mieloma múltiple

Un método ideado en el CIC averigua si el paciente tiene la enfermedad mínima residual

4

Localizan la primera diana para frenar el cáncer de mama más agresivo

El Centro de Investigación del Cáncer ha descubierto un sistema para neutralizar el tumor y evita que la metástasis llegue al pulmón. La revista Nature ha publicado este avance científico



7

Un director del Vall D'Hebron, premiado por sus estudios de tumores cerebrales

6

contra el

8

El Centro del Cáncer descubre cómo se activan proteínas malignas

El importante hallazgo de los científicos del CIC abre nuevas vías para inhibir estas proteínas en pacientes con cáncer o en personas con trastornos del metabolismo

Salamanca

María Barreira: «Permitirá diseñar fármacos más precisos»

PRESS CLIPPINGS

2015

1 **El Norte de Castilla** (diciembre)
2 **El País** (diciembre)
3 **ABC** (enero)
4 **Diario Médico** (junio)
5 **Diario de Ávila** (noviembre)
6 **El Mundo de Castilla y León / Innovadores** (febrero)
7 **El Periódico** (diciembre)
8 **www.jano.es** (marzo)

1

Un momento de la inauguración del simposio en el Centro de Investigación del Cáncer.

Un simposio visibiliza en el CIC las nuevas aplicaciones de la proteómica clínica

El análisis masivo de las proteínas congrega en un encuentro internacional a especialistas de España, Estados Unidos, Holanda, Suecia y Suiza

RICARDO SÁBADE / SALAMANCA

EE UU aprueba tres fármacos contra el mieloma múltiple

>PERSONAJES ÚNICOS / PEDRO LAZO

Fue sevillano uno de los fundadores del CIC de manejar retrovirus en los años duros del SIDA, descubre proteínas «sin querer» pero que dan

'Completar' a Ram

Pedro Lazo, científico del Centro de Investigación del Cáncer, en los pasillos

«Castilla y León no tiene capacidad para atraer científicos de fuera»

5

'Tan alta como un ciprés' dona 2.000 euros a la investigación del cáncer

Con esta cifra recaudada en la marcha 'Compartiendo camino' ya son 37.000 euros los entregados al CIC situado en Salamanca

• Al dinero obtenido con la venta del libro 'Tan alta como un ciprés' y con otros actos solidarios se suman ahora los 2.000 aportados por los participantes en la mucha.

M. R. | ÁVILA

'Tan alta como un ciprés' junto a personal del Centro de Investigación del Cáncer.

La asociación 'Tan alta como un ciprés' ha hecho entrega de una donación en metálico de dos mil euros al Centro de Investigación del Cáncer (CIC) de Salamanca. Esta cantidad fue recaudada entre los participantes en la marcha 'Compartiendo camino', realizada el mes pasado por las mujeres que forman parte del citado colectivo y sus allegados junto al personal sanitario de la Unidad de Oncología del Hospital Nuestra Señora de Sonsoles de Ávila, por lo que agradecen la participación y la solidaridad.

Con esta reciente entrega de 2.000 mil euros, ya suciende a 37.000 euros la cantidad total donada por 'Tan alta como un ciprés' al Centro de Investigación del Cáncer de Salamanca, dinero obtenido con la venta del libro que comparte título con el nombre de la asociación, en el que las mujeres que forman parte de la misma narran su experiencia personal con el cáncer, así como con los distintos actos solidarios organizados precisamente para recaudar fondos destinados a facilitar que los profesionales que trabajan en el CIC de Salamanca sigan investigando la enfermedad, informan desde la misma.

2

6

-Salamanca; tras recorrer medio mundo y el recién nombrado presidente de la Aseica ...in que hablar. Por M. Ángel Rodríguez

...nón y Cajal

3

Una joven investigadora realiza una de las operaciones en su laboratorio

Fundación Memoria D. Samuel Solórzano Barruso

Ayudas a la investigación

INVESTIGACIÓN

Unidos contra el cáncer

La Universidad de Valladolid y la Asociación Española contra el Cáncer financian un estudio centrado en los carcinomas papilares de tiroides

LA INVESTIGACIÓN PERMITIRÁ LOCALIZAR BIOMARCADORES FIABLES

4

AstraZeneca

MEDICIN...

|PROMESAS EN INVESTIGACIÓN|

Una fuga de cerebros bidireccional

PERFIL

Una carrera que arranca en Argentina y se consolida en España

7

PUBLICADO EN 'PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES'

Investigadores españoles participan en un trabajo que describe el patrón genético del linfoma folicular

Los autores logran identificar genes mutados en el 96% de los tumores analizados y confirmar, en el 76%, la presencia de 2 o más genes modificadores de cromatina.

SCIENTIFIC REPORT

2014 | 2015

CENTRO DE INVESTIGACIÓN DEL CÁNCER

INSTITUTO DE BIOLOGÍA MOLECULAR Y CELULAR DEL CÁNCER (USAL - CSIC)

CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

CAMPUS DE EXCELENCIA INTERNACIONAL

Unión Europea

Fondo Europeo de Desarrollo Regional "Una manera de hacer Europa"