Scientific Report

2012 | 2013

CIC
CENTRO DE INVESTIGACIÓN DEL CÁNCER

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

CSIC
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

VNiVERSiDAD D SALAMANCA
CAMPUS DE EXCELENCIA INTERNACIONAL

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)

Phone: +34 923 294 720
Fax: +34 923 294 743
E-mail: cicancer@usal.es

http://www.cicancer.org/memoria-2012-2013

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Scientific Report

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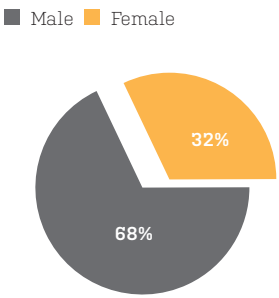
CENTRO
DE INVESTIGACIO
DEL CANCER

1 Foreword

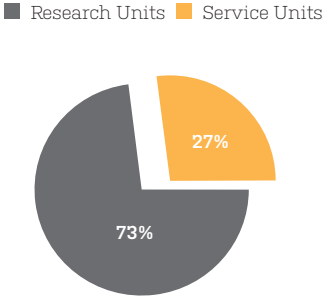
This report describes the scientific activities of the CIC-IBMCC (Centro de Investigación del Cáncer-Instituto de Biología Molecular y Celular del Cáncer) de Salamanca (CSIC-USAL) for the **years 2012 and 2013**. As in previous times, the CIC-IBMCC has focused its activity during this period on basic, clinical and translational research of tumoral events applying a multidisciplinar approach reminiscent of the US Comprehensive Cancer Centers in an effort to achieve a quick and efficient transfer of laboratory results to society and the patients. In this regard, our center continues 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.

As of december 2013, the CIC-IBMCC was composed by 16 independent **Research Units** whose activities were supported by 9 **Scientific Service Units** and 8 **Technical Support Units**. The following pages contain in-depth descriptions of the composition and functions of each of those Units during 2012 and 2013. As our center is a joint enterprise (Instituto Mixto) of the University of Salamanca (**USAL**) and the Spanish Research Council (**CSIC**), about 50% of our personnel were formally affiliated with either USAL or CSIC, whereas the remainder 50% were supported by work contracts (102 contracts in 2012 and 111 contracts in 2013) underwritten by our supporting **FICUS** Foundation (Fundación de Investigación del Cáncer en la Universidad de Salamanca).

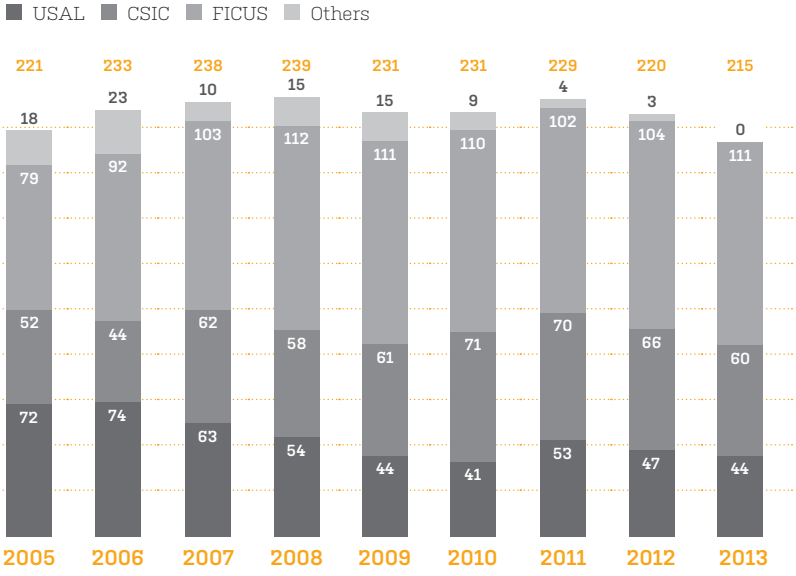
Average distribution by gender 2012-2013



Staff Research Units vs Service Units

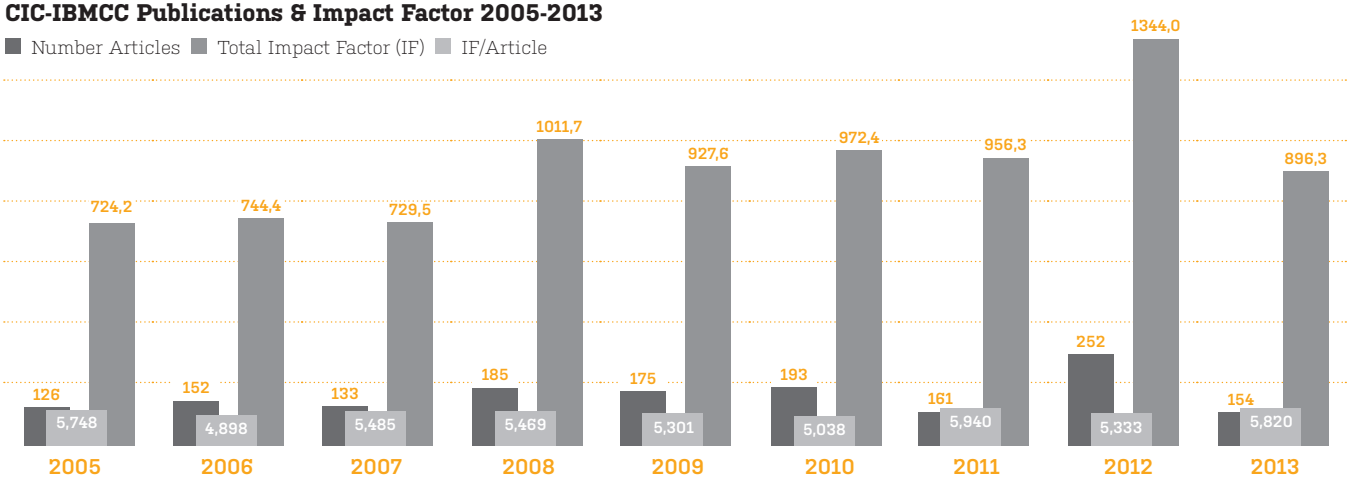


Distribution by institutions 2005-2013



During 2012 and 2013 the CIC-IBMCC scientists published more than **405 original scientific articles** covering different aspects of the cancer field in over 175 indexed journals, most of which (>70%) rank in the Q1 (first quartile) Category of their cancer scientific specialty. The production for the years 2012-2013 represents a growth of more than 10% over the average year production measured in our previous multiyear report (2005-2011) and yields a remarkable **average impact factor per publication of 5.53**. A detailed listing of the publications generated by the individual research groups of ours institution is presented in the following pages of this Report. Our production in this period included high quality publications touching different subjects of cancer research such as characterization of various oncogenes and signal transduction pathways, animal models relevant for tumorigenesis, or studies focused on molecular diagnostics or therapy of various solid or hematologic tumors.

CIC-IBMCC Publications & Impact Factor 2005-2013

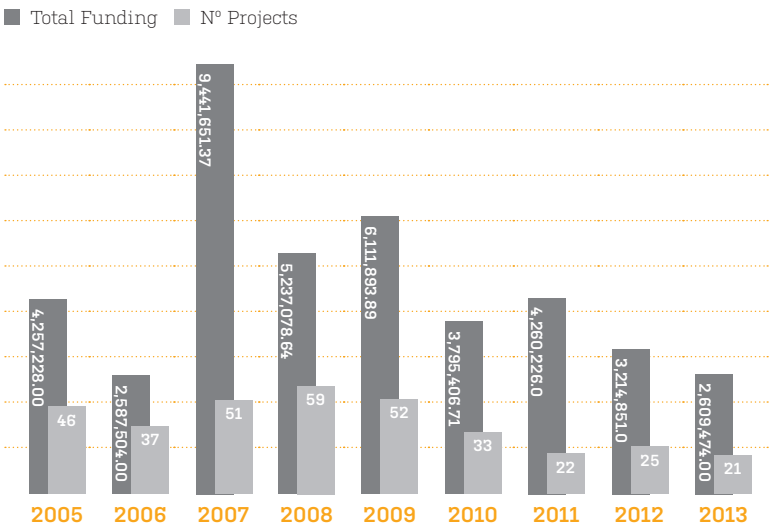


Significant scientific contributions of several individual IPs from the CIC IBMCC were also recognized with prestigious national and international **awards** during this period. In 2012, Dr. Alberto Orfao received the Premio Castilla y León de Investigación Científica y Técnica 2012, and Dr. Atanasio Pandiella and his associates Drs. S. Seoane and J.C Montero received the XIII Premio de Investigación from Fundación Dr. Antonio Esteve. In 2013 Dr. Jesús San Miguel received the Jaime I Award for Medical Research, the Kyle Life achievement Award from the International Myeloma Foundation (IMF), and the Jose Carreras Award from the European Hematology Association-José Carreras Foundation.

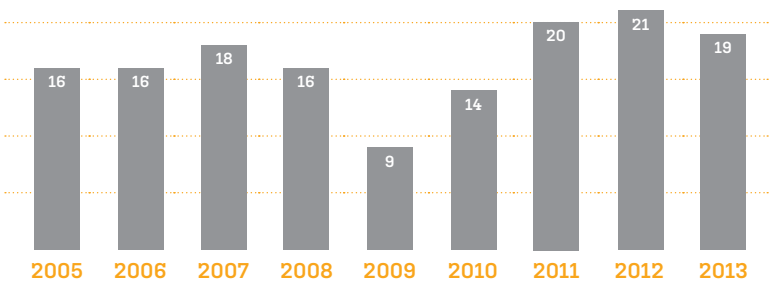
The CIC IBMCC scientists have also developed significant **scientific collaborations** with outside scientists or institutions during this period. Special mention should be made here to the contributions of several CIC-IBMCC groups to the Chronic Lymphocytic Leukemia (CLL) sequencing project in the context of the International Cancer Genome Consortium (ICGC), or the participation of 7 different groups of our Center in the Spanish Cancer Research Network (Red Temática de Investigación Cooperativa en Cáncer (RTICC), which is sponsored by the national Instituto de Salud Carlos III (ISCIII) and coordinated by Dr E. Santos.

During this two-year period, our IPs were also awarded **competitive grant** money for almost 5.9 million euros corresponding to 48 separate research projects. In comparison to previous periods this, in fact, represents a reduction reflecting the major recent cuts in research money available from Spanish granting Agencies. Anyhow, despite the significant cuts in the R+D Spanish research budget, the CIC scientists kept generating intellectual property during this period and registered 7 different patents which are currently at different stages of development in the corresponding patent offices.

CIC-IBMCC Nº Projects and funding 2005-2013



Thesis / year



Only minor changes are worth reporting regarding our building infrastructures during this period. They included the remodeling of our -2 Library in order to provide better accommodation for predoctoral and postdoctoral students and to generate an additional classroom for courses and seminars. A new Cytometry Sorter was added to our Molecular Diagnostic Units and various minor equipment was also incorporated to some Research and Service Units of our building. During 2012-2013 we also received full approval in different audits by various evaluating Agencies monitoring the Quality control processes (ISO 9001) and the Risk Prevention policies (OHSAS 18001) applied in our Service and Support Units.

As an accredited University Institute belonging to the USAL academic community, the CIC IBMCC was also responsible for a variety of **teaching activities** on different cancer areas at the graduate and postgraduate level during 2012-2013. Among others, these activities included a **Master program** on "Biology and Clinics of Cancer" taught in full by our PIs, from which 81 students have graduated in the last three courses. In this period we also started a **PhD program** entitled "Bioscience: Biology and Clinics of Cancer and Translational Medicine" sponsored by the CIC-IBMCC in collaboration with the department of Microbiology& Genetics (School of Biology) and the department of Medicine (School of Medicine) of USAL. Our PhD program is fully compliant with the "European Space for Higher Education" and 91 alumni have participated in it in the last two years since its inception. During 2012-1013, a total **40 Doctoral Theses** (PhD) directed by CIC-IBMC scientists have been presented and successfully defended. Other activities during 2012-2013 included the continuation of our open Cancer Seminar Series program, which involved 77 different national and international speakers. In addition, 8 specialized congresses/symposia were also organized in our institution that involved the participation of more than 50 different speakers and the attendance of more than 500 participants.

Communicating with the outside cancer scientific community at large, and implementing outreaching activities directed to patients, society and the general public are also important goals for an integral, comprehensive cancer research center like ours. With those aims in mind, the CIC-IBMCC established in 2011 the "**Doctores Diz Pintado Award**" in order to recognize yearly the excellence of the most outstanding Spanish cancer researcher younger than 45. The awardees in 2012 and 2013 were, respectively, Dr. Óscar Fernández Capetillo (CNIO, Madrid) and Dr. Eduard Batlle (IRB, Barcelona), two of the most relevant and recognized young cancer scientists at the current Spanish and European cancer scene.

In addition, during this period our Center has also continued its regular outreaching activities to the community by producing several videos and publications geared at cancer prevention and promotion of healthy habits in the general population, as well as by receiving visits to our research laboratories of more than 400 young students (ages 10-14) from various local elementary and high schools from the Salamanca area.

Perhaps the most striking and noticeable events affecting our Center during this two-year period have been the **losses of three of our leading IPs**, who moved recently to other research institutions in our country. Thus, on March 2012 Dr. Sergio Moreno (Lab 10) transferred his research group, working on cell growth, differentiation and cancer, to our sister institution IBFG (CSIC-USAL) in Salamanca. Later, on May 2013, Dr. Enrique de Álava (Lab 20), the IP leading the Molecular Pathology Program and Tumor Bank at the CIC-IBMCC, got a position as Head of the Pathology of Virgen del Rocío Hospital (Sevilla, Spain) and moved his research team to that institution. Finally, on September 2013, Dr. Jesús San Miguel, who for many years directed a highly recognized Oncohematology research team in our Center (Lab 12) and headed the Hematology Service at our neighboring University Hospital, moved to the University of Navarra (Pamplona, Spain) as Director of Clinical and Translational Medicine at their University Clinic, School of Medicine and CIMA institute.

While feeling sadness for their departure, on behalf of all of us remaining at the CIC-IBMCC, here I wish the very best for their future scientific endeavors to Sergio, Enrique and Jesús. I also want to convey to them our deepest, heartfelt gratefulness for their tremendous contributions and dedication during the years they have shared with us at the CIC-IBMCC.

Although the professional and scientific promotion of our three colleagues is a clear indication of the high quality and competitiveness of the CIC-IBMCC researchers, it also entails an enormous loss, with very negative long term implications, for our Center. It is my heartfelt conviction that the **chronic lack of stable budget support from our sponsoring institutions** to cover fixed costs of regular operations at the CIC IBMCC, and our subsequent inability to match the offers of resources

and economic support made by our competing institutions, contributed significantly to our colleagues´ decision to move to other Spanish institutions. We will also be unable to correct the loss of veteran IPs through the **recruitment of new, young independent researchers** because of our lack of funds to offer competitive starting packages to potential, high quality young recruits. To make matters worse, the tremendous **reduction in competitive R+D project calls** made by Spanish granting agencies (attributed to the current economic crisis) has caused an almost 50% reduction in the number of competitive grant awards received by CIC IBMCC investigators during 2012-13 in comparison to previous years. All in all, the protracted budget constraints caused by our lack of institutional support have created a situation of progressive deterioration making it very difficult, and compromising the progression and long-term survival of the CIC IBMCC as a competitive cancer research center.

The main challenge facing the CIC IBMCC for the near future is **maintaining and improving our past scientific productivity and competitiveness** at the national and international levels. For this purpose it is clear that, in the current situation, we will need a more definite and stable show of **economic support from our sponsoring institutions** in order to compete under equal opportunity conditions with our peers in other national and international in cancer research centers.

I want to conclude this foreword by expressing **the most sincere gratitude and recognition** to the scientific and support staff of our center, whose commitment and hard work made it possible for the CIC IBMCC to achieve its scientific goals and reputation at the national and international level during 2012-2013. Our deep gratitude is also due to our External Scientific Advisory Board that has 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 have helped our center during the past two years. I am convinced that adding up all these internal and external contributions 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 of CIC-IBMCC


CENTRO
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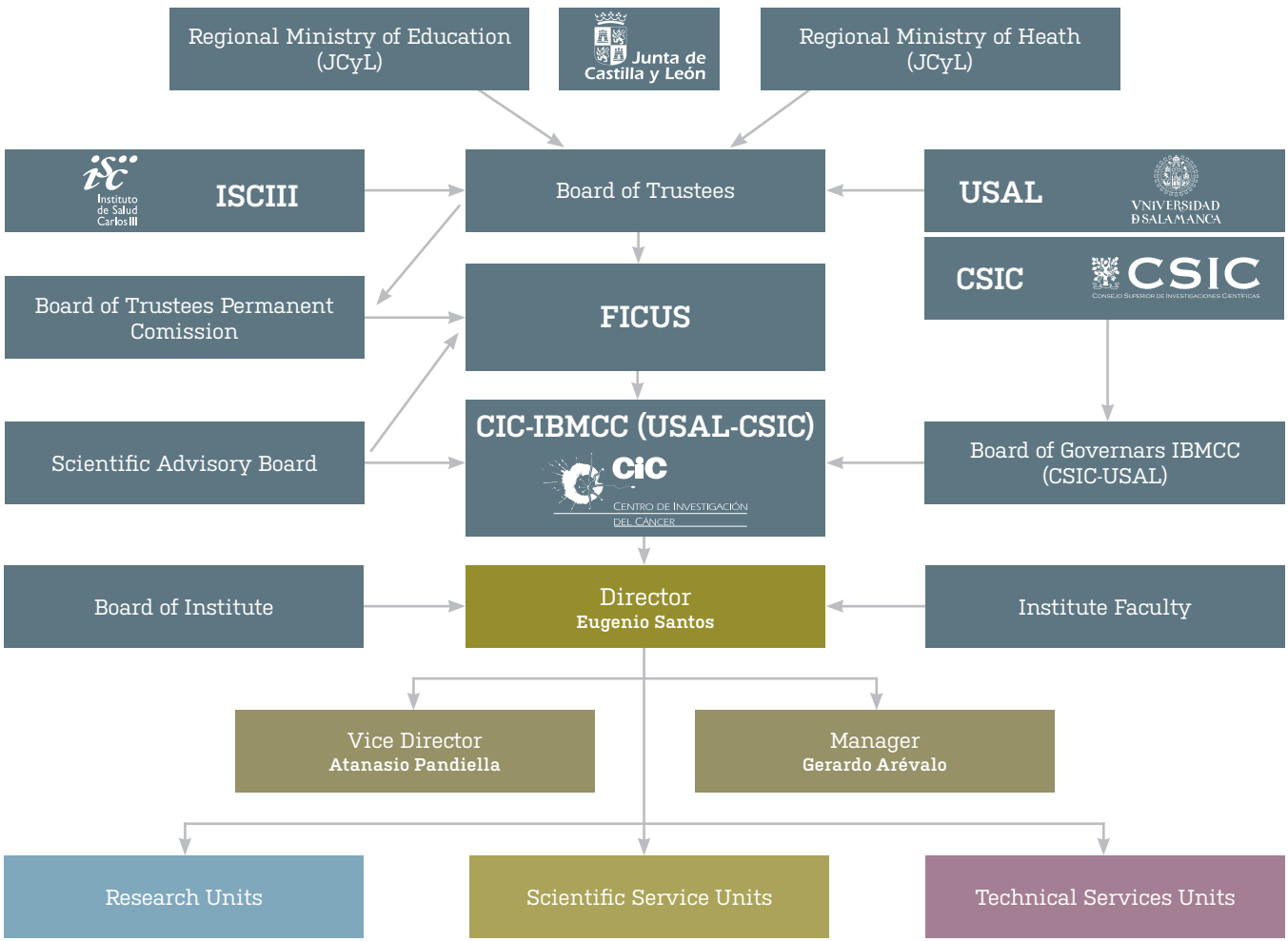
DEL CANCER

2 Organization

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.


Regional Ministry of Education (JCyL)
Junta de Castilla y León
Regional Ministry of Heath (JCyL)
ISCIII
Board of Trustees
USAL
Board of Trustees Permanent Comission
FICUS
CSIC
Scientific Advisory Board
CIC-IBMCC (USAL-CSIC)
Board of Governars IBMCC (CSIC-USAL)
Board of Institute
Director
Eugenio Santos
Institute Faculty
Vice Director
Atanasio Pandiella
Manager
Gerardo Arévalo
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Scientific Service Units
Technical Services Units

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President of the Spanish National Research Council (CSIC)

Members
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Health Counsellor of Castilla y León Government

D. Juan José Mateos Otero
Education Counsellor of Castilla y León Government

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Vice rector for Research of the Salamanca University

D. Ricardo López Fernández
Vice rector for Economics of the Salamanca University

D. Antonio L. Andreu Périz
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

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Chairman
Dr. Elías Campo Hospital Clinic, Barcelona






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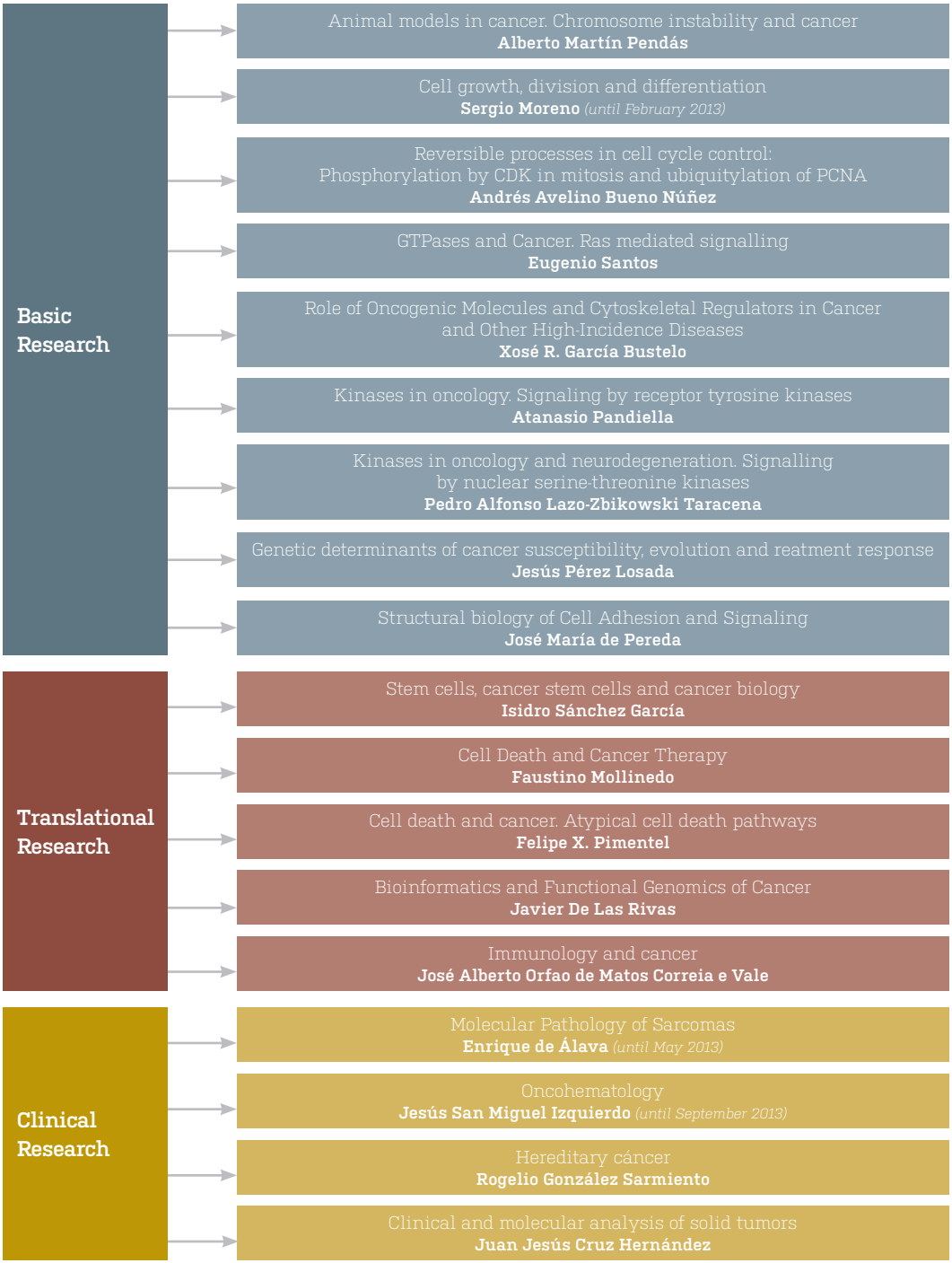
Dr. Juan Bernal Instituto de Investigaciones Biomédicas "Alberto Sols", Madrid
Dr. Carlos López Otín Universidad de Oviedo, Oviedo
Dr. Francisco Sánchez Madrid Hospital Universitario de la Princesa, Madrid
Dr. Julio R. Villanueva Vice president, Consejo Científico de la Fundación Ramón Areces, Madrid
Dr. Eugenio Santos Director, Instituto de Biología Molecular y Celular del Cáncer (IBMCC), Salamanca

Research Units



Scientific Services Units

Genomic Unit
Scientific Coordinator: **Xosé R. García Bustelo**

Proteomic Unit
Scientific Coordinator: **Xosé R. García Bustelo**

Oncopharmacology Traslational Unit
Scientific Coordinator: **Atanasio Pandiella**

Bioinformatics Unit
Scientific Coordinator: **Javier De Las Rivas**

Molecular & Celular Diagnosis Unit
Scientific Coordinators: **Jose Alberto Orfao de Matos Correia e Vale, Jesús María Hernández Rivas y Marcos González Díaz**

Molecular Pathology and Tumor Bank / Comparative Molecular Pathology
Scientific Coordinators: **Enrique de Álava y Carmen García Macías**

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

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

Microscopy Unit
Scientific Coordinators: **Atanasio Pandiella y Alberto Martín Pendás**

Technical Services Units

Management Secretary

Administration

Glassware Cleaning and Sterilization

Equipment & Building Maintenance

Quality Control & Risk Prevention

Central Warehouse & Radiological Protection

Communication & Marketing Unit

Information Technologies Service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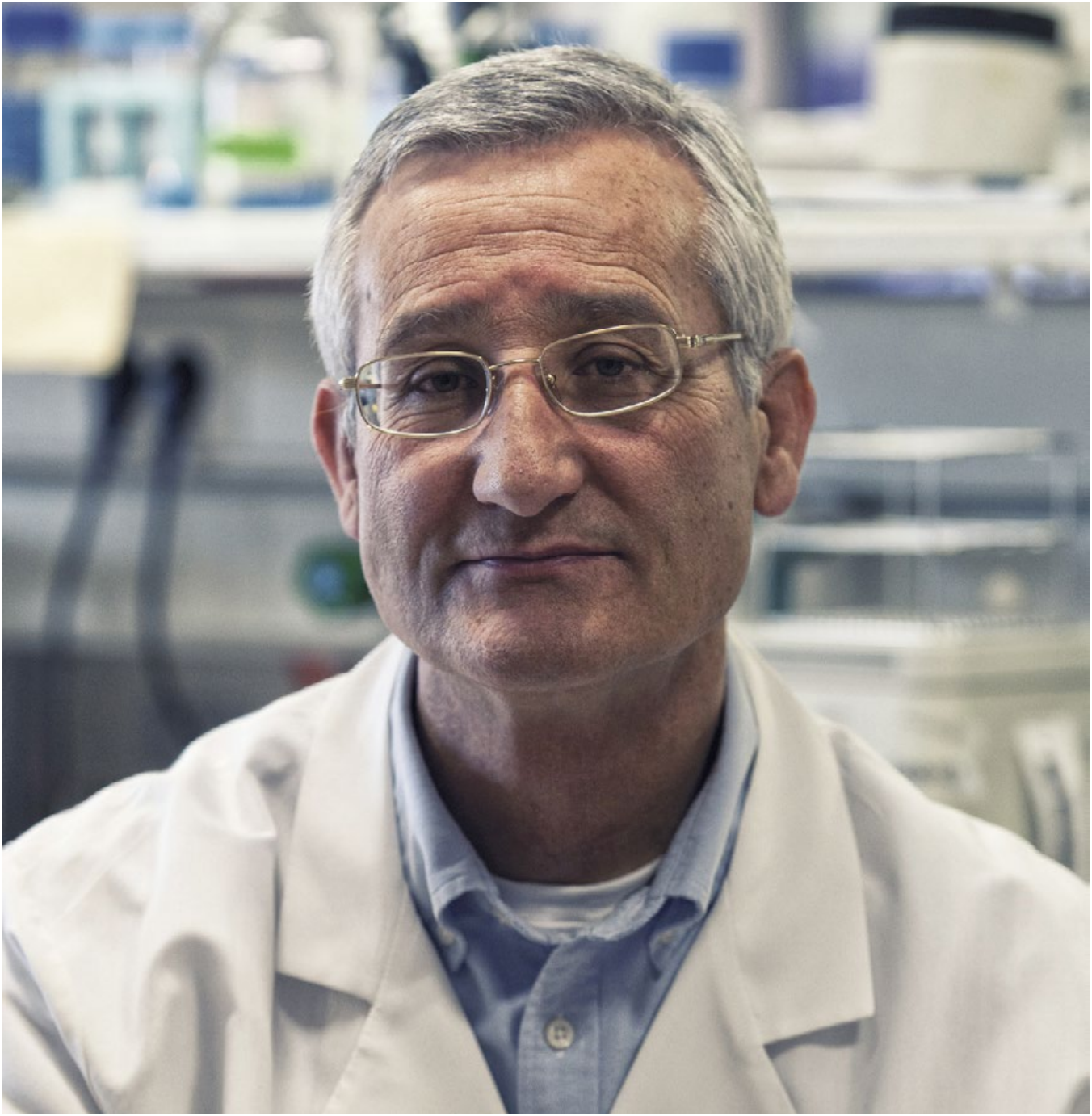
3 Research Units



GTPases and cancer. Ras mediated signalling

Team Leader

Eugenio Santos
Phone.: +34 923 294 801
E-mail: esantos@usal.es

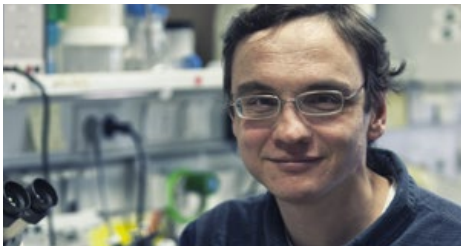
Research Team
Senior Researcher
Alberto Fernández Medarde
Postdoctoral
Fernando Calvo Baltanás
Carmela Gómez Rodríguez
David Jimeno García
Predoctoral
Alicia Ginel Picardo
Lara Manyes Font
Pilar Liceras Boillos
Technicians
Nuria Calzada Nieto
Ximena Marcela Bonilla Fore
María Luz Hernández Mulas

RESEARCH SUMMARY

Our work during this period was focused on genomic/proteomic and functional analyses of knockout mice strains lacking individual ras or GEF genes (H-ras, N-ras, K-ras RasGrf1, RasGrf2, Sos1, Sos2) or combinations thereof. Research was aimed at (i) identifying transcriptomic patterns dependent on each of those individual loci and (ii) determining the functional specificity -or redundancy- of different Ras and Ras-GEF isoforms in various physiological or pathological contexts. The bulk of the experimental evidence thus generated supports the notion of functional specificity for the different Ras and RasGEF isoforms analyzed.

The functional specificity of Ras isoforms was supported by various experimental approaches including: (a) studies on functional analysis of H-Ras and N-Ras in a variety of cellular contexts and/or subcellular locations as well as characterization of specific contributions of H-Ras or N-Ras to a variety of altered renal conditions including fibrosis; (b) analysis of transcriptional networks and functional characterization of constitutive H-ras and N-ras knockout cell lines under conditions of active growth or during early stages of the cell cycle, demonstrating that different Ras isoforms play functionally distinct cellular roles and indicating that N-Ras is significantly involved in immune modulation/host defense and apoptotic responses; (c) characterization of inducible, triple knockout [H-, N-, K-ras] cells, documenting an essential role of K-Ras for progression through the G1/S phase of the cycle.

The study of our single or double knockout mice for RasGrf1 or Rasgrf2 has also shown differential functionality for these RasGEF family members. We demonstrated that RasgGrf1 plays a significant, specific role in control of visual photoreception processes and that RasGrf2 cooperates with Vav proteins in T cell signaling and lymphomagenesis. In addition, recent collaborative studies of GWAS (genome wide association study meta-analysis of directly genotyped or inputted human SNPs) support a role of RasGrf1 in predisposition to myopia and refractive errors of vision and of RasGrf2 in predisposition to alcohol consumption.



Role for Ras guanine nucleotide exchange factors RasGrf1 and RasGrf2 in central nervous system

Alberto Fernández Medarde
Phone.: +34 923 294 801
E-mail: afm@usal.es

RESEARCH SUMMARY

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

Strategic objectives

(i) Involvement of RasGrfs in adult neurogenesis.
(ii) Role for RasGrf1 and RasGrf2 in Alzheimer disease.
(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 Hebp1 and Clasp2 proteins in RasGrf1 mediated signaling at the CNS.
(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) How does RasGrf1 control memory formation?
(b) RasGrf1 and microtubule dynamics in the CNS. Implications in human illness.
(c) Mechanisms underlying the photoreception problems and the changes in the lens parameters of the RasGrf1 KO animals.
(d) Analysis of RasGrf2 role in addiction to alcohol and drugs.
(e) Implication of RasGrf1 and RasGrf2 in neuronal differentiation and adult neurogenesis.

Publications

1 **H-Ras isoform modulates extracellular matrix synthesis, proliferation, and migration in fibroblasts** Fuentes-Calvo I, Blázquez-Medela AM, Eleno N, Santos E, López-Novoa JM, Martínez-Salgado C. ***Am J Physiol Cell Physiol. 2012 Feb 15;302(4):C686-97. doi: 10.1152/ajpcell.00103.2011. Epub 2011 Nov 16.*** PMID: 22094331 **IF: 3,711 /Q1**

2 **The Ras-like protein R-Ras2/TC21 is important for proper mammary gland development** Larive RM, Abad A, Cardaba CM, Hernández T, Cañamero M, de Álava E, Santos E, Alarcón B, Bustelo XR. ***Mol Biol Cell. 2012 Jun;23(12):2373-87. doi: 10.1091/mbc.E12-01-0060. Epub 2012 Apr 25.*** PMID: 22535521 **IF: 4,803 / Q2**

3 **RASGRF2 regulates alcohol-induced reinforcement by influencing mesolimbic dopamine neuron activity and dopamine release** Stacey D, Bilbao A, Maroteaux M, Jia T, Easton AC, Longueville S, Nymberg

C, Banaschewski T, Barker GJ, Büchel C, Carvalho F, Conrod PJ, Desrivières S, Fauth-Bühler M, Fernandez-Medarde A, Flor H, Gallinat J, Garavan H, Bokde AL, Heinz A, Ittermann B, Lathrop M, Lawrence C, Loth E, Lourdusamy A, Mann KF, Martinot JL, Nees F, Palkovits M, Paus T, Pausova Z, Rietschel M, Ruggeri B, Santos E, Smolka MN, Staehlin O, Jarvelin MR, Elliott P, Sommer WH, Mameli M, Müller CP, Spanagel R, Girault JA, Schumann G; IMAGEN Consortium. ***Proc Natl Acad Sci U S A. 2012 Dec 18;109(51):21128-33. doi: 10.1073/pnas.1211844110. Epub 2012 Dec 5.*** PMID: 23223532 **IF: 9,737 / D1**

4 **N-ras couples antigen receptor signaling to Eomesodermin and to functional CD8+ T cell memory but not to effector differentiation** Iborra S, Ramos M, Arana DM, Lázaro S, Aguilar F, Santos E, López D, Fernández-Malavé E, Del Val M. ***J Exp Med. 2013 Jul 1;210(7):1463-79. doi: 10.1084/jem.20112495. Epub 2013 Jun 17.*** PMID: 23776078 **IF: 13,214 / D1**

5 **The small GTPase N-Ras regulates extracellular matrix synthesis, proliferation and migration in fibroblasts** Fuentes-Calvo I, Crespo P, Santos E, López-Novoa JM, Martínez-Salgado C. ***Biochim Biophys Acta. 2013 Dec;1833(12):2734-44. doi: 10.1016/j.bbamcr.2013.07.008. Epub 2013 Jul 18.*** PMID: 23871832 **IF: 4,808/ Q1**

6 **Functional redundancy of Sos1 and Sos2 for lymphopoiesis and organismal homeostasis and survival** Baltanás FC, Pérez-Andrés M, Ginel-Picardo A, Diaz D, Jimeno D, Liceras-Boillos P, Kortum RL, Samelson LE, Orfao A, Santos E. ***Mol Cell Biol. 2013 Nov;33(22):4562-78. doi: 10.1128/MCB.01026-13. Epub 2013 Sep 16.*** PMID: 24043312 **IF: 5,372 / Q1**

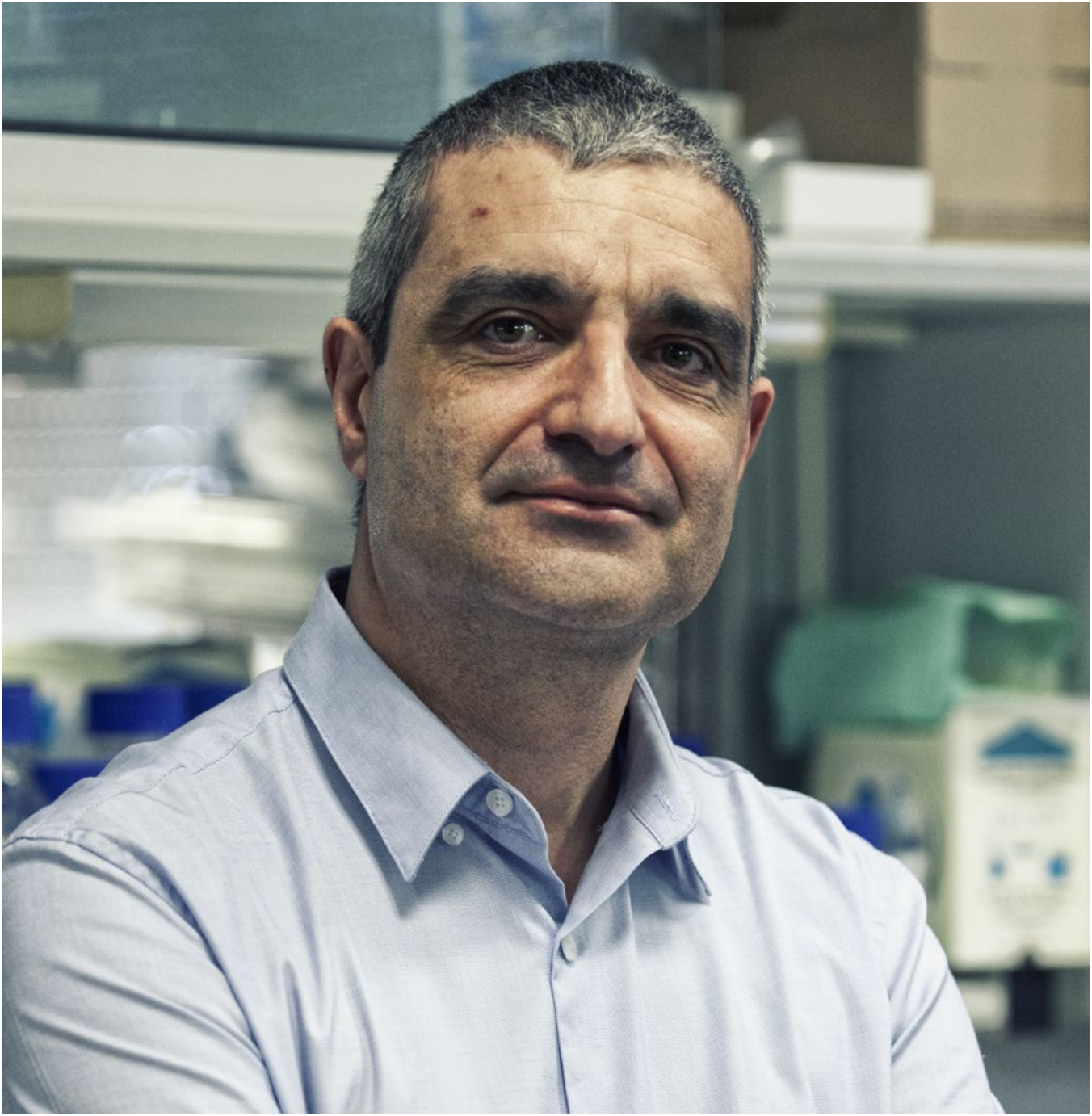
7 **Reversible, interrelated mRNA and miRNA expression patterns in the transcriptome of Rasless fibroblasts: functional and mechanistic implications** Azrak SS, Ginel-Picardo A, Drosten M, Barbacid M, Santos E. ***BMC Genomics. 2013 Oct 25;14:731. doi: 10.1186/1471-2164-14-731.*** PMID: 24156637 **IF: NI**

Other publications & Book chapters

- **RasGrf (RAS Protein-Specific Guanine Nucleotide-Releasing Factor)** Santos E and Fernández-Medarde A. Encyclopedia of Signaling Molecules pp 1605-1612, 2012. DOI 10.1007/978-1-4419-0461-4. Springer Science, New York Heidelberg Dordrecht London.

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Desarrollo y distribución de nuevas tecnologías oncológicas en áreas de diagnóstico y monitorización de la enfermedad	Eugenio Santos	Fundación Marcelino Botín	2005-2012	1,060,000.00 €
Red Temática en Investigación Cooperativa en Cáncer	Eugenio Santos (national coordinator)	Instituto de Salud Carlos III (RD06/0020/0000)	2007-2012	2,161,632.01 €
Mecanismos de especificidad funcional de oncoproteínas RAS y sus activadores celulares específicos GEF en procesos fisiológicos y patológicos	Eugenio Santos	Instituto de Salud Carlos III (PS09/01979)	2010-2013	523,325.00 €
Papel de los activadores de las oncoproteínas Ras: Sos y RasGrf en procesos fisiológicos y su relación con patologías humanas	Alberto Fernández Medarde	Fundación Solórzano	2012	5,500.00 €
Subvención directa Consejería Sanidad a la Fundación de Investigación del Cáncer	Eugenio Santos	Junta de Castilla y León	2012	300,000.00 €
Subvención directa Consejería Educación a la Fundación de Investigación del Cáncer	Eugenio Santos	Junta de Castilla y León	2012	325,000.00 €
Red Temática en Investigación Cooperativa en Cáncer	Eugenio Santos (national coordinator)	Instituto de Salud Carlos III (RD12/0036/0001)	2013	442,343.65 €
Papel de las proteínas Sos en el desarrollo y maduración de linfocitos B y T	Eugenio Santos	Fundación Solorzano. Univ de Salamanca	2013	6,714.00 €
Los ratones KNOCKOUT para RASGRF1 y RASGRF2 como modelos de degeneración retiniana	Eugenio Santos	Fundación Lucha Contra La Ceguera	2013-2014	24,000.00 €
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 €



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

RESEARCH SUMMARY

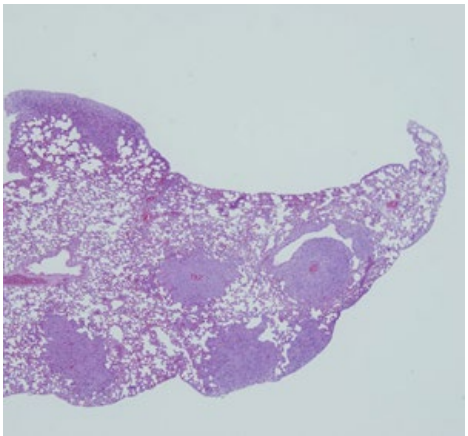
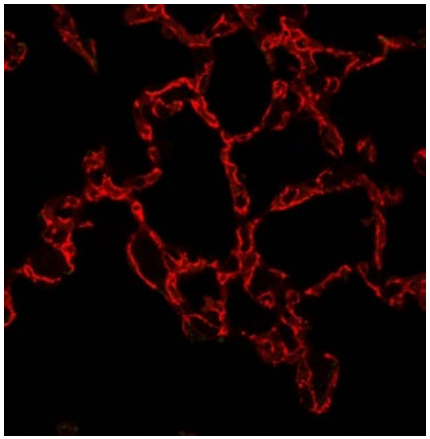
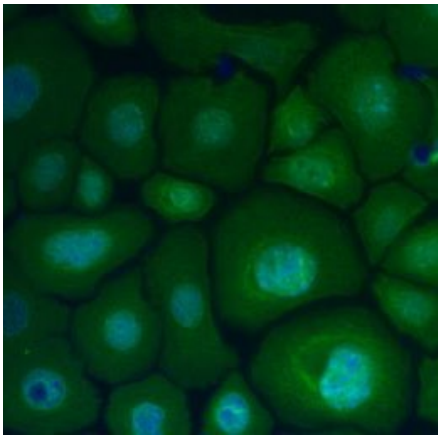
Our research is focused on the functional characterization of signal transduction molecules with oncogenic potential and, particularly, on the functional analysis of oncoproteins specialized in connecting the stimulation of membrane receptors with signaling routes that lead to both cytoskeletal change and mitogenic processes. Within this general objetive, 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 intracellular positive and negative regulators of Rho/Rac GTPases.
(4) Study of the cross-talk between cytoskeletal routes and other biological processes.
(5) 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.

Team Leader

Xosé R. Bustelo
Phone.: +34 923 294 802
E-mail: xbustelo@usal.es

Research Team
Senior Researcher
Mercedes Dosil Castro
Postdoctoral
Clara Moyano Cardaba
Romain M. Larive
Mauricio A. Menacho-Márquez
Javier Robles Valero
Ana Belén Rodríguez de la Peña
Mª Isabel Fernández Pisonero
Myriam Cuadrado López
Predoctoral
María Barreira
Salvatore Fabbiano
Virginia Ojeda Seijas
Guilia Moriggi
Blanca Nieto Bernáldez
Technicians
Antonio Luis Abad
María Teresa Blázquez
Fellow initiation AECC
Francisco Lorenzo Martín
Fellow initiation CSIC
Sonia Rodríguez-Fernández

(6) Characterization of the role of these signal transduction pathways in other high incidence health problems such as cardiovascular disease and the metabolic syndrome.
(7) Development of new therapeutic avenues to treat those diseases using molecular targets belonging to those signaling routes.

To achieve these aims, our laboratory utilizes a quite diverse collection of experimental tools, including biochemical analysis (i.e., determination of enzyme activities, post-translational modifications, protein-protein interactions), structural biology (i.e., determination of the three-dimensional structure of proteins), cell biology, cell signaling (i.e., characterization of the signaling routes used by the oncoproteins under study) transgenic and knockout mice, genetic models available in invertebrate species (Drosophila, yeast) as well as genomics, proteomics, and cellomics techniques.

Ribosome synthesis and cell growth

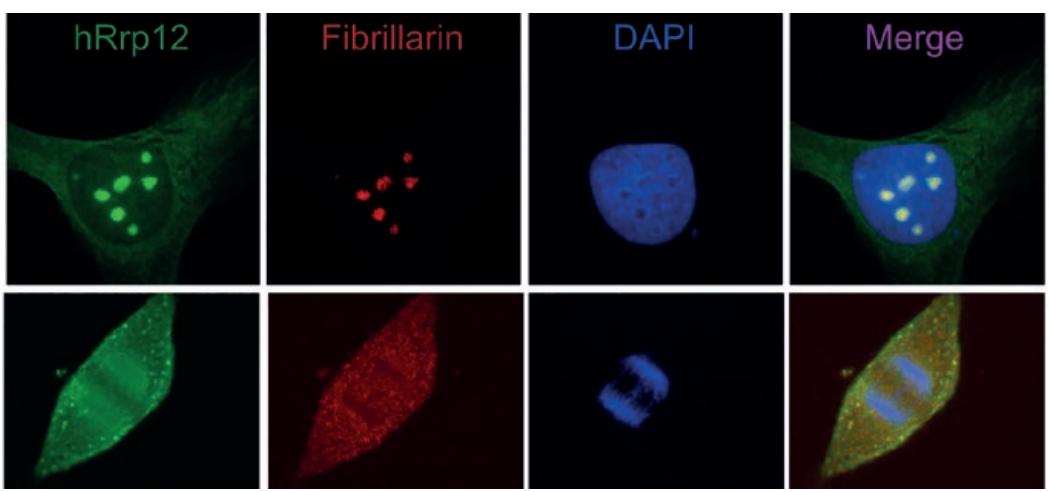
Mercedes Dosil
Phone.: +34 923 294 803
E-mail: mdosil@usal.es

RESEARCH SUMMARY

It is currently known that some alterations in ribosome production or function lead to cellular transformation or cancer susceptibility. The focus of our laboratory is to provide molecular detail to the ribosome synthesis pathway. This will contribute to get the basic knowledge required to understand the relationship between ribosome biogenesis and cancer. The current challenge in the field is to unveil the molecular functions and mode of regulation of the many factors (>200) implicated in the formation of ribosomes. We specifically aim at characterizing two types of factors: the ones that drive the initial steps of ribosome assembly, and the ones that integrate ribosome synthesis with other cellular processes. Such aims require multifaceted strategies that combine proteomic techniques, biochemical assays and genetic studies. Previous contributions of the group include the elucidation of assembly events during early pre-ribosome formation, and the identification of ribosome synthesis factors that influence cell cycle progression.

Lines of research

(1) Functional characterization of proteins that initiate ribosome formation.
(2) Identification and functional analysis of factors that coordinate ribosome synthesis and cell-cycle related processes.



Localization of two ribosome synthesis factors during mitosis in human cervical cancer cells.

Publications

1 **Reduction of NADPH-oxidase activity ameliorates the cardiovascular phenotype in a mouse model of Williams-Beuren Syndrome** Campuzano V, Segura-Puimedon M, Terrado V, Sánchez-Rodríguez C, Coustets M, Menacho-Márquez M, Nevado J, Bustelo XR, Francke U, Pérez-Jurado LA. ***PLoS Genet. 2012 Feb;8(2):e1002458. doi: 10.1371/journal.pgen.1002458. Epub 2012 Feb 2.*** PMID: 22319452 **IF: 8,517 / D1**

2 **The Ras-like protein R-Ras2/TC21 is important for proper mammary gland development.** Larive RM, Abad A, Cardaba CM, Hernández T, Cañamero M, de Álava E, Santos E, Alarcón B, Bustelo XR. ***Mol Biol Cell. 2012 Jun;23(12):2373-87. doi: 10.1091/mbc.E12-01-0060. Epub 2012 Apr 25.*** PMID: 22535521 **IF: 4,803 / Q2**

3 **Vav3 collaborates with p190-BCR-ABL in lymphoid progenitor leukemogenesis, proliferation, and survival.** Chang KH, Sanchez-Aguilera A, Shen S, Sengupta A, Madhu MN, Ficker AM, Dunn SK, Kuenzi AM, Arnett JL, Santho RA, Agirre X, Perentesis JP, Deininger MW, Zheng Y, Bustelo XR, Williams DA, Cancelas JA. ***Blood. 2012 Jul 26;120(4):800-11. doi: 10.1182/blood-2011-06-361709. Epub 2012 Jun 12.*** PMID: 22692505 **IF: 9,06 / D1**

4 **Intratumoral stages of metastatic cells: a synthesis of ontogeny, Rho/Rac GTPases, epithelial-mesenchymal transitions, and more.** Bustelo XR. ***Bioessays. 2012 Sep;34(9):748-59. doi: 10.1002/bies.201200041. Epub 2012 Jun 18. Review.*** PMID: 22706877 **IF: 5,423 / Q1**

5 **Rac-ing to the plasma membrane: the long and complex work commute of Rac1 during cell signaling.** Bustelo XR, Ojeda V, Barreira M, Sauzeau V, Castro-Castro A. ***Small GTPases. 2012 Jan-Mar;3(1):60-6. doi: 10.4161/sgtp.19111.*** PMID: 22714419 **IF: NI**

6 **Expression of VAV1 in the tumour microenvironment of glioblastoma multiforme.** Garcia JL, Couceiro J, Gomez-Moreta JA, Gonzalez Valero JM, Briz AS, Sauzeau V, Lumbreras E, Delgado M, Robledo C, Almunia ML, Bustelo XR, Hernandez JM. ***J Neurooncol. 2012 Oct;110(1):69-77. doi: 10.1007/s11060-012-0936-y. Epub 2012 Aug 4.*** PMID: 22864683 **IF: 3,115 / Q2**

7 **The rho exchange factors vav2 and vav3 control a lung metastasis-specific transcriptional program in breast cancer cells.** Citterio C, Menacho-Márquez M, García-Escudero R, Larive RM, Barreiro O, Sánchez-Madrid F, Paramio JM, Bustelo XR. ***Sci Signal. 2012 Oct 2;5(244):ra71. doi: 10.1126/scisignal.2002962.*** PMID: 23033540 **IF: 7,648 / D1**

8 **Role of Src homology domain binding in signaling complexes assembled by the murid herpesvirus M2 protein.** Pires de Miranda M, Lopes FB, McVey CE, Bustelo XR, Simas JP. ***J Biol Chem. 2013 Feb 8;288(6):3858-70. doi: 10.1074/jbc.M112.439810. Epub 2012 Dec 20.*** PMID: 23258536 **IF: 4,651 / Q1**

9 **The dioxin receptor has tumor suppressor activity in melanoma growth and metastasis.** Contador-Troca M, Alvarez-Barrientos A, Barrasa E, Rico-Leo EM, Catalina-Fernández I, Menacho-Márquez M, Bustelo XR, García-Borrón JC, Gómez-Durán A, Sáenz-Santamaría J, Fernández-Salguero PM. ***Carcinogenesis. 2013 Dec;34(12):2683-93. doi: 10.1093/carcin/bgt248. Epub 2013 Jul 10.*** PMID: 23843039 **IF: 5,635 / Q1**

10 **Chronic sympathoexcitation through loss of Vav3, a Rac1 activator, results in divergent effects on metabolic syndrome and obesity depending on diet.** Menacho-Márquez M, Nogueiras R, Fabbiano S, Sauzeau V, Al-Massadi O, Diéguez C, Bustelo XR. ***Cell Metab. 2013 Aug 6;18(2):199-211. doi: 10.1016/j.cmet.2013.07.001.*** PMID: 23931752 **IF: 14,619 / D1**

11 **The Rho exchange factors Vav2 and Vav3 favor skin tumor initiation and promotion by engaging extracellular signaling loops.** Menacho-Márquez M, García-Escudero R, Ojeda V, Abad A, Delgado P, Costa C, Ruiz S, Alarcón B, Paramio JM, Bustelo XR. ***PLoS Biol. 2013 Jul;11(7):e1001615. doi: 10.1371/journal.pbio.1001615. Epub 2013 Jul 23.*** PMID: 23935450 **IF: 12,96 / D1**

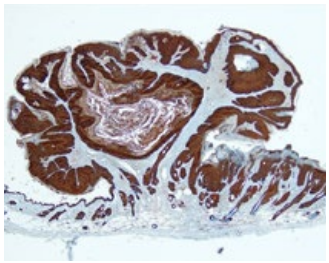
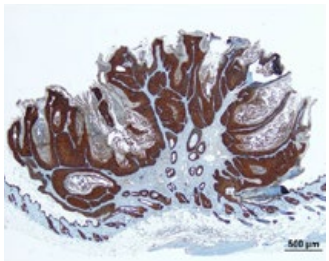
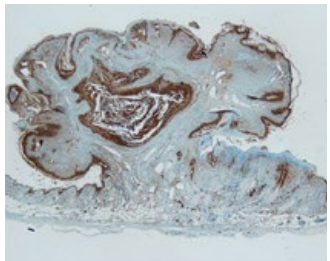
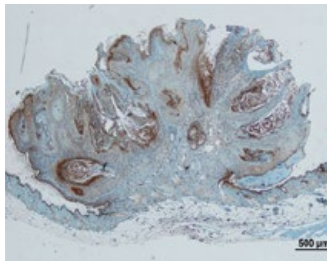
Other publications & Book chapters

- **Vav family** Bustelo, X.R. Encyclopedia of Signaling Molecules S. Choi (Editor). Part 23 pp 1963-1976, 2012. DOI: 10.1007/978-1-4419-0461-4_513 Springer Science, New York Heidelberg Dordrecht London.

Other activities & Relevant facts

Editorial Boards in Scientific Journals:
Front. Immunol.
Small GTPases
Encyclopedia of Signaling Molecules

Miembro de Comités Científicos:
Scientific Committee of the area of Oncology of the University Hospital Complex of Santiago de Compostela
External Scientific Committee of the Galician Network of Research on Colorectal Cancer (Galicia, Spain)
External Scientific Committee of the Institute for Research and Training Marqués de Valdecilla (Santander)
External Scientific Committee of the Institute for Research and Training Marqués de Valdecilla (Santander)

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
ProteoRed: plataforma tecnológica para análisis proteómicos	Xosé R. Bustelo. (Leader node and co-principal investigator of the coordinated project)	Fundación Genoma-España	2005-2013	550,000.00 €
Red Temática en Investigación Cooperativa en Cáncer	Xosé R. Bustelo	Instituto de Salud Carlos III (RD06/0020/0001)	2007-2012	1,021,000.00 €
Importancia de la GTPasa oncogénica TC21 en procesos tumorigénicos	Xosé R. Bustelo	Asociación Española contra el Cáncer	2009-2014	1,200,000.00 €
Oncoproteínas de la familia Vav: regulación, señalización y participación en patologías humanas	Xosé R. Bustelo	Ministerio de Ciencia e Innovación (SAF2009-07172)	2010-2012	571,120.00 €
Importancia de la GTPasa oncogénica TC21 en cáncer de mama	Xosé R. Bustelo	Consejería de Educación de la Junta de Castilla y León (CSI039A12-1)	2012	30,000.00 €
Funciones moleculares de factores de biogénesis de ribosomas	Mercedes Dosil	Ministerio de Ciencia e Innovación (BFU2011-23668)	2012-2014	113,740.00 €
Red Temática en Investigación Cooperativa en Cáncer	Xosé R. Bustelo	Grant Instituto de Salud Carlos III (RD12/0036/0002)	2013	92,575.00 €
Oncoproteínas de la familia VAV: nuevos avances sobre su regulación, señalización y valor potencial como dianas terapéuticas en enfermedades de alta incidencia	Xosé R. Bustelo	Ministerio de Economía y Competitividad (SAF2012-31371)	2013-2016	468,000.00 €

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

Team Leader:

Pedro Alfonso Lazo-Zbikowski Taracena
Phone.: +34 923 294 804
E-mail: plazozbi@usal.es

Research Team
Postdoctoral
Alberto Valbuena González
Marcela Salzano
Predoctoral
Lara Cantarero Abad
Isabel Fernández Fernández
Diana Monsalve Carmona
Marta Vázquez Cedeira
David da Silva Moura
Technician
Virginia Gascón Galán
Students
Ignacio Campillo Marcos
Ana Clara de Tomaso Portaz
Elena Martín Doncel

RESEARCH SUMMARY

Description

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. The group is focused on the human VRK family of the kinome studying its implications in different phenotypes in relation with oncology in the context of DNA damage and neurodegeneration. These kinases regulate asymmetric division of stem cells and chromatin structure.

Main aim

Determine the steps that constitute the novel signaling pathways where human VRK proteins participate in biological processes associated to DNA damage response in the context of cancer and neurodegenerative syndromes and also its role in asymmetric division of stem cells.

Specific aims

1 Identify upstream elements for each VRK protein, which are likely to be either a part of the pathway or a regulatory element.
2 Identify downstream elements of VRK proteins. This are likely to be intracellular substrates proteins of the kinases, but may also be interacting proteins.
3 Determine how VRK proteins are regulated in response to specific stimulation. This regulation may be covalent modifications of the protein, or alternatively represent regulation of gene expression.
4 Study the role of VRK proteins in the context of cell response to genetic damage either natural (estres oxidative, luz 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.

Publications

1 **Vaccinia-related kinase 1 (VRK1) is an upstream nucleosomal kinase required for the assembly of 53BP1 foci in response to ionizing radiation-induced DNA damage.** Sanz-García M, Monsalve DM, Sevilla A, Lazo PA. ***J Biol Chem. 2012 Jul 6;287(28):23757-68. doi: 10.1074/jbc.M112.353102. Epub 2012 May 22.*** PMID: 22621922 **IF:4,651 / Q1**

2 **VRK2 anchors KSR1-MEK1 to endoplasmic reticulum forming a macromolecular complex that compartmentalizes MAPK signaling.** Fernández IF, Pérez-Rivas LG, Blanco S, Castillo-Dominguez AA, Lozano J, Lazo PA. ***Cell Mol Life Sci. 2012 Nov;69(22):3881-93. doi: 10.1007/s00018-012-1056-8. Epub 2012 Jul 4.*** PMID: 22752157 **IF: 5,615 / Q1**

3 **Guidelines for the use and interpretation of assays for monitoring autophagy.** Klionsky DJ, Abdalla FC, Abeliovich H, Abraham RT, several authors, Lazo PA, López-Otín C, Mollinedo F, Moscat J, several authors. ***Autophagy. 2012 Apr;8(4):445-544.*** PMID: 22966490 **IF: 12,042 / D1**

4 **Human VRK2 (vaccinia-related kinase 2) modulates tumor cell invasion by hyperactivation of NFAT1 and expression of cyclooxygenase-2.** Vázquez-Cedeira M, Lazo PA. ***J Biol Chem. 2012 Dec 14;287(51):42739-50. doi: 10.1074/jbc.M112.404285. Epub 2012 Oct 26.*** PMID: 23105117 **IF: 4,651/ Q1**

5 **Human VRK2 modulates apoptosis by interaction with Bcl-xL and regulation of BAX gene expression.** Monsalve DM, Merced T, Fernández IF, Blanco S, Vázquez-Cedeira M, Lazo PA. ***Cell Death Dis. 2013 Feb 28;4:e513. doi: 10.1038/cddis.2013.40.*** PMID: 23449449 **IF: 6,044 / Q1**

6 **Sensitivity of the kinase activity of human vaccinia-related kinase proteins to toxic metals.** Barcia-Sanjurjo I, Vázquez-Cedeira M, Barcia R, Lazo PA. ***J Biol Inorg Chem. 2013 Apr;18(4):473-82. doi: 10.1007/s00775-013-0992-6. Epub 2013 Mar 13.*** PMID: 23483238 **IF: 3,353 / Q1**

7 **Gene amplification of the histone methyltransferase SETDB1 contributes to human lung tumorigenesis.** Rodriguez-Paredes M, Martinez de Paz A, Simó-Riudalbas L, Sayols S, Moutinho C, Moran S, Villanueva A, Vázquez-Cedeira M, Lazo PA, Carneiro F, Moura CS, Vieira J, Teixeira MR, Esteller M. Oncogene. ***2013 Jun 17. doi: 10.1038/onc.2013.239.*** PMID: 23770855 **IF: 7,357 / Q1**

8 **Human JC polyomavirus in normal colorectal mucosa, hyperplastic polyps, sporadic adenomas, and adenocarcinomas in Portugal.** Coelho TR, Gaspar R, Figueiredo P, Mendonça C, Lazo PA, Almeida L. ***J Med Virol. 2013 Dec;85(12):2119-27. doi: 10.1002/jmv.23705. Epub 2013 Sep 5.*** PMID: 24009184 **IF: 2,373 / Q3**

9 **VRK2 identifies a subgroup of primary high-grade astrocytomas with a better prognosis.** Rodríguez-Hernández I, Vázquez-Cedeira M, Santos-Briz A, García JL, Fernández IF, Gómez-Moreta JA, Martin-Vallejo J, González-Sarmiento R, Lazo PA. ***BMC Clin Pathol. 2013 Oct 1;13(1):23. doi: 10.1186/1472-6890-13-23.*** PMID: 24079673 **IF: NI**

Other publications & Book chapters

- **Scaffold Proteins** Lazo P.A., Lozano J. (2012). In: Encyclopedia of Cancer: SpringerReference. Schwab M. (Ed.) Springer-Verlag Berlin, Heidelberg, 2012. ISBN: 978-3-642-16482-8. DOI: 10.1007/SpringerReference_176820. http://www.springerreference.com/docs/html/chapterdbid/176820.html

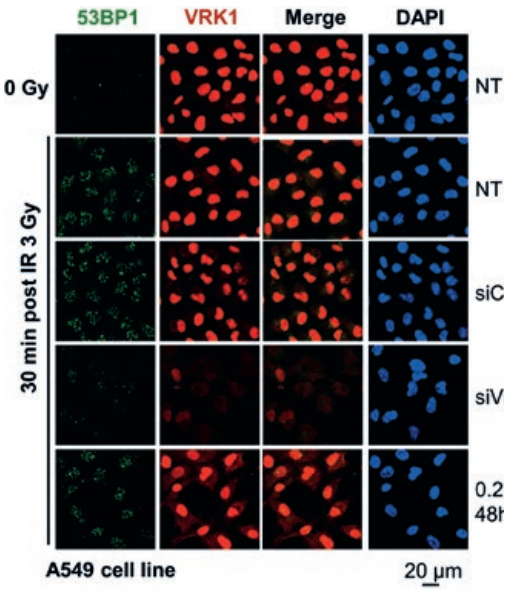
- **VRK1: vaccinia-related kinase 1** Valbuena, A., Sanz-García, M., López-Sánchez, I, Vega, F. M., Sevilla, A. & Lazo, P.A. (2012) " Encyclopedia of Signalling Molecules. Choi, S. (ed.) Springer-Verlag. ISBN: 978-1-4419-0461-4. pp : 1992-1996.

- **VRK2: vaccinia-related kinase 2** Blanco, S., Fernández, I.F., Vázquez-Cedeira, M., Monsalve, D. M. & Lazo, P. A. (2012) Encyclopedia of Signalling Molecules. Choi, S. (Ed.). Springer-Verlag. ISBN: 978-1-4419-0461-4. Pp : 1996-2000.

  VRK3: vaccinia-related kinase 3 Vázquez-Cedeira, M., Monsalve, D. M. & and Lazo, P.A. (2012). Encyclopedia of Signalling Molecules. Choi, S. (Ed.). Springer-Verlag. ISBN: 978-1-4419-0461-4. pp: 1955-1957.

- **Tetraspanin CD53** Lazo, P.A. & Barcia, R. (2012). Encyclopedia of Signalling Molecules. Choi, S. (Ed.). Springer-Verlag. ISBN: 978-1-4419-0461-4. Pp: 343-347.

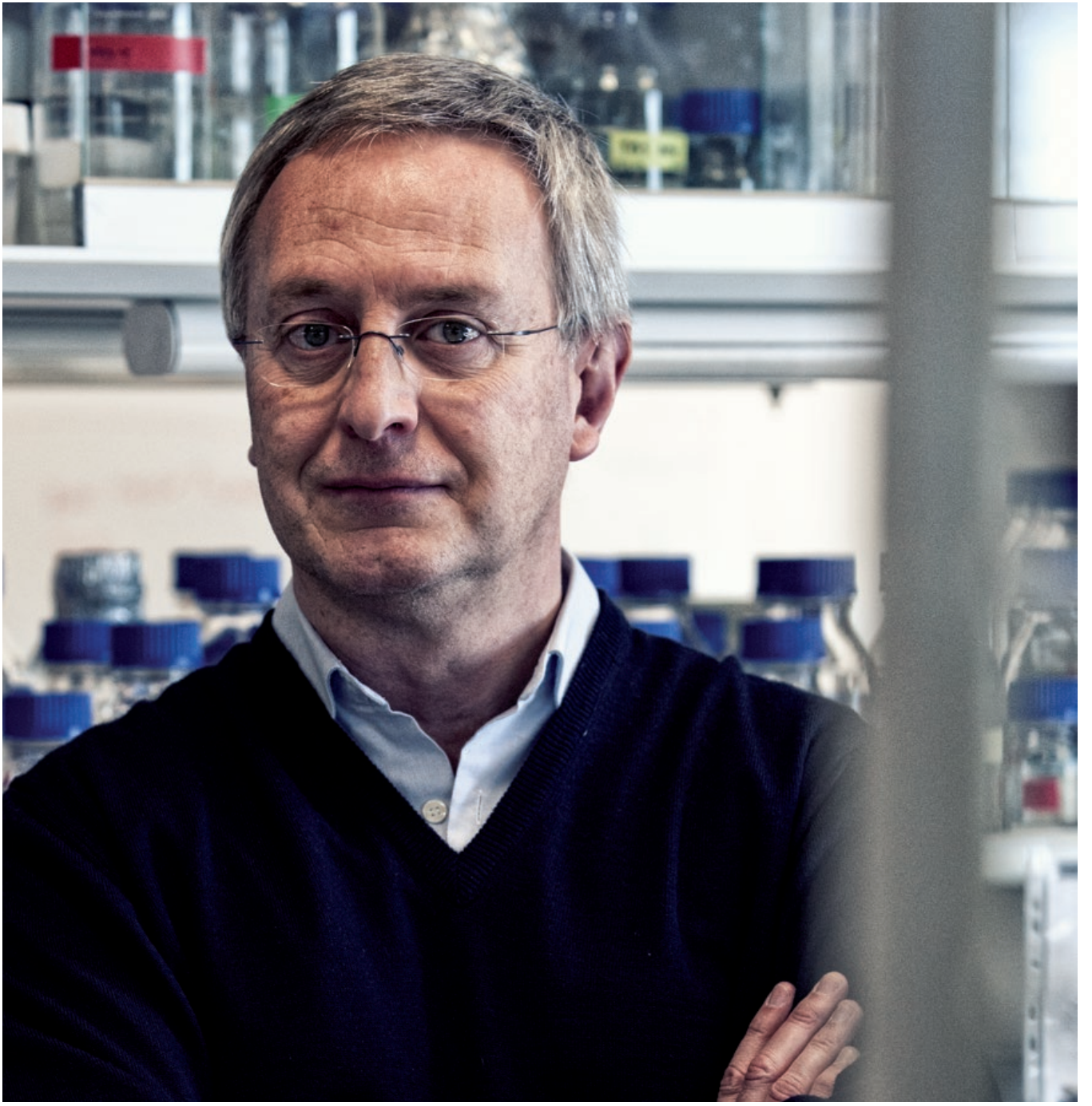
- **VRK2 (Vaccinia-Related Kinase 2)** Vázquez-Cedeira, M., Blanco, S., Fernández, I. F., Monsalve, D. M. & Lazo, P. A. (2012). Atlas Genet. Cytogenet. Oncol. Haematol. 16: 841-843. DOI : 10.4267/2042/48233.



VRK1 kock-down prevents formation of 53BP1 DNA-repair foci in response to DNA double-strand breaks induced by ionizing radiation.

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Biología del Cáncer	Pedro A. Lazo-Zbikowski Taracena	Ministerio de Ciencia y Tecnología CSD2007-00017(Programa Consolider Oncostem)	2007-2012	528,000.00 €
Caracterización de la ruta de señalización por quinasas VRK humanas y sus funciones en biología celular y tumoral	Pedro A. Lazo-Zbikowski Taracena	Ministerio de Educación y Ciencia (SAF2010-14935)	2011-2013	350,900.00 €
Función de proteínas VRK en cáncer de mama	Pedro A. Lazo-Zbikowski Taracena	Kutxa-Fundación INBIOMED (San Sebastian)	2011-2013	50,000.00 €



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

Team Leader:

Avelino Bueno
Phone.: +34 923 294 805
E-mail: abn@usal.es

Research Team
Senior Researcher
María Sacristán Martín
Predoctoral
Alfonso Gallego-Sánchez
Laura Viñas de la Cruz
Sara Ovejero Merino
Patricia Ayala de la Roca
Vanesa Álvarez Álvarez
Technician
Sonia Andrés Recio
Students
Beatriz Sáenz Narciso
Sara Villa Hernández
Janine Wörthmüller Rodríguez
Laura Ahumada Arranz
Amalia Muñiz Carrillo

RESEARCH SUMMARY

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 different 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 effects 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.

Publications

1 **WEE1 accumulation and deregulation of S-phase proteins mediate MLN4924 potent inhibitory effect on Ewing sarcoma cells** Mackintosh C, García-Domínguez DJ, Ordóñez JL, Ginel-Picardo A, Smith PG, Sacristán MP, de Álava E. ***Oncogene. 2013 Mar 14;32(11):1441-51. doi: 10.1038/onc.2012.153. Epub 2012 May 28.*** PMID: 22641220 **IF: 7,357/Q1**

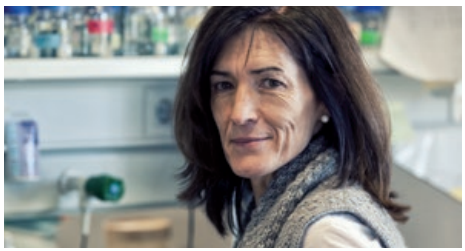
2 **Reversal of PCNA ubiquitylation by Ubp10 in Saccharomyces cerevisiae.** Gallego-Sánchez A, Andrés S, Conde F, San-Segundo PA, Bueno A. ***PLoS Genet. 012;8(7):e1002826. doi: 10.1371/journal.pgen.1002826. Epub 2012 Jul 19.*** PMID: 22829782 **IF: 8,517 / D1**

3 **Human Cdc14A regulates Wee1 stability by counteracting CDK-mediated phosphorylation.** Ovejero S, Ayala P, Bueno A, Sacristán MP. ***Mol Biol Cell. 2012 Dec;23(23):4515-25. doi: 10.1091/mbc.E12-04-0260. Epub 2012 Oct 10.*** PMID: 23051732 **IF: 4,803 / Q2**

4 **Analysis of the tolerance to DNA alkylating damage in MEC1 and RAD53 checkpoint mutants of Saccharomyces cerevisiae.** Gallego-Sánchez A, Ufano S, Andrés S, Bueno A. ***PLoS One. 2013 Nov 19;8(11):e81108. doi: 10.1371/journal.pone.0081108. eCollection 2013.*** PMID: 24260543 **IF: 3,730 / Q1**

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Mecanismos de regulación de la respuesta a estrés replicativo en levaduras (BFU2009-06938)	Avelino Bueno	Ministerio de Ciencia e Innovación (BFU2009-06938)	2010-2012	242,000.00 €
Estudio de procesos reversibles en el control del ciclo celular: fosforilación por CDK en mitosis y ubiquitina de PCNA	María Sacristán	Fundación Solórzano	2013	6,000.00 €
Estudio de procesos reversibles en el control del ciclo celular: fosforilación por CDK en mitosis y ubiquitina de PCNA	Avelino Bueno	Ministerio de Economía y Competitividad (BFU2012-30787)	2013-2016	196,560.00 €

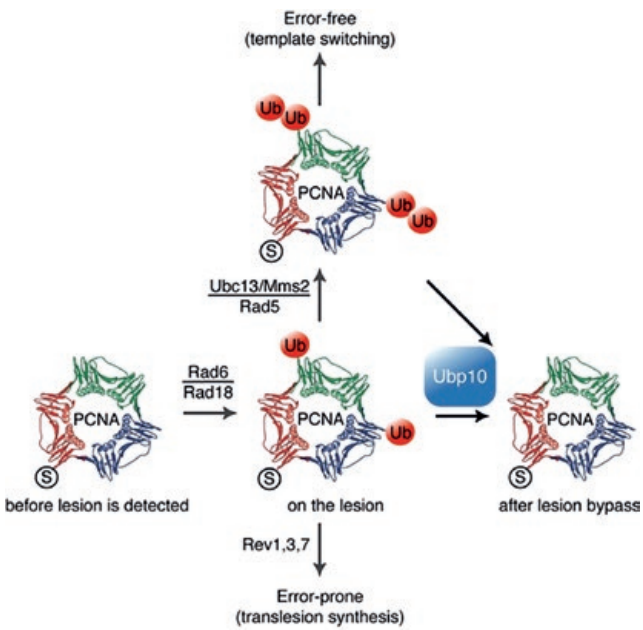


Reversible phosphorylation processes in cell cycle control: role of Cdc14 protein phosphatases

María Sacristán Martín
Phone.: +34 923 294 805
E-mail: msacristan@usal.es

RESEARCH SUMMARY

The process of cell division is complex and involves multiple independent regulatory steps, most of which are controlled by reversible phosphorylation. 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 effects and allow the cell exiting mitosis. The Cdc14 phosphatase is essential for most of these processes in the budding yeast Saccharomyces cerevisiae. 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.



Model for ubiquitin proteases role on the control of PCNA ubiquitylation in *S.cerevisiae* yeast cells. SUMOylated PCNA progress with the replisome at replication forks. Detection of bulky lesions on DNA stall replication fork progression and induces Rad6/Rad18 ubiquitylation of PCNA, thus, enhacing ubPCNA-TLS DNA polymerases interaction or ubPCNA polyubiquitylation. After lesion bypass, an ubiquitin protease, Ubp10, deubiquitylates ubPCNA to switching back to replicative DNA polymerases, resuming rapid and processive DNA replication fork progression.

Our research group studies some aspects of the cell division cycle. Particularly, we are interested on 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 understanding the functions of Cdc14 proteins and to contribute with it to the knowledge of the cellular proliferation mechanisms.


Webster's New
Encyclopedic Dictionary

Cell death and cancer therapy

RESEARCH SUMMARY

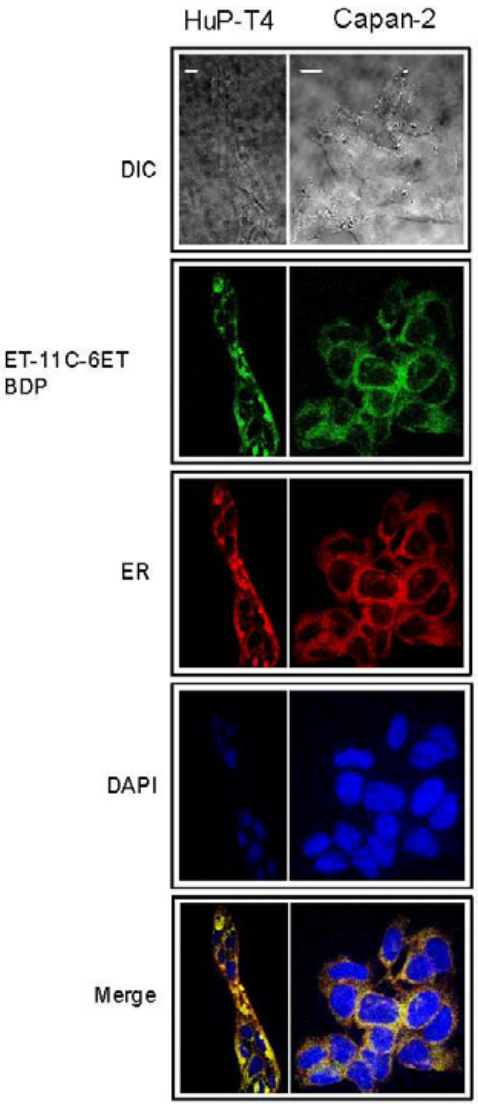
Description

One of the major hallmarks of a 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, and apoptosis-targeted therapy can be a new way to kill tumor cells. We have found that death receptors as well as downstream signaling molecules are recruited into lipid raft membrane domains upon the 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 of additional proteins involved in dictating the 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 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

Team Leader:

Faustino Mollinedo García
Phone.: +34 923 294 806
E-mail: fmollin@usal.es

Research Team
Senior Researcher
María Consuelo Gajate Fraile
Postdoctoral
EL Habib Dakir
Adolfo Sánchez Blanco
Predoctoral
Álvaro Cuesta Marbán
Mariana Reis Sobreiro
Verónica Alonso Pérez
Sara Lima Tavares de Sousa Melo
Reyna Alejandra Jiménez Flores
Rósula García Navas
Students
Ana Catarina Pinho Ferreira Bento
Cynthia Oliveira
Alberto García Rodríguez
Amaya Ortega Pajares
Laurentius Rumokoy
Marta Morte Corvinos
Jorge Mata Garrido
Julia Mayor Pillado
Cristina Mollinedo Gajate
Sara Puente Martín



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.

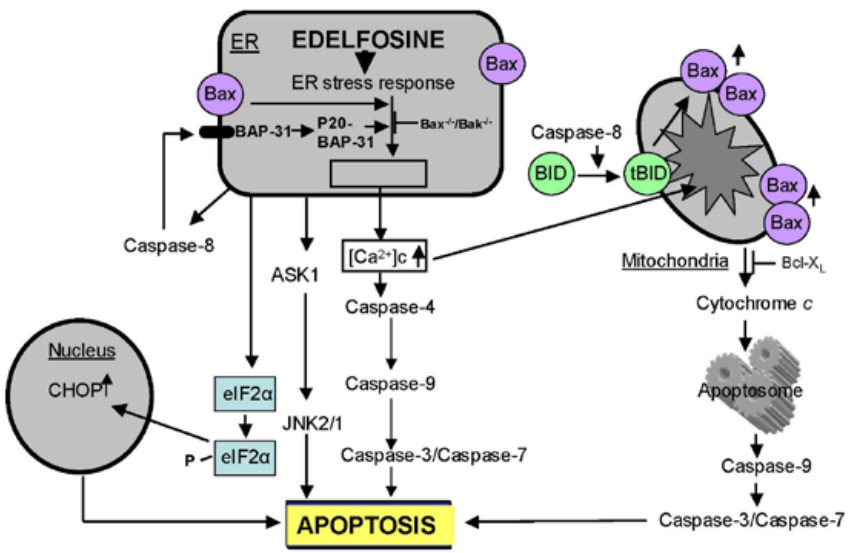
Objectives

- 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.
- 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 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.

The antitumor ether lipid edelfosine (ET-11C-6ET BDP fluorescent analog) accumulates at the endoplasmic reticulum (ER) in edelfosine-treated human pancreatic cancer cell lines HuP-T4 and Capan-2.

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 identifyng 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 postulated the concept of 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, especially the ether phospholipid edelfosine, as anticancer drugs against both hematological and solid tumors. Major interests in our lab 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 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*. 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.



Schematic model of endoplasmic reticulum (ER) involvement in edelfosine-induced apoptosis in pancreatic cancer cells.

Publications

1 **Antitumor alkyl-lysophospholipid analog edelfosine induces apoptosis in pancreatic cancer by targeting endoplasmic reticulum.** Gajate C, Matos-da-Silva M, Dakir el-H, Fonteriz RI, Alvarez J, Mollinedo F. ***Oncogene. 2012 May 24;31(21):2627-39. doi: 10.1038/onc.2011.446. Epub 2011 Nov 7.*** PMID: 22056873 ***Featured article in the Oncogene issue of 24 May 2012 (Oncogene, Volume 31, No. 21).*** **IF: 7,357 / Q1**

2 **In vitro and in vivo efficacy of ether lipid edelfosine against Leishmania spp. and SbV-resistant parasites.** Varela-M RE, Villa-Pulgarin JA, Yepes E, Müller I, Modolell M, Muñoz DL, Robledo SM, Muskus CE, López-Abán J, Muro A, Vélez ID, Mollinedo F. ***PLoS Negl Trop Dis. 2012;6(4):e1612. doi: 10.1371/journal.pntd.0001612. Epub 2012 Apr 10.*** PMID: 22506086 **IF: 4,569 / D1**

3 **Complete inhibition of extranodal dissemination of lymphoma by edelfosine-loaded lipid nanoparticles.** Estella-Hermoso de Mendoza A, Campanero MA, Lana H, Villa-Pulgarin JA, de la Iglesia-Vicente J, Mollinedo F, Blanco-Prieto MJ. ***Nanomedicine (Lond). 2012 May;7(5):679-90. doi: 10.2217/nnm.11.134.*** PMID: 22630151 **IF: 5,26 / D1**

4 **Relationship between arginase activity and the storage time of packed red blood cells.** Palomero Rodríguez MA, García Navas R, Laporta Báez Y, Al Kassam Martínez D, de Vicente Sánchez J, Cacharro Moras LM, Sánchez Conde P, Mollinedo F, Muriel Villoria C. ***Rev Esp Anestesiol Reanim. 2012 Jun;59(6):315-20. doi: 10.1016/j.redar.2012.04.021. Epub 2012 Jun 15. Spanish.*** PMID: 22703829 **IF: NI**

5 **Depletion of L-arginine induces autophagy as a cytoprotective response to endoplasmic reticulum stress in human T lymphocytes.** García-Navas R, Munder M, Mollinedo F. ***Autophagy. 2012 Nov;8(11):1557-76. doi: 10.4161/auto.21315. Epub 2012 Aug 9.*** PMID: 22874569 **IF: 12,042 / D1**

6 **Apoptotic mechanisms are involved in the death of Strongyloides venezuelensis after triggering of nitric oxide.** Ruano AL, López-Abán J, Gajate C, Mollinedo F, De Melo AL, Muro A. ***Parasite Immunol. 2012 Dec;34(12):570-80. doi: 10.1111/pim.12004.*** PMID: 22897441 **IF: 2,208 / Q2**

7 **Guidelines for the use and interpretation of assays for monitoring autophagy.** Klionsky DJ, Abdalla FC, Abeliovich H, Abraham RT, several authors, Lazo PA, López-Otín C, Mollinedo F, Moscat J, several authors. ***Autophagy. 2012 Apr;8(4):445-544.*** PMID: 22966490 **IF: 12,042 / D1**

8 **Saiyacenols A and B: the key to solve the controversy about the configuration of aplysiols.** Cen-Pacheco F, Mollinedo F, Villa-Pulgarin Janny JA, Norte M, Fernandez JJ, Daranas AH. ***Tetrahedron 2012 Sep 9; 68(36):7275-9. doi: 10.1016/j.tet.2012.07.005*** **IF: 2,803 / Q2**

9 **Synthesis of 12-epi-ent-polyalthenol an antitumour indole sesquiterpene alkaloid.** Marcos IS, Moro RF, Costales I, Basabe P, Diez D, Mollinedo F, Urones JG. ***Tetrahedron 2012 Sep 23; 68(38):7932-40. doi: 10.1016/j.tet.2012.07.010*** **IF: 2,803 / Q2**

10 **Lipid raft involvement in yeast cell growth and death.** Mollinedo F. ***Front Oncol. 2012;2:140. doi: 10.3389/fonc.2012.00140. Epub 2012 Oct 10.*** PMID: 23087902 **IF: NI**

11 **Lignopurines: a new family of hybrids between cyclolignans and purines.** Synthesis and biological evaluation. Castro MÁ, Miguel del Corral JM, García PA, Rojo MV, Bento AC, Mollinedo F, Francesch AM, San Feliciano A. ***Eur J Med Chem. 2012 Dec;58:377-89. doi: 10.1016/j.ejmech.2012.10.026. Epub 2012 Oct 26.*** PMID: 23153810 **IF: 3,499 / Q1**

12 **Edelfosine and perifosine disrupt hepatic mitochondrial oxidative phosphorylation and induce the permeability transition.** Burgeiro A, Pereira CV, Carvalho FS, Pereira GC, Mollinedo F, Oliveira PJ. ***Mitochondrion. 2013 Jan;13(1):25-35. doi: 10.1016/j.mito.2012.11.003. Epub 2012 Nov 16.*** PMID: 23164800 **IF: 4,025 / Q2**

13 **Drug uptake, lipid rafts, and vesicle trafficking modulate resistance to an anticancer lysophosphatidylcholine analogue in yeast.** Cuesta-Marbán Á, Botet J, Czyz O, Cacharro LM, Gajate C, Hornillos V, Delgado J, Zhang H, Amat-Guerri F, Acuña AU, McMaster CR, Revuelta JL, Zaremberg V, Mollinedo F. ***J Biol Chem. 2013 Mar 22;288(12):8405-18. doi: 10.1074/jbc.M112.425769. Epub 2013 Jan 18.*** PMID: 23335509 **IF: 4,651/ Q1**

14 **Alteration of plasma membrane organization by an anticancer lysophosphatidylcholine analogue induces intracellular acidification and internalization of plasma membrane transporters in yeast.** Czyz O, Bitew T, Cuesta-Marbán A, McMaster CR, Mollinedo F, Zaremberg V. ***J Biol Chem. 2013 Mar 22;288(12):8419-32. doi: 10.1074/jbc.M112.425744. Epub 2013 Jan 23.*** PMID: 23344949 **IF: 4,651/ Q1**

15 **Edelfosine lipid nanosystems overcome drug resistance in leukemic cell lines.** Lasa-Saracíbar B, Estella-Hermoso de Mendoza A, Mollinedo F, Odero MD, Blanco-Príeto MJ. ***Cancer Lett. 2013 Jul 1;334(2):302-10. doi: 10.1016/j.canlet.2013.01.018. Epub 2013 Jan 23.*** PMID: 23353057 **IF: 4,258 / Q1**

16 **Endowing indole-based tubulin inhibitors with an anchor for derivatization: highly potent 3-substituted indolephenstatins and indoleisocombretastatins.** Álvarez R, Puebla P, Díaz JF, Bento AC, García-Navas R, de la Iglesia-Vicente J, Mollinedo F, Andreu JM, Medarde M, Peláez R. ***J Med Chem. 2013 Apr 11;56(7):2813-27. doi: 10.1021/jm3015603. Epub 2013 Mar 20.*** PMID: 23470139 **IF: 5,614 / D1**

17 **Rapid human melanoma cell death induced by sanguinarine through oxidative stress.** Burgeiro A, Bento AC, Gajate C, Oliveira PJ, Mollinedo F. ***Eur J Pharmacol. 2013 Apr 5;705(1-3):109-18. doi: 10.1016/j.ejphar.2013.02.035. Epub 2013 Mar 13.*** PMID: 23499690 **IF: 2,592 / Q2**

18 **Lipid raft-mediated Akt signaling as a therapeutic target in mantle cell lymphoma.** Reis-Sobreiro M, Roué G, Moros A, Gajate C, de la Iglesia-Vicente J, Colomer D, Mollinedo F. ***Blood Cancer J. 2013 May 31;3:e118. doi: 10.1038/bcj.2013.15.*** PMID: 23727661 **IF: 1,400/ Q4**

19 **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, Suarez-Gonzalo L. ***Blood Transfus. 2013 May 29:1-2. doi: 10.2450/2013.0237-12.*** PMID: 23736936 **IF: 1,858 / Q3**

20 **Edelfosine and miltefosine effects on lipid raft properties: membrane biophysics in cell death by antitumor lipids.** Castro BM, Fedorov A, Hornillos V, Delgado J, Acuña AU, Mollinedo F, Prieto M. ***J Phys Chem B. 2013 Jul 3;117(26):7929-40. doi: 10.1021/jp401407d. Epub 2013 Jun 24.*** PMID: 23738749 **IF: 3,607 / Q2**

21 **Ipilimumab and vemurafenib: two different routes for targeting melanoma.** Burgeiro A, Mollinedo F, Oliveira PJ. ***Curr Cancer Drug Targets. 2013 Oct;13(8):879-94.*** PMID: 23862981 **IF: 4,000 / Q2**

22 **Antitumor activity of new enantiopure pybox-ruthenium complexes.** Menéndez-Pedregal E, Díez J, Manteca Á, Sánchez J, Bento AC, García-Navas R, Mollinedo F, Gamasa MP, Lastra E. ***Dalton Trans. 2013 Oct 14;42(38):13955-67. doi: 10.1039/c3dt51160j. Epub 2013 Aug 8.*** PMID: 23925580 **IF: 3,806 / Q1**

23 **Synthesis and evaluation as antitumor agents of 1,4-naphthohydroquinone derivatives conjugated with amino acids and purines.** Molinari A, Oliva A, Ojeda C, Miguel del Corral JM, Castro MA, Mollinedo F, San Feliciano A. ***Arch Pharm (Weinheim). 2013 Dec;346(12):882-90. doi: 10.1002/ardp.201300137. Epub 2013 Oct 14.*** PMID: 2412314 **IF: 1,540 / Q2**

24 **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. 2013 Dec 1;131C:32-36. doi: 10.1016/j.actatropica.2013.11.018.*** PMID: 24299925 **IF: 2,787 / Q1**

25 **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. 2013 Dec 25;73C:265-279. doi: 10.1016/j.ejmech.2013.12.012.*** PMID: 24412720 **IF: 3,499 / Q1**

Other publications & Book chapters

- **Lipid rafts, cholesterol and apoptosis in cancer and neurodegenerative diseases** Mollinedo F. and Gajate C. In "A Toxicological/Pharmacological Approach to Chemico-Biological Interactions at a Membrane Level" (Jurado, A.S., Pedroso, M.C., and de Almeida, L., eds),pp. 27-40, Transworld Research Network, Kerala, India (2012). ISBN: 978-81-308-0494-1

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Red Temática en Investigación Cooperativa en Cáncer	Faustino Mollinedo	Instituto de Salud Carlos III (RD06/0020/1037)	2007-2012	127,629.62 €
Apoptosis y terapia antitumoral en cáncer de páncreas	Consuelo Gajate Fraile	Instituto de Salud Carlos III (PI09/1915)	2010-2012	122,815.00 €
Consorcio Oncológico	Faustino Mollinedo	FAES Pharma (Proyecto CENIT)	2011-2012	60,000.00 €
Integrating chemical approaches to treat pancreatic cancer: making new leads for a cure	Faustino Mollinedo	European Union (European Community's Seventh Framework Programme [FP7-2007-2013] under grant agreement HEALTH-F2-2011-256986, PANACREAS)	2011-2016	365,250.00 €
Estudios in vivo en modelos animales de la capacidad antitumoral de análogos alquil-lisofosfolípidos y papel de células del microentorno tumoral	Faustino Mollinedo	Junta de Castilla y León (CSI221A12-2)	2012	29,996.00 €
Mecanismos de acción y estudios preclínicos de análogos alquil-lisofosfolípidos antitumorales	Faustino Mollinedo	Junta de Castilla y León (CSI052A11-2)	2012	30,000.00 €
Estructuras subcelulares, regulación de apoptosis, y microentorno tumoral como dianas de agentes antitumorales: análogos alquil-lisofosfolípidos	Faustino Mollinedo	Ministerio de Ciencia e Innovación (SAF2011-30518)	2012-2014	338,800.00 €
Red Temática en Investigación Cooperativa en Cáncer	Faustino Mollinedo	Instituto de Salud Carlos III (RD12/0036/0065)	2013	39,013.75 €

Other activities & Relevant facts

- **Editorial Boards in Scientific Journals**
  - Anti-Cancer Drugs
  - International Journal of Biochemistry and Molecular Biology
  - Recent Patents on Anti-Cancer Drug Discovery
  - World Journal of Biological Chemistry
  - World Journal of Pharmacology
  - World Journal of Translational Medicine
  - Inmunología (until January 2013).

Genetic determinants of cancer susceptibility, evolution and treatment response

Team Leader:

Jesús Pérez Losada
Phone.: +34 923 294 807
E-mail: jperezlosada@usal.es

Research Team
Postdoctoral
Andrés Castellanos Martín
Sonia Castillo Lluva
Predoctoral
Lourdes Hontecillas Prieto
María del Mar Sáez Freire
Adrián Blanco Gómez
Technician
María Luz Hernández Mulas
Student
Facundo Nehuén Ramos Ochoa

RESEARCH SUMMARY

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 hystopathologic 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.

Cancer is not a cellular autonomous process; instead, it is an aberrant tissue that grows in a not controlled manner in the context of the physiology and pathophysiology of an organism. Therefore, it is a disease that not only depends on the properties of the tumour cells, but also of other compartments, like the immune and endocrine systems, stroma, angiogenesis, etc., which are key pieces in the development and evolution of cancer. Consequently, tumour susceptibility, development and evolution are not only determined by factors intrinsic to the tumour cell, involved in processes like proliferation, apoptosis, etc, but they are also influenced by extrinsic factors. Modifier genes control molecular and cellular factors of these two compartments, and explain differences in the susceptibility, development and the different clinical evolution among patients who seemingly suffer the same disease.

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 **New models towards assessing anti-cancer therapeutics.** Romero-Camarero I, Barajas-Diego M, Castellanos-Martín A, García-Martín Á, Varela G, Abad M, Ludeña MD, Pérez-Losada J, Sánchez-García I. ***Histol Histopathol. 2012 Feb;27(2):157-70. Review.*** PMID: 22207550 **IF: 2,281 / Q2**

2 **Allele-specific deletions in mouse tumors identify Fbxw7 as germline modifier of tumor susceptibility.** Perez-Losada J, Wu D, DelRosario R, Balmain A, Mao JH. ***PLoS One. 2012;7(2):e31301. doi: 10.1371/journal.pone.0031301. Epub 2012 Feb 13.*** PMID: 22348067 **IF: 3,730 / Q1**

3 **Pten regulates Aurora-A and cooperates with Fbxw7 in modulating radiation-induced tumor development.** Kwon YW, Kim IJ, Wu D, Lu J, Stock WA Jr, Liu Y, Huang Y, Kang HC, DelRosario R, Jen KY, Perez-Losada J, Wei G, Balmain A, Mao JH. ***Mol Cancer Res. 2012 Jun;10(6):834-44. doi: 10.1158/1541-7786.MCR-12-0025. Epub 2012 Apr 18.*** PMID: 22513362 **IF: 4,353 / Q1**

4 **Multiple novel alternative splicing forms of FBXW7\have a translational modulatory function and show specific alteration in human cancer.** Liu Y, Ren S, Castellanos-Martin A, Perez-Losada J, Kwon YW, Huang Y, Wang Z, Abad M, Cruz-Hernandez JJ, Rodriguez CA, Sun Y, Mao JH. ***PLoS One. 2012;7(11):e49453. doi: 10.1371/journal.pone.0049453. Epub 2012 Nov 14.*** PMID: 23166673 **IF: 3,730 / Q1**

5 **CD133+ cell content correlates with tumour growth in melanomas from skin with chronic sun-induced damage.** González-Herrero I, Romero-Camarero I, Cañueto J, Cardeñoso-Álvarez E, Fernández-López E, Pérez-Losada J, Sánchez-García I, Román-Curto C. ***J Dermatol. 2013 Oct;169(4):830-7. doi: 10.1111/bjd.12428.*** PMID: 23662851 **IF: 1,765 / Q2**

6 **C2ORF40 suppresses breast cancer cell proliferation and invasion through modulating expression of M phase cell cycle genes.** Lu J, Wen M, Huang Y, He X, Wang Y, Wu Q, Li Z, Castellanos-Martin A, Abad M, Cruz-Hernandez JJ, Rodriguez CA, Pérez-Losada J, Mao JH, Wei G. ***Epigenetics. 2013 Jun;8(6):571-83. doi: 10.4161/epi.24626. Epub 2013 Apr 26.*** PMID: 23770814 **IF: 4,920 / Q1**

7 **Schistosoma mansoni experimental infection in Mus spretus (SPRET/EiJ strain) mice.** Pérez Del Villar L, Vicente B, Galindo-Villardón P, Castellanos A, Pérez-Losada J, Muro A. ***Parasite. 2013;20:27. Epub 2013 Aug 29.*** PMID: 23985166 **IF: NI**

Other activities & Relevant facts

- Andrés Castellanos Martín , Lourdes Hontecillas Prieto, María del Mar Sáez Freire, Luis Pérez del Villar, Adrián Blanco Gómez, M. Luz Mulas, José F. Pérez-Fontán, Carmen Martín Seisdedos, María Isidoro, Rogelio González Sarmiento, Carmen Patino Alonso, Purificación Galindo Villardó, Jian Hua Mao, and **Jesús Pérez Losada**. Identification of Genetic Determinants of Breast Cancer Evolution and Susceptibility in an Erbb2/Neu Breast Cancer Mouse Model. **Complex Trait Community 2012. Institut Pasteur, Paris, France. June 12-15, 2012 . Congress communication.**

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Biología del Cáncer (PROGRAMA CONSOLIDER ONCOSTEM)	Jesús Pérez Losada	Ministerio de Ciencia y Tecnología (CSD2007-00017)	2007-2012	528,000.00 €
Identificación del componente genético responsable de la influencia de las células madre sobre la respuesta al tratamiento del cáncer de mama	Jesús Pérez Losada	Ministerio de Educación y Ciencia (PLE2009-0119)	2009-2012	400,000.00 €
Identificación de determinantes genéticos de la respuesta terapéutica y evolución del cáncer de mama	Jesús Pérez Losada	Instituto de Salud Carlos III (PI10/00328)	2011-2013	294,030.00 €
Identificación del papel de las células madre stem normales y tumorales en la susceptibilidad y desarrollo del cáncer de mama	Jesús Pérez Losada	Proyecto de Red de Investigación en Células Madre Tumorales en Cáncer de Mama. Fundación Inbiomed, Instituto Oncológico, Obra Social de la Caja Guipozkoa-San Sebastián (Kutxa) (11-13-JPLTS)	2011-2013	90,000.00 €
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 €
Estudio de los miRNAs en la evolución y pronóstico del carcinoma epidermoide cutáneo	Jesús Pérez Losada	Fundación Eugenio Rodríguez Pascual	2012	20,000.00 €
Papel de la Inmunoglobulina Intravenosa en el tratamiento del Cáncer-2	Jesús Pérez Losada	Instituto Grifols S.A.	2012-2014	370,800.00 €

Animal models in cancer. Chromosome instability and cancer

Team Leader:

Alberto Martín Pendás
Phone.: +34 923 294 809
E-mail: amp@usal.es

Research Team
Postdoctoral
Elena Llano Cuadra
Ignacio García Tuñón Llanio
Antonio M. Barrientos Durán
Predoctoral
Luis Ramírez Cebollero
Laura Gómez Hernández
Students
Juan Lorenzo Corral Moreno
Natalia Felipe Medina

RESEARCH SUMMARY

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. The disruption of the gene encoding the mouse Sgol2 does not cause any alteration in sister chromatid cohesion in embryonic cultured fibroblasts and adult somatic tissues. Besides, mutant mice developed normally and survive to adulthood without any apparent alteration. However, Sgol2 deficient mice, both male and female are sterile. We showed for the first time that SGOL2 is necessary for protecting cohesin from mammalian chromosome arms at anaphase I. In vivo loss of SGOL2 provoked a premature release of the meiotic-specific REC8 cohesin subunit from the centromeres. This molecular alteration was manifested cytologically with the complete loss of chromatid cohesion at metaphase II leading to single chromatids and physiologically with the formation of aneuploid spermatids giving rise to infertility (Llano et al., 2008).

More recently, we identified and characterized biochemically, cytologically, and functionally a new subunit of the α-kleisin of the Cohesin Complex which is evolutionary conserved from fish to mammals. The new protein, named RAD21L1, showed homology to the RAD21/REC8 kleisin subfamily. We showed trough a proteomic approach that RAD21L1 interacts with other cohesin subunits (SMC3, SMC1α/β) and specifically with the meiosis-specific STAG3 protein. Accordingly, RAD21L1 was expressed in mouse oocytes/spermatocytes localizing to the SC of autosomes (Gutierrez-Caballero et al., 2011). In addition, we developed and characterized a KO mouse of RAD21L1. Whereas female mice deficient for RAD21L1 were fertile, displaying no overt phenotype, mutant males showed a severe defect in synapsis and impaired sex body formation which provoked a meiotic arrest at late zygotene that ultimately led to azoospermia. Thus, RAD21L1 was the only cohesin subunit essential for male-specific fertility, challenging the view that REC8was the only key meiotic kleisin (Herrán et al., 2011).

It was known for a decade that Yeast, but not mice, depleted of the cohesin subunit Rec8 are defective in the formation of the axial elements (AEs) of the SC, suggesting

that, in mammals, this function was not conserved. We now show, that spermatocytes from mice lacking the two meiosis-specific cohesin subunits RAD21L and REC8 (depletion of the meiotic cohesins) were unable to initiate RAD51- but not DMC1-mediated double-strand break repair. More interestingly, spermatocytes were not able to assemble their AEs, and arrested as early as the leptotene stage of prophase I, demonstrating for the first time that cohesin plays an essential role in AE assembly and that thi function is conserved from yeast to mammals.

Based on our results, we have postulated that non obstructive azoospermia and POF with genetic basis (which are idiopathic in a large fraction) can be due to genetic mutations in the cohesin pathway. We are now enrolled with several groups trying to elucidate the participation of the cohesin pathway in human infertility.

Publications

1 **Shugoshins: from protectors of cohesion to versatile adaptors at the centromere.** Gutiérrez-Caballero C, Cebollero LR, Pendás AM. ***Trends Genet. 2012 Jul;28(7):351-60. doi: 10.1016/j.tig.2012.03.003. Epub 2012 Apr 27. Review.*** PMID: 22542109 **IF: 9,772 / D1**

2 **Meiotic cohesin complexes are essential for the formation of the axial element in mice.** Llano E, Herrán Y, García-Tuñón I, Gutiérrez-Caballero C, de Álava E, Barbero JL, Schimenti J, de Rooij DG, Sánchez-Martín M, Pendás AM. ***J Cell Biol. 2012 Jun 25;197(7):877-85. doi: 10.1083/jcb.201201100. Epub 2012 Jun 18.*** PMID: 22711701 **IF: 10,822 / D1**

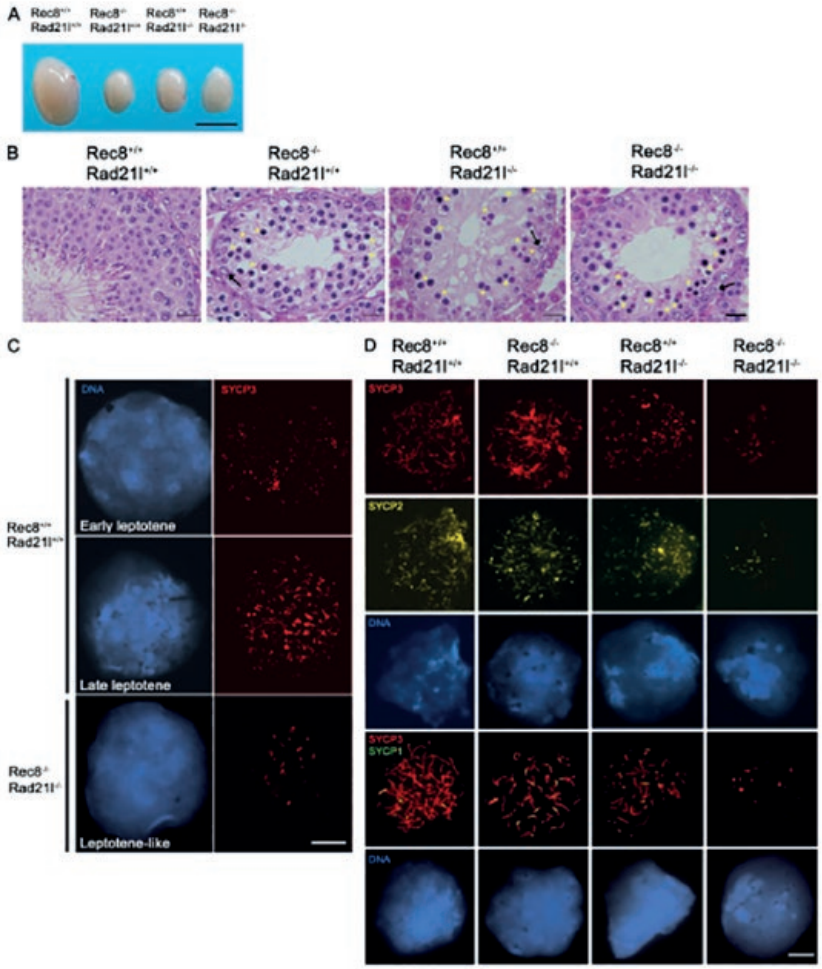
3 **Oxysterol-induced soluble endoglin release and its involvement in hypertension.** Valbuena-Diez AC, Blanco FJ, Oujo B, Langa C, Gonzalez-Nuñez M, Llano E, Pendas AM, Díaz M, Castrillo A, Lopez-Novoa JM, Bernabeu C. ***Circulation. 2012 Nov 27;126(22):2612-24. doi: 10.1161/CIRCULATIONAHA.112.101261. Epub 2012 Oct 30.*** PMID: 23110859 **IF: 15,202 / D1**

4 **Dynamic localization of SMC5/6 complex proteins during mammalian meiosis and mitosis suggests functions in distinct chromosome processes.** Gómez R, Jordan PW, Viera A, Alsheimer M, Fukuda T, Jessberger R, Llano E, Pendás AM, Handel MA, Suja JA. ***J Cell Sci. 2013 Sep 15;126(Pt 18):4239-52. doi: 10.1242/jcs.130195. Epub 2013 Jul 10.*** PMID: 23843628 **IF: 5,877 / Q1**

5 **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. 2013 Sep 8.*** PMID: 24013524 **IF: 3,34 / Q2**

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Análisis funcional de genes implicados en cohesión cromosómica y su posible implicación en cohesinopatías	Alberto Martín Pendás	Junta de Castilla y León (CSI006A10-2)	2010-2012	40,000.00 €
Análisis in vivo de la pérdida de cohesión en el ratón y su papel en enfermedades humanas	Alberto Martín Pendás	Ministerio de Ciencia e Innovación (SAF2011-25252)	2012-2014	217,800.00 €



Absence of RAD21L and REC8 arrest mouse spermatogenesis in early prophase I. (A) dKO-kls mice show a 70% reduction in testes size compared with wild type. Similar reductions are observed in Rad21l–/– and Rec8–/– males. (B) Mutation of both Rad21l and Rec8 elicits an arrest of spermatogenesis at stage IV characterized by intermediate spermatogonia (arrows) in a representative section of a seminiferous tubule. Massive apoptosis of spermatocytes (condensed nuclei indicated by asterisks) and absence of mature spermatozoa/spermatids are observed in the dKO-kls tubules. A similar arrest is observed in seminiferous tubules from singly mutant Rad21l and Rec8mice. (C) Immunolabeling for SYCP3 in spermatocytes from a wild-type mouse at early and late leptonema and spermatocytes arrested at a leptotene-like stage from a dKO-kls mouse. (D) dKO-kls spermatocytes arrested at the leptotene-like stage show absence of chromosomal synapsis. Double immunolabeling for SYCP3 and SYCP2 or SYCP1 shows SYCP3/SYCP2 aggregates without synapsis as indicated by the lack of SYCP1 labeling in double mutant spermatocytes. Spermatocytes from Rad21l–/– (zygotene-like arrest), Rec8–/– (zygotene-like arrest), and wild-type (zygotene stage) mice show AEs and synapsed LEs with stretches of SYCP1. Bars: (A) 5 mm; (B) 25 µm; (C and D) 100 µm.

Cell growth, division and differentiation *(until February 2013)*

RESEARCH SUMMARY

Our laboratory is interested in understanding the molecular mechanisms that control the coordination between cell division, cell differentiation and apoptosis. We use the fission yeast Schizosaccharomyces pombe, as unicellular model system, and the mouse, as multicellular model system to study these processes.

We have studied

1 The nutritional signals that regulate cell cycle exit and cell differentiation; in particular, the role of the TOR and the protein kinase A (PKA) pathways.
2 The role of the Anaphase Promoting Complex or Cyclosome (APC/C) in cell cycle exit and cell differentiation in mice.
3 The mechanism of action of the antitumour compounds Yondelis, Zalypsis and Kahalalide F developed by PharmaMar.

Lines of research

1 Role of the TOR pathway in cell growth and cell differentiation.
2 Role of the APC-Cdh1 (Fzr1) complex in cell cycle, cancer and neurodegeneration.
3 Identification of molecular targets of the antitumour compounds Yondelis, Zalypsis and Kahalalide F.

Main achievements

1 We have shown that the TOR and the PKA pathways act sinergistically to inhibit cell differentiation in the fission yeast S. pombe.
2 We have shown that Cdh1 (Fzr1) is a tumour supressor required to maintain genome stability. We have also shown that Cdh1 is required terminally differentiated neurones to prevent cell death.
5 We have identified the molecular targets and the possible mechanism of action of Yondelis and Kahalalide F, two antitumour drugs developed by PharmaMar.

Team Leader:

Sergio Moreno
Phone.: +34 923 294 810
E-mail: smo@usal.es

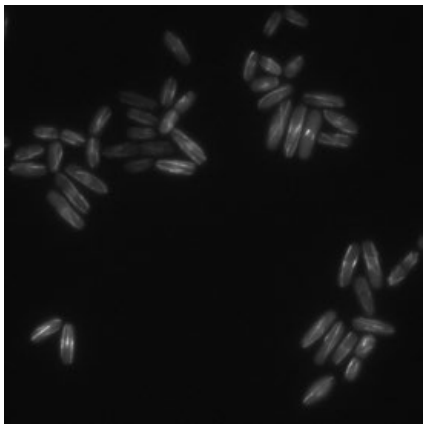
Research Team

Postdoctoral
Javier Botet Rodríguez
Myriam Cuadrado López
Irene García Higuera
Livia Pérez Hidalgo

Predoctoral
Nathalia Chica Balaguera
Javier Garzón Hidalgo
Marta Tormos Pérez

Technicians
Silvia González Fernández
Ana Elisa Rozalén de la Cruz

Student
Jorge Maldonado Fernández de Gatta


Publications

1 **The Vam6 and Gtr1-Gtr2 pathway activates TORC1 in response to amino acids in fission yeast.** Valbuena N, Guan KL, Moreno S. ***J Cell Sci. 2012 Apr 15;125(Pt 8):1920-8. doi: 10.1242/jcs.094219. Epub 2012 Feb 17.*** PMID: 22344254 **IF: 5,877 / Q1**

2 **AMPK phosphorylation by Ssp1 is required for proper sexual differentiation in fission yeast.** Valbuena N, Moreno S. ***J Cell Sci. 2012 Jun 1;125(Pt 11):2655-64. doi: 10.1242/jcs.098533. Epub 2012 Feb 28.*** PMID: 22375066 **IF: 5,877 / Q1**

3 **Chemical inactivation of Pat1: a novel approach to synchronize meiosis.** Pérez-Hidalgo L, Moreno S. ***Cell Cycle. 2012 May 15;11(10):1875. doi: 10.4161/cc.20512. Epub 2012 May 15.*** PMID: 22580453 **IF: 5,321 / Q1**

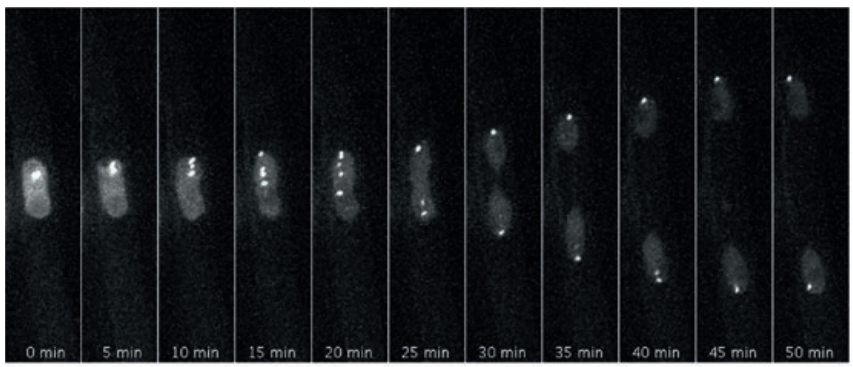
4 **APC(FZR1) prevents nondisjunction in mouse oocytes by controlling meiotic spindle assembly timing.** Holt JE, Lane SI, Jennings P, García-Higuera I, Moreno S, Jones KT. ***Mol Biol Cell. 2012 Oct;23(20):3970-81. doi: 10.1091/mbc.E12-05-0352. Epub 2012 Aug 23.*** PMID: 22918942 **IF: 4,803 / Q2**

5 **The APC activator fizzy-related-1 (FZR1) is needed for preimplantation mouse embryo development.** Seah MK, Holt JE, García-Higuera I, Moreno S, Jones KT. ***J Cell Sci. 2012 Dec 15;125(Pt 24):6030-7. doi: 10.1242/jcs.110155. Epub 2012 Oct 24.*** PMID: 23097041 **IF: 5,877 / Q1**

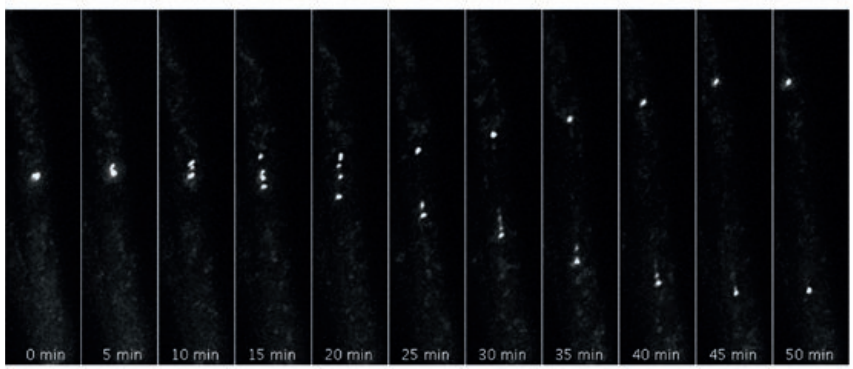
6 **Fission yeast TORC1 prevents eIF2γ phosphorylation in response to nitrogen and amino acids via Gcn2 kinase.** Valbuena N, Rozalén AE, Moreno S. ***J Cell Sci. 2012 Dec 15;125(Pt 24):5955-9. doi: 10.1242/jcs.105395. Epub 2012 Oct 29.*** PMID: 23108671 **IF: 5,877 / Q1**

Grants for research in progress

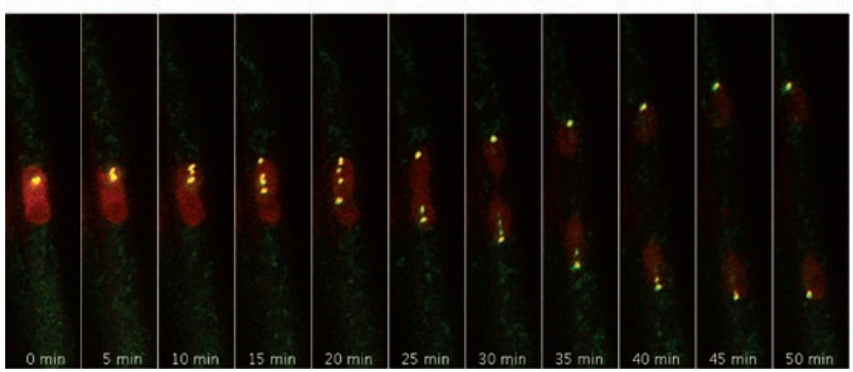
PROJECT	IP	GRANT	TIME	FUNDING
Inestabilidad Genómica CSD2007-00015 CONSOLIDER INGENIO 2010 (2007)	Sergio Moreno	Ministerio de Ciencia y Tecnología	2008-2013	40,000.00 €



mhf1-tdT



ndc80-GFP



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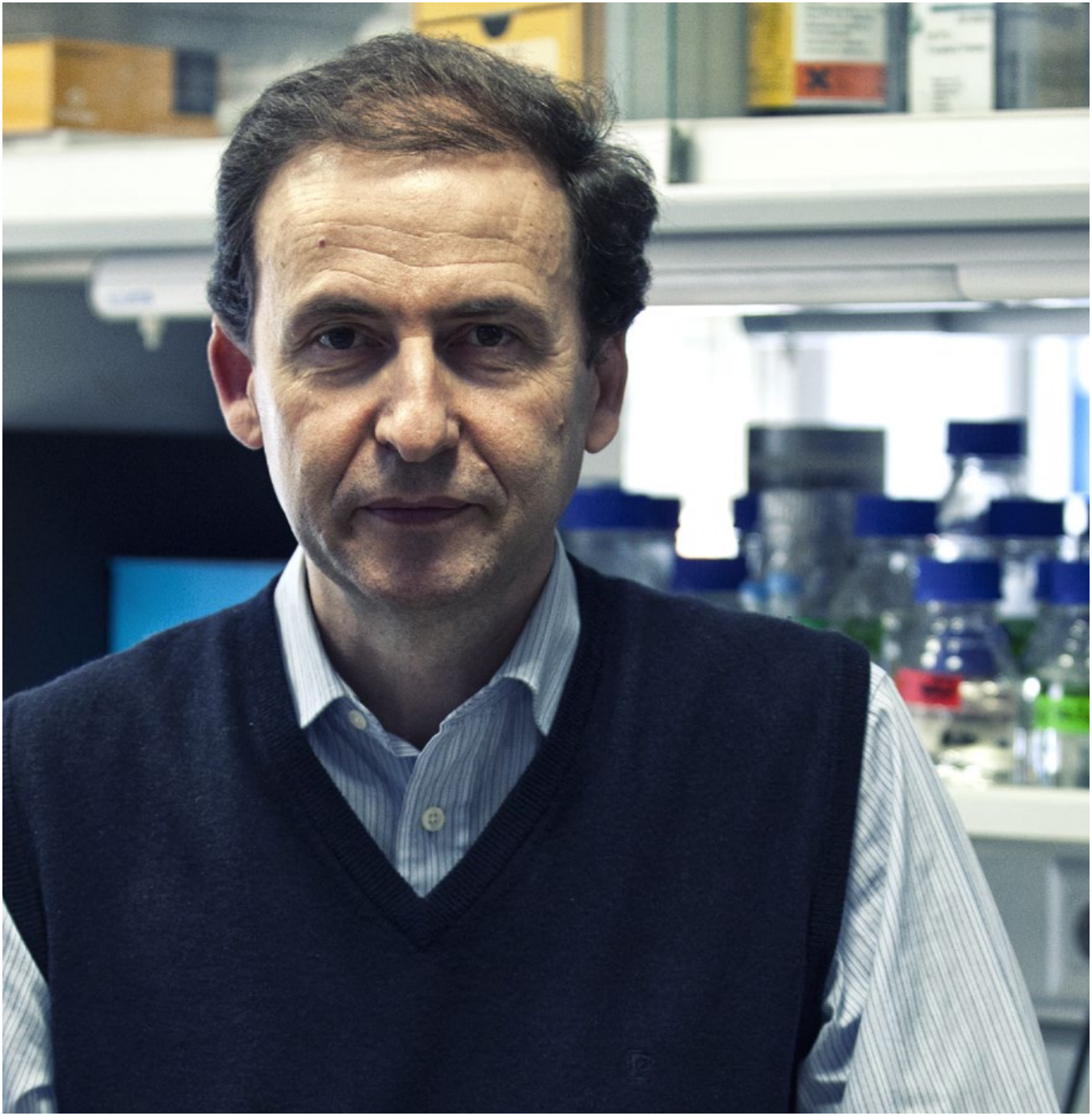

Immunology and cancer

RESEARCH SUMMARY

Description

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.

Team Leader:

Jose Alberto Orfao de Matos Correia e Vale
Phone.: +34 923 294 811
E-mail: orfao@usal.es

Research Team

Senior Researchers
Andrés Celestino García Montero
Julia Almeida Parra
José María Sayagués Manzano
Manuel Fuentes García
María Dolores Tabernero Redondo
Rafael Góngora Fernández

Carlos Eduardo Pedreira

Postdoctoral
María Aranzazu Rodríguez Caballero
Sergio Matarraz Sudón
Martín Pérez de Andrés
Belén Espinosa Fernández
Quentin Lecrevisse
Andrea Mayado Colino
Elaine Sobral da Costa
Elena Blanco Álvarez

Predoctoral
Raquel Bartolomé Casado
Juan Alejandro Flores Montero
Cristina Isabel Goncalves Grunho Teodosio
María González González

María Jara Acevedo
Paula Laranjeira
María Lourdes Martín Martín
Ignacio Criado García

Technicians
María Campos Terrón
Patricia Herniques Domingues
Esther Martín González
Ana Belén Nieto Librero
Wendy Nieto Pérez
Guillermo Tabernero Redondo

Students
Paula Díez García

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 suffereing 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.

JUNIOR GROUPS

Phenotypic and molecular characterization of Systemic Mastocytosis: correlation between disease progression, immunophenotype and the specific genetic background

Andrés Celestino García Montero
Phone.: +34 923 294 811
E-mail: angarmon@usal.es

RESEARCH SUMMARY

Description

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; 106 citations). 2) Mast cells from different molecular and prognostic subtypes of SM display distinct immunophenotypes (J Allergy Clin Immunol. 2010; 125:719-26. IF: 9.773; 21 citations). 3) 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; 30 citations). 4) An immature immunophenotype of bone marrow MC predicts for multilineage D816V KIT mutation in SM (Leukemia 2012 [in press] IF: 8.966). Future research: To design new methodologies to be applied in any clinical laboratory for the diagnosis and prediction of progression of SM.

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

Julia Almeida Parra
Phone.: +34 923 294 811
E-mail: jalmeida@usal.es

RESEARCH SUMMARY

Description and general objetive

"Immunology and Cancer", particularly in the field of hematological malignancies (Leukemias and lymphomas), from the onto-pathogenesis to clinical settings, particularly in diagnosis, classification and treatment monitoring of these neoplasms. Main lines of research: 1.-Definition of aberrant protein expression profiles in neoplastic cells from hematological malignancies and their relationship with their genetic origin. 2.- Identification of potential factors involved in the onto-pathogenesis of T- and B-cell clonal lymphocytosis / chronic lymphoproliferative disorders. 3.- Development and evaluation of new methodological approaches and automated data analyses applied to diagnosis, classification and monitoring of hematological malignancies by flow cytometry. Results: Line 1: Definition of new entities or diagnosis strategies of hematological malignancies of T/NK and B-cell CLPD ((Lima et al, Cytometry 2003, Hematologica 2003, Am J Hematol 2003 and Am J Hematol 2004; Sánchez et al Blood 2003 and Hematologica 2006; Barrena et al, Leukemia 2005 and Histopatholgy 2011; Sandberg et al Leukemia 2006; Quijano et al, Blood 2008; Martin-Martin Transfusion 2009). Line 2: LGL CD4+ Clonal lymphocytosis / T-cell CLPD are antigen-driven proceses against certain peptides from CMV (Garrido et al, Blood 2007; Rodríguez-Caballero et al, Blood 2008); The frequency of detection of circulating B-cell clones in the general population of Salamanca might be a usual finding in subjetcs older than 70 years, which suggests that these cells may correspond to the normal counterpart of CLL (chronic lymphocytic leukemia), and not a leukemic precursor (Nieto et al, Blood 2009; Almeida et al, Leukemia 2011). Line 3: Verification of the utilitly of novel automated tools applied to flow cytometry data analysis, with diagnostic purposes (Pedreira et al IEEE 2008, Cytometry 2008; Costa et al Leukemia 2006, Cytometry B 2010, Leukemia 2010). Future research: to deeply know those mechanisms involved in the transformation of clonal lymphocytosis into malignant diseases; application of novel estrategies of automated data analysis of FCM files to diagnosis, classification and treatmente monitoring of hematological malignancies.

Immunotechnological, nanotechnological, and proteomics approaches for biomarker discovery in cancer

Manuel Fuentes García
Phone.: +34 923 294 811
E-mail: mfuentes@usal.es

RESEARCH SUMMARY

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. 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,...) 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.

Molecular Genetics and Cytogenetics in Colorectal Cancer

José María Sayagués Manzano
Phone.: +34 923 294 811
E-mail: ppmari@usal.es

RESEARCH SUMMARY

Colorectal cancer is one of the most common malignant tumours and is frequently lethal due to metastatic spreading to the liver. The metastatic process is considered, at least in part, to be related to a specific background of genetic alterations accumulated in cells from primary tumors, the identification of such genetic alterations being critical for the identification of colorectal cancer patients at risk of developing metastates. Objetives: 1) To establish the intratumoural pathways of clonal evolution associated with chromosomal instability in individual primary versus metastatic tumours from colorectal carcinoma patients, 2) to define the most frequent recurrent breakpoint regions in metastatic CRC and the commonly gained and/or deleted genes in the altered chromosomes, 3) to search for recurrent genetic differences between paired primary versus metastatic tumor samples that might contain candidate genes highly characteristic of metastatic liver disease, and 4) to investigate the prognostic value of structural/numerical abnormalities of the most frequently altered chromosomes in liver metastatic colorectal carcinomas.

Results: 1) the liver metastases typically contained tumour cell clones similar to those found in the primary tumours, suggesting the absence of selective selection of specific tumour clones (J Pathol 2010; 221: 308–319), 2) Detailed characterization of the breakpoint regions for the altered chromosomes showed four recurrent breakpoints at chromosomes 1p12, 8p12, 17p11.2 and 20p12.1; interestingly, the most frequently observed recurrent chromosomal breakpoint was localized at 17p11.2 and systematically targeted the FAM27L gene, whose role in CRC deserves further investigations (PLoS ONE 2010; 5(10): e13752. doi:10.1371), 3) Overall, metastatic tumors systematically contained those genetic abnormalities observed in the primary tumor sample from the same subject.

However, liver metastases from many cases (up to 8 out of 20) showed acquisition of genetic aberrations that were not found in their paired primary tumors (Modern Pathology (2012) 25, 590–601), and 4) the results show that the occurrence of del(17p) involving the 17p11.2 breakpoint region is an independent prognostic factor for overall survival (PLoS ONE 2012; 7(8): e42683. doi:10.1371). Future research: To define differential gene expression profile between metastatic and non-metastatic tumors, for a better undestanding of the genetics of the metastatic process in colorectal tumors.

Publications

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2 **Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms.** Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, García-Montero A, Morgado JM, Orfao A, Escribano L. ***Int Arch Allergy Immunol. 2012;157(3):275-80. doi: 10.1159/000329856. Epub 2011 Oct 28.*** PMID: 22042301 **IF: 2,248 / Q3**

3 **An immature immunophenotype of bone marrow mast cells predicts for multilineage D816V KIT mutation in systemic mastocytosis.** Teodosio C, García-Montero AC, Jara-Acevedo M, Alvarez-Twose I, Sánchez-Muñoz L, Almeida J, Morgado JM, Matito A, Escribano L, Orfao A. ***Leukemia. 2012 May;26(5):951-8. doi: 10.1038/leu.2011.293. Epub 2011 Nov 4.*** PMID: 22051531 **IF: 10,164 / D1**

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70 **Correction: Common Infectious Agents and Monoclonal B-Cell Lymphocytosis: A Cross-Sectional Epidemiological Study among Healthy Adults.** Casabonne D, Almeida J, Nieto WG, Romero A, Fernández-Navarro P, Rodriguez-Caballero A, Muñoz-Criado S, Díaz MG, Benavente Y, de Sanjosé S, Orfao A; the Primary Health Care Group of Salamanca for the Study of MBL. ***PLoS One. 2013 Oct 11;8(10). doi: 10.1371/annotation/6f57f3c7-2f86-4d3a-a646-cb54de56ddba. eCollection 2013.*** PMID: 24146721 **IF: 3,730 / Q1**

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Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Red Temática en Investigación Cooperativa en Cáncer	Jose Alberto Orfao de Matos Correia e Vale	Instituto de Salud Carlos III (RD06/0020/0035)	2007-2012	468,088.86 €
Technology for diagnosis and classification of malignancies	Jose Alberto Orfao de Matos Correia e Vale	Cytognos	2009-2012	300,000.00 €
Caracterización detallada de las alteraciones genéticas y de las vías de señalización implicadas en el desarrollo clonal y transformación neoplásica de células B de sujetos con linfocitos B Clonal (MBL) Vs pacientes con leucemia linfática crónica	Jose Alberto Orfao de Matos Correia e Vale	Instituto de Salud Carlos III (PS09/02430)	2010-2012	241,395.00 €
Diseño y desarrollo de técnicas Nano-Proteómicas de alto rendimiento para el descubrimiento de biomarcadores y nuevos fármacos, emplando como modelo leucemia linfoides B y tirosina quinasas	Manuel Fuentes García	Instituto de Salud Carlos III (PI11/02114)	2011-2012	98,241.11 €
Identificación de factores predictivos de progresión clonal en mastocitosis sistémica	Andrés García Montero	Junta de Castilla y León	2011-2012	22,379.00 €
Análisis de las alteraciones genéticas con valor pronóstico en cáncer colorectal esporádico	José María Sayagués	Junta de Castilla y León	2011-2012	25,553.00 €
Banco Nacional de ADN colección de muestras biológicas de hemoglobinuria paroxística nocturna	María Almeida Parra	Junta de Castilla y León	2012-2014	98,241.11 €
Diseño de un método de análisis de severidad en Mastocitosis Sistémica	Andrés García Montero	Instituto de Salud Carlos III (PI11/02399)	2012-2014	42,360.89 €
Identificación de factores predictivos de progresión clonal en mastocitosis sistémica	Andrés García Montero	Fundación Ramón Areces	2012-2015	76,440.00 €

Oncohematology *(until September 2013)*

RESEARCH SUMMARY

Description

The main characteristic of Prof. San Miguel'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 syndrome

Team Leader:

Jesús San Miguel Izquierdo
Phone.: +34 923 294 812
E-mail: sanmiguel@usal.es

Research Team

Senior Researchers

Mª Consuelo del Cañizo Fernández-Roldán
Marcos González Díaz
Mª Dolores Caballero Barrigón
Jesús María Hernández Rivas
Belén Vidriales Vicente
Ramón García Sanz
Norma C. Gutiérrez Gutiérrez
Mª Victoria Mateos Manteca
Fermín M. Sánchez-Guijo
Enrique M. Ocio San Miguel
Mª Mercedes Garayoa Berrueta
Juan Luis García Hernández

Postdoctoral

Miguel Alcoceba Sánchez
Mª Eugenia Alonso Sarasquete
Mª Rocío Benito Sánchez
Ana Belén Herrero Hernández
Patryk Krzeminski
Irena Misiewicz-Krzeminska
Teresa Paíno Gómez
Cristina Robledo Montero
Ana E. Rodríguez Vicente
Belén Blanco Durango
Bruno Paiva
Sandra Muntión Olave
Antonio García Gómez

Predoctoral

María Abáigar Alvarado
Luis A. Corchete Sánchez
Mª Isabel Forero Castro
José González Valero
Mª Carmen Herrero Sánchez
María Hernández Sánchez
Eva Lumbreras González
Dalia Salim Quwarider
Mónica del Rey González
Carlos Romo Gonzalo
Laura San Segundo Payo
Verena González Rodríguez
Mª Carmen Herrero Sánchez
Kamila Janusz
Cristina Jiménez Sánchez
Ana Alicia López Iglesias
Rodrigo Prieto Bermejo
Elizabeta Rojas Ricardo

Technicians

Irene Aires Mejia
María García Álvarez
Lorena González Méndez
Sara González Briones
Isabel María Isidro Hernández
María Almudena Martín Martín
Mª Montserrat Martín Sánchez
Mª Teresa Prieto Martín
Sandra Pujante Fernández
Mª Ángeles Ramos Rodríguez
Concepción Rodríguez Serrano
Irene Rodríguez Iglesias

Student

Jenny Lorena Brito Hoyos

Data Manager

Irene Real Ibáñez
Fátima Méndez Ambel
María José Rodrigo Egido
Magdalena García Astorga
Eva María Diez Baeza
Manuel Delgado Criado

(MDS) and chronic lymphoproliferative disorders (CLL) / lymphomas.

Strategic objectives

1 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 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 areas of research:

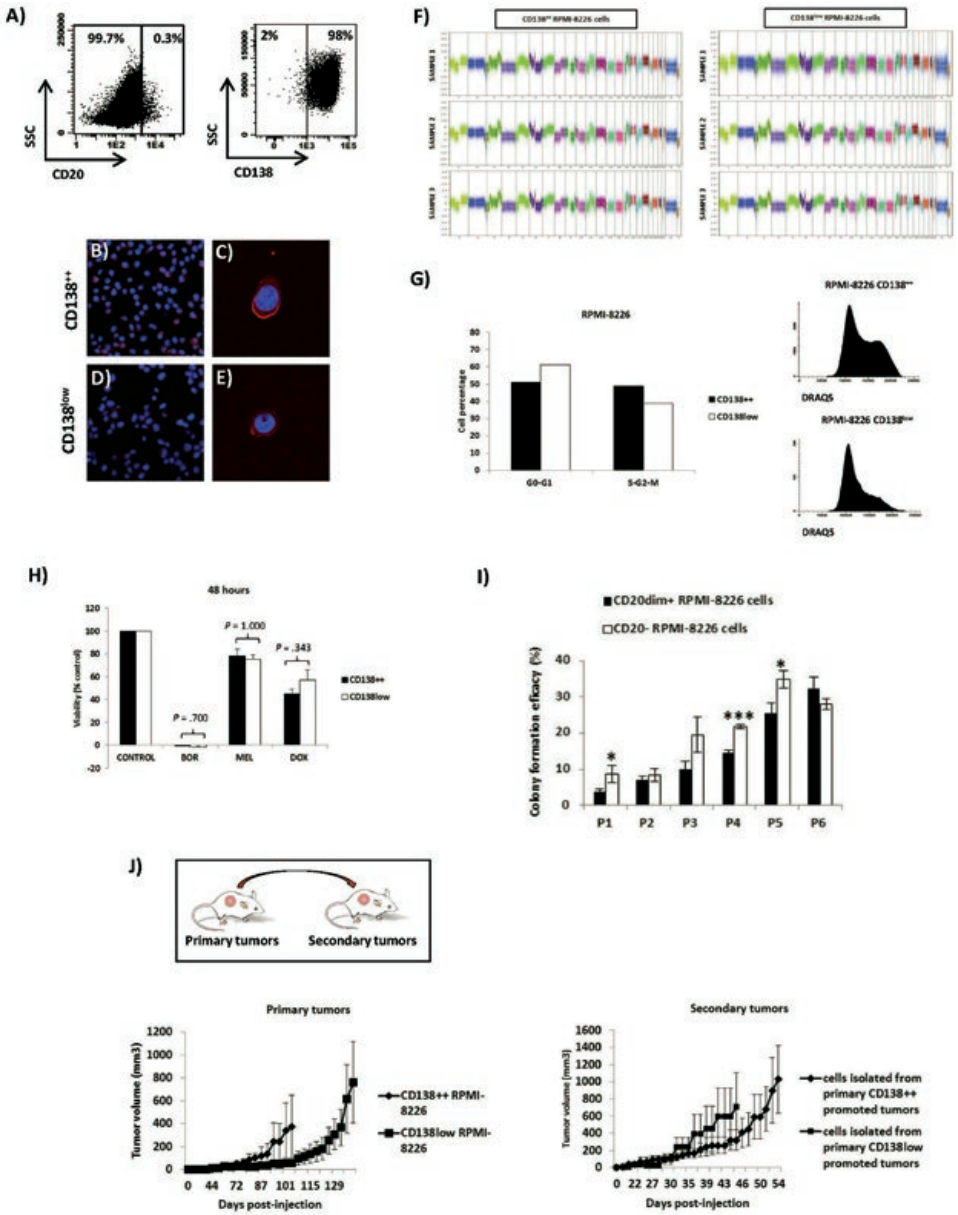
1 Onco-Haematologic Molecular Cytogenetics
   - Molecular cytogenetics and genomic arrays in haematological malignancies
   - Analysis of the tumor transcriptome and exome
2 Molecular Biology and Immunopathology
   - Study of genomic expression and mutations in genes associated with cancer: clinico-biological 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) description of 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 chronic lymphocytic leukemia. 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, and which has allowed the leadership of several clinical trials (phase I/II and phase III for registration).

Future challenges

- Deepen into the genomic mechanisms responsible for the development of haematological neoplasms.
- Identify and characterize the tumoral stem cells and to gain further insights into the role of the tumor microenvironment.
- Analyze mechanisms responsible for the development of drug-resistance.
- Activation of novel therapeutic trials.



Study of subpopulations with cancer stem cell properties in multiple myeloma cell lines. (A) Percentages of CD20-, CD20dim+ (left dot plot), CD138++ and CD138low subpopulations (right dot plot) in RPMI-8226 cell line (B-E) Immunocytochemistry for CD138 (red) in CD138++ and CD138low RPMI-8226 cells. Nuclear DNA was stained with DAPI (blue). Magnification of the lens, 63x. Specific "4x zoom" was made in C and E. (F) Copy number variation analysis corresponding to CD138++ RPMI-8266 cells (n=3; left panel) and CD138low RPMI-8266 cells (n=3; right panel) on the basis of Cytoscan HD array. (G) Left: Cell percentage of CD138++ and CD138low RPMI-8226 cells in G0-G1 and S-G2-M phases. The results correspond to one representative experiment that was repeated at least twice with similar results. Right: Representative DRAQ5 histograms for each indicated population. (H) Sorted CD138++ or CD138low RPMI-8226 cells were incubated in the absence (control) or presence of bortezomib (10 nM), melphalan (10 μM) or doxorubicin (250 nM) for 48 hours. The percentage of cell viability was calculated considering control as 100%. Results are the means ± SEM (n=3). (I) Serial colony assays for sorted CD20dim+ and CD20- RPMI-8226 cells. Results are expressed as mean ± SEM (n=3) and represent the percentage of the number of colonies scored compared to the number of cells plated in each passage (P1, P2, P3, P4, P5 and P6). Statistically significant differences are given as *P<0.05 and ***P<0.001. (J) 3x104 sorted CD138++ RPMI-8226 or CD138low RPMI-8226 cells were subcutaneously injected into CB17-SCID mice to generate primary tumors. Subsequently, 3x106 cells isolated from selected primary tumors were serially transplanted into new CB17-SCID mice to generate secondary tumors. Tumor growth curves for CB17-SCID mice that developed measurable primary and secondary tumors. Results are the means ± SEM (n=4-6).

Genetics in Oncohematology

Jesús María Hernández Rivas
Phone.: +34 923 294 812
E-mail: jmhr@usal.es

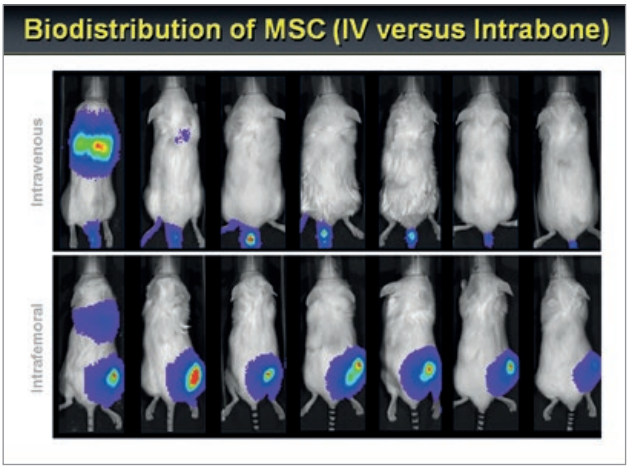
RESEARCH SUMMARY

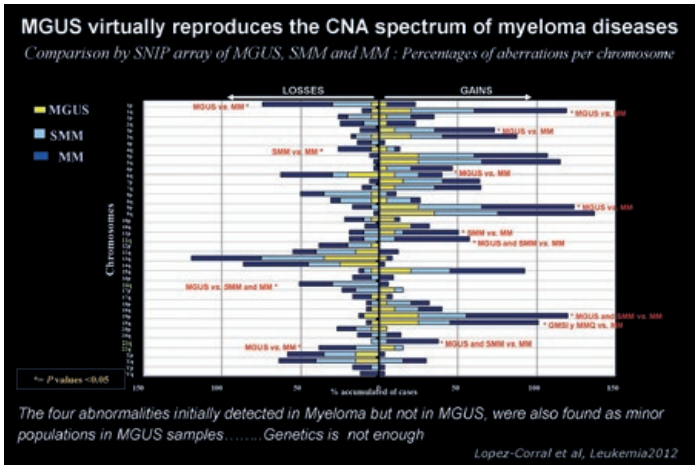
Research group in Molecular Cytogenetics

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.





Bone marrow microenvironment in multiple myeloma and bone lesions

Mercedes Garayoa Berrueta
Phone.: +34 923 294 812
E-mail: mgarayoa@usal.es

RESEARCH SUMMARY

Description

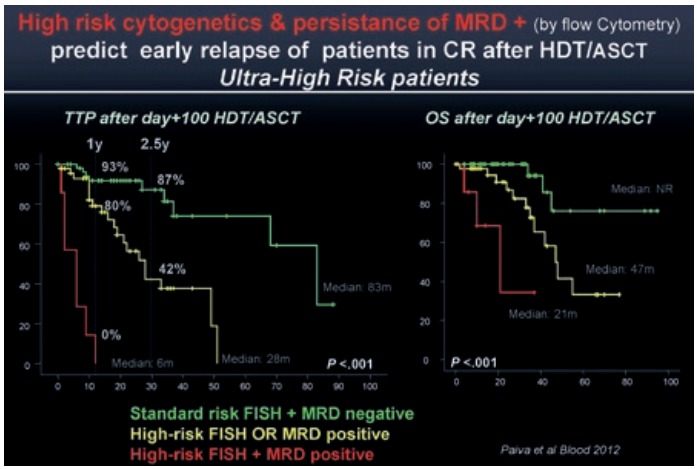
Our group has focused on the study of the role of the bone marrow microenvironment in the pathogenesis of multiple myeloma and in the development of bone lesions associated to this disease and other malignancies. We are also involved in preclinical studies of anti-myeloma agents with a specific effect 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 use of mesenchymal stromal cells as vehicles for anti-myeloma therapy.

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 which may have a role in myeloma pathophysiology and bone lesions.

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 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.

Publications

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118 **IMWG consensus on risk stratification in multiple myeloma.** Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, Munshi N, Palumbo A, Miguel JS, Sonneveld P, Cavo M, Usmani S, Durie BG, Avet-Loiseau H; International Myeloma Working Group. ***Leukemia. 2014 Feb;28(2):269-77. doi: 10.1038/leu.2013.247. Epub 2013 Aug 26.*** **PMID: 23974982 IF: 10,164 / D1**

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122 **Clinical applicability and prognostic significance of molecular response assessed by fluorescent-PCR of immunoglobulin genes in multiple myeloma. Results from a GEM/PETHEMA study.** Martinez-Lopez J, Fernández-Redondo E, García-Sánz R, Montalbán MA, Martínez-Sánchez P, Pavia B, Mateos MV, Rosiñol L, Martín M, Ayala R, Martínez R, Blanchard MJ, Alegre A, Besalduch J, Bargay J, Hernandez MT, Sarasquete ME, Sanchez-Godoy P, Fernández M, Blade J, San Miguel JF, Lahuerta JJ; GEM (Grupo Español Multidisciplinar de Melanoma)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) cooperative study group. ***Br J Haematol. 2013 Dec;163(5):581-9. doi: 10.1111/bjh.12576. Epub 2013 Oct 3.*** PMID: 24117042 **IF: 4,942 / Q1**

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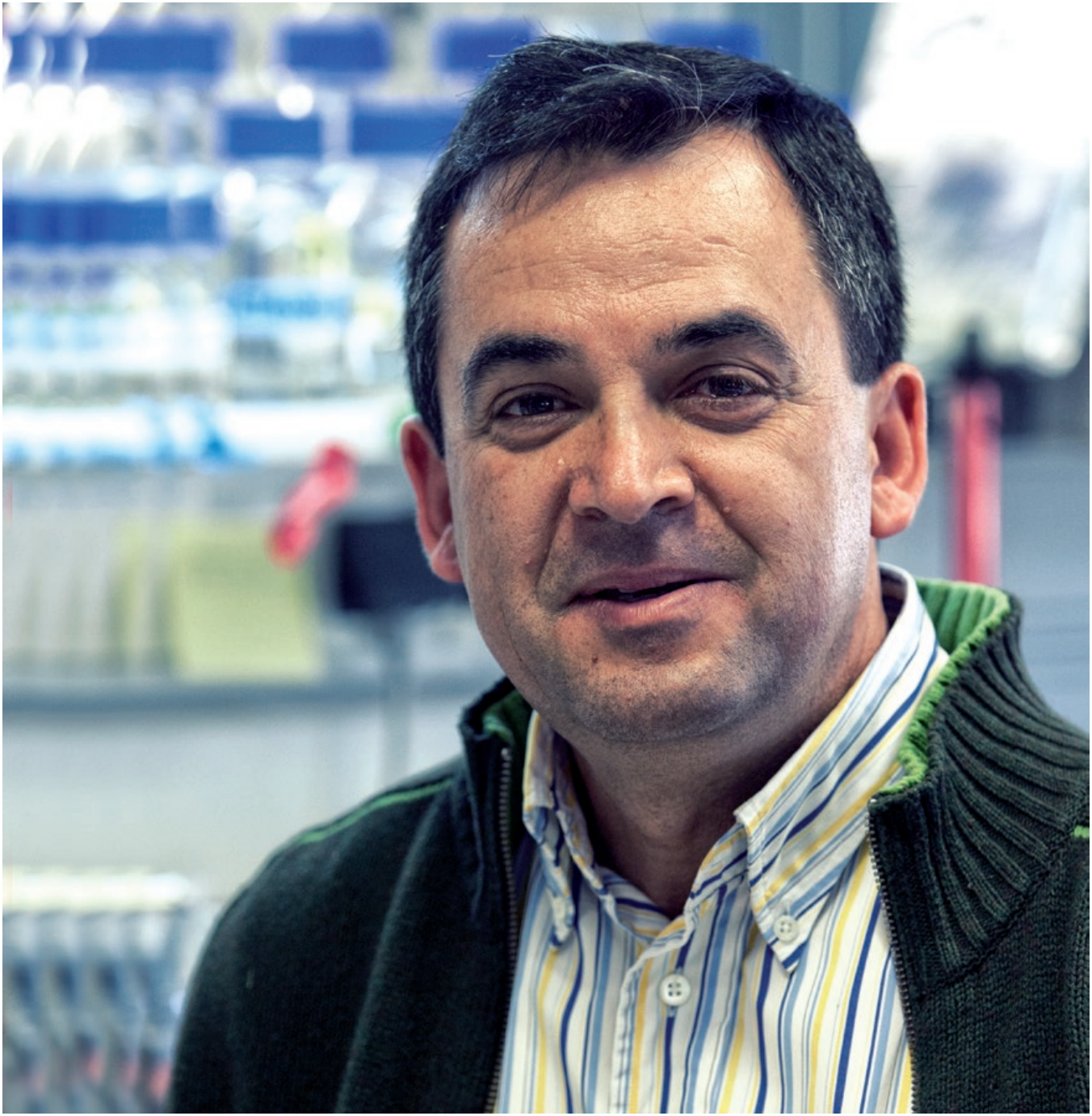
Other publications & Book chapters

- **Gammapatías monoclonales** J. Bladé, J. San Miguel. Medicina Interna (XVII edición). Farreras-Rozman. Ed. Elservier. Capítulo: 207, Pag:1619-1628, 2012.
- **Haematopoietic Stem Cell Transplantation for multiple myeloma in adults** J. San Miguel, J. Perez Simón, MV Mateos. The EBMT handbook (6th edition). Chapter 19.6: 387-401, 2012
- **Sequencing of available agents in Multiple Myeloma: the role of cambination therapy** Sagar Lonial, Donna Reece, Jonathan Kaufman, Jesús F. San Miguel. Multiple myeloma State of the Art. 2nd edition. Paul Richardson, Kenneth Anderson. Ed. Redemedica. Chapter 9, 2012
- **Mieloma multiple** J. San Miguel, J. Bladé. Manual Práctico de Hematología Clínica. Miguel A. Sanz Alonso, Enric Carreras. Ed. Antares. Capítulo 4, 361-368, 2012
- **Prognosis and staging of multiple mieloma** Jesús F. San-Miguel, Ramón García-Sanz, Norma Gutierrez. Neoplastic diseases of the blood (5th edition). Editors: Peter H. Wiernik, John Goldman, Janice Dutcher, Robert A. Kyle. Chapter 32: 615-636, 2013

Grants for research in progress

PROJECT	IP	GRANT	TIME
Red Nacional de Terapia Celular (TerCel)	Consuelo del Cañizo	ISCIII (RD06/0010/0021)	2007-2013
Red Temática de Investigación Cooperativa en Cáncer (RTICC)	Jesús San Miguel	Instituto de Salud Carlos III (RD06/0020/0006)	2007-2013
Estudio de la eficacia y mecanismo de acción de fármacos inhibidores de tirosina quinasas sobre las células mielomatosas y el microambiente de la médula ósea.	Jesús San Miguel	Fundación Mutua Madrileña (AP27262008)	2008-2011
Translating genomic and epigenetic studies of MDS and AML (EUGESMA)	Ken Mills, vice chairman: JM Hernández	Unión Europea (COST). BMBS Action BM0801	2008-2012
Mejora de la Sala Blanca del Servicio de Hematología del Hospital Universitario de Salamanca	Consuelo del Cañizo	MICINN (PLE2009-0094)	2009-2013
Heterogeneidad evolutiva del mieloma: en busca de respuestas biológicas	Jesús San Miguel Izquierdo	Instituto de Salud Carlos III (PS09/01897)	2009-2013
Células madre mesenquimales (MSC) de médula ósea y fisiopatología de los síndromes mielodisplásicos	Consuelo del Cañizo	ISCIII (PS09/01530)	2010-2012
Tratamiento de la discopatía degenerativa intervertebral lumbar mediante artrodesis posterolateral instrumentada y células madre mesenquimales autólogas	Consuelo del Cañizo	Ministerio de Sanidad y política social (TRA-138)	2010-2012
ExGenEx	Jesús María Hernández Rivas	Norvatis Farmacéutica S.A.	2010-2012
Análisis comparativo del exoma en las variantes genéticas de la leucemia linfática crónica B (LLC-B)	Jesús M Hernández	FIS 09/01543	2010-2012
Proyecto Genoma en Leucemia Linfática Crónica dentro del "International Cancer Genome Consortium"	En Salamanca los investigadores participantes: a) Hospital Universitario: Prof. San Miguel, Marcos González Díaz, Jesús Hernández Rivas b) Centro de Investigación del Cáncer: Prof. Eugenio Santos, Enrique de Álava	Proyecto internacional financiado por el Instituto Carlos III (Coordinador: Prof. Elías Campo. Hospital Clinic, Barcelona, España)	2010-2012
Polimorfismos Genéticos en Linfoma B Difuso de Célula Grande. Implicaciones Clínico-biológicas y pronósticas en pacientes incluidos en un protocolo terapéutico del Grupo GEL-TAMO	Marcos González Díaz	Beca del Fondo de Investigaciones Sanitarias de la Seguridad Social (PS09/01382)	2010-2012
Evaluation of focal adhesions as a new therapeutic target in acute myeloid leukemia	Marcos González Díaz (Investigador del Proyecto unitario: Dr J. Sierra)	Convocatoria Publica Fundació La Mataró de TV3: Nº Orphan: 519, Nº Omin: 601626	2010-2012
Análisis de diferenciación B en sangre periférica y medula ósea en macroglobulinemia de waldenström, gammapatía monoclonal se significado incierto IgM y amiloidosis sistémica primaria mediante citometría de flujo de alta sensibilidad	M. Belén Vidriales	Junta de Castilla y León	2010-2012
Determinación de la alteración 5q- en pacientes diagnosticados de SMD	Jesús M Hernández	Celgene	2010-2014
Comparación entre células mesenquimales de médula ósea (MSC-MO) y de tejido adiposo (MSC-TA) para su uso en programas de medicina regenerativa osteoarticular	Consuelo del Cañizo	Consejería de Sanidad de la Junta de Castilla y León (BIO113/SA59/11)	2011-2012

PROJECT	IP	GRANT	TIME
Análisis olfativo del cáncer humano "in vivo" e "in vitro"	Jesús M Hernández	Ministerio de Ciencia e Innovación (subprograma INNPACTO) IPT-2011-0925-900000	2011-2012
Estudio de las bases genéticas de la recaída del mieloma múltiple mediante la integración del análisis genómico y de la metilación global	Norma C. Gutiérrez Gutiérrez	Gerencia Regional de Salud (Junta de Castilla y León) (GRS702/A/11)	2011-2013
Análisis olfativo del cáncer humano in vivo e in vitro	Jesús María Hernández Rivas	Ministerio de Ciencia e Innovación (IPT-2011-0925-900000-DIAFANO)	2011-2014
Estudio genómico y epigenético de los síndromes mielodisplásicos (SMD) mediante microarrays de alta densidad. Evaluación de la respuesta terapéutica	Jesús María Hernández Rivas	Fundación Solórzano (FS/15-2011)	2012
Subvención directa al centro en red de medicina regenerativa y terapia celular de Castilla y León	Jesús San Miguel Izquierdo	Junta de Castilla y León	2012
Changes in gene expression levels in patients treated with 5-azacytidine: A pharmacogenomic study in AML or MDS patients treated with 5-azacytidine	Jesús M Hernández	Celgene	2012-2013
Valor diagnóstico y pronóstico del perfil de expresión génica, mutaciones somáticas y nivel de enfermedad mínima residual en la leucemia mieloblástica aguda (LMA)	Marcos González Díaz	Fondo de Investigaciones Sanitarias de la Seguridad Social: (Expte: PI12/02321)	2012-2014
Resistencia adquirida a nuevos fármacos frente al mieloma múltiple. Estudio de sus características, mecanismos responsables y reversibilidad	Enrique Ocio	Instituto de Salud Carlos III	2012-2014
Next Generation Sequencing platform for targeted Personalized Therapy of Leukemia (NGS-PTL)	Jesús María Hernández Rivas	Unión Europea	2012-2015
Análisis de resistencia en mieloma múltiple y desarrollo de alternativas terapéuticas para superarla: proyecto basado en dos ensayos multicéntricos nacionales	Jesús San Miguel Izquierdo	Fundación AECC (GCB120981SAN)	2012-2017
Estudio de las alteraciones en el gen ikaros en leucemia aguda linfoblástica.	Rocío Benito Sánchez	Junta de Castilla y León (BIO/SA31/13)	2013
Interacciones entre las células de mieloma y estroma de la médula ósea: papel en la progresión de las gammapatías asistomáticas, fisiopatología y lesiones osteolíticas del mieloma múltiple	Mercedes Garayoa	Instituto de Salud Carlos III (PI12/02591)	2013-2015
In vivo evaluation of the antitumor effect of PharmaMar compounds (Zalypsis and Aplidin) in preclinical models of multiple myeloma following the co-administration with other compounds	Enrique Ocio	PharMamar	2013-2015
Red Temática de Investigación Cooperativa en Cáncer (RTICC)	Marcos González Díaz	Instituto de Salud Carlos III (RD12/0036/0069)	2013-2016
Red Temática de Investigación Cooperativa en Cáncer (RTICC)	Jesús San Miguel	Instituto de Salud Carlos III (RD12/0036/0058)	2013-2016
Minimal residual disease monitoring for multiple myeloma: automation of highly-sensitive conventional flow cytometric bone marrow-based approaches and development of novel minimally invasive blood procedures	Jesús San Miguel	International Myeloma Foundation	2013-2016



Stem cells, cancer stem cells and cancer biology

Team Leader:

Isidro Sánchez García
Phone.: +34 923 294 813
E-mail: isg@usal.es

Research Team
Postdoctoral
Inés González Herrero
Carolina Vicente Dueñas
Predoctoral
Marcos Barajas Diego
Isabel Romero Camarero
Idoia García Ramírez
Alberto Martín Lorenzo
Lucía Ruiz Roca
Technician
Esther Alonso Escudero
Students
Esther Arnaiz González
Mónica Patricia Cazar Cifuentes
Elia H. Cornejo Muñoz
Carlos del Pilar Rodríguez
Mª Goretti Llamas Arriba
Alba Rodríguez Meira
Guillermo Rodríguez Hernández
Visiting Researcher
Carlos Samuel Marqués Boto

RESEARCH SUMMARY

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 (Perez-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 **New models towards assessing anti-cancer therapeutics.** Romero-Camarero I, Barajas-Diego M, Castellanos-Martín A, García-Martín Á, Varela G, Abad M, Ludeña MD, Pérez-Losada J, Sánchez-García I. ***Histol Histopathol. 2012 Feb;27(2):157-70. Review.*** PMID: 22207550 **IF: 2,281 / Q2**

2 **Essential role for telomerase in chronic myeloid leukemia induced by BCR-ABL in mice.** Vicente-Dueñas C, Barajas-Diego M, Romero-Camarero I, González-Herrero I, Flores T, Sánchez-García I. ***Oncotarget. 2012 Mar;3(3):261-6.*** PMID: 22408137 **IF: 6,636 / Q1**

3 **Understanding telomerase in cancer stem cell biology.** Vicente-Dueñas C, Romero-Camarero I, Sánchez-García I. ***Cell Cycle. 2012 Apr 15;11(8):1479-80. doi: 10.4161/cc.20108. Epub 2012 Apr 15.*** PMID: 22487683 **IF: 5,321 / Q1**

4 **Identification of LMO2 transcriptome and interactome in diffuse large B-cell lymphoma.** Cubedo E, Gentles AJ, Huang C, Natkunam Y, Bhatt S, Lu X, Jiang X, Romero-Camarero I, Freud A, Zhao S, Bacchi CE, Martínez-Climent JA, Sánchez-García I, Melnick A, Lossos IS. ***Blood. 2012 Jun 7;119(23):5478-91. doi: 10.1182/blood-2012-01-403154. Epub 2012 Apr 19.*** PMID: 22517897 **IF: 9,060 / D1**

5 **Expression of MALT1 oncogene in hematopoietic stem/progenitor cells recapitulates the pathogenesis of human lymphoma in mice.** Vicente-Dueñas C, Fontán L, Gonzalez-Herrero I, Romero-Camarero I, Segura V, Aznar MA, Alonso-Escudero E, Campos-Sanchez E, Ruiz-Roca L, Barajas-Diego M, Sagardoy A, Martinez-Ferrandis JI, Abollo-Jimenez F, Bertolo C, Peñuelas I, Garcia-Criado FJ, García-Cenador MB, Tousseyn T, Agirre X, Prosper F, Garcia-Bragado F, McPhail ED, Lossos IS, Du MQ, Flores T, Hernandez-Rivas JM, Gonzalez M, Salar A, Bellosillo B, Conde E, Siebert R, Sagaert X, Cobaleda C, Sanchez-Garcia I, Martinez-Climent JA. ***Proc Natl Acad Sci U S A. 2012 Jun 26;109(26):10534-9. doi: 10.1073/pnas.1204127109. Epub 2012 Jun 11.*** PMID: 22689981 **IF: 9,737 / D1**

6 **MALT lymphoma meets stem cells.** Vicente-Dueñas C, Cobaleda C, Martínez-Climent JÁ, Sánchez-García I. ***Cell Cycle. 2012 Aug 15;11(16):2961-2. doi: 10.4161/cc.21264. Epub 2012 Jul 24.*** PMID: 22825253 **IF: 5,321 / Q1**

7 **A novel molecular mechanism involved in multiple myeloma development revealed by targeting MafB to haematopoietic progenitors.** Vicente-Dueñas C, Romero-Camarero I, González-Herrero I, Alonso-Escudero E, Abollo-Jiménez F, Jiang X, Gutierrez NC, Orfao A, Marín N, Villar LM, Criado MC, Pintado B, Flores T, Alonso-López D, De Las Rivas J, Jiménez R, Criado FJ, Cenador MB, Lossos IS, Cobaleda C, Sánchez-García I. ***EMBO J. 2012 Sep 12;31(18):3704-17. doi: 10.1038/emboj.2012.227. Epub 2012 Aug 17.*** PMID: 22903061 **IF: 9,822 / D1**

8 **The cellular architecture of multiple myeloma.** Vicente-Dueñas C, Romero-Camarero I, García-Criado FJ, Cobaleda C, Sánchez-García I. ***Cell Cycle. 2012 Oct 15;11(20):3715-7. doi: 10.4161/cc.22178. Epub 2012 Sep 14.*** PMID: 22983005 **IF: 5,321 / Q1**

9 **Loss of p53 exacerbates multiple myeloma phenotype by facilitating the reprogramming of hematopoietic stem/progenitor cells to malignant plasma cells by MafB.** Vicente-Dueñas C, González-Herrero I, García Cenador MB, García Criado FJ, Sánchez-García I. ***Cell Cycle. 2012 Oct 15;11(20):3896-900. doi: 10.4161/cc.22186. Epub 2012 Sep 14.*** PMID: 22983007 **IF: 5,321 / Q1**

10 **p53 restoration kills primitive leukemia cells in vivo and increases survival of leukemic mice.** Velasco-Hernández T, Vicente-Dueñas C, Sánchez-García I, Martin-Zanca D. ***Cell Cycle. 2013 Jan 1;12(1):122-32. doi: 10.4161/cc.23031. Epub 2012 Dec 19.*** PMID: 23255106 **IF: 5,321 / Q1**

11 **Germinal centre protein HGAL promotes lymphoid hyperplasia and amyloidosis via BCR-mediated Syk activation.** Romero-Camarero I, Jiang X, Natkunam Y, Lu X, Vicente-Dueñas C, Gonzalez-Herrero I, Flores T, Garcia JL, McNamara G, Kunder C, Zhao S, Segura V, Fontan L, Martínez-Climent JA, García-Criado FJ, Theis JD, Dogan A, Campos-Sánchez E, Green MR, Alizadeh AA, Cobaleda C, Sánchez-García I, Lossos IS. ***Nat Commun. 2013;4:1338. doi: 10.1038/ncomms2334.*** PMID: 23299888 **IF: 10,015 / D1**

12 **Back to the beginning: The initiation of cancer.** Cobaleda C, Sánchez-García I. ***Bioessays. 2013 May;35(5):413. doi: 10.1002/bies.201300024. Epub 2013 Apr 2.*** PMID: 23553938 **IF: 5,423 / Q1**

13 **Function of oncogenes in cancer development: a changing paradigm.** Vicente-Dueñas C, Romero-Camarero I, Cobaleda C, Sánchez-García I. ***EMBO J. 2013 May 29;32(11):1502-13. doi: 10.1038/emboj.2013.97. Epub 2013 Apr 30. Review.*** PMID: 23632857 **IF: 9,822 / D1**

14 **CD133+ cell content correlates with tumour growth in melanomas from skin with chronic sun-induced damage.** González-Herrero I, Romero-Camarero I, Cañueto J, Cardeñoso-Álvarez E, Fernández-López E, Pérez-Losada J, Sánchez-García I, Román-Curto C. ***Br J Dermatol. 2013 Oct;169(4):830-7. doi: 10.1111/bjd.12428.*** PMID: 23662851 **IF: 3,759 / D1**

15 **Genetic background affects susceptibility to tumoral stem cell reprogramming.** García-Ramírez I, Ruiz-Roca L, Martín-Lorenzo A, Blanco O, García-Cenador MB, García-Criado FJ, Vicente-Dueñas C, Sánchez-García I. ***Cell Cycle. 2013 Aug 1;12(15):2505-9. doi: 10.4161/cc.25544. Epub 2013 Jul 8.*** PMID: 23839033 **IF: 5,321 / Q1**

16 **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: 9,737 / D1**

Other publications & Book chapters

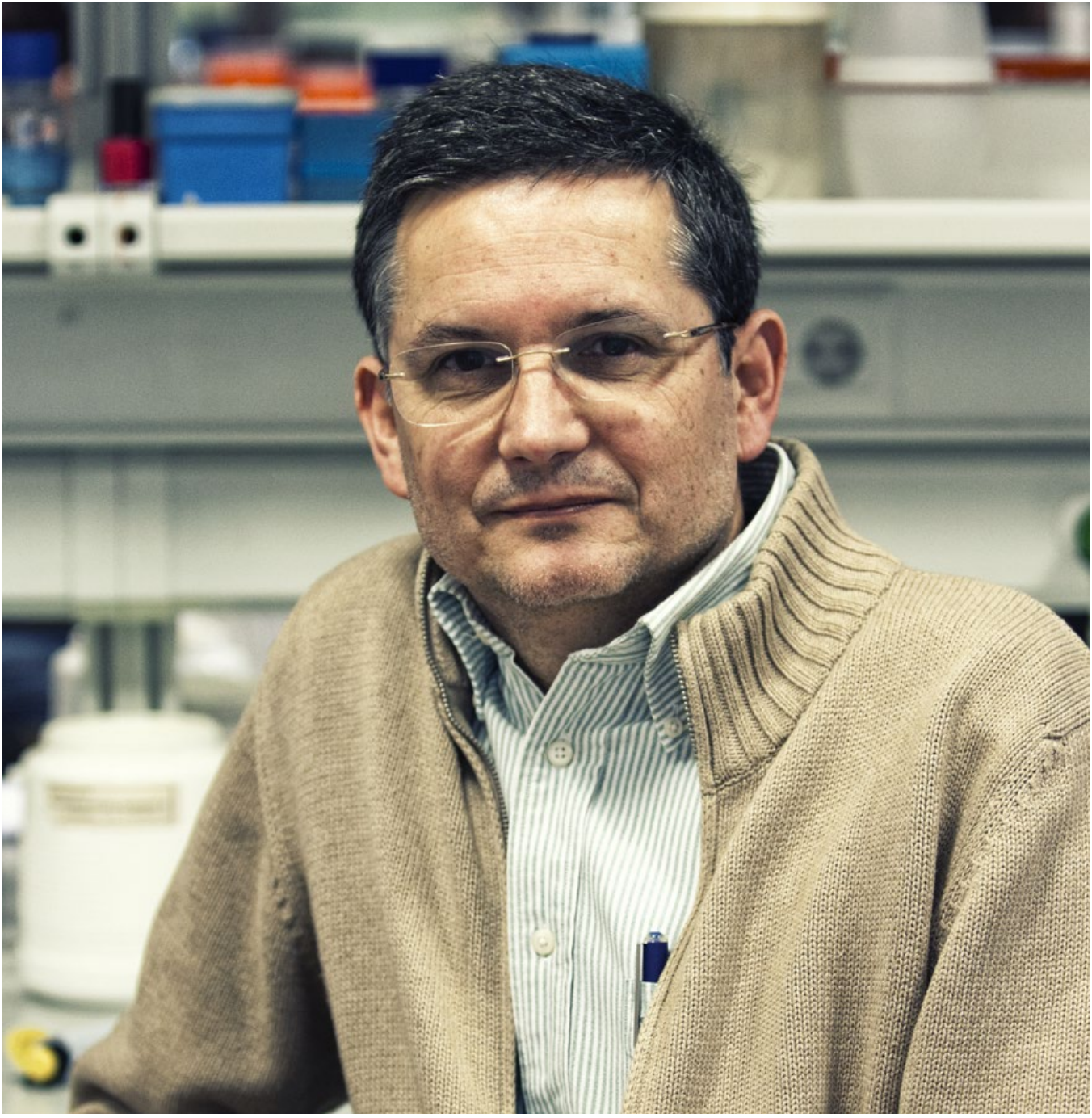
- **Plasticity and Tumorigenicity. Atlas Genet Cytogenet Oncol Haematol** Campos-Sanchez E, Sanchez-Garcia I, Cobaleda C. 2012; 16(3):238-251. http://atlasgeneticsoncology.org/Deep/PluripotencyID20103.html
- **Cancer Stem Cells. In: Encyclopaedia of Life Sciences (eLS)** Cobaleda, C; Vicente-Duenas, C; Romero-Camarero, I; and Sanchez-Garcia, I (January 2012). 2012, John Wiley & Sons, Ltd: Chichester http://www.els.net/ [DOI: 10.1002/9780470015902.a0020860.pub2]

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Biología del Cáncer	Isidro Sánchez García	Ministerio de Ciencia y Tecnología CSD2007-00017(PROGRAMA CONSOLIDER ONCOSTEM)	2007-2012	528,600.00 €
Significance and Function of HGAL in Lymphoma.	Isidro Sánchez García	NIH grant (2R01 CA109335-04A1)	2009-2014	250,000.00 $
Papel de las células madre cancerígenas en la biología tumoral y en la oncología traslacional	Isidro Sánchez García	Ministerio de Ciencia e Innovación (SAF2009-08803)	2010-2012	211,750.00 €
Convenio específico de colaboración entre la Consejería de Sanidad de la JCYL, Caja Guipúzcoa San Sebastián "Kutxa", la FIECSCYL, la FICUS y la Fundación Inbiomed, para la puesta en marcha y desarrollo en Castilla y León del proyecto en red de investigación en células madre tumorales en cáncer de mama	Isidro Sánchez García	La Kutxa	2011-2013	408,000.00 €
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 €
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)	Isidro Sánchez García	European Union (Marie Curie initial training programme)	2013-2016	
Papel de la Células Stem Cancerígenas en la biología del mieloma múltiple	Isidro Sánchez García	Junta de Castilla y León (BIO/SA06/13)	2013	27,669.00 €

Other activities & Relevant facts

- 3-09-2009-present. Member of the European Stem Cell Group. Associate PI (API) of EuroSyStem (http://www.eurosystemproject.eu/associate-principal-investigators).
- 2012-present. PI of the CANC-15 group within the Institute of Biomedical Research of Salamanca (IBSAL).
- June 2012: member of the meeting in conclave on shaping future research on the **Childhood leukaemia risks: Towards a better understanding of unexplained results MELODI scientific workshop. Jointly Organised by BfS and IRSN** 8-22 June 2012, Bombon, France
- October 2012-present: member of the Halifax project (www.gettingtoknowcancer.org)
- The technological and scientific achievements mentioned above have also been the basis for collaborations with companies and institutions like SUINSA, GRIFOLS, Schmid & Partner Engineering AG (SPEAG, Zurich, Switzerland), and University of Miami.



Hereditary cancer

RESEARCH SUMMARY

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. 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.

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 the to Lynch Syndrome.

A third aim is the analysis of the modifications induced in cell lines derived from colon cancer, breast cancer and myeloma treated with histone deacetylase inhibitors.

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

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

Team Leader:

Rogelio González Sarmiento
Phone.: +34 923 294 814
E-mail: gonzalez@usal.es

Research Team

Predoctoral

Carlos Jiménez Criado
María Jesús García Salgado
Catia Daniela Quintas Faria
Ricardo Usategui Martín
Javier Fernández Mateos
Juan Luis Blázquez Román
Marta Fernández Prieto
Leonor López Almeida
Vanessa Carolina Rivero Perdomo
Iskander Aurrekoetxwa Rodríguez
Jesús Mª Hernández Sánchez
Diego Martín Sánchez
Fernando Mesías Recamán

Technicians

Jessica Pérez García (Genetic Council)
Atenea Pascual Rodríguez

Publications

1 **Two novel mutations in the thyroglobulin gene as cause of congenital hypothyroidism: identification a cryptic donor splice site in the exon 19.** Targovnik HM, Edouard T, Varela V, Tauber M, Citterio CE, González-Sarmiento R, Rivolta CM. ***Mol Cell Endocrinol. 2012 Jan 2;348(1):313-21. doi: 10.1016/j.mce.2011.09.024. Epub 2011 Sep 21.*** PMID: 21958696 **IF: 4,039 / Q2**

2 **Meta-analysis: glutathione-S-transferase allelic variants are associated with alcoholic liver disease.** Marcos M, Pastor I, Chamorro AJ, Ciria-Abad S, González-Sarmiento R, Laso FJ. ***Aliment Pharmacol Ther. 2011 Nov;34(10):1159-72. doi: 10.1111/j.1365-2036.2011.04862.x. Epub 2011 Oct 3.*** PMID: 21967547 **IF: 4,548 / Q1**

3 **Congenital goitrous hypothyroidism: mutation analysis in the thyroid peroxidase gene.** Belforte FS, Miras MB, Olcese MC, Sobrero G, Testa G, Muñoz L, Gruñeiro-Papendieck L, Chiesa A, González-Sarmiento R, Targovnik HM, Rivolta CM. ***Clin Endocrinol (Oxf). 2012 Apr;76(4):568-76. doi: 10.1111/j.1365-2265.2011.04249.x.*** PMID: 21981063 **IF: 3,396 / Q2**

4 **Prevalence of autosomal recessive congenital ichthyosis: a population-based study using the capture-recapture method in Spain.** Hernández-Martín A, Garcia-Doval I, Aranegui B, de Unamuno P, Rodríguez-Pazos L, González-Enseñat MA, Vicente A, Martín-Santiago A, Garcia-Bravo B, Feito M, Baselga E, Círia S, de Lucas R, Ginarte M, González-Sarmiento R, Torrelo A. ***J Am Acad Dermatol. 2012 Aug;67(2):240-4. doi: 10.1016/j.jaad.2011.07.033. Epub 2011 Oct 14.*** PMID: 22000705 **IF:NI**

5 **Cannabinoid receptor 1 gene is associated with alcohol dependence.** Marcos M, Pastor I, de la Calle C, Barrio-Real L, Laso FJ, González-Sarmiento R. ***Alcohol Clin Exp Res. 2012 Feb;36(2):267-71. doi: 10.1111/j.1530-0277.2011.01623.x. Epub 2011 Nov 15.*** PMID: 22085192 **IF: 3,421 / Q1**

6 **Clinical, molecular and biochemical characterization of nine Spanish families with Conradi-Hünermann-Happle syndrome: new insights into X-linked dominant chondrodysplasia punctata with a comprehensive review of the literature.** Cañueto J, Girós M, Ciria S, Pi-Castán G, Artigas M, García-Dorado J, García-Patos V, Virós A, Vendrell T, Torrelo A, Hernández-Martín A, Martín-Hernández E, Garcia-Silva MT, Fernández-Burriel M, Rosell J, Tejedor M, Martínez F, Valero J, García JL, Sánchez-Tapia EM, Unamuno P, González-Sarmiento R. ***Br J Dermatol. 2012 Apr;166(4):830-8. doi: 10.1111/j.1365-2133.2011.10756.x. Epub 2012 Mar 2. Review.*** PMID: 22121851 **IF: 3,759 / D1**

7 **[Analysis of TRPV1 gene polymorphisms in Spanish patients with neuropathic pain].** Armero P, Muriel C, López M, Santos J, González-Sarmiento R. ***Med Clin (Barc). 2012 Jun 2;139(1):1-4. doi: 10.1016/j.medcli.2011.10.028. Epub 2012 Mar 6. Spanish.*** PMID: 22401740 **IF: 1,399 / Q2**

8 **Shorter telomere length is associated with increased ovarian cancer risk in both familial and sporadic cases.** Martinez-Delgado B, Yanowsky K, Inglada-Perez L, de la Hoya M, Caldes T, Vega A, Blanco A, Martin T, Gonzalez-Sarmiento R, Blasco M, Robledo M, Urioste M, Song H, Pharoah P, Benitez J. ***J Med Genet. 2012 May;49(5):341-4. doi: 10.1136/jmedgenet-2012-100807. Epub 2012 Apr 6.*** PMID: 22493152 **IF: 5,703 / Q1**

9 **Association of μ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis.** Chamorro AJ, Marcos M, Mirón-Canelo JA, Pastor I, González-Sarmiento R, Laso FJ. ***Addict Biol. 2012 May;17(3):505-12. doi: 10.1111/j.1369-1600.2012.00442.x. Review.*** PMID: 22515274 **IF: 5,914 / D1**

10 **Prognostic value of telomere length in acute coronary syndrome.** Perez-Rivera JA, Pabon-Osuna P, Cieza-Borrella C, Martin-Herrero F, Gonzalez-Porras JR, Gonzalez-Sarmiento R. ***Mech Ageing Dev. 2012 Nov-Dec;133(11-12):695-7. doi: 10.1016/j.mad.2012.09.003. Epub 2012 Sep 23.*** PMID: 23010295 **IF: 3,264 / Q2**

11 **New insights into thyroglobulin gene: molecular analysis of seven novel mutations associated with goiter and hypothyroidism.** Citterio CE, Machiavelli GA, Miras MB, Gruñeiro-Papendieck L, Lachlan K, Sobrero G, Chiesa A, Walker J, Muñoz L, Testa G, Belforte FS, González-Sarmiento R, Rivolta CM, Targovnik HM. ***Mol Cell Endocrinol. 2013 Jan 30;365(2):277-91. doi: 10.1016/j.mce.2012.11.002. Epub 2012 Nov 16.*** PMID: 23164529 **IF: 4,039 / Q2**

12 **The p53 codon 72 polymorphism (rs1042522) is associated with proliferative vitreoretinopathy: the Retina 4 Project.** Pastor-Idoate S, Rodriguez-Hernández I, Rojas J, Fernández I, García-Gutierrez MT, Ruiz-Moreno JM, Rocha-Sousa A, Ramkissoon Y, Harsum S, Maclaren RE, Charteris D, van Meurs J, González-Sarmiento R, Pastor JC; Genetics on PVR Study Group. ***Ophthalmology. 2013 Mar;120(3):623-8. doi: 10.1016/j.ophtha.2012.08.019. Epub 2012 Dec 1.*** PMID: 23207172 **IF: 5,563 / D1**

13 **First symposium of ichthyosis experts.** Hernández-Martín A, Torrelo-Fernández A, de Lucas-Laguna R, Casco F, González-Sarmiento R, Vega A, Pedreira-Massa JL, de Unamuno-Pérez P, Larcher F, Arroyo I, Traupe H. ***Actas Dermosifiliogr. 2013 Dec;104(10):877-82. doi: 10.1016/j.ad.2012.11.018. Epub 2013 Jan 30. English, Spanish.*** PMID: 23375695 **IF: NI**

14 **Influence of CFH, HTRA1 and ARMS2 haplotype polymorphisms in the development of age-related macular disease.** Cruz-González F, Lorenzo-Pérez R, Cañete-Campos C, Hernández-Galilea E, González-Sarmiento R. ***Arch Soc Esp Oftalmol. 2013 Jan;88(1):3-10. doi: 10.1016/j.oftal.2012.04.019. Epub 2012 Jun 2. English, Spanish.*** PMID: 23414945 **IF: NI**

15 **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. 2013 Mar 27. [Epub ahead of print]*** PMID: 23534868 **IF: 1,070 / Q3**

16 **Common susceptibility alleles and SQSTM1 mutations predict disease extent and severity in a multinational study of patients with Paget's disease.** Albagha OM, Visconti MR, Alonso N, Wani S, Goodman K, Fraser WD, Gennari L, Merlotti D, Gianfrancesco F, Esposito T, Rendina D, di Stefano M, Isaia G, Brandi ML, Giusti F, Del Pino-Montes J, Corral-Gudino L, Gonzalez-Sarmiento R, Ward L, Rea SL, Ratajczak T, Walsh JP, Ralston SH. ***J Bone Miner Res. 2013 Nov;28(11):2338-46. doi: 10.1002/jbmr.1975.*** PMID: 23658060 **IF: 6,128 / Q1**

17 **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, Garcia 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: NI**

18 **Molecular evidence of type 2 mosaicism in Gorlin syndrome.** Torrelo A, Hernández-Martín A, Bueno E, Colmenero I, Rivera I, Requena L, Happle R, González-Sarmiento R. ***Br J Dermatol. 2013 Dec;169(6):1342-5. doi: 10.1111/bjd.12458.*** PMID: 23746055 **IF: 3,759 / D1**

19 **The highly prevalent BRCA2 mutation c.2808_2811del (3036delACAA) is located in a mutational hotspot and has multiple origins.** Infante M, Durán M, Acedo A, Sánchez-Tapia EM, Díez-Gómez B, Barroso A, García-González M, Feliubadaló L, Lasa A, de la Hoya M, Esteban-Cardeñosa E, Díez O, Martínez-Bouzas C, Godino J, Teulé A, Osorio A, Lastra E, González-Sarmiento R, Miner C, Velasco EA. ***Carcinogenesis. 2013 Nov;34(11):2505-11. doi: 10.1093/carcin/bgt272. Epub 2013 Aug 8.*** PMID: 23929434 **IF: 5,635 / Q1**

20 **Novel mutational mechanism in the thyroglobulin gene: imperfect DNA inversion as a cause for hereditary hypothyroidism.** Citterio CE, Rossetti LC, Souchon PF, Morales C, Thouvard-Viprey M, Salmon-Musial AS, Mauran PL, Doco-Fenzy M, González-Sarmiento R, Rivolta CM, De Brasi CD, Targovnik HM. ***Mol Cell Endocrinol. 2013 Dec 5;381(1-2):220-9. doi: 10.1016/j.mce.2013.07.034. Epub 2013 Aug 7.*** PMID: 23933148 **IF: 4,039 / Q2**

21 **Association of a novel polymorphism of the ϒ-chimaerin gene (CHN2) with smoking.** Barrio-Real L, Barrueco M, González-Sarmiento R, Caloca MJ. ***J Investig Med. 2013 Oct;61(7):1129-31. doi: 10.231/JIM.0b013e3182a32ff9.*** PMID: 23941981 **IF: 1,746 / Q2**

22 **VEGF A (rs699947 and rs833061) and VEGFR2 (rs2071559) gene polymorphisms are not associated with AMD susceptibility in a Spanish population.** Cruz-González F, Cieza-Borrella C, Cabrillo-Estévez L, Cañete-Campos C, Escudero-Domínguez F, González-Sarmiento R. ***Curr Eye Res. 2013 Dec;38(12):1274-7. doi: 10.3109/02713683.2013.819926. Epub 2013 Aug 23.*** PMID: 23971975 **IF: 1,710 / Q2**

23 **Evaluation of rare variants in the new fanconi anemia gene ERCC4 (FANCQ) as familial breast/ovarian cancer susceptibility alleles.** Osorio A, Bogliolo M, Fernández V, Barroso A, de la Hoya M, Caldés T, Lasa A, Ramón y Cajal T, Santamariña M, Vega A, Quiles F, Lázaro C, Díez O, Fernández D, González-Sarmiento R, Durán M, Piqueras JF, Marín M, Pujol R, Surrallés J, Benítez J. ***Hum Mutat. 2013 Dec;34(12):1615-8. doi: 10.1002/humu.22438. Epub 2013 Oct 7.*** PMID: 24027083 **IF: 5,213 / Q1**

24 **The role of the abnormalities in the distal pathway of cholesterol biosynthesis in the Conradi-Hünermann-Happle syndrome.** Cañueto J, Giros M, González-Sarmiento R. ***Biochim Biophys Acta. 2014 Mar;1841(3):336-344. doi: 10.1016/j.bbalip.2013.09.002. Epub 2013 Sep 11. Review.*** PMID: 24036494 **IF: 4,134 / Q1**

25 **[Pharmacogenetics and age-related macular degeneration, towards an individualized treatment of the disease].** Cruz-González F, Cabrillo Estévez L, López-Valverde G, Escudero-Domínguez F, González-Sarmiento R. ***Arch Soc Esp Oftalmol. 2013 Oct;88(10):371-2. doi: 10.1016/j.oftal.2013.03.006. Epub 2013 May 15. Spanish.*** PMID: 24060299 **IF:NI**

26 **Integrated analysis of mismatch repair system in malignant astrocytomas.** Rodríguez-Hernández I, Garcia JL, Santos-Briz A, Hernández-Laín A, González-Valero JM, Gómez-Moreta JA, Toldos-González O, Cruz JJ, Martin-Vallejo J, González-Sarmiento R. ***PLoS One. 2013 Sep 20;8(9):e76401. doi: 10.1371/journal.pone.0076401. eCollection 2013.*** PMID: 24073290 **IF: 3,730 / Q1**

27 **Ectodermal dysplasia-skin fragility syndrome: a novel mutation in the PKP1 gene.** Hernández-Martín A, Torrelo A, Ciria S, Colmenero I, Aguilar A, Grimalt R, González-Sarmiento R. ***Clin Exp Dermatol. 2013 Oct;38(7):787-90. doi: 10.1111/ced.12109.*** PMID: 24073657 **IF: 1,329 / Q3**

28 **VRK2 identifies a subgroup of primary high-grade astrocytomas with a better prognosis.** Rodríguez-Hernández I, Vázquez-Cedeira M, Santos-Briz A, García JL, Fernández IF, Gómez-Moreta JA, Martin-Vallejo J, González-Sarmiento R, Lazo PA. ***BMC Clin Pathol. 2013 Oct 1;13(1):23. doi: 10.1186/1472-6890-13-23.*** PMID: 24079673 **IF: NI**

29 **Influence of Uridine Diphosphate-Glucuronyltransferase 2B7 (UGT2B7) Variants on Postoperative Buprenorphine Analgesia.** Sastre JA, Varela G, López M, Muriel C, González-Sarmiento R. ***Pain Pract. 2013 Nov 20. doi: 10.1111/papr.12152. [Epub ahead of print]*** PMID: 24256307 **IF: 2,605 / Q2**

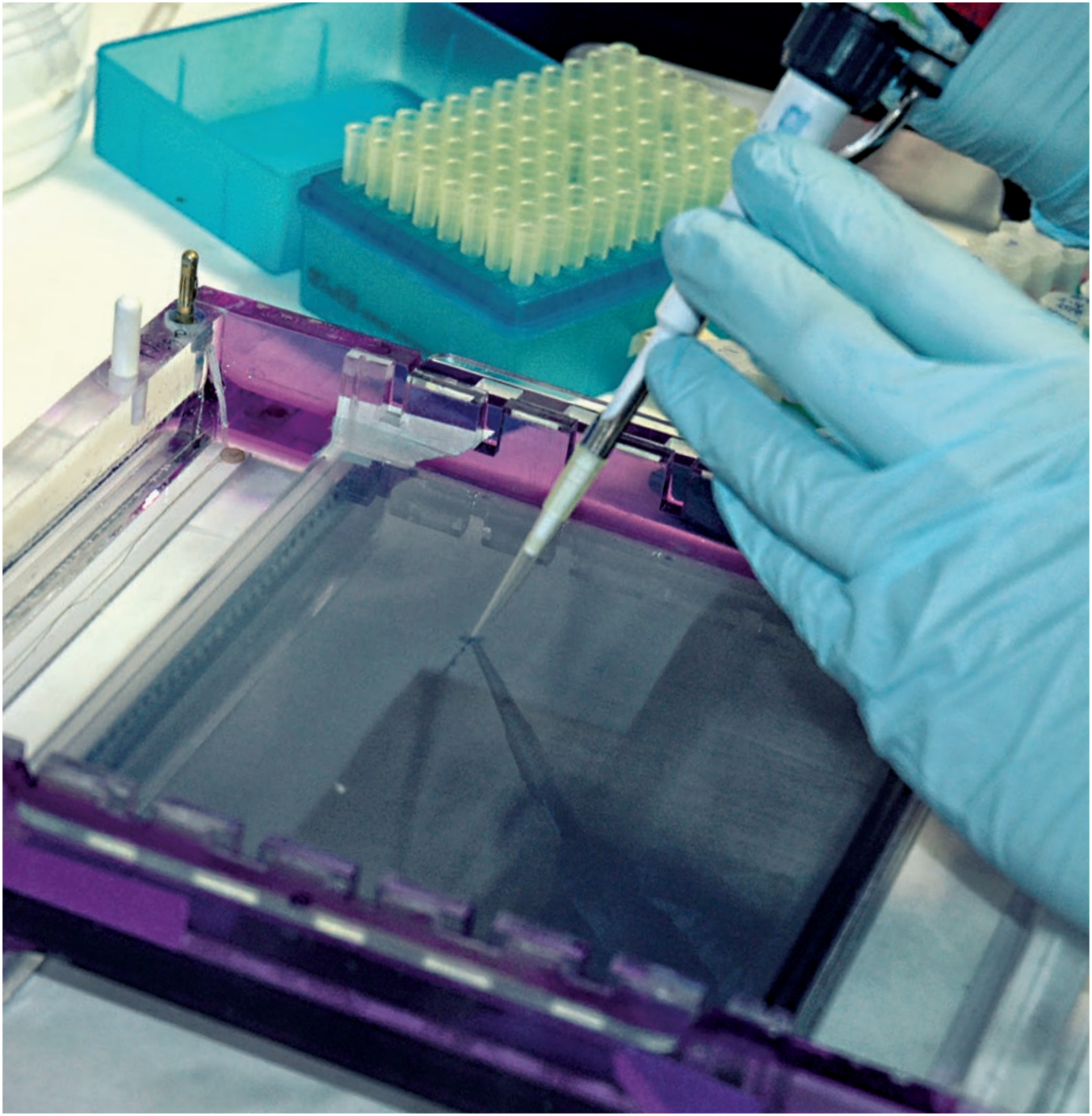
30 **Effect of telomere length on prognosis in men with acute coronary syndrome.** Perez-Rivera JA, Pabon-Osuna P, Cieza-Borrella C, Duran-Bobin O, Martin-Herrero F, Gonzalez-Porras JR, Gonzalez-Sarmiento R. ***Am J Cardiol. 2014 Feb 1;113(3):418-21. doi: 10.1016/j.amjcard.2013.10.009. Epub 2013 Nov 7.*** PMID: 24290493 **IF: 3,209 / Q2**

31 **Analysis of DNA repair gene polymorphisms in glioblastoma.** Rodriguez-Hernandez I, Perdomo S, Santos-Briz A, Garcia JL, Gomez-Moreta JA, Cruz JJ, Gonzalez-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: 2,196 / Q3**

32 **The T309G MDM2 gene polymorphism is a novel risk factor for proliferative vitreoretinopathy.** Pastor-Idoate S, Rodríguez-Hernández I, Rojas J, Fernández I, García-Gutiérrez MT, Ruiz-Moreno JM, Rocha-Sousa A, Ramkissoon Y, Harsum S, MacLaren RE, Charteris D, VanMeurs JC, González-Sarmiento R, Pastor JC; Genetics on PVR Study Group. ***PLoS One. 2013 Dec 9;8(12):e82283. doi: 10.1371/journal.pone.0082283. eCollection 2013.*** PMID: 24349246 **IF: 3,73 / Q1**

Other activities & Relevant facts

- **Miembro del Consejo de Gobierno de la Universidad de Salamanca**



Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Caracterización de alteraciones genéticas y epigenéticas comunes a tumores asociados a síndrome de Lynch	Rogelio González Sarmiento	Junta de Castilla y León (PI10/00219)	2011-2012	122,815.00 €
Convocatoria de Proyectos de Investigación en Biomedicina, Biotecnología y Ciencias de la Salud. Importancia del microARN en la inflamación y esteatohepatitis asociada a la obesidad	Rogelio González Sarmiento (Coinvestigador)	Gerencia Regional de Salud de Castilla y León (GRS 681/A/11)	2011-2013	
Valor de los polimorfismos del gen CHRNA5 en la adicción al tabaco. Influencia de los mismos en el proceso de adicción y en la terapia de abandono	Rogelio González Sarmiento (Coinvestigador)	Consejería de Sanidad Junta de Castilla y León (GRS553/A/10)	2010-2012	12,000 €

Kinases in oncology. Signaling by receptor tyrosine kinases

Team Leader:

Atanasio Pandiella Alonso
Phone.: +34 923 294 815
E-mail: atanasio@usal.es

Research Team
Senior Researcher
Azucena Esparís Ogando
Postdoctoral
María Elena Díaz Rodríguez
Juan Carlos Montero González
Elena Vela Sarrión
Carla Patricia Ríos Luci
Predoctoral
Mª Florencia Re Louhau
Xi Chen
Stela Álvarez Fernández
Sara García Alonso
Yolanda Mª Guillén Pérez
Students
Ester García Casarrubios Pimentel
Ruana Calado
Gema Fuerte Hortigón
Pablo Rodríguez Núñez
Sandra Moro Villa
Adrián Sánchez Fernández
Visiting Scientific
Gamal Eldein Fathi Abdellatef
Technician
Virginia Fernández Chanca
Isabel Ramos Fernández

RESEARCH SUMMARY

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 signalling intermediates, such as P-Rex1 is being analyzed.

Objectives: To understand the role of RTK signalling pathways in cancer, with the purpose of developing therapeutic strategies to fight cancer.

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.

The ERK5 pathway in cancer

Azucena Esparís Ogando
Phone.: +34 923 294 815
E-mail: esparis@usal.es

RESEARCH SUMMARY

Breast cancer is the most common tumor in the female population. We have shown that ERK5 is frequently overexpressed and activated in human breast cancer, is related to prognosis, and its overexpression impairs the action of antineoplastic drugs. Currently active research lines are:

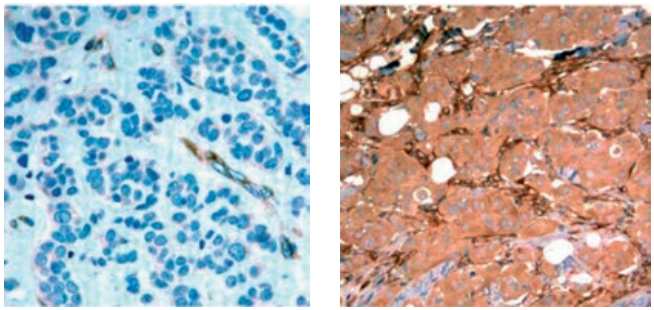
1. Mek5/ERK5 pathway in cancer

(i) We are analyzing the tumorigenic capacity of ERK5 in the breast by generating an animal model of expression of MEK5DD (the constitutively active form of MEK5) in the breast epithelia.
(ii) We intend to identify genes regulated by either gain or loss-of-function of ERK5, by using several cellular models.
(iii) We are investigating the participation of ERK5 in the proliferation of triple negative breast cancer cells, as we have also observed increased levels of ERK5 in this subtype of breast cancer.

2. Therapies directed against ERK5

Because ERK5 pathway could represent a new therapeutic target, we aim to:

(i) study the efficiency, in breast cancer, of an inhibitor directed against ERK5, designed by an US-based company
(ii) identify proteins that are associated with ERK5.



Immunohistochemical staining of Erk5 in human breast cancer showing samples scored as low (left panel) or high expression level (right panel).

Publications

1 **Sox2 expression in breast tumours and activation in breast cancer stem cells.** Leis O, Eguiara A, Lopez-Arribillaga E, Alberdi MJ, Hernandez-Garcia S, Elorriaga K, Pandiella A, Rezola R, Martin AG. ***Oncogene. 2012 Mar 15;31(11):1354-65. doi: 10.1038/onc.2011.338. Epub 2011 Aug 8.*** PMID: 21822303 **IF: 7,357 / Q1**

2 **Differential action of small molecule HER kinase inhibitors on receptor heterodimerization: therapeutic implications.** Sánchez-Martín M, Pandiella A. ***Int J Cancer. 2012 Jul 1;131(1):244-52. doi: 10.1002/ijc.26358. Epub 2011 Sep 22.*** PMID: 21826647 **IF: 6,198 / Q1**

3 **CD20 positive cells are undetectable in the majority of multiple myeloma cell lines and are not associated with a cancer stem cell phenotype.** Paíno T, Ocio EM, Paiva B, San-Segundo L, Garayoa M, Gutiérrez NC, Sarasquete ME, Pandiella A, Orfao A, San Miguel JF. ***Haematologica. 2012 Jul;97(7):1110-4. doi: 10.3324/haematol.2011.057372. Epub 2012 Feb 7.*** PMID: 22315496 **IF: 5,935 / Q1**

4 **Clinical significance of CD81 expression by clonal plasma cells in high-risk smoldering and symptomatic multiple myeloma patients.** Paiva B, Gutiérrez NC, Chen X, Vídriales MB, Montalbán MÁ, Rosiñol L, Oriol A, Martínez-López J, Mateos MV, López-Corral L, Díaz-Rodríguez E, Pérez JJ, Fernández-Redondo E, de Arriba F, Palomera L, Bengoechea E, Terol MJ, de Paz R, Martin A, Hernández J, Orfao A, Lahuerta JJ, Bladé J, Pandiella A, Miguel JF; GEM (Grupo Español de Mieloma)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) cooperative. ***Leukemia. 2012 Aug;26(8):1862-9. doi: 10.1038/leu.2012.42. Epub 2012 Feb 15.*** PMID: 22333880 **IF: 10,164 / D1**

5 **Predominance of mTORC1 over mTORC2 in the regulation of proliferation of ovarian cancer cells: therapeutic implications.** Montero JC, Chen X, Ocaña A, Pandiella A. ***Mol Cancer Ther. 2012 Jun;11(6):1342-52. doi: 10.1158/1535-7163.MCT-11-0723. Epub 2012 Apr 10.*** PMID: 22496482 **IF: 5,599 / Q1**

6 **Dasatinib as a bone-modifying agent: anabolic and anti-resorptive effects.** Garcia-Gomez A, Ocio EM, Crusoe E, Santamaria C, Hernández-Campo P, Blanco JF, Sanchez-Guijo FM, Hernández-Iglesias T, Briñón JG, Fisac-Herrero RM, Lee FY, Pandiella A, San Miguel JF, Garayoa M. ***PLoS One. 2012;7(4):e34914. doi: 10.1371/journal.pone.0034914. Epub 2012 Apr 23.*** PMID: 22539950 **IF: 3,730 / Q1**

7 **Lapachone analogs with enhanced antiproliferative activity.** Ríos-Luci C, Bonifazi EL, León LG, Montero JC, Burton G, Pandiella A, Misico RI, Padrón JM. ***Eur J Med Chem. 2012 Jul;53:264-74. doi: 10.1016/j.ejmech.2012.04.008. Epub 2012 Apr 19.*** PMID: 22560628 **IF: 3,499 / Q1**

8 **A dominant-negative N-terminal fragment of HER2 frequently expressed in breast cancers.** Morancho B, Parra-Palau JL, Ibrahim YH, Bernadó Morales C, Peg V, Bech-Serra JJ, Pandiella A, Canals F, Baselga J, Rubio I, Arribas J. ***Oncogene. 2013 Mar 14;32(11):1452-9. doi: 10.1038/onc.2012.152. Epub 2012 May 28.*** PMID: 22641219 **IF: 7,357 / Q1**

9 **Androgen-independent prostate cancer cells circumvent EGFR inhibition by overexpression of alternative HER receptors and ligands.** Carrión-Salip D, Panosa C, Menendez JA, Puig T, Oliveras G, Pandiella A, De Llorens R, Massaguer A. ***Int J Oncol. 2012 Sep;41(3):1128-38. doi: 10.3892/ijo.2012.1509. Epub 2012 Jun 6.*** PMID: 22684500 **IF: 2,657 / Q2**

10 **The evolving landscape of protein kinases in breast cancer: clinical implications.** Ocaña A, Amir E, Seruga B, Martin M, Pandiella A. ***Cancer Treat Rev. 2013 Feb;39(1):68-76. doi: 10.1016/j.ctrv.2012.05.004. Epub 2012 Jun 15. Review.*** PMID: 22703833 **IF: 6,024 / Q1**

11 **The epoxyketone-based proteasome inhibitors carfilzomib and orally bioavailable oprozomib have anti-resorptive and bone-anabolic activity in addition to anti-myeloma effects.** Hurchla MA, Garcia-Gomez A, Hornick MC, Ocio EM, Li A, Blanco JF, Collins L, Kirk CJ, Piwnica-Worms D, Vij R, Tomasson MH, Pandiella A, San Miguel JF, Garayoa M, Weilbaecher KN. ***Leukemia. 2013 Feb;27(2):430-40. doi: 10.1038/leu.2012.183. Epub 2012 Jul 5.*** PMID: 22763387 **IF: 10,164 / D1**

12 **RAF265, a dual BRAF and VEGFR2 inhibitor, prevents osteoclast formation and resorption. Therapeutic implications.** Garcia-Gomez A, Ocio EM, Pandiella A, San Miguel JF, Garayoa M. ***Invest New Drugs. 2013 Feb;31(1):200-5. doi: 10.1007/s10637-012-9845-3. Epub 2012 Jul 7.*** PMID: 22773056 **IF: 3,498 / Q1**

13 **Targeting HER receptors in cancer.** Ocaña A, Pandiella A. ***Curr Pharm Des. 2013;19(5):808-17. Review.*** PMID: 22973952 **IF: 3,311 / Q1**

14 **HER3 overexpression and survival in solid tumors: a meta-analysis.** Ocana A, Vera-Badillo F, Seruga B, Templeton A, Pandiella A, Amir E. ***J Natl Cancer Inst. 2013 Feb 20;105(4):266-73. doi: 10.1093/jnci/djs501. Epub 2012 Dec 8. Erratum in: J Natl Cancer Inst. 2013 Jul 3;105(13):944.*** PMID: 23221996 **IF:NI**

15 **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: 7,357 / Q1**

16 **ErbBs inhibition by lapatinib blocks tumor growth in an orthotopic model of human testicular germ cell tumor.** Juliachs M, Castillo-Ávila W, Vidal A, Piulats JM, Garcia Del Muro X, Condom E, Hernández-Losa J, Teixidó C, Pandiella A, Graupera M, Casanovas O, Germà JR, Villanueva A, Viñals F. ***Int J Cancer. 2013 Jul;133(1):235-46. doi: 10.1002/ijc.28009. Epub 2013 Feb 12.*** PMID: 23292912 **IF: 6,198 / Q1**

17 **Cellular plasticity confers migratory and invasive advantages to a population of glioblastoma-initiating cells that infiltrate peritumoral tissue.** Ruiz-Ontañon P, Orgaz JL, Aldaz B, Elosegui-Artola A, Martino J, Berciano MT, Montero JA, Grande L, Nogueira L, Diaz-Moralli S, Esparís-Ogando A, Vazquez-Barquero A, Lafarga M, Pandiella A, Cascante M, Segura V, Martinez-Climent JA, Sanz-Moreno V, Fernandez-Luna JL. ***Stem Cells. 2013 Jun;31(6):1075-85. doi: 10.1002/stem.1349.*** PMID: 23401361 **IF: 7,701 / D1**

18 **Potent antimyeloma activity of a novel ERK5/CDK inhibitor.** Álvarez-Fernández S, Ortiz-Ruiz MJ, Parrott T, Zaknoen S, Ocio EM, San Miguel J, Burrows FJ, Esparís-Ogando A, Pandiella A. ***Clin Cancer Res. 2013 May 15;19(10):2677-87. doi: 10.1158/1078-0432.CCR-12-2118. Epub 2013 Mar 26.*** PMID:23532886 **IF: 7,837 / D1**

19 **Scientific literature among smoking and respiratory system: repercussion and collaboration.** de Granda-Orive JI, Alonso-Arroyo A, García-Río F, Villanueva-Serrano S, Pandiella A, Aleixandre-Benavent R. ***Arch Bronconeumol. 2013 Jul;49(7):282-8. doi: 10.1016/j.arbres.2013.01.009. Epub 2013 Apr 4. Review. English, Spanish.*** PMID: 23562409 **IF:NI**

20 **ERK5/BMK1 is a novel target of the tumor suppressor VHL: implication in clear cell renal carcinoma.** Arias-González L, Moreno-Gimeno I, del Campo AR, Serrano-Oviedo L, Valero ML, Esparís-Ogando A, de la Cruz-Morcillo MÁ, Melgar-Rojas P, García-Cano J, Cimas FJ, Hidalgo MJ, Prado A, Callejas-Valera JL, Nam-Cha SH, Giménez-Bachs JM, Salinas-Sánchez AS, Pandiella A, del Peso L, Sánchez-Prieto R. ***Neoplasia. 2013 Jun;15(6):649-59.*** PMID: 23730213 **IF: 5,470 / Q1**

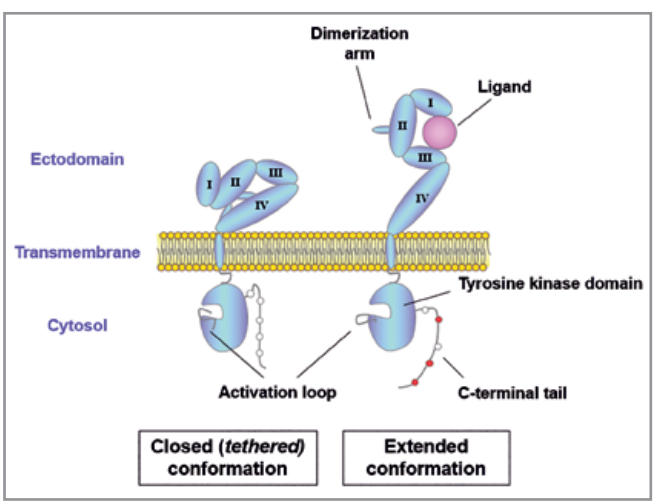
21 **Molecular pathways: P-Rex in cancer.** Pandiella A, Montero JC. ***Clin Cancer Res. 2013 Sep 1;19(17):4564-9. doi: 10.1158/1078-0432.CCR-12-1662. Epub 2013 Jun 10.*** PMID: 23753921 **IF: 7,837 / D1**

22 **Phosphorylation of P-Rex1 at serine 1169 participates in IGF-1R signaling in breast cancer cells.** Montero JC, Seoane S, Pandiella A. ***Cell Signal. 2013 Nov;25(11):2281-9. doi: 10.1016/j.cellsig.2013.07.018. Epub 2013 Jul 27.*** PMID: 23899556 **IF: 4,304 / Q2**

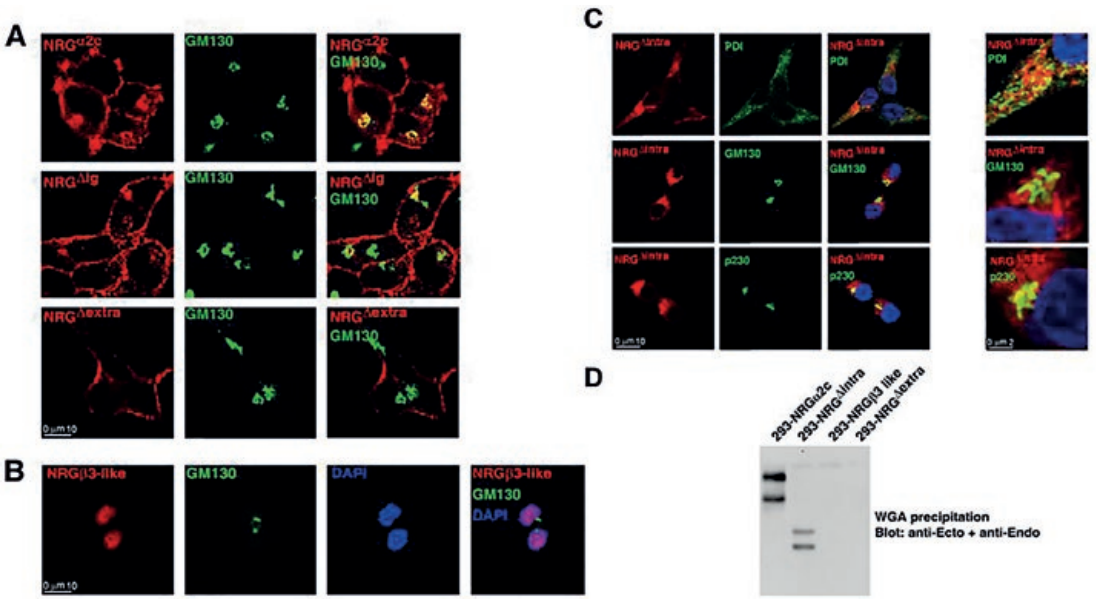
23 **Biological insights into effective and antagonistic combinations of targeted agents with chemotherapy in solid tumors.** Ocaña A, Freedman O, Amir E, Seruga B, Pandiella A. ***Cancer Metastasis Rev. 2013 Dec 15. [Epub ahead of print]*** PMID: 24338003 **IF: 7,787 / D1**

Grants for research in progress

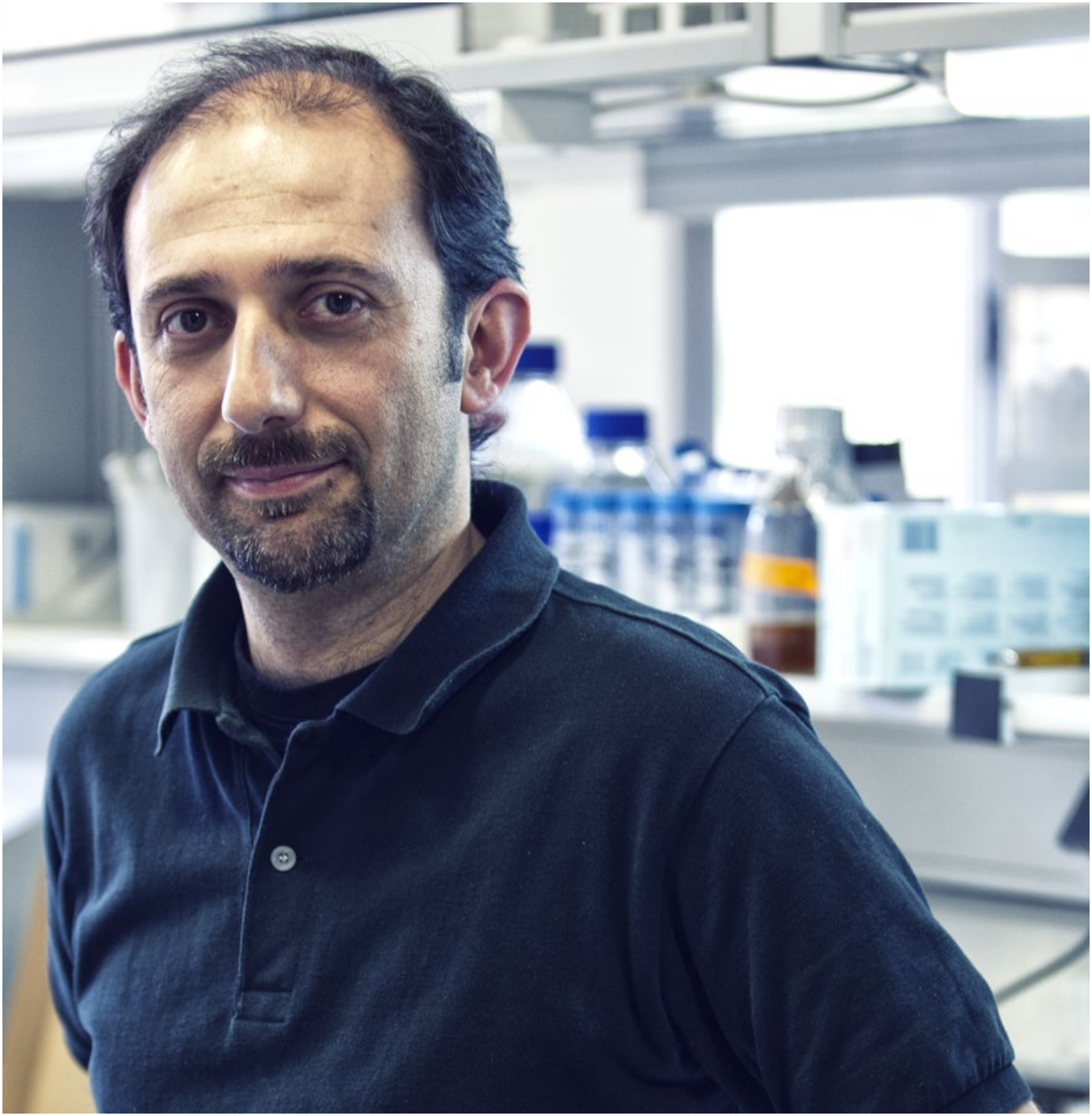
PROJECT	IP	GRANT	TIME	FUNDING
Red Temática en Investigación Cooperativa en Cáncer. (RD06/0020/0041)	Atanasio Pandiella Alonso	Instituto de Salud Carlos III	2007-2012	528,249.45 €
La red de señalización neuregulinas-receptores erbb (BFU2009-07728)	Atanasio Pandiella Alonso	Ministerio de Ciencia e Innovación	2010-2012	376,310.00 €
La ruta de ERK5 en cáncer (PS09/00868)	Azucena Esparis Ogando	Instituto de Salud Carlos III	2010-2012	116,765.00 €
Red Temática de Investigación Cooperativa en Cáncer.	Atanasio Pandiella Alonso	Instituto de Salud Carlos III (RD12/0036/0003)	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	2012-2017	600,000.00 €
Papel de PDCD4 como intermediario en la señalización por receptores ERBS	Juan Carlos Montero González	Junta de Castilla y León (BIO/SA28/13)	2013	13,444.00 €
Identification of new molecular targets in triple negative breast cancer	Juan Carlos Montero González	Instituto de Salud Carlos III (CP12/03073)	2013-2015	121,500.00 €
Señalización por receptores ERBB/HER	Atanasio Pandiella Alonso	Ministerio de Economía y Competitividad (BFU2012-39151)	2013-2016	351,000.00 €



Structure of ErbB/HER receptors. The figure shows a schematic representation of inactive (closed) and active (extended) ErbB receptors. Interaction of ligands with the extracellular region of ErbB receptors triggers conformational changes that provoke activation of the ErbB receptors through extension of the dimerization arm, present in their ectodomain. Interaction of two dimerization arms stabilizes the ErbB receptors as dimers favoring transautophosphorylation and activation.



Subcellular localization of pro-NRG2c mutatnts. Distribution of NRG2c, pro-NRG1g, and pro-NRGextra (*A*) and NRG3-like (*B*) in 293 cells was assessed by immunofluorescence using the anti-NRG or anti-endodomain antibodies as described under "Experimental was performed whit DAPI. *C*, detection of the pro-NRGintra mutant in 293 cells by immunofluorescence with the anti-endodomain antibody. Colocalization with the *cis*-Golgi was determined using anti-GM130 antibody, and colocalization with the *trans*-Golgi apparatus was determined with the anti-P230 antibody. The endoplastic reticulum was stained with the anti-protein-disulfide isomerase (*PDI*) antibody. *D*, glycosylation of the different pro-NRG2c mutants. Protein extracts of 293 cells expressing each construct were precipitated with wheat germ agglutinin-agarose (*WGA*) for 2 h and centrifuged, and complexes were resolved in a 10% SDS-polyacrylamide gels. Detection of pro-NRG forms was carried out by Western blot using the anti-ectodomain and anti-endodomain antibodies.



Structural biology of cell adhesion and signaling

Team Leader:

José María de Pereda Vega
Phone.: +34 923 294 817
E-mail: pereda@usal.es

Research Team
Senior Researcher
Carmen Guerrero Arroyo
Postdoctoral
Rubén Martínez-Buey
José Antonio Manso
Beatriz Escudero Paniagua
Patricia Esther González Sáenz
Víctor Martín Granado
Predoctoral
Noelia Alonso García
Ana M. Carballido Vázquez
María Gómez Hernández
Esther Ortega Portero
Sara Gutiérrez Herrero
Vera Susana Carneiro Maia
Visiting Scientific
Pablo Alcón Hernández
Sara Ortíz Rivero
Students
Beatriz Escudero Paniagua
Patricia Esther González Sáenz
Víctor Martín Granado
Arturo Carabias del Rey

RESEARCH SUMMARY

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 α6 integrin exhorts its functions in cell adhesion and signal transduction and how it is regulated. In epithelial tissues, α6 is an essential component of hemidesmosomes, which are adhesion complexes that mediate the anchoring of cells to the basement membrane. In carcinoma cells, α6-mediated signaling favors migration, invasion, and survival. The roles of α6 in carcinomas correlate with an inhibition of the assembly of hemidesmosomes. Plectin, a member of the plakin family, connects the integrin α6 to the intermediate filaments at the hemidesmosomes. We have elucidated the structural basis of the interaction between α6 and plectin. Our results show that missense mutations in the α subunit that cause a skin blistering disease, termed epidermolysis bullosa, prevent important intermolecular contacts. In addition we have solved the crystal structure of the Calx-α domain of the integrin α subunit, which is located adjacent to the plectin-binding site. 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 sub-domains of the "spectrin repeat" type and a SH3 domain. This region is responsible for the sub-cellular localization of plakins and harbors binding sites for other proteins.

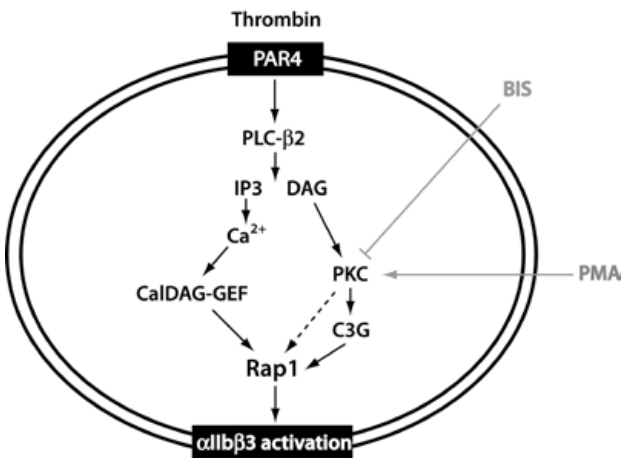
Finally, in collaboration with the group of Dra Carmen Guerrero we are characterizing the structural basis of the regulation of C3G, a guanine nucleotide exchange factor for small GTPases, mainly Rap1 and R-Ras.

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

Carmen Guerrero Arroyo
Phone.: +34 923 294 817
E-mail: cguerrero@usal.es

RESEARCH SUMMARY

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 recently 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.



Schematic representation of thrombin-triggered pathways leading to αIIbβ3 activation in mouse platelets. C3G participates in the second peak of Rap1 activation, which is mediated by the PKC pathway.

Publications

1 **Risk of placenta-mediated pregnancy complications or pregnancy-related VTE in VTE-asymptomatic families of probands with VTE and heterozygosity for factor V Leiden or G20210 prothrombin mutation.** Cordoba I, Pegenaute C, González-López TJ, Chillon C, Sarasquete ME, Martin-Herrero F, Guerrero C, Cabrero M, Garcia Sanchez MH, Pabon P, Lozano FS, Gonzalez M, Alberca I, González-Porras JR. ***Eur J Haematol. 2012 Sep;89(3):250-5. doi: 10.1111/j.1600-0609.2012.01809.x. Epub 2012 Jun 29.*** PMID: 22642978 **IF: 2,548 / Q3**

2 **C3G transgenic mouse models with specific expression in platelets reveal a new role for C3G in platelet clotting through its GEF activity.** Gutiérrez-Herrero S, Maia V, Gutiérrez-Berzal J, Calzada N, Sanz M, González-Manchón C, Pericacho M, Ortiz-Rivero S, González-Porras JR, Arechederra M, Porras A, Guerrero C. ***Biochim Biophys Acta. 2012 Aug;1823(8):1366-77. doi: 10.1016/j.bbamcr.2012.05.021. Epub 2012 May 29.*** PMID: 22659131 **IF: 4,808 / Q1**

3 **Sequence determinants of a microtubule tip localization signal (MtLS).** Buey RM, Sen I, Kortt O, Mohan R, Gfeller D, Veprintsev D, Kretzschmar I, Scheuermann J, Neri D, Zoete V, Michielin O, de Pereda JM, Akhmanova A, Volkmer R, Steinmetz MO. ***J Biol Chem. 2012 Aug 17;287(34):28227-42. doi: 10.1074/jbc.M112.373928. Epub 2012 Jun 13.*** PMID: 22696216 **IF: 4,651 / Q1**

4 **C3G forms complexes with Bcr-Abl and p38γ MAPK at the focal adhesions in chronic myeloid leukemia cells: implication in the regulation of leukemic cell adhesion.** Maia V, Ortiz-Rivero S, Sanz M, Gutierrez-Berzal J, Alvarez-Fernández I, Gutierrez-Herrero S, de Pereda JM, Porras A, Guerrero C. ***Cell Commun Signal. 2013 Jan 23;11(1):9. doi: 10.1186/1478-811X-11-9.*** PMID: 23343344 **IF: 5,093 / Q1**

5 **The autoimmunity risk variant LYP-W620 cooperates with CSK in the regulation of TCR signaling.** de la Puerta ML, Trinidad AG, Rodríguez Mdel C, de Pereda JM, Sánchez Crespo M, Bayón Y, Alonso A. ***PLoS One. 2013;8(1):e54569. doi: 10.1371/journal.pone.0054569. Epub 2013 Jan 24.*** PMID: 23359562 **IF: 3,730 / Q1**

6 **Met signaling in cardiomyocytes is required for normal cardiac function in adult mice.** Arechederra M, Carmona R, González-Nuñez M, Gutiérrez-Uzquiza A, Bragado P, Cruz-González I, Cano E, Guerrero C, Sánchez A, López-Novoa JM, Schneider MD, Maina F, Muñoz-Chápuli R, Porras A. ***Biochim Biophys Acta. 2013 Dec;1832(12):2204-15. doi: 10.1016/j.bbadis.2013.08.008. Epub 2013 Aug 28.*** PMID: 23994610 **IF: 4,910 / Q1**

7 **Exploiting tertiary structure through local folds for crystallographic phasing.** Sammito M, Millán C, Rodríguez DD, de Ilarduya IM, Meindl K, De Marino I, Petrillo G, Buey RM, de Pereda JM, Zeth K, Sheldrick GM, Usón I. ***Nat Methods. 2013 Nov;10(11):1099-101. doi: 10.1038/nmeth.2644. Epub 2013 Sep 15.*** PMID: 24037245 **IF: 23,565 / D1**

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Bases estructurales de interacciones en hemidesmosomas: integrina A6B4, BPAG1E y Tetraspanina	José María de Pereda	Ministerio de Ciencia e Innovación (BFU2009-08389)	2010-2012	153,760.00 €
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	Carmen Guerrero Arroyo	Junta de Castilla y León (SA069A11-2)	2011-2013	30,000.00 €
Modulating EB proteína interactions through small molecules	Rubén Martínez Buey	Junta de Castilla y León (PEOPLE-CIG/1387)	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	Carmen Guerrero Arroyo	Junta de Castilla y León (SA157A12-1)	2012-2014	30,000.00 €
Bases estructurales de la función de plakinas en adhesión celular, implicación en enfermedades.	José María de Pereda	Ministerio de Economía y Competitividad (BFU2012-32847)	2013-2016	134,550.00 €

Cell death and cancer. Atypical cell death pathways

Team Leader:

Felipe X. Pimentel-Muiños
Phone.: +34 923 294 818
E-mail: fxp@usal.es

Research Team
Postdoctoral
Michal Letek Polberg
Predoctoral
Emilio Boada Romero
Cristina Mesa Núñez
Cristina Ramón Barros
Students
Inmaculada Serramito Gómez
Álvaro Murillo Bartolomé
Mª José Conde Dusmán

RESEARCH SUMMARY

Description

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 autophagy-inducing molecules were cloned before in the laboratory and will be subjected to further characterization.

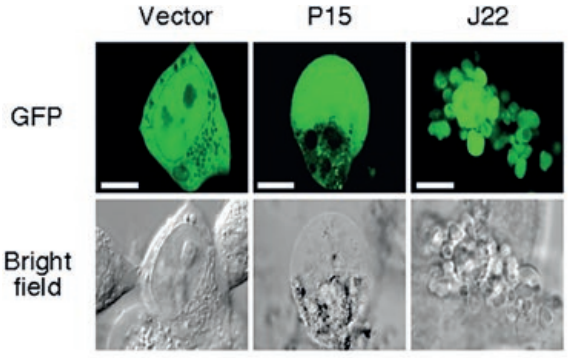
Objectives and Main Research Avenues

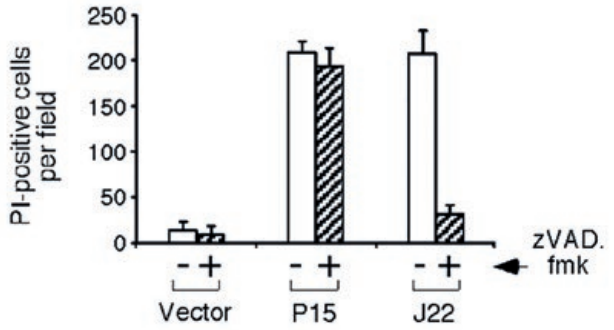
- To understand the signaling events governing the apoptotic communication between the endoplasmic reticulum and mitochondria.
- To investigate the mechanisms that mediate cytochrome c release from apoptotic mitochondria in the absence of the conventional Bak and Bax-dependent pathway.
- To identify 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

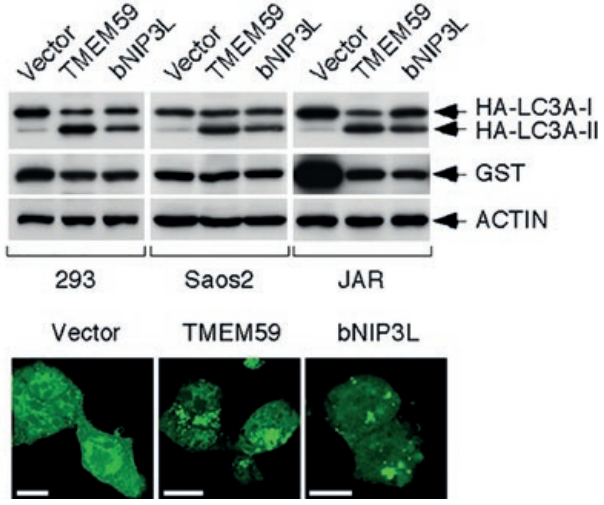
In previous years the laboratory has identified several signaling pathways to cell death that function in non-conventional ways. First, we have discovered that multiple apoptotic inducers function normally in the exclusive presence of the critical apoptotic mediator Bak expressed at the endoplasmic reticulum, 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.

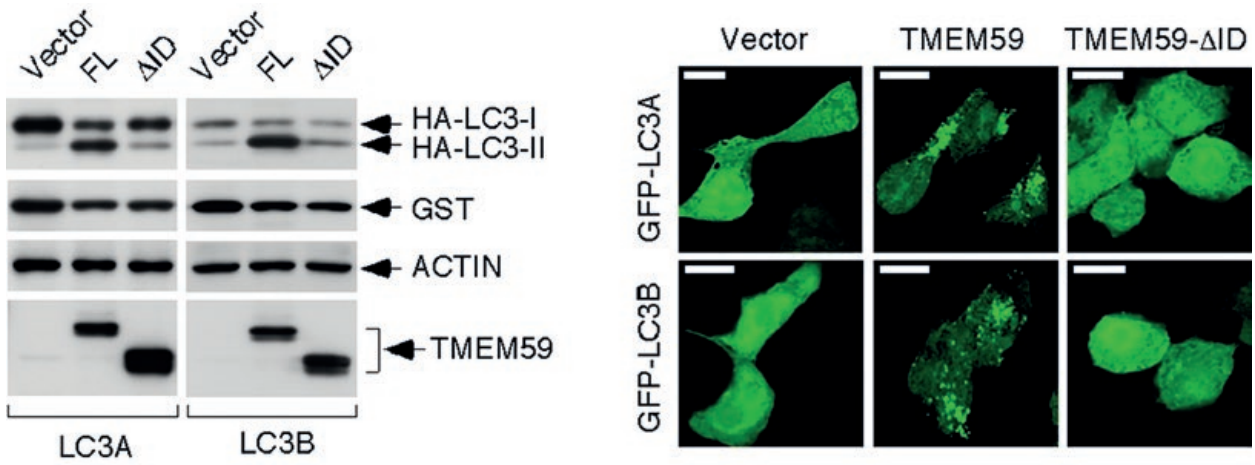




Different forms of cell death caused by molecules identified in a functional screening for death-inducing genetic elements. Left: Cells were transfected with the indicated constructs combined with GFP and subjected to in vivo confocal microscopy. The figure shows the atypical morphology that accompanies P15-induced death compared with the conventional apoptotic phenotype induced by clone J22. Right: Cells were transfected as indicated in the absence or presence of the pan-caspase inhibitor zVAD. fmk. The figure shows that P15 induces a form of cell death that proceeds independently of caspases.



TMEM59 induces autophagy. Cells were transfected with TMEM59 in combination with the autophagic reporters HA-LC3 (top) or GFP-LC3 (bottom). The figure shows the capacity of TMEM59 to cause generation of LC3II (top) or clustering of GFP-LC3 into vesicular structures (bottom).



The probable intracellular domain of TMEM59 is required for induction of autophagy. Cells were transfected with the indicated versions of TMEM59 plus the autophagic reporters HA-LC3 (left) or GFP-LC3 (right). The figure shows the inability of the truncated form of TMEM59 that lacks the possible intracellular domain (ΔD) to induce generation of LC3II (left) or aggregation of GFP-LC3 into a vesicular pattern (right).

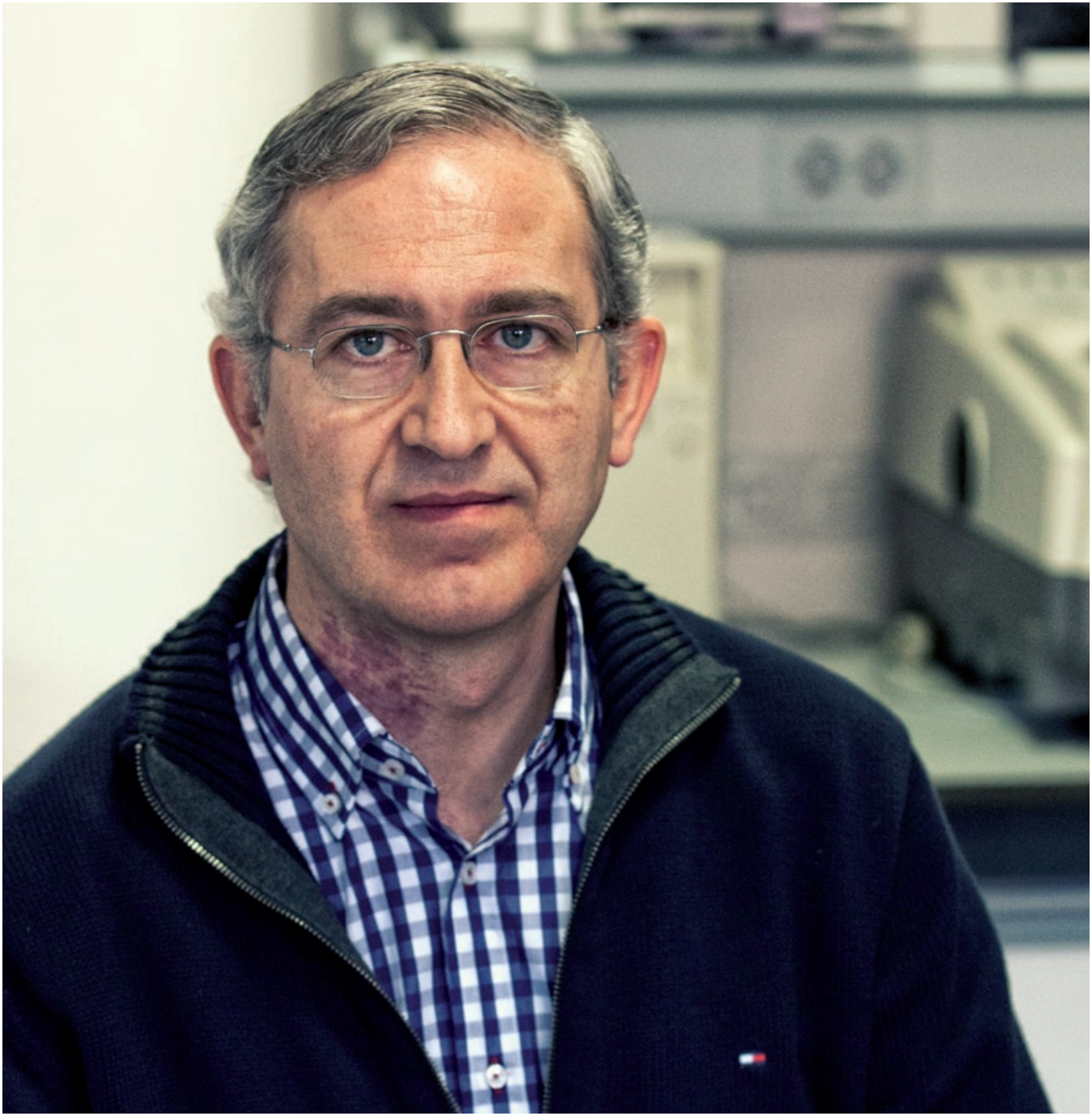
Publications

1 **BH3-only proteins are part of a regulatory network that control the sustained signalling of the unfolded protein response sensor IRE1α** Rodriguez DA, Zamorano S, Lisbona F, Rojas-Rivera D, Urra H, Cubillos-Ruiz JR, Armisen R, Henriquez DR, Cheng EH, Letek M, Vaisar T, Irrazabal T, Gonzalez-Billault C, Letai A, Pimentel-Muiños FX, Kroemer G, Hetz C. ***EMBO J. 2012 May 16;31(10):2322-35. doi: 10.1038/emboj.2012.84. Epub 2012 Apr 17.*** PMID: 22510886 **IF: 9,822 / D1**

2 **TMEM59 defines a novel ATG16L1-binding motif that promotes local activation of LC3.** Boada-Romero E, Letek M, Fleischer A, Pallauf K, Ramón-Barros C, Pimentel-Muiños FX. ***EMBO J. 2013 Feb 20;32(4):566-82. doi: 10.1038/emboj.2013.8. Epub 2013 Feb 1.*** PMID: 23376921 **IF: 9,822 / D1**

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Estudio estructural y funcional de una nueva molécula de membrana inductora de muerte celular autofágica. Implicación en supresión tumoral	Felipe Pimentel Muiños	Junta de Castilla y León (CSI001A10-2)	2010-2012	40,000.00 €
Implicaciones de la autofagia en patología humana	Felipe Pimentel Muiños	Junta de Castilla y León (SA157A12-1)	2011-2012	23,878.00 €
Caracterización de nuevas proteínas y vías señalizadoras implicadas en la regulación de la autofagia en mamíferos. Implicaciones en patología	Felipe Pimentel Muiños	Ministerio de Ciencia e Innovación (SAF2011-23714)	2011-2014	151,250.00 €
Identification of novel ATG16L1 regulators involved in Crohn´s disease	Felipe Pimentel Muiños	The Broad Foundation (IBD-0369)	2013-2014	110,000.00 $



Bioinformatics and functional genomics of cancer

RESEARCH SUMMARY

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: Development of a unified and integrated database with all known and experimentally determined protein-protein interactions (PPIs) including stategies to evaluate quality and confidence on the interactions. Use of this data source to build a comprehensive human interactome network and derive cancer-related subnetworks.
- Integrative Bioinformatics: Integration of genome-wide expression data with proteomic interaction data to build human biomolecular networks incluiding several relational layers.
- Machine Learning (ML) and Reverse Engineering (RE) methods applied to genomic and proteomic data to discover the biomolecular signatures and profiles associated to cancer states and survival, focused on the study of onco-hematological diseases (in collaboration with MDs of HUS).

Team Leader:

Javier De Las Rivas
Phone.: +34 923 294 819
E-mail: jrivas@usal.es

Research Team

Predoctoral

Sara Aibar Santos
Celia Fontanillo Fontanillo
Alberto Risueño Pérez
Beatriz Rosón Burgo
Conrad Droste
Francisco José Campo Laborie

Publications

1 **Bioinformatics Training Network (BTN): a community resource for bioinformatics trainers.** Schneider MV, Walter P, Blatter MC, Watson J, Brazas MD, Rother K, Budd A, Via A, van Gelder CW, Jacob J, Fernandes P, Nyrönen TH, De Las Rivas J, Blicher T, Jimenez RC, Loveland J, McDowall J, Jones P, Vaughan BW, Lopez R, Attwood TK, Brooksbank C. ***Brief Bioinform. 2012 May;13(3):383-9. doi: 10.1093/bib/bbr064. Epub 2011 Nov 22. Review.*** PMID: 22110242 **IF: 5,298 / D1**

2 **Unique genetic profile of sporadic colorectal cancer liver metastasis versus primary tumors as defined by high-density single-nucleotide polymorphism arrays.** Muñoz-Bellvis L, Fontanillo C, González-González M, Garcia E, Iglesias M, Esteban C, Gutierrez ML, Abad MM, Bengoechea O, De Las Rivas J, Orfao A, Sayagués JM. ***Mod Pathol. 2012 Apr;25(4):590-601. doi: 10.1038/modpathol.2011.195. Epub 2012 Jan 6.*** PMID: 22222638 **IF: 5,253 / D1**

3 **Identification of a novel recurrent gain on 20q13 in chronic lymphocytic leukemia by array CGH and gene expression profiling.** Rodríguez AE, Robledo C, García JL, González M, Gutiérrez NC, Hernández JA, Sandoval V, García de Coca A, Recio I, Risueño A, Martín-Núñez G, García E, Fisac R, Conde J, de las Rivas J, Hernández JM. ***Ann Oncol. 2012 Aug;23(8):2138-46. doi: 10.1093/annonc/mdr579. Epub 2012 Jan 6.*** PMID: 22228453 **IF: 7,384 / D1**

4 **Cortactin (CTTN) overexpression in osteosarcoma correlates with advanced stage and reduced survival.** Folio C, Zalacain M, Zandueta C, Ormazábal C, Sierrasesúmaga L, San Julián M, de las Rivas J, Toledo G, Lecanda F, Patiño-García A. ***Cancer Biomark. 2011-2012;10(1):35-41. doi: 10.3233/CBM-2012-0227.*** PMID: 22297550 **IF: 0,972 / Q4**

5 **Impaired expression of DICER, DROSHA, SBDS and some microRNAs in mesenchymal stromal cells from myelodysplastic syndrome patients.** Santamaría C, Muntión S, Rosón B, Blanco B, López-Villar O, Carrancio S, Sánchez-Guijo FM, Díez-Campelo M, Alvarez-Fernández S, Sarasquete ME, de las Rivas J, González M, San Miguel JF, Del Cañizo MC. ***Haematologica. 2012 Aug;97(8):1218-24. doi: 10.3324/haematol.2011.054437. Epub 2012 Feb 27.*** PMID: 22371183 **IF: 5,935 / Q1**

6 **Receptor of activated protein C promotes metastasis and correlates with clinical outcome in lung adenocarcinoma.** Antón I, Molina E, Luis-Ravelo D, Zandueta C, Valencia K, Ormazabal C, Martínez-Canarias S, Perurena N, Pajares MJ, Agorreta J, Montuenga LM, Segura V, Wistuba II, De Las Rivas J, Hermida J, Lecanda F. ***Am J Respir Crit Care Med. 2012 Jul 1;186(1):96-105. doi: 10.1164/rccm.201110-1826OC. Epub 2012 Mar 29.*** PMID: 22461368 **IF: 11,041 / D1**

7 **Integrating literature-constrained and data-driven inference of signalling networks.** Eduati F, De Las Rivas J, Di Camillo B, Toffolo G, Saez-Rodriguez J. ***Bioinformatics. 2012 Sep 15;28(18):2311-7. doi: 10.1093/bioinformatics/bts363. Epub 2012 Jun 25.*** PMID: 22734019 **IF: 5,323 / D1**

8 **Protein interactions: mapping interactome networks to support drug target discovery and selection.** De Las Rivas J, Prieto C. ***Methods Mol Biol. 2012;910:279-96. doi: 10.1007/978-1-61779-965-5_12. Review.*** PMID: 22821600 **IF: NI**

9 **A novel molecular mechanism involved in multiple myeloma development revealed by targeting MafB to haematopoietic progenitors.** Vicente-Dueñas C, Romero-Camarero I, González-Herrero I, Alonso-Escudero E, Abollo-Jiménez F, Jiang X, Gutierrez NC, Orfao A, Marín N, Villar LM, Criado MC, Pintado B, Flores T, Alonso-López D, De Las Rivas J, Jiménez R, Criado FJ, Cenador MB, Lossos IS, Cobaleda C, Sánchez-García I. ***EMBO J. 2012 Sep 12;31(18):3704-17. doi: 10.1038/emboj.2012.227. Epub 2012 Aug 17.*** PMID: 22903061 **IF: 9,822 / D1**

10 **Protein-protein interaction networks: unraveling the wiring of molecular machines within the cell.** De Las Rivas J, Fontanillo C. ***Brief Funct Genomics. 2012 Nov;11(6):489-96. doi: 10.1093/bfgp/els036. Epub 2012 Aug 20.*** PMID: 22908212 **IF: 4,210 / Q1**

11 **Prognostic Impact of del(17p) and del(22q) as assessed by interphase FISH in sporadic colorectal carcinomas.** González-González M, Muñoz-Bellvis L, Mackintosh C, Fontanillo C, Gutiérrez ML, Abad MM, Bengoechea O, Teodosio C, Fonseca E, Fuentes M, De Las Rivas J, Orfao A, Sayagués JM. ***PLoS One. 2012;7(8):e42683. doi: 10.1371/journal.pone.0042683. Epub 2012 Aug 17.*** PMID: 22912721 **IF: 3,730 / Q1**

12 **Genome-wide profiling of methylation identifies novel targets with aberrant hypermethylation and reduced expression in low-risk myelodysplastic syndromes.** del Rey M, O'Hagan K, Dellett M, Aibar S, Colyer HA, Alonso ME, Díez-Campelo M, Armstrong RN, Sharpe DJ, Gutiérrez NC, García JL, De Las Rivas J, Mills KI, Hernández-Rivas JM. ***Leukemia. 2013 Mar;27(3):610-8. doi: 10.1038/leu.2012.253. Epub 2012 Aug 31.*** PMID: 22936014 **IF: 10,164 / D1**

13 **Combined analysis of genome-wide expression and copy number profiles to identify key altered genomic regions in cancer.** Fontanillo C, Aibar S, Sanchez-Santos JM, De Las Rivas J. ***BMC Genomics. 2012;13 Suppl 5:S5. doi: 10.1186/1471-2164-13-S5-S5. Epub 2012 Oct 19.*** PMID: 23095915 **IF: 4,397 / Q1**

14 **Molecular characterization of chronic lymphocytic leukemia patients with a high number of losses in 13q14.** Rodríguez AE, Hernández JÁ, Benito R, Gutiérrez NC, García JL, Hernández-Sánchez M, Risueño A, Sarasquete ME, Fermiñán E, Fisac R, de Coca AG, Martín-Núñez G, de Las Heras N, Recio I, Gutiérrez O, De Las Rivas J, González M, Hernández-Rivas JM. ***PLoS One. 2012;7(11):e48485. doi: 10.1371/journal.pone.0048485. Epub 2012 Nov 13.*** PMID: 23152777 **IF: 3,730 / Q1**

15 **iAnn: an event sharing platform for the life sciences.** Jimenez RC, Albar JP, Bhak J, Blatter MC, Blicher T, Brazas MD, Brooksbank C, Budd A, De Las Rivas J, Dreyer J, van Driel MA, Dunn MJ, Fernandes PL, van Gelder CW, Hermjakob H, Ioannidis V, Judge DP, Kahlem P, Korpelainen E, Kraus HJ, Loveland J, Mayer C, McDowall J, Moran F, Mulder N, Nyronen T, Rother K, Salazar GA, Schneider R, Via A, Villaveces JM, Yu P, Schneider MV, Attwood TK, Corpas M. ***Bioinformatics. 2013 Aug 1;29(15):1919-21. doi: 10.1093/bioinformatics/btt306. Epub 2013 Jun 5.*** PMID: 23742982 **IF: 5,323 / D1**

16 **Best practices in bioinformatics training for life scientists.** Via A, Blicher T, Bongcam-Rudloff E, Brazas MD, Brooksbank C, Budd A, De Las Rivas J, Dreyer J, Fernandes PL, van Gelder C, Jacob J, Jimenez RC, Loveland J, Moran F, Mulder N, Nyrönen T, Rother K, Schneider MV, Attwood TK. ***Brief Bioinform. 2013 Sep;14(5):528-37. doi: 10.1093/bib/bbt043. Epub 2013 Jun 25.*** PMID: 23803301 **IF: 5,298 / D1**

17 **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. 2013 Oct 28. doi: 10.1038/onc.2013.440.*** PMID: 24166494 **IF: 7,357 / Q1**

18 **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: 6,701 / Q1**

19 **Transcriptome analysis in prenatal IGF1-deficient mice identifies molecular pathways and target genes involved in distal lung differentiation.** Pais RS, Moreno-Barriuso N, Hernández-Porras I, López IP, De Las Rivas J, Pichel JG. ***PLoS One. 2013 Dec 31;8(12):e83028. doi: 10.1371/journal.pone.0083028. eCollection 2013.*** PMID: 24391734 **IF: 3,730 / Q1**

Other publications & Book chapters

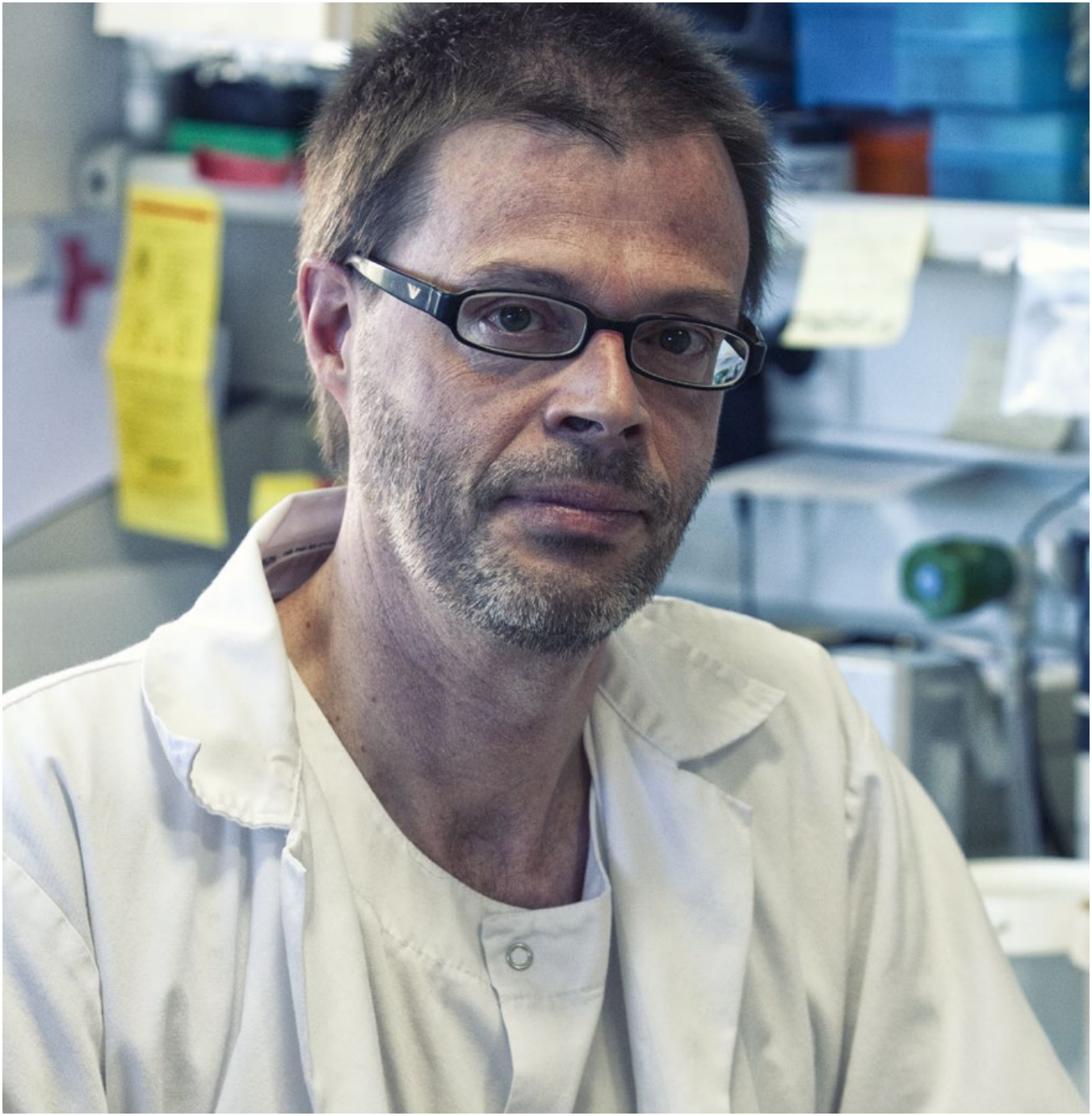
- **Protein interactions: mapping interactome networks to support drug target discovery and selection.** De Las Rivas J, Prieto C. Methods Mol Biol. 2012; 910: pg. 279-296. Book Title: Bioinformatics and Drug Discovery. doi: 10.1007/978-1-61779-965-5_12. PMID: 22821600

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
PSIMEx Consortium Agreement. Proteomics standards International Molecular Exchange - Systematics Capture of Published Molecular Interaction data	Javier De Las Rivas	Unión Europea (PSIMEx)	2009-2012	26,750.00 €
PROTEIN INTERACTOME: Construction a new human protein nteractome Reference Set (hsRS-PPI) combining proteomic and bioinformatic work; steps to build a more comprehensive human interaction network	Javier De Las Rivas	Ministerio de Economía y Competitividad (I-LING0398)	2011-2014	16,285.00 €
Genómica integrativa de leucemias y mieloma: estudio bioinformática de transcriptomas e interactomas a nivel omico para desentrañar los estados patológicos, redes derivadas y nodos críticos de estas enfermedades	Javier De Las Rivas	Instituto de Salud Carlos III (PS09/00843)	2010-2012	92,565.00 €
CELGENE Sponsored Research Agreement	Javier De Las Rivas	CELGENE S.L.U.	2013-2015	100,000.00 €
Transcriptómica y epigenómica de células stem mesnquimales (MSC) normales y alteradas en hemopatías malignas	Javier De Las Rivas	Junta de Castilla y León (BIO/SA68/13)	2013	23,500.00 €

Other activities & Relevant facts

- **Algorithms and tools for transcriptomics and multiple gene profiling using the open source platforms R and Bioconductor** Santiago de Chile (Chile), 17.Mar.2012 / 8 horas / ISCB-LatinAmerica 2012 / Dr. Javier De Las Rivas / http://www.iscb.org/iscb-latinamerica2012
- **In Silico Systems Biology** Cambridge (UK), 23-27. Apr.2012 / 3 horas / Joint EMBL-EBI and Wellcome Trust / Dr. Javier De Las Rivas / http://www.ebi.ac.uk/training/handson/course_121203_sysbiol
- **Bioinformatics & Comparative Genome Analyses** Naples (Italy), 7-19.May.2012 / 8 horas / EMBO Practical Course and Institut Pasteur / Dr. Javier De Las Rivas / http://events.embo.org/12-comparative-genomics/
- **Bioinformatics and Functional Genomics using R** Lisbon (Portugal), 18-20. Jun.2012 / 24 horas (3 días) / Instituto Gulbenkian de Ciencia (GTPB) / Dr. Javier De Las Rivas y Celia Fontanillo / http://gtpb.igc.gulbenkian.pt/bicourses/BFG12/
- **Visualising and exploring biological networks with Cytoscape** Gent (Belgium), 23.Nov.2012 / 8 horas / BioInformatics Training & Services, Vlaams Instituut voor Biotechnologie (BITS, VIB) / Dr. Javier De Las Rivas / http://www.bits.vib.be/index.php/training/119-analyzing-biological-networks



Molecular pathology of sarcomas *(until May 2013)*

RESEARCH SUMMARY

Sarcomas –malignant tumours of the mesenchymal tissues-- are rare, accounting ~2% of the cancer burden. Children and young adolescents are frequently affected. Their aggressiveness has major impact on morbidity and mortality. Though progress has been made in pathological and genetic typing, the aetiology is largely unknown. Advances in therapeutic approaches increased survival. Significant numbers of patients (~40%) still die from disease. Sarcoma research is favoured by the existence of networks of sarcoma groups where an exchange of material, knowledge and technology is achieved to obtain statistical significant datasets, otherwise not achievable due to the rareness and the large number of sub entities (the 2002 WHO classification recognises over 90 different sarcomas). We focus on the molecular level, which is expedient since the availability of the wealth of information from the Human Genome Project. Most sarcomas yield a complex and as yet not tumour-specific genetic make-up. Some specific genetic events, such as translocations, are reported, but this knowledge is not translated into comprehensive understanding, nor does it give an anchoring point for designing tumour specific therapy. Our subline is focused on Ewing sarcoma, as a model of developmental tumor with well characterized translocations and fusion genes.

Objectives

This subline is focused on translational research in sarcomas, mostly based on the use of high throughput genomic and proteomic methodologies for molecular classification of sarcomas, and individualization of their therapy. Among our current research program we include:

a) Assessment of study of bone marrow mesenchymal stem cells as the likely histogenetic origin of Ewing sarcoma,
b) discover the downstream targets of the fusion proteins of Ewing sarcoma,
c) assessment of key sarcoma signaling pathways through in vitro studies with specific drugs (IGF1R and KIT inhibitors), inducible models (of EWS-FLI1 and other fusion types) and stable shRNA systems (of the fusion genes and translocation targets).
d) molecular profiling of sarcomas, using multiple expression techniques, and its validation using immunohistochemistry on tissue microarrays,
e) proteomic studies to characterise cell lines and their response to drugs,
f) development of genetically engineered models (GEM) of sarcomas particularly Ewing sarcoma to be used in preclinical studies, and
g) using the knowledge acquired in aims a-f: design, validation, and intellectual property protection of new patentable diagnostic tools which can be used in the clinical diagnostic setting to diagnose sarcomas.

Team Leader:

Enrique de Álava
Phone.: +34 923 294 820
E-mail: edealava@usal.es

Research Team
Postdoctoral
José Luis Ordóñez García
Predoctoral
Daniel José García Domínguez
Ana Pastora Otero Motta
Technician
Mª Victoria Sevillano González

Publications

1 **1q gain and CDT2 overexpression underlie an aggressive and highly proliferative form of Ewing sarcoma.** Mackintosh C, Ordóñez JL, García-Domínguez DJ, Sevillano V, Llombart-Bosch A, Szuhai K, Scotlandi K, Alberghini M, Sciot R, Sinnaeve F, Hogendoorn PC, Picci P, Knuutila S, Dirksen U, Debiec-Rychter M, Schaefer KL, de Álava E. ***Oncogene. 2012 Mar 8;31(10):1287-98. doi: 10.1038/onc.2011.317. Epub 2011 Aug 8.*** PMID: 21822310 **IF: 7,357 / Q1**

2 **Activated growth signaling pathway expression in Ewing sarcoma and clinical outcome.** Mora J, Rodríguez E, de Torres C, Cardesa T, Ríos J, Hernández T, Cardesa A, de Alava E. ***Pediatr Blood Cancer. 2012 Apr;58(4):532-8. doi: 10.1002/pbc.23348. Epub 2011 Oct 12.*** PMID: 21994054 **IF: 2,353 / Q1**

3 **Primary vaginal Ewing sarcoma: case report and review of the literature.** Bancalari E, de Álava E, Tardío JC. ***Int J Surg Pathol. 2012 Jun;20(3):305-10. doi: 10.1177/1066896911424898. Epub 2011 Oct 17. Review.*** PMID: 22007080 **IF: 0,756 / Q4**

4 **Delineation of commonly deleted chromosomal regions in meningiomas by high-density single nucleotide polymorphism genotyping arrays.** Tabernero MD, Maíllo A, Nieto AB, Diez-Tascón C, Lara M, Sousa P, Otero A, Castrillo A, Patino-Alonso Mdel C, Espinosa A, Mackintosh C, de Alava E, Orfao A. ***Genes Chromosomes Cancer. 2012 Jun;51(6):606-17. doi: 10.1002/gcc.21948. Epub 2012 Feb 27.*** PMID: 22371336 **IF: 3,546 / Q2**

5 **The Ras-like protein R-Ras2/TC21 is important for proper mammary gland development.** Larive RM, Abad A, Cardaba CM, Hernández T, Cañamero M, de Álava E, Santos E, Alarcón B, Bustelo XR. ***Mol Biol Cell. 2012 Jun;23(12):2373-87. doi: 10.1091/mbc.E12-01-0060. Epub 2012 Apr 25.*** PMID: 22535521 **IF: 4,803 / Q2**

6 **A new multidisciplinary Spanish Working Group on Cancer Biomarkers: presentation and aims.** Colomer R, Garrido P, de Álava E, García Alfonso P, Palacios J, Ariza A; Multidisciplinary Working Group on Cancer Biomarkers of the Spanish Society of Medical Oncology (SEOM) and the Spanish Society of Pathology (SEAP). ***Clin Transl Oncol. 2012 May;14(5):323-4.*** PMID: 22551536 **IF: NI**

7 **WEE1 accumulation and deregulation of S-phase proteins mediate MLN4924 potent inhibitory effect on Ewing sarcoma cells.** Mackintosh C, García-Domínguez DJ, Ordóñez JL, Ginel-Picardo A, Smith PG, Sacristán MP, de Álava E. ***Oncogene. 2013 Mar 14;32(11):1441-51. doi: 10.1038/onc.2012.153. Epub 2012 May 28.*** PMID: 22641220 **IF: 7,357 / Q1**

8 **The first European interdisciplinary ewing sarcoma research summit.** Kovar H, Alonso J, Aman P, Aryee DN, Ban J, Burchill SA, Burdach S, De Alava E, Delattre O, Dirksen U, Fourtouna A, Fulda S, Helman LJ, Herrero-Martin D, Hogendoorn PC, Kontny U, Lawlor ER, Lessnick SL, Llombart-Bosch A, Metzler M, Moriggl R, Niedan S, Potratz J, Redini F, Richter GH, Riedmann LT, Rossig C, Schäfer BW, Schwentner R, Scotlandi K, Sorensen PH, Staege MS, Tirode F, Toretsky J, Ventura S, Eggert A, Ladenstein R. ***Front Oncol. 2012;2:54. doi: 10.3389/fonc.2012.00054. Epub 2012 May 29.*** PMID: 22662320 **IF: NI**

9 **Meiotic cohesin complexes are essential for the formation of the axial element in mice.** Llano E, Herrán Y, García-Tuñón I, Gutiérrez-Caballero C, de Álava E, Barbero JL, Schimenti J, de Rooij DG, Sánchez-Martín M, Pendás AM. ***J Cell Biol. 2012 Jun 25;197(7):877-85. doi: 10.1083/jcb.201201100. Epub 2012 Jun 18.*** PMID: 22711701 **IF: 10,822 / D1**

10 **Transcription factors Sp1 and p73 control the expression of the proapoptotic protein NOXA in the response of testicular embryonal carcinoma cells to cisplatin.** Grande L, Bretones G, Rosa-Garrido M, Garrido-Martin EM, Hernandez T, Fraile S, Botella L, de Alava E, Vidal A, Garcia del Muro X, Villanueva A, Delgado MD, Fernandez-Luna JL. ***J Biol Chem. 2012 Aug 3;287(32):26495-505. doi: 10.1074/jbc.M112.376319. Epub 2012 Jun 20.*** PMID: 22718761 **IF: 4,651 / Q1**

11 **Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** ESMO / European Sarcoma Network Working Group. ***Ann Oncol. 2012 Oct;23 Suppl 7:vii100-9.*** PMID: 22997441 **IF: 7,384 / D1**

12 **Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** ESMO / European Sarcoma Network Working Group. ***Ann Oncol. 2012 Oct;23 Suppl 7:vii49-55.*** PMID: 22997454 **IF: 7,384 / D1**

13 **Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** ESMO / European Sarcoma Network Working Group. ***Ann Oncol. 2012 Oct;23 Suppl 7:vii92-9.*** PMID: 22997462 **IF: 7,384 / D1**

14 **The calcium-sensing receptor is silenced by genetic and epigenetic mechanisms in unfavorable neuroblastomas and its reactivation induces ERK1/2-dependent apoptosis.** Casalà C, Gil-Guiñón E, Ordóñez

JL, Miguel-Queralt S, Rodríguez E, Galván P, Lavarino C, Munell F, de Alava E, Mora J, de Torres C. ***Carcinogenesis. 2013 Feb;34(2):268-76. doi: 10.1093/carcin/bgs338. Epub 2012 Oct 29.*** PMID: 23108190 **IF: 5,635 / Q1**

15 **Endometrial stromal tumors: immunohistochemical and molecular analysis of potential targets of tyrosine kinase inhibitors.** Sardinha R, Hernández T, Fraile S, Tresserra F, Vidal A, Gómez MC, Astudillo A, Hernández N, Saenz de Santamaría J, Ordi J, Gonçalves L, Ramos R, Balañá C, de Álava E. ***Clin Sarcoma Res. 2013 Mar 7;3(1):3. doi: 10.1186/2045-3329-3-3.*** PMID: 23497641 **IF: NI**

16 **Fluorescence in situ hybridization analysis of CCND3 gene as marker of progression in bladder carcinoma.** Beltran AL, Ordonez JL, Otero AP, Blanca A, Sevillano V, Sanchez-Carbayo M, Kirkali Z, Cheng L, Montironi R, Prieto R, De Alava E. ***J Biol Regul Homeost Agents. 2013 Apr-Jun;27(2):559-67.*** PMID: 23830405 **IF: NI**

17 **EphA2-induced angiogenesis in ewing sarcoma cells works through bFGF production and is dependent on caveolin-1.** Sáinz-Jaspeado M, Huertas-Martinez J, Lagares-Tena L, Martin Liberal J, Mateo-Lozano S, de Alava E, de Torres C, Mora J, Del Muro XG, Tirado OM. ***PLoS One. 2013 Aug 12;8(8):e71449. doi: 10.1371/journal.pone.0071449. eCollection 2013.*** PMID: 23951165 **IF: 3,730 / Q1**

Grants for research in progress

PROJECT	IP	GRANT	TIME	FUNDING
Red Temática en Investigación Cooperativa en Cáncer	Enrique de Álava Casado	Instituto de Salud Carlos III (RD06/0020/0059)	2007-2012	355,652.81 €
Puesta a punto de métodos inmunohistoquímicos para el análisis de marcadores de respuesta a fármacos. Procesamiento y análisis de muestras tumorales procedentes de pacientes participantes en ensayos clínicos de trabectedina, plitidepsina, PM02734, PM00104 y PM01183	Enrique de Álava Casado	Pharmamar S.A	2010-2012	52,500.00 €
Análisis olfativo del cáncer humano in vivo e in vitro	Enrique de Álava Casado	Ministerio de Ciencia e Innovación (IPT-2011-0925-900000-DIAFANO)	2011-2014	84,550.00 €
Búsqueda, validación y tralación clínica de nuevas dianas terapéuticas a partir de estudios de genómica integrativa en sarcoma de Ewing	Enrique de Álava Casado	Instituto de Salud Carlos III (PI11/00018)	2011-2015	330,714.78 €
Eurosarc: European clinical trials in rare sarcomas within an integrated translational trial network	Enrique de Álava Casado	Unión Europea (EUROSARC-EAC)	2011-2015	259,800.00 €
Estudio de los inhibidores de PARP como tratamiento en el sarcoma de Ewing: estudio preclínico	Enrique de Álava Casado	Fundación María García-Estrada	2012-2014	104,400.00 €
Red Temática en Investigación Cooperativa en Cáncer.	Enrique de Álava Casado	Instituto de Salud Carlos III (RD12/0036/0017)	2013-2016	92,575.00 €

Clinical and molecular analysis of solid tumors

RESEARCH SUMMARY

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.

Team Leader:

Juan Jesús Cruz Hernández
Phone.: +34 923 291 342
E-mail: jjcruz@usal.es

Research Team
Medical Oncologists
Amalia Gómez Bernal
Emilio Fonseca Sánchez
Rocío García Domínguez
Germán Martín García
César Rodríguez Sánchez
Teresa Martín Gómez
Elvira del Barco Morillo
Luis Miguel Navarro Martín
Lorena Bellido Hernández
Beatriz María Rivas López
Raquel Seijas Tamayo
Mª Rosario Vidal Tocino
Resident Medical Intern
Sara Alfonso Hernández
Rosa Ana Marcos González
Cristina González Velasco
Ignacio Matos García
Rebeca Lozano Mejorada
Rosa Ana Marcos Sánchez
Sara Alfonso Hernández
Cecilia Guillén Gacoto
Alba Noguerido Castro
Oliver Rúa Fernández
Soledad Medina Valdivieso
Mª Jesús Valdeón Conde
Leydy Paredes Durán
Julia Ayuso Martín-Romo
Roberto Andrés Escala Cornejo
Predoctoral
Javier Fernández Mateos
Assays Clinical Unit Coordinator
Juan Carlos Adansa
Data Manager
Adriana Armellini
Administrative Staff
Felicidad Alisente Frías

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 Drs Pandiella y de Álava and several national hospitals.

Publications

1 **Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck.** Hitt R, Irigoyen A, Cortes-Funes H, Grau JJ, García-Sáenz JA, Cruz-Hernandez JJ; ***Spanish Head and Neck Cancer Cooperative Group (TTCC). Ann Oncol. 2012 Apr;23(4):1016-22. doi: 10.1093/annonc/mdr367. Epub 2011 Aug 23.*** PMID: 21865152 **IF: 7,384 /D1**

2 **Spanish Society of Medical Oncology (SEOM) Cancer and Thrombosis Working Group.** Muñoz Martín AJ, Pachón Olmos V, Martín Jiménez M, Alba Conejo E, Cruz Hernández JJ ***SEOM Cancer and Thrombosis Working Group.Clin Transl Oncol. 2012 Feb;14(2):160.*** PMID: 22301407 **IF: NI**

3 **Pain in clinical oncology: patient satisfaction with management of cancer pain.** Antón A, Montalar J, Carulla J, Jara C, Batista N, Camps C, Cassinello J, Sanz-Ortiz J, Díaz-Rubio E, Martínez C, Ledesma F, Zubillaga E; ALGOS Group; DOME III Study Group ***Eur J Pain. 2012 Mar;16(3):381-9. doi: 10.1002/j.1532-2149.2011.00036.x. Epub 2011 Dec 23.*** PMID: 22337158 **IF: 3,067 / Q1**

4 **Functions and workload of medical oncologists in Spain.** Grávalos C, Salvador J, Albanell J, Barnadas A, Borrega P, García-Mata J, Garrido P, González-Flores E, Isla D, Lomas M, Rodríguez-Lescure Á, Cruz JJ, Alba E; Spanish Society for Medical Oncology (SEOM) ***Clin Transl Oncol. 2012 Jun;14(6):423-9. Review.*** PMID: 22634530 **IF: NI**

5 **SEOM clinical guidelines: a consolidated project.** Cruz Hernández JJ, Rodríguez CA. ***Clin Transl Oncol. 2012 Jul;14(7):489-90.*** PMID: 22721791 **IF: NI**

6 **Pilot study on workload estimate in breast cancer, lung cancer and colorectal cancer in a Medical Oncology Service at Valme hospital.** Salvador J, Grávalos C, Albanell J, Barnadas A, Borrega P, García-Mata J, Garrido P, Gonzalez-Flores E, Isla D, Lomas M, Rodríguez-Lescure A, Cruz JJ, Alba E. ***Clin Transl Oncol. 2012 Nov;14(11):820-6. doi: 10.1007/s12094-012-0873-4. Epub 2012 Aug 2.*** PMID: 22855162 **IF: NI**

7 **Comments to SEOM clinical guidelines for the treatment of thyroid cancer.** Riesco-Eizaguirre G, Galofré JC, Zafón C, Alvarez-Escolá C, Anda E, Calleja A, Donnay S, Lucas-Martín A, Menéndez-Torre E, Pereg V, Pérez-Corral B, Santamaría J, Gómez-Sáez JM. ***Clin Transl Oncol. 2012 Sep;14(9):709-10; author reply 711-2. doi: 10.1007/s12094-012-0910-3. Epub 2012 Jul 24.*** PMID: 22855192 **IF: NI**

8 **SEOM recommendations on the structure and operation of hereditary cancer genetic counseling units (HCGCUs).** Lastra-Aras E, Robles-Díaz L, Guillén-Ponce C, Alba E, Cruz JJ. ***Clin Transl Oncol. 2013 Jan;15(1):20-5. doi: 10.1007/s12094-012-0920-1. Epub 2012 Aug 22.*** PMID: 22911548 **IF: NI**

9 **Multiple novel alternative splicing forms of FBXW7 have a translational modulatory function and show specific alteration in human cancer.** Liu Y, Ren S, Castellanos-Martin A, Perez-Losada J, Kwon YW, Huang Y, Wang Z, Abad M, Cruz-Hernandez JJ, Rodriguez CA, Sun Y, Mao JH. ***PLoS One. 2012;7(11):e49453. doi: 10.1371/journal.pone.0049453. Epub 2012 Nov 14.*** PMID: 23166673 **IF: 3,730 / Q1**

10 **Breakthrough cancer pain - still a challenge.** Margarit C, Juliá J, López R, Anton A, Escobar Y, Casas A, Cruz JJ, Galvez R, Mañas A, Zaragozá F. ***J Pain Res. 2012;5:559-66. doi: 10.2147/JPR.S36428. Epub 2012 Nov 19.*** PMID: 23204865 **IF: NI**

11 **Optimal management of breakthrough cancer pain (BCP).** Escobar Y, Mañas A, Juliá J, Gálvez R, Zaragozá F, Margarit C, López R, Casas A, Antón A, Cruz JJ. ***Clin Transl Oncol. 2013 Jul;15(7):526-34. doi: 10.1007/s12094-012-0981-1. Epub 2012 Dec 21. Review.*** PMID: 23263914 **IF: NI**

12 **Incidence of -93 MLH1 promoter polymorphism in familial and sporadic colorectal cancer.** Martínez-Urueña N, Macías L, Pérez-Cabornero L, Infante M, Lastra E, Cruz JJ, Miner C, González R, Durán M. ***Colorectal Dis. 2013 Mar;15(3):e118-23. doi: 10.1111/codi.12112.*** PMID: 23374646 **IF: 2,081 / Q3**

13 **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, Garcia 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: NI**

14 **C2ORF40 suppresses breast cancer cell proliferation and invasion through modulating expression of M phase cell cycle genes.** Lu J, Wen M, Huang Y, He X, Wang Y, Wu Q, Li Z, Castellanos-Martin A, Abad M, Cruz-Hernandez JJ, Rodriguez CA, Pérez-Losada J, Mao JH, Wei G. ***Epigenetics. 2013 Jun;8(6):571-83. doi: 10.4161/epi.24626. Epub 2013 Apr 26.*** PMID: 23770814 **IF: 4,920 / Q1**

15 **Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group.** Blanchard P, Bourhis J, Lacas B, Posner MR, Vermorken JB, Hernandez JJ, Bourredjem A, Calais G, Paccagnella A, Hitt R, Pignon JP; Meta-Analysis of Chemotherapy in Head and Neck Cancer, Induction Project, Collaborative Group. ***J Clin Oncol. 2013 Aug 10;31(23):2854-60. doi: 10.1200/JCO.2012.47.7802. Epub 2013 Jul 8.*** PMID: 23835714 **IF: 18,038 / D1**

16 **SEOM guidelines 2013: a response to the needs of Spanish oncologists.** Cruz-Hernández JJ, Rodríguez CA. ***Clin Transl Oncol. 2013 Dec;15(12):975-6. doi: 10.1007/s12094-013-1097-y. Epub 2013 Aug 8.*** PMID: 23925725 **IF: NI**

17 **Integrated analysis of mismatch repair system in malignant astrocytomas.** Rodríguez-Hernández I, Garcia JL, Santos-Briz A, Hernández-Laín A, González-Valero JM, Gómez-Moreta JA, Toldos-González O, Cruz JJ, Martin-Vallejo J, González-Sarmiento R. ***PLoS One. 2013 Sep 20;8(9):e76401. doi: 10.1371/journal.pone.0076401. eCollection 2013.*** PMID: 24073290 **IF: 3,730 / Q1**

18 **Analysis of DNA repair gene polymorphisms in glioblastoma.** Rodriguez-Hernandez I, Perdomo S, Santos-Briz A, Garcia JL, Gomez-Moreta JA, Cruz JJ, Gonzalez-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: 2,196 / Q3**

4
Scientific Service Units


Agilent Technologies
1-3
4-6
7-9
10-11
High Sensitivity DNA Chip
On-Chip Electrophoresis
LOT#:RA17BK50
EXP:17.JAN.2014

4.1 Genomic

Scientific Coordinator:
Xosé R. Bustelo
Phone: (+34) 923 294 816
E-mail: xbustelo@usal.es / encarnaf@usal.es

Location and Contact:
Unidad de Genómica
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)
María Encarnación Fermiñán Benito
Phone: (+34) 923 294 816
E-mail: encarnaf@usal.es




Personnel:
María Encarnación Fermiñán Benito, Eva María García, Mª Estela Hernández, Ana Isabel Sánchez

DESCRIPTION

In this Facility we provide complete services for: a) Analysis of expression profiles and genotyping using Affymetrix technology. b) Printing and processing of home-made chips. c) Sequencing. d) Genomics related techniques such as RT-PCR.

The philosophy of this Unit is to provide full services to both internal and external customers. By full services we understand carrying out the whole analytic process: starting with the experimental sample (total RNA, genomic DNA), we carry out all the genomics steps, including technical advice about the design of the experiment, quality control of the samples provided, microarray analysis, and a standard bioinformatics analysis.

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

- DNA Sequencing. Sequencing of DNA contained in plasmids or PCR fragments using ABI-3130 xl sequencer (Applied Biosystems). This system is able to do genotyping and SNPs analysis too.
- Genomics studies using Affymetrix technology. The main services includes in this category are:
  – Analysis of expression profiles using Gene Chip System of Affymetrix in different organisms. The main arrays used are:

- Gene Chip Human Genome U133 Plus 2.0
- Gene Chip Mouse Genome 430 2.0
- Gene Chip Rat Genome 230 2.0 Array
- Gene Chip Arabidopsis ATH1 Genome Array
- Gene Chip Drosophila Genome 2.0 Array
- Gene Chip Yeast Genome 2.0 Array.
- Prime View Human Genome

– Analysis of expression profiles using Gene ST System of Affymetrix in different organisms. The main arrays used are:

- Gene Chip Human Gene 1.0 and 2.0 ST Array
- Gene Chip Mouse Gene 1.0 and 2.0ST Array
- Gene Chip Rat Gene 1.0 and 2.0 ST Array

These arrays are a new version (2007) for analysis of expression profiles cheaper and more complete than Gene Chip System.

– Analysis of expression profiles and splicing alternative using Exon ST System of Affymetrix. The main arrays used are:

- Gene Chip Human Exon 1.0 and 2.0 ST Array
- Gene Chip Mouse Exon 1.0 and 2.0 ST Array
- Gene Chip Rat Exon 1.0 and 2.0 ST Array
- HTA Array

– Identification of regulatory promoter sites by inmunoprecipitation (ChIP on chip) and other kind of studies which involve complete genome. The main arrays used are:

- Gene Chip S.pombe Tiling 1.0 FR Array
- Gene Chip S.cerevisiae Tiling 1.0 FR Array
- Gene Chip Human Tiling 1.0 R Array

– Analysis of polymorphisms (SNPs) and copy number studies. The main arrays used are:

- Gene Chip Human Mapping 250K NspI/StyI Arrays
- Genome-Wide Human SNP Array 6.0
- CytoScan 750K Array
- CytoScan HD Array

– Analysis of miRNAs and its precursors. The main arrays used are:

- Gene Chip miRNA 2.0, 3.0 and 4.0 Array

For more information visit www.affymetrix.com

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

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

EQUIPMENT

Analysis of RNA quality:

- Agilent 2100 Bioanalyzer

Platform for the analysis of Affymetrix arrays:

- GeneChip Hybridization Oven 640
- GeneChip Fluidics Station 450
- Gene Array Scanner 3000 7G

Platform for the manufacture of home-made arrays

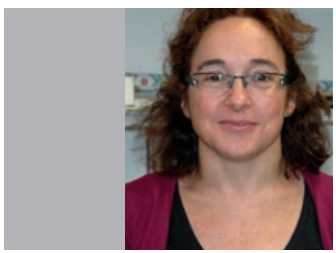
- Biorobot 3000 (Qiagen)
- Arrayer (Biorobotics)
- HS4800Pro Hybridization Station (Tecan)
- GenePix 4000B (Axon)

Automatic sequencer, 16-capillary ABI Prism 3130xl (Applied Biosystems)

4.2 Proteomic

Scientific Coordinator:
Xosé R. Bustelo
Phone: (+34) 923 294 816
E-mail: xbustelo@usal.es

Location and Contact:
Unidad de Proteómica
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)
Nieves Ibarrola de Andrés
Phone: (+34) 923 294 720 Ext 1904
E-mail: nibarrola@usal.es




Personnel:
Nieves Ibarrola de Andrés, Rosa Mª Dégano Blázquez

DESCRIPTION

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

These technologies are implemented with a broad spectrum of techniques for protein and peptide separation, and mass spectrometry based techniques to characterize and quantify analytes from complex biological samples. We provide services for: a) Protein separation, b) Protein identification, c) Analysis of posttranslational modifications, d) Characterization of proteome dynamics and e) Protein-protein interaction studies.

The philosophy of this Resource is to provide full services to both internal and external customers. We provide technical advice about proteomics experimental design and carry out quality control of the processes undertaken.

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

SERVICES

- Protein separation by electrofocusing in IPG strips. Separation of proteins according to their pI is done in an Ettan IPGphor. http://www5.gelifesciences.com/aptrix/upp01077.nsf/Content/2d_electrophoresis~2delectrophoresis_handbook
- Protein separation by SDS-PAGE. Separation of proteins in a SDS-acrylamide:bis-acrylamide denaturing gel according to their molecular weight. http://www5.gelifesciences.com/aptrix/upp01077.nsf/Content/2d_electrophoresis~2delectrophoresis_handbook
- Protein separation by 2D-electroforesis. Protein separation by electrofocusing in IPG strips is followed by SDS-PAGE separation. http://www5.gelifesciences.com/aptrix/upp01077.nsf/Content/2d_electrophoresis~2delectrophoresis_handbook
- Gel staining with Coomassie. Staining of gel separated proteins with Coomassie brilliant blue G-250. • Gel staining with silver. Staining of gel separated proteins with silver using a modification of Heukeshoven and Dernick protocol, Electrophoresis 6, 103-112, (1988), mass spectrometry compatible.
- Protein or peptide fractionation by in solution IEF. Protein or peptide in solution fractionation by IEF using the 3100 OFFGEL fractionator. http://www.chem.agilent.com/Library/usermanuals/Public/G3100-90001_OFFGEL_UserManual_ ebook.pdf
- Protein or peptide fractionation by HPLC. Protein or peptide separation by gel filtration, ion exchange or reverse phase chromatography using HPLC 1100.
- Enrichment of phosphopeptides by IMAC. Phosphopeptides are enriched by Fe3+ chromatography following SIMAC procedure. (Thingholm et al. Molecular & Cellular Proteomics 7:661-671,2008.)
- Enrichment of phosphopeptides by TiO2. Phosphopeptides are enriched by TiO2chromatography following SIMAC procedure.
- In gel protein digestion. Digestion with trypsin of a protein gel spot or band. (Schevchenko et al. Anal. Chem. 1996, 68, 850-858.)
- In solution protein digestion. Digestion with trypsin of a protein sample in solution.
- Desalting and concentration of peptide digests by C18. Low abundance or dirty tryptic peptide samples are cleaned and concentrated using reverse phase C18 columns before MS analysis.(Rappsilber J, Anal Chem. 2003 Feb 1;75(3):663-70.)
- Peptide Mass Fingerprinting analysis by MALDI-TOF MS. Identification of a protein by peptide mass fingerprinting analysis. The masses of the tryptic peptides generated by digestion of single protein are analyzed by a MALDI-TOF mass spectrometer. The pattern of masses obtained is compared against the pattern of masses of each protein in a database of the same organism digested "in silico" with the same endoprotease. (Pappin et al. Current Biol. 1993, 3, 327-332.)
- Protein analysis by LC-MS/MS of low, medium or high complexity protein samples. Peptides derived from digested protein mixtures will be separated by reverse phase chromatography using a nanoUPLC coupled to the mass spectrometer. Different gradient lengths are used depending on the complexity of the protein sample. Eluting peptides are directly analyzed by MS/MS with the LTQ-Orbitrap velos (Olsen et al. Mol Cell Proteomics. 2009 Dec;8(12):2759-69.)
- 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

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

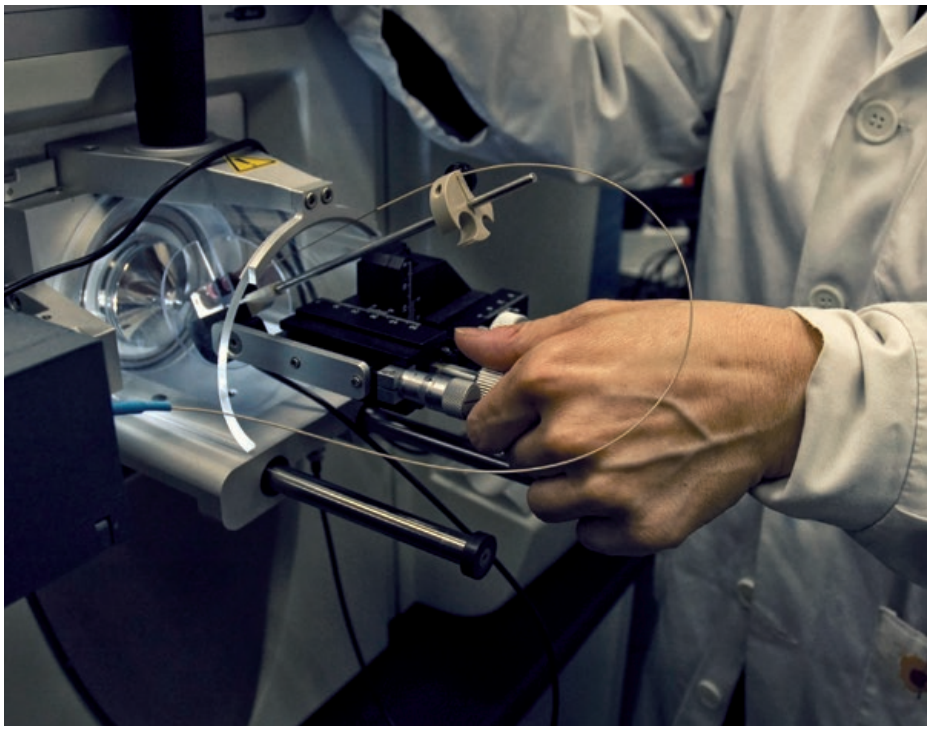
- 3100 OFF GEL fractionator (Agilent).

Mass Spectrometers

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

Protein interaction

- Biacore X (Biacore, GE Healthcare).



4.3 Traslational Oncopharmacology

Scientific Coordinator:
Atanasio Pandiella
Phone: (+34) 923 294 815
E-mail: atanasio@usal.es

Location and Contact:
Unidad de Oncofarmacología Traslacional
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)
Susana Hernández García
Phone: (+34) 923 294 720 / Ext. 3043
E-mail: suherga@usal.es / veranag@usal.es



Personnel:
Susana Hernández García, Verena González Rodríguez, Virginia Gascón Galán

DESCRIPTION

The traslational oncopharmacology laboratory has recently been created (april 2007) in response to the needs of several groups of our institute that work on antitumor drug development. This unit performs screening of antitumoral activities of drugs, 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 sporadically to assess drug activity on tumoral cells.
- Bioluminescence Assay. Two types of protocols are usually performed. One is based on the incubation of the agent of interest in the presence of bone marrow cells. In this case, BM cells from patients or the HS-5 cell line can be used. The latter is preferred 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://www.cicancer.org/lot/screening.php

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

STRATEGIC OBJECTIVES

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

ACHIEVEMENTS

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

Goals for the future

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

EQUIPMENT

Among the equipment of the unit are included:

BECKMAN Refrigerated Centrifuge, Heraeus CO2 Incubator, Biological Safety Cabinet TELSTAR BIO-II-A, Nikon Microscope for cell culture, BOECO PSU 2T plate shaker and OS-20 Orbital Shaker, ASYS UVM 340 Reader plate reader with the ASYS Software DigiRead / Scan plus, Bunsen Water Bath, Zeiss inverted microscope, equipment for electrophoresis, freezers (-80°C), liquid nitrogen tank at -180°C, etc. It is also available all the equipment present at the IBMCC, where the unit is located.

4.4 Bioinformatics

Scientific Coordinator:
Javier De Las Rivas
Phone: (+34) 923 294 819
E-mail: jrivas@usal.es

Location and Contact:
Unidad de Bioinformática
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)

Diego Alonso López
Phone: (+34) 923 294 821
E-mail: diego.alonso@usal.es

Personnel:
Diego Alonso López

DESCRIPTION

The Bioinformatics Unit works in the CIC-IBMCC with the help and support of the Bioinformatics and Functional Genomics Research Group, to provide technical and scientific service on bioinformatics data analyses. The Unit has major expertise in the analysis of data from Affymetrix platforms, either genome-wide DNA-associated or RNA-associated data.

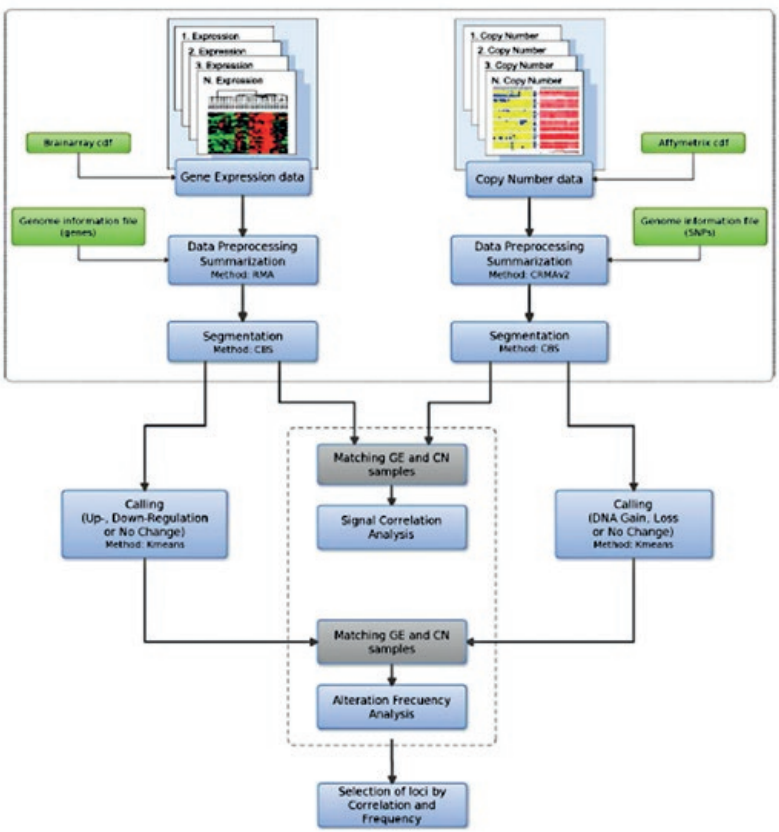
The Bioinformatics Unit was launched to provide services in June 2008 and in the last 5 years has performed more than 3000 analyses on about 1300 samples coming from different labs and research centers in Spain.

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

SERVICES

- Multiple comparative analyses of two states. Analysis for search and identification of genes - or other biomolecular entity as miRNAs, etc.- that are statistically significant obtained through statistical techniques of differential contrast of two states (Normal vs. Altered) with a minimum of 2 biological replicates for each state.

- Expression profiles of specific genes across multiple states / conditions /individuals. Integrated analysis of data for the identification of gene expression profiles.
- Functional analysis. Annotation and biological functional assignation based on enrichment studies and clustering methods. 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 and GeneTerm Linker
- Custom Analysis. The unit also offers custom analysis for data sets of non-standard platforms and the expansion and deepening of studies and data sets that have been analyzed before.
- Advice and assistance. Frequently, regardless of budget studies, the unit performs numerous works of advice and assistance to the scientists and researchers of the CIC-IBMCC and the University Campus demanding concrete assistance in Bioinformatics.



4.5 Molecular & Cellular Diagnostic

Scientific Coordinator:
Alberto Orfao (Cytometry Service)
Phone: (+34) 923 294 811
E-mail: orfao@usal.es
Jesús María Hernández Rivas (Molecular Cytogenetics Service)
Phone: (+34) 923 291 100 Ext. 55764
E-mail: jmhr@usal.es
Marcos González Díaz (Molecular Biology Service)
Phone: (+34) 923 291 100 Ext. 55629
E-mail: margondi@usal.es

Location and Contact:
Unidad de Diagnóstico Molecular y Celular
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)
Alberto Orfao (Cytometry Service)
Phone: (+34) 923 294 811
E-mail: orfao@usal.es
Jesús María Hernández Rivas (Molecular Cytogenetics Service)
Phone: (+34) 923 291 100 Ext. 55764
E-mail: jmhr@usal.es
Marcos González Díaz (Molecular Biology Service)
Phone: (+34) 923 291 100 Ext. 55629
E-mail: margondi@usal.es

Personnel:
Cytometry Service: Juana Ciudad Pizarro, Antonio López Fernández, Carolina Pontes Caldas, Rosa Ana Rivas Amoedo, Susana Barrena Delfa, Laura Gutiérrez Troncoso, Carlos Fernández Giménez, Miriam Fierro, Miriam Santos, Paloma Bárcena Carrasco, Mª Luz Sánchez García

Cytometry Service

DESCRIPTION

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

EQUIPMENT

- Cytometer Analyzer FACScanto II (BDB) for analisis in 8 fluorescence
- 2 Citometer separating FACAria (BDB), for analisis in 8 fluorescence
- 2 Cytometer Analyzer FACScaliburI (BDB) for analisis in 4 fluorescence
- Termocyclers
- Fluoresence microscopies
- Auxiliar equipment: centrifuges, refrigerators, freezers, bathrooms...

Personnel:

Molecular Cytogenetics Service: Jesús María Hernández Rivas, Norma C. Gutiérrez, Juan Luis García Hernández, Eva Lumbreras González, Cristina Robledo Montero, Rocío Benito Sánchez, María del Pozo Hernández, Ana Belén Díaz Martín, Micaela Fonseca García, Sara González Briones, Mª Ángeles Hernández García, María Almudena Martín Martín, Mª Ángeles Ramos Rodríguez, Irene Rodríguez Iglesias, Ana María Simón Muñoz, Isabel Mª Isidro Hernández, Vanesa Gutiérrez Moreta, Mª Teresa Prieto Martín

Molecular Cytogenetics Service

DESCRIPTION

Molecular Cytogenetics Unit (MCU) is a facility devoted to the karyotypic analysis, fluorescence "in situ" hybridization, comparative genomic hybridization, microarrays and nextgeneration sequencing of cancer patients. Most than 100 hospitals in Spain, and occasionally others from the EU, have used the MCU services. The Unit collaborates with the most relevant groups in the treatment of the hematological malignancies such as Pethema, GEL-TAMO, GEM or GETH providing technical support and 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-II).

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

EQUIPMENT

- Full authomatised system for karyotyping and FISH (Cytovision) with 3 analysis stations
- Full authomatised system for karyotyping and FISH (Metasystems) including a karyotype finder with 3 analysis stations
- Microbeads-based system for cellular isolation (Miltenyi)
- Microscopes of light and fluorescence
- Pirosequencer

Personnel:

Molecular Biology Service: Marcos González Díaz, Ramón García-Sanz, Luis Marín, Rocío Corral, Ana Balanzategui, M. Carmen Chillón, M. Eugenia A. Sarasquete, Miguel Alcoceba, Elena Sebastián, Cristina Jiménez, Mª Isabel Prieto Conde, María García-Álvarez, Alicia Antón, Montserrat Hernández-Ruano, Rebeca Maldonado, Alejandra Martín, Isabel Sánchez, Mercedes Jiménez

Molecular Biology Service

DESCRIPTION

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), and next generation sequencing (EuroClonality-NGS Consortium).

SERVICES

- B-cell and T-cell clonality for diagnosis or MRD detection in fresh cells (bone marrow, peripheral blood, lymph node, spleen, etc...) and/or formalin-fixed paraffin-embedded.
- Screening and quantification of chromosomal translocations (qualitative and real-time quantitative PCR, RT-PCR) for diagnosis and MRD monitoring in hematological malignancies.
- Analysis of somatic mutations: prognostic value, screening of potential MRD markers and/or identification of therapeutic targets.
- Gene expression: RT-PCR for diagnosis, prognosis and MRD detection.
- 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*).
- 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*)

4.6 Molecular Pathology and Tumor Bank / Comparative Molecular Pathology

Scientific Coordinator:
Enrique de Álava Casado (until May 2013)
Phone: (+34) 923 294 820
E-mail: edealava@usal.es
Carmen García Macías (from July 2013)
Phone: (+34) 923 294 832
E-mail: janagm@usal.es

Location and Contact:
Patología Molecular Comparada
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)
Carmen García Macías (from July 2013)
Phone: (+34) 923 294 832
E-mail: janagm@usal.es




Personnel:
Carmen García Macías, Susana Fraile Martín, Jairo Nieto Castro, Telmo Rodrigues Teixeira

DESCRIPTION

This is a core lab with two different aims:

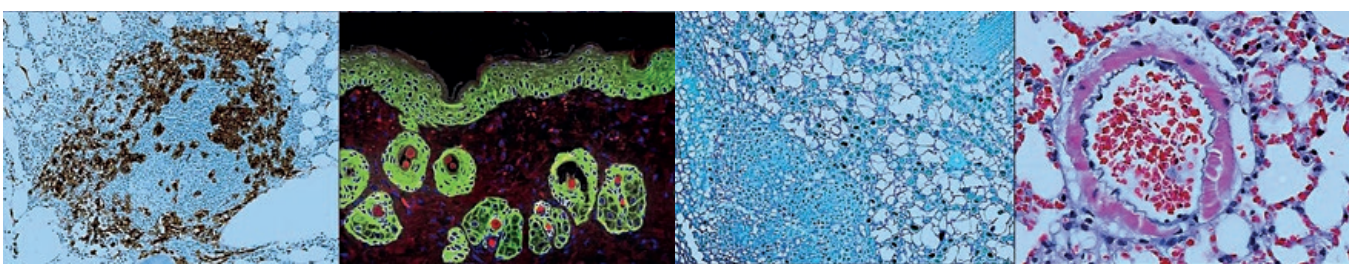
1 It serves as the Coordinating Node for the Biobank Network Oncological Diseases of Castilla and Leon, managing all tissue transactions between Hospitals of the Network (n=7) and researchers inside or outside the region. About 10 requests for tumor samples are received/served per year, which represents 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 5.300 samples are processed a year, from 502 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)
- 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.
  - 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 Coordinator:
José María de Pereda
Phone: (+34) 923 294 817
E-mail: pereda@usal.es

Location and Contact:
Unidad de Biología Estructural
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)
José María de Pereda
Phone: (+34) 923 294 817
E-mail: pereda@usal.es

DESCRIPTION

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

The main service offered by the Unit is the access to instrumentation for the analysis of macromolecular crystals and the collection of diffraction data. In addition, it provides consultations and assistance on optimization of crystallization, data collection and processing, and structure solution.

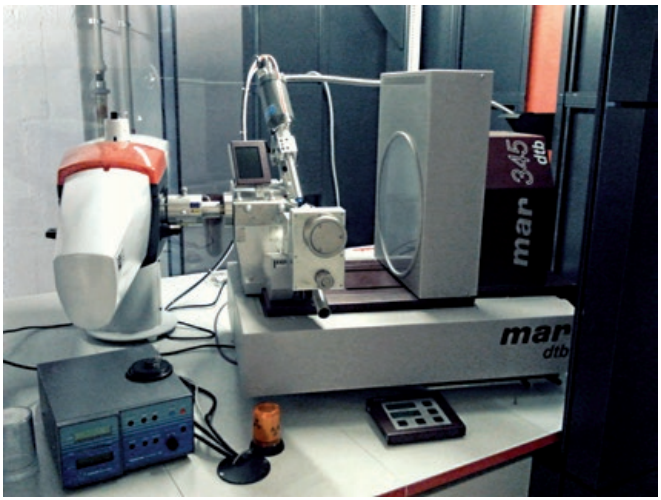
EQUIPMENT

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

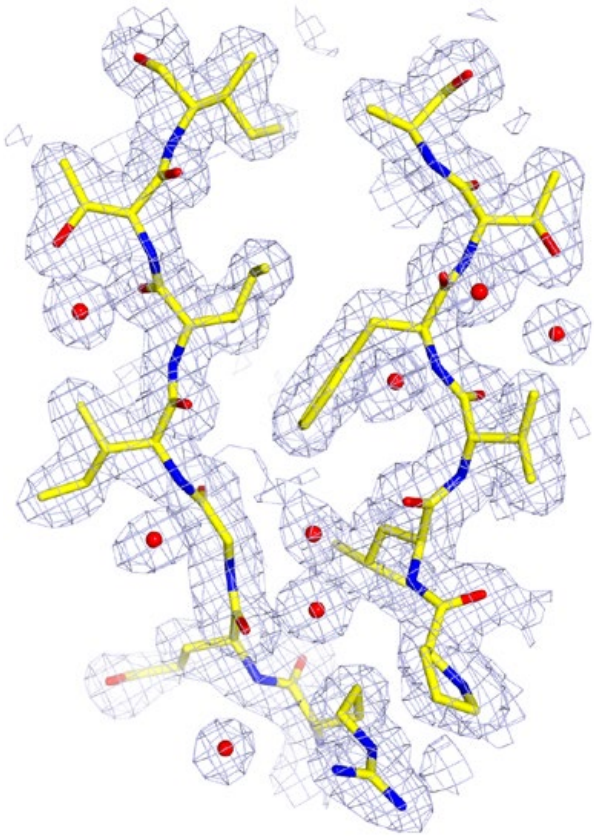
- Microstar (Bruker AXS) rotating anode micro-focus x-ray generator.
- Helios high-brightness multilayer X-ray optics (Bruker AXS).
- Mardtb goniostat (Marresearch) that integrates automated collimator, goniometer and detector mount.

- 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.



View of the difractometer of the Structural Biology Unit for the analysis of macromolecular crystals.



Electron density map of a fragment of the cytoplasmic domain of the integrin α and the corresponding refined model. The map was calculated using phases obtained by the SIRAS method and data collected at the Structural Biology Unit from a native crystal and a second crystal derivatized with a mercurial compound.

4.8 Microscopy

Scientific Coordinator:
Atanasio Pandiella
Phone: (+34) 923 294 815
E-mail: atanasio@usal.es
Alberto Martín Pendás
Phone: (+34) 923 294 809
E-mail: amp@usal.es

Location and Contact:
Unidad de Microscopía
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)
Ángel Luis Prieto Martín
Phone: (+34) 923 492 720 Ext: 3016
E-mail: microscopia_cic@usal.es


Personnel:
Ángel Luis Prieto Martín, María Nistal Chimeno

DESCRIPTION

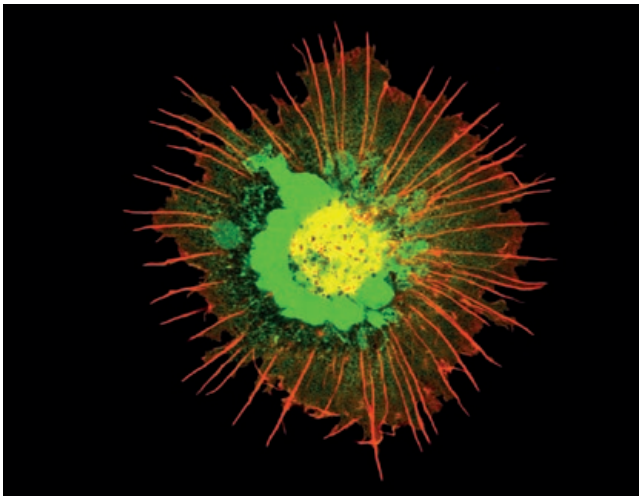
The IBMCC Microscopy Unit provides the following services:

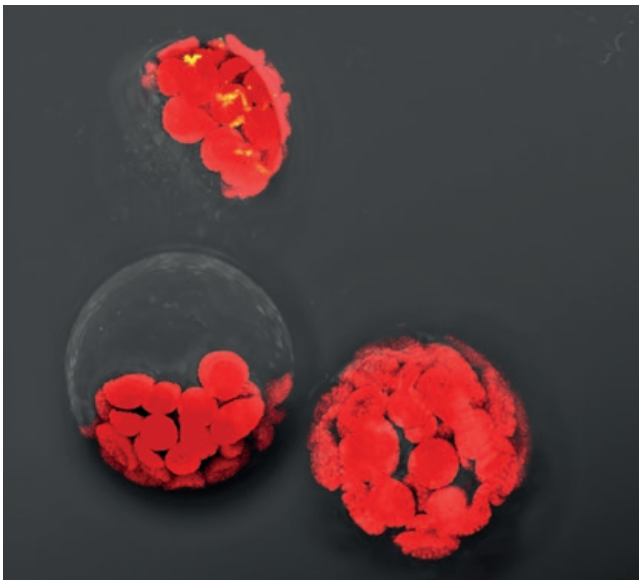
(1) Confocal microscopy: two confocal microscopes, one Zeiss LSM510 and one brand new Leica SP5.
(2) Live cell imaging and Deconvolution: one Olympus IX71 with Delta-Vision system, for live cell imaging. A chamber that controls CO2 and temperature is connected.
(3) Live cell imaging: one Nikon Eclipse TE-2000 fluorescent microscope with CO2 and temperature controlled.
(4) The Unit also looks after additional microscopes in the IBMCC: 9 fluorescent microscopes, 10 inverted microscopes for tissue culture, 1 microinjector, 1 microscope for cytogenetic and 1 microscope for histology.

The Unit personnel:

- Runs the confocal microscopes doing Z-Series, Timelapse, FRAP and FRET.
- Runs the in vivo systems (Delta-Vision and Nikon TE-2000).

- Gives tutorials on the correct use of the microscopes and deals with the day to day problems.
- Helps the users with the different imaging software: MetaMorph®, Openlab®, AxioVision®, LSM Image Browser® y DPManager®.





- Carries out monthly revisions of the microscopes, including phase adjustment, Kohler adjustment and objective cleaning and weekly revisions of the different microscope rooms (material reposition).
- Changes and fixes the mercury and halogen lamps.
- Writes guides and tutorials about the use, basic configurations and programs on the Unit website.
- Looks after the Unit quality system.

ISO Certifications: ISO 9001:2000

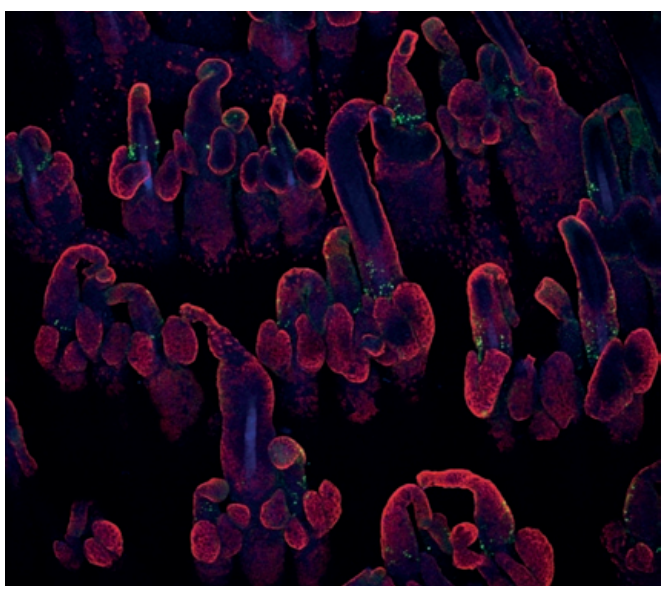
SERVICES

- Confocal microscopy to external users. This service offers microscopy both to internal and external users. Electronic management allows remote communication with the service to book the use of different microscopes, especially confocal.
- Training and advicing about the use of programs for image capture, including basic training and solving of inquiries about the programs of capture, image analysis and processing (Metamorph, Leica LAS AF, Image Browser LSM and Openlab).
- Creating, updating and maintaining the Web Unit, including a constant update of technical specifications for new equipment incorporated by the Center, as well as tutorials and guides. Basic use of major hardware and software associated analysis. Image for downloading by users of the center.
- Advicing about in vivo microscopy. Use of Nikon Eclipse TE2000, with CO2 and temperature controlled, including the handling of the equipment, as well as the associated software configuration (Metamorph). Designing Timelapse experiments and processing images and videos.
- Development of Tutorials with instructions for the use of image analysis programs to facilitate the microscopes manipulation and the capture and image analysis.
- Review and monthly maintenance of microscopy equipment of the Center, including setting stage for microscopy in cell culture rooms and adjustment for Kohler in fluorescence microscopes. Control, replacement and adjustment of fluorescent lamps of fluorescence microscopes.

EQUIPMENT

The Microscopy Unit of Cancer Research Center owns a great collection of microscopes that offers a high range of analysis possibilities. There are four main equipments due to their cost and the service they give:

- Laser Scan Confocal Microscopy Leica SP5: the machine was co-paid by FEDER, Ministerio de Sanidad y Consumo and Instituto de Salud Carlos III. It is the Unit main equipment – nearly 80% of the staff job is related to it. The microscopy has four lasers which have seven excitation lines, which, in combination with the spectral detection technology, allows the observation of every fluorocrome in the visible range. Due to its confocal module, it is the most demanded facility by users in order to obtain high resolution images of cell cultures or tissues. Besides, due to its software and the motorized stage techniques such as FRAP, FRET or co-localization analysis can be performed.



- Live Cell Microscopy Delta-Vision: acquired with FEDER and CSIC founding, this machine is mainly used in in vivo time-lapse experiments. Its principal application is observation and image acquisition of yeasts (cell-wall eukaryotic organisms). Anyway, this equipment is widely used – experiments in animal cells, cultures or fixed cells are run as well. The microscopy main advantages are the ultra-precise stage, the lighting system which combines a xenon lamp with a excitation filters wheel, and a high sensitive CCD camera. Hence, the machine acquires images with high speed and low exposition time, which decreases the damages that the live cells can suffer. In the other hand, the deconvolution module treatment gets high quality images.
- Laser Scan Confocal Microscopy Zeiss LSM 510: It's older equipment and the demand for its use has decreased since the arrival of the Leica SP5. It's useful when the demand is over possibilities of the Leica and for external users, who can use this microscopy under technician unit control.
- In vivo experiments microscope Nikon TE2000: This equipment is very useful to performance assays with living cells. In addition, this microscope is combined with Metamorph, a very powerful software tool in microscopy. Metamorph provides a lot aplications such as transforming images or making measurements.

In addition, the Microscopy Facility of the Cancer Research Center is completed with several fluorescence machines, inverted microscopes for culture checking and microscopes for FISH and histological analysis.

4.9 Hereditary Cancer & Genetic Counseling

Scientific Coordinator:
Rogelio González Sarmiento
Phone: (+34) 923 294 814
E-mail: gonzalez@usal.es
Juan Jesús Cruz Hernández
Phone: (+34) 923 291 342
E-mail: jjcruz@usal.es

Location and Contact:
Unidad de Consejo Genético & Cáncer Hereditario
Centro de Investigación del Cáncer (CSIC-USAL)
Campus Universitario Miguel de Unamuno s/n E- 37007 Salamanca (ESPAÑA)
Eva María Sánchez Tapia
Phone: (+34) 923 294 814
E-mail: emstapia@usal.es




Personnel:
Teresa Martín, Eva María Sánchez Tapia, Jéssica Pérez García, Rosario Miguel Tocino

DESCRIPTION

Cancer is a very heterogeneous disease caused by different factors. Those factors can be environmental and genetic and both are responsible for its etiopathogeny. It is estimated that between 5% and 10% of all tumors are hereditary. In those cases, the genetic alterations which determine the appearance of a series of cancer types can be transmitted from parents to their offspring together with a high possibility that the carriers of this particular mutation can therefore develop a tumor. This implies the necessity to carry out a genetic check-up of the entire family who then will be informed not only about the probability of a neoplasm appearance and transmitting the cancer predisposition to the descendants, but also about the prognosis, early detection strategies and proper treatment.

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

better knowledge of the disease that will help transfer this information onto other types of tumors.

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

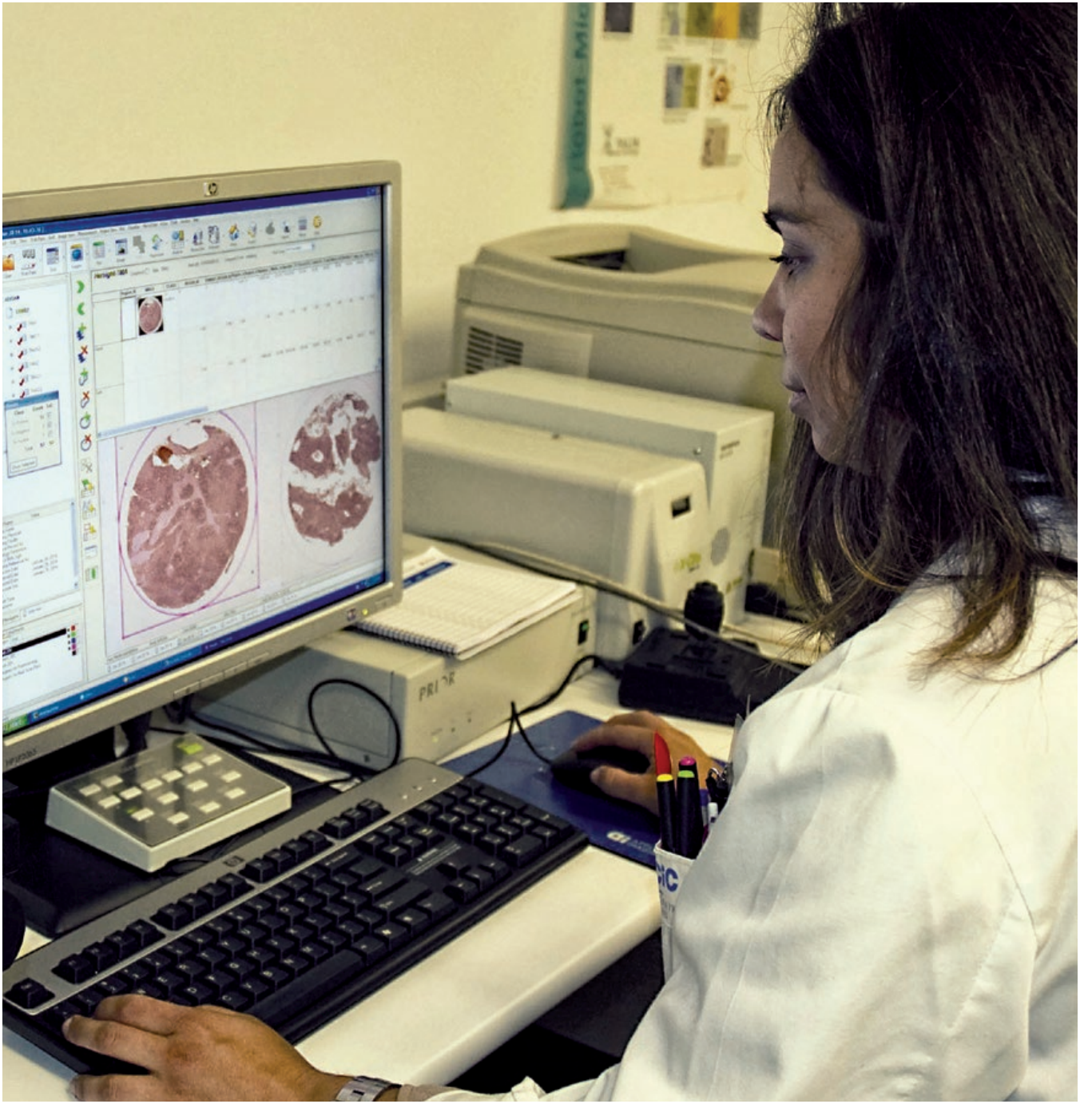
The main objective of the Laboratory of Hereditary Cancer of CIC-IBMCC (Institute of Molecular and Cellular Biology of Cancer) is to pay attention, prevent from and investigate the hereditary and family cancer. It can be fulfilled through counseling, evaluation, and study of the family with an increased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

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

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

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

5 Technical Support Units



5.1 Secretary Manager

Personnel:
Nuria Morán Aguirre

DESCRIPTION

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

5.2 Administration

Personnel:
Javier Beltrán Lurueña, Antonio Mata Domínguez, Cristina Santos Gallego, Álvaro Menéndez Sanchez, Margarita Villamor Carba, Miguel Ángel Moreno Valle, María Manuela Calvo González

DESCRIPTION

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):

1 Budgetary and financial management
- Annual budget institutional and financial management operations of the CSIC and USAL.
- Budget derived from competitive grant funding obtained by PIs (research projects).
- Management of contracts and agreements made by the center and / or researchers with public and private institutions.
- Monitoring and justification of expenditures to the granting agencies.
- Administration of revenues derived from direct services delivered by our technical scientific units.

2 Human resources
- Recruitment of scientific, technical, and administrative personnel.
- Payroll Management for staff employed by each of the institutions.
- Management of the payment of social security obligations.
- Payroll Management for staff employed by each of the institutions.

3 Management of the payment of social security obligations

4 Administrative management
- National and international scientific projects.
- Presentation of scientific and economic justification dossiers to the granting agencies.
- Administrative coordination with the USAL, CSIC, FICUS and other institutions.
- Administrative work related to Ph.D. and Master program of the Institute.

5.3 Glassware Cleaning and Sterilization




Personnel:
Ana Brufau Redondo, Mª Eugenia Fernández de la Torre, Mª del Rosario García Rubia, Gloria González Holgado

DESCRIPTION

The Washing and 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 and cleaning of labware.
- Sterilization of material.
- Preparation of 39 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 of material used in laboratories.
- Sterilization of material needed in laboratories.
- Stocking of reagents and research material.
- Management of dangerous waste Biohazard disposal.

5.4 Equipment & Building Maintenance


Personnel:
Celso Collazo López, Carlos Miguel de los Dolores Redondo

DESCRIPTION

The Equipment & Building Maintenance unit has the following functions:

- Performs maintenance programs of laboratory equipment and building facilities of the IBMCC.
- Management maintenance contracts, externals repairs and supplies for laboratory equipment and building facilities.
- Oversees the work of outside contractors in the repair and maintenance of laboratory equipment and building facilities.
- Modifies and repairs laboratory equipment and instruments.
- Modifies and repairs building facilities, and laboratory facilities.
- Helps research laboratories and core services in scientific equipment verification, purchases or replacement, or any technical problem.
- Verification and Internal calibration of laboratory equipment into the IBMCC Quality Management System.
- Registration of all equipment 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 of lab equipment
- Complex repair of laboratory equipment using some specific maintenance tools or equipment.
- CO2 cell culture incubators and spectrophotometer maintenance
- Simple laboratory equipment repairs
- Verification/calibration of balances, pipettes, dry heat incubators, refrigerators, thermoblocks, etc.
- Maintenance, corrective and preventive on the building and individual laboratories
- Programmed routine maintenance building (fancoil filters, oil vacuum replacement, etc.)
- Request of an intervention, Overseeing of the work of outside contractors and Management of repairs made by external companies
- Steam checkout.

5.5 Quality Control & Risk Prevention

Personnel:
María José Campo Beneítez

DESCRIPTION

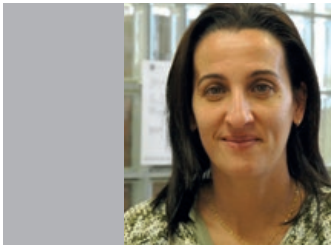
The Quality & Risk Unit Labor is responsible for:

- Quality control, assurance and improvement in the centre.
- Control of occupational and environmental safety and health in the institute.
- Management of ISO 9001 and OSHAS 18001 standards.
- Elaboration of general quality procedures applicable to all Units and review of standard operation protocols of the certified service Units.
- Elaboration of customized procedures for labor risks prevention and safety instructions.
- Training and education of newly incorporated personnel on occupational safety and emergency procedures.
- Training and education of all personnel with regards to Environmental Safety and Health programs.
- Organization of annual drills, annual revision and update of Emergency Plans.
- Organization of annual health monitoring and checkups.
- Channeling communication between centralized Risk Prevention Services from CSIC and the University of Salamanca.
- Record keeping and management of occupational accidents/incidents.
- Permanent update on current regulations on safety and health, ensuring their compliance.

SERVICES

- Preparation, follow-up and modification of quality procedures.
- Preparation , follow-up and modification of occupational risks prevention.
- Internal quality and prevention audits .Preparation of paperwork, data filling, and elaboration of annual report to be reviewed by the Direction.
- Follow-up control of the units and laboratories certified to check for the compliance of rules under the OHSAS 18001 and ISO 9001 requirements.
- Training of new personnel joining the center.
- Yearly health monitoring.
- Emergency drill preparation and execution.
- Quality and prevention external audits.

5.6 Central Warehouse & Radiological Protection



Personnel:
María Sonia Pérez Díez

SERVICES

- Supply of fungible material, reactive materials, solvents and culture medium.
- Maintenance of stock in warehouse.
- Monitoring of user expenses, internal invoicing and information.
- Files and acquisitions of inventorial material.
- Evaluations, previous and periodic of radiological risk.
- Management of the acquisition of radioisotopes, equipment and instruments of counting and protection. Edition of procedures.
- Managing the production and conditioning of radioactive waste. Internal handling and final storage up to the transfer to an authorized company of waste management.
- Controlled disposal of disclassified radioactive waste.
- Cooperation in the management of medical and dosimetric surveillance of the exposed personnel. Maintenance of medical and dosimetric reports of the exposed personnel.
- Acting in incidents, accidents and emergency situations following the previously established procedures.
- Training and information to the exposed personnel. Safety and Health seminars for the personnel exposed to ionizing radiation. Permanent practical advising for the exposed personnel.

5.7 Communication & Marketing

Personnel:
Almudena Timón Sánchez

DESCRIPTION

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:

1 Social Marketing. The marketing and communication unit is developing 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.

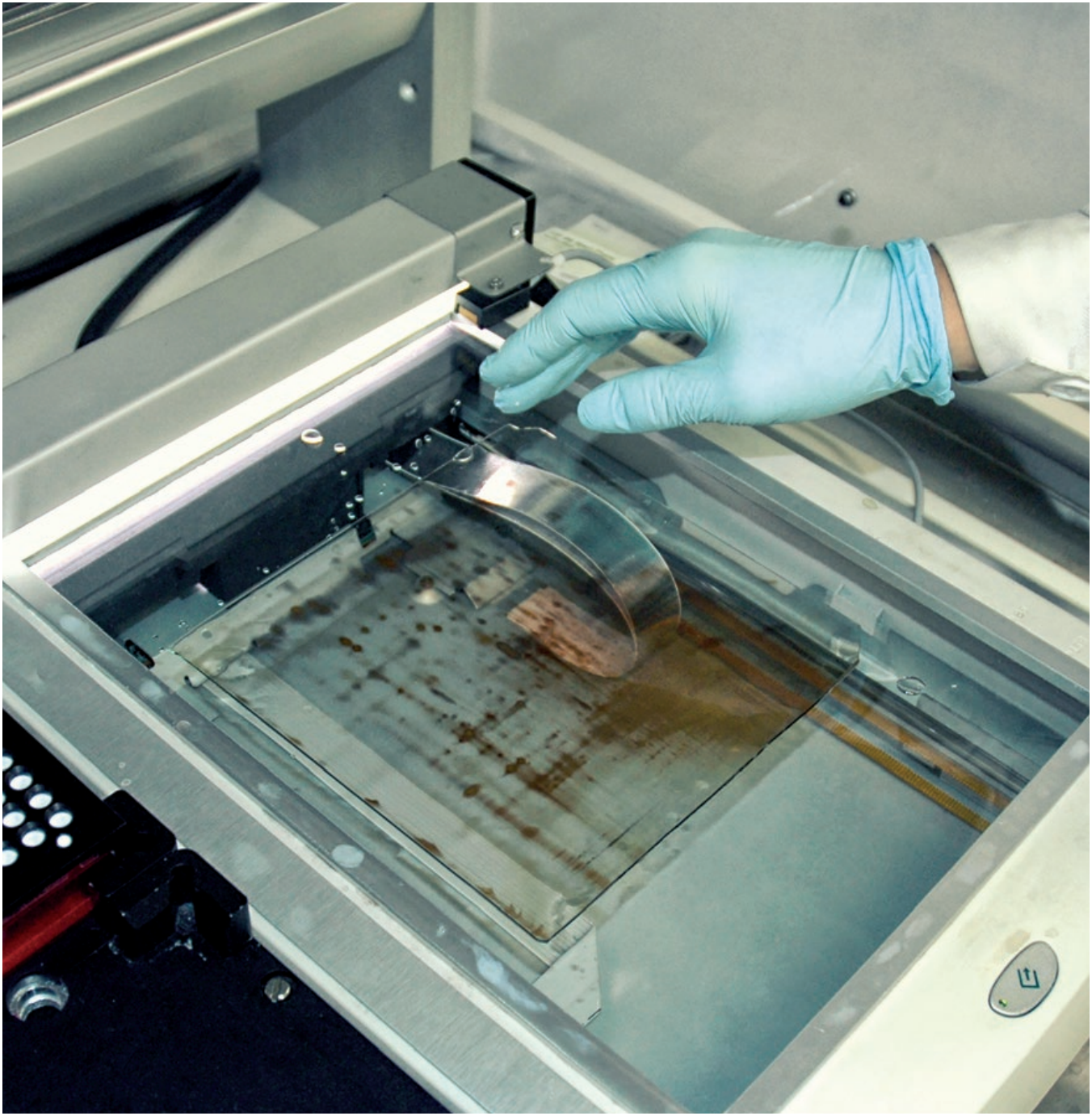
2 Corporate Public Communications.
This service includes.
- Media Relations
- Press releases
- Press conferences
- Social networking services
- Media monitoring and evaluation

3 Internal Communications.

Some more information (examples) on these activities can be found at News (website CIC)

SERVICES

- CIC Scientific seminars series. Diffusion and support in the organization of the CIC Scientific weekly seminars.
- Attention to the guided tours requested to visit of schools, university students and society in general organized within the "Week of Science", the "Open-Door days" or through agreements with the City hall of Salamanca.
- 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 for the diffusion of scientific achievements or project presentations.
- Attention to the consults and managements of the donations to the CIC through its foundation (FICUS).
- Attention to the media.



5.8 Information Technologies Service (IT)


Personnel:
Sonia Pedraza Flores, Pablo González Delgado

SERVICES

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, 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).

6 Scientific Activities


THE JOURNAL OF
Allergy and Clinical
Immunology
AAAAI
American Academy of
Allergy Asthma
& Immunology

6.1 List of journal

This list reflects all the journals in which the investigators of the CIC-IBMCC have published original articles during 2012-2013. The publications with an impact factor over 10 points are highlighted.

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Acta Tropica	1	2,787	2,787	Q1
Actas Dermo-Sifiliográficas	1	NI	NI	NI
Addiction Biology	1	5,914	5,914	D1
Advances in Experimental Medicine and Biology	2	1,825	3,65	Q2
Alcoholism-Clinical and Experimental Research	2	3,421	6,842	Q1
Alimentary Pharmacology & Therapeutics	1	4,548	4,548	Q1
Allergy	3	5,883	17,649	D1
American Journal of Cardiology	1	3,209	3,209	Q2
American Journal of Clinical Pathology	2	2,881	5,762	Q1
American Journal of Hematology	1	4,138	4,138	Q2
American Journal of Pathology	4	4,522	18,088	Q1
American Journal of Physiology-Cell Physiology	1	3,711	3,711	Q1
American Journal of Respiratory and Critical Care Medicine	**1**	**11,041**	**11,041**	**D1**
American Society of Clinical Oncology Educational Book	1	NI	NI	NI
Annals of Hematology	4	2,866	11,464	Q2
Annals of Oncology	6	7,384	44,304	D1
Annals of Surgical Oncology	1	4,12	4,12	D1
Antimicrobial Agents and Chemotherapy	1	4,565	4,565	Q1
Archiv der Pharmazie (Weinheim)	1	1,54	1,54	Q2
Archivos de la Sociedad Española de Oftalmología	2	NI	NI	NI
Autophagy	**3**	**12,042**	**36,126**	**D1**
Biochimica et Biophysica Acta (BBA) - Molecular Cell Research	3	4,808	14,424	Q1
Biochimica et Biophysica Acta (BBA) - Molecular And Cell Biology of Lipids	1	4,134	4,134	Q1
Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease	1	4,91	4,91	Q1
Bioessays	2	5,423	10,846	Q1

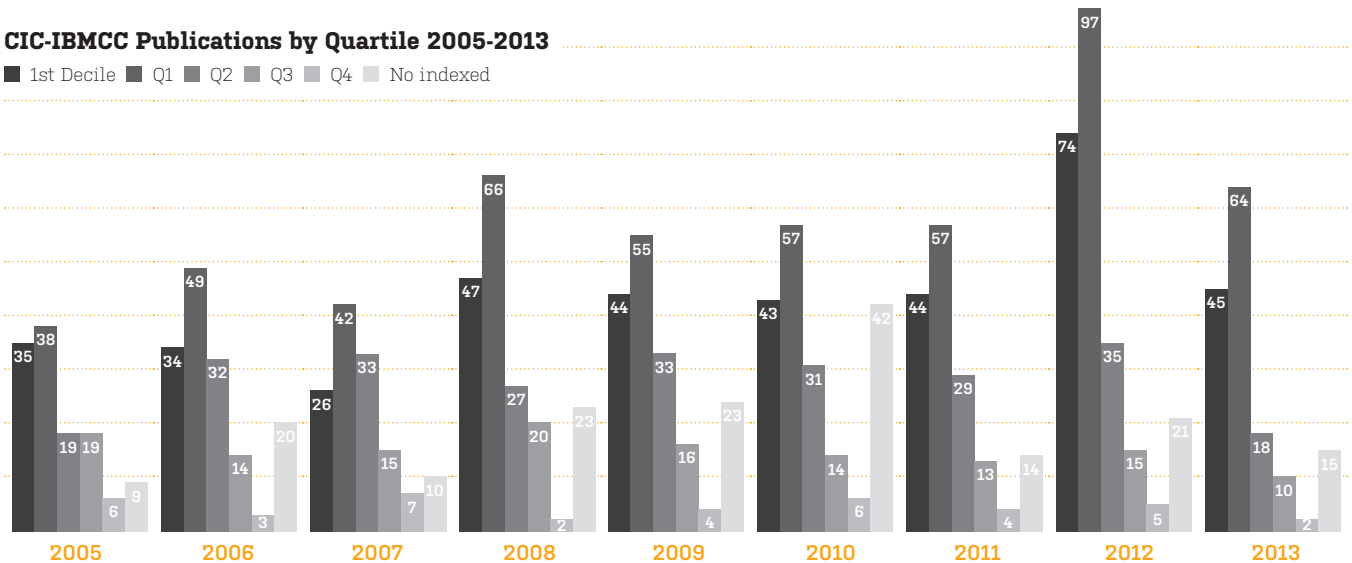
JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Bioinformatics	2	5,323	10,646	D1
Biology of Blood and Marrow Transplantation	2	3,94	7,88	Q1
Blood	14	9,06	126,84	D1
Blood Cancer Journal	1	1,4	1,4	Q4
Blood Transfusion	1	1,858	1,858	Q3
BMC Clinical Pathology	2	NI	NI	NI
BMC Genomics	2	4,397	8,794	Q1
BMC Medical Genetics	1	2,536	2,536	Q3
British Journal of Dermatology	3	3,759	11,277	D1
British Journal of Haematology	9	4,942	44,478	Q1
Briefings in Bioinformatics	2	5,298	10,596	D1
Briefings in Functional Genomics	1	4,21	4,21	Q1
Archivos de Bronconeumología	1	1,372	1,372	Q3
Cancer	1	5,201	5,201	Q1
Cancer Biomarkers	1	0,972	0,972	Q4
Cancer Genomics Proteomics	1	NI	NI	NI
Cancer Letters	1	4,258	4,258	Q1
Cancer and Metastasis Reviews	1	7,787	7,787	D1
Cancer Treatment Reviews	1	6,024	6,024	Q1
Carcinogenesis	3	5,635	16,905	Q1
Cell Communication and Signaling	1	5,093	5,093	Q1
Cell Cycle	7	5,321	37,247	Q1
Cell Death & Disease	1	6,044	6,044	Q1
Cell Metabolism	**1**	**14,619**	**14,619**	**D1**
Cellular and Molecular Life Sciences	1	5,615	5,615	Q1
Cellular Signalling	1	4,304	4,304	Q2
Cell Transplantation	1	4,422	4,422	Q1
Chromosome	1	3,34	3,34	Q2
Chromosomes Cancer	1	NI	NI	NI
Circulation	**1**	**15,202**	**15,202**	**D1**
Clinical Cancer Research	5	7,837	39,185	D1
Clinical Endocrinology (Oxf)	2	3,396	6,792	Q2
Clinical and Experimental Dermatology	1	1,329	1,329	Q3
Clinical Lymphoma Myeloma & Leukemia	2	1,667	3,334	Q3

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Clinical Sarcoma Research	1	NI	NI	NI
Clinical and Translational Oncology	2	NI	NI	NI
Clinics (Sao Paulo)	1	NI	NI	NI
Current Cancer Drug Targets	1	4	4	Q2
Current Eye Research	1	1,71	1,71	Q2
Current Hematologic Malignancy Reports	1	1,852	1,852	Q3
Current Pharmaceutical Design	1	3,311	3,311	Q1
Cytometry Part B-Clinical Cytometry	1	2,231	2,231	Q2
Cytotherapy	1	3,055	3,055	Q2
Dalton Transactions	1	3,806	3,806	Q1
Embo Journal	7	9,822	68,754	D1
Encyclopedia of Signaling Molecules	1	NI	NI	NI
Epigenetics	1	4,92	4,92	Q1
European Journal of Clinical Investigation	1	3,365	3,365	Q1
European Journal of Haematology	6	2,548	15,288	Q3
European Journal of Medicinal Chemistry	3	3,499	10,497	Q1
European Journal of Pharmacology	1	2,592	2,592	Q2
European Journal of Vascular And Endovascular Surgery	1	2,82	2,82	Q1
Expert Opinion on Investigational Drugs	1	4,744	4,744	D1
Frontiers in Oncology	2	NI	NI	NI
Gene	1	2,196	2,196	Q3
Genes Chromosomes Cancer	1	3,546	3,546	Q2
Haematologica-The Hematology Journal	26	5,935	154,31	Q1
Hematology	1	1,393	1,393	Q4
Histology and Histopathology	2	2,281	4,562	Q2
Histopathology	1	2,857	2,857	Q1
Human Mutation	1	5,213	5,213	Q1
International Archives of Allergy And Immunology	2	2,248	4,496	Q3
International Journal of Cancer	2	6,198	12,396	Q1
International Journal of Cardiology	1	5,509	5,509	Q1
International Journal of Hematology	2	1,681	3,362	Q3
International Journal of Laboratory Hematology	1	1,293	1,293	Q4
International Journal of Oncology	2	2,657	5,314	Q2
International Journal of Surgical Pathology	1	0,756	0,756	Q4

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Investigational New Drugs	3	3,498	10,494	Q1
Journal of Allergy and Clinical Immunology	3	**12,047**	36,141	D1
Journal of the American Academy of Dermatology	1	NI	NI	NI
Journal of Biological Chemistry	8	4,651	37,208	Q1
Journal of Biological Regulators & Homeostatic Agents	1	NI	NI	NI
Journal of Bone And Mineral Research	1	6,128	6,128	Q1
Journal of Cell Biology	**2**	**10,822**	**21,644**	**D1**
Journal of Cell Science	5	5,877	29,385	Q1
Journal of Clinical Oncology	**4**	**18,038**	**72,152**	**D1**
Journal of Dermatology	1	1,765	1,765	Q2
Journal of Experimental Medicine	**2**	**13,214**	**26,428**	**D1**
Journal of Hematology & Oncology	1	4,458	4,458	Q1
Journal of Immunology	1	5,52	5,52	Q1
Journal of Immunological Methods	1	2,225	2,225	Q3
Journal of Inorganic Biochemistry	2	3,197	6,394	Q1
Journal of Investigative Medicine	1	1,746	1,746	Q2
Journal of Medicinal Chemistry	1	5,614	5,614	D1
Journal of Medical Genetics	1	5,703	5,703	Q1
Journal of Medical Virology	1	2,373	2,373	Q3
Journal of the National Cancer Institute	1	NI	NI	NI
Journal of Neuro-Oncology	2	3,115	6,23	Q2
Journal of Pathology	1	7,585	7,585	D1
Journal of Physical Chemistry B	1	3,607	3,607	Q2
Journal of Proteome Research	1	5,056	5,056	Q1
Journal of Proteomics	1	4,088	4,088	Q1
Leukemia & Lymphoma	4	2,301	9,204	Q3
Leukemia Research	3	2,764	8,292	Q2
Leukemia	**30**	**10,164**	**304,92**	**D1**
Mechanisms of Ageing And Development	2	3,264	6,528	Q2
Medicina Clinica (Barc)	4	1,399	5,596	Q2
Mediterranean Journal of Hematology and Infectious Diseases	1	NI	NI	NI
Methods in Molecular Biology	1	NI	NI	NI
Mitochondrion	1	4,025	4,025	Q2
Modern Pathology	3	5,253	15,759	D1

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Molecular Biology of The Cell	5	4,803	24,015	Q2
Molecular Cancer Research	1	4,353	4,353	Q1
Molecular Cancer Therapeutics	1	5,599	5,599	Q1
Molecular and Cellular Biology	2	5,372	10,744	Q1
Molecular and Cellular Endocrinology	3	4,039	12,117	Q2
Molecular Oncology	1	6,701	6,701	Q1
New England Journal of Medicine	**1**	**51,658**	**51,658**	**D1**
Nanomedicine	1	5,26	5,26	D1
Nature Communications	**1**	**10,015**	**10,015**	**D1**
Nature Methods	**1**	**23,565**	**23,565**	**D1**
Nature Reviews Clinical Oncology	**1**	**15,031**	**15,031**	**Q1**
Nature	**1**	**38,597**	**38,597**	**D1**
Neoplasia	1	5,47	5,47	Q1
Oncogene	9	7,357	66,213	Q1
Oncologist	1	4,095	4,095	Q2
Oncotarget	1	6,636	6,636	Q1
Ophthalmic Genetics	1	1,07	1,07	Q3
Ophthalmology	1	5,563	5,563	D1
Pain Practice	1	2,605	2,605	Q2
Parasite	1	NI	NI	NI
Parasite Immunology	1	2,208	2,208	Q2
Pediatric Blood & Cancer	1	2,353	2,353	Q1
Pharmacogenetics and Genomics	1	3,608	3,608	Q1
Plos Biology	**1**	**12,96**	**12,96**	**D1**
Plos Genetics	2	8,517	17,034	D1
Plos Neglected Tropical Diseases	1	4,569	4,569	D1
Plos One	23	3,73	85,79	Q1
Proceedings of The National Academy of Sciences of The United States of America	4	9,737	38,948	D1
Recent Patents on Biotechnology	1	NI	NI	NI
Revista Española de Anestesiología y Reanimación	1	NI	NI	NI
Revista Espanola de Cardiología	1	3,204	3,204	Q2
Revista Española de Quimioterapia	1	0,836	0,836	Q4
Rheumatology International	1	2,214	2,214	Q3

JOURNAL	Nº ITEMS	IF	TOTAL IF	QUARTILE
Science Signaling	1	7,648	7,648	D1
Science	**1**	**31,027**	**31,027**	**D1**
Seminars in Oncology	1	4,327	4,327	Q1
Sensors (Basel)	1	1,953	1,953	Q1
Small Gtpases	1	NI	NI	NI
Stem Cells	1	7,701	7,701	D1
Tetrahedron	2	2,803	5,606	Q2
Therapeutic Advances in Hematology	1	NI	NI	NI
Transfusion Medicine	1	1,259	1,259	Q4
Transfusion	1	3,526	3,526	Q2
Transplant Infectious Disease	1	1,984	1,984	Q3
Trends in Biotechnology	1	9,66	9,66	D1
Trends in Genetics	1	9,772	9,772	D1
Wiener Klinische Wochenschrift	1	0,813	0,813	Q3



6.2 Patents

REFERENCE	TITLE	INVENTORS	PRIORITY DATE
PCT/NL2011/050781	Methods and means for detecting IgE-expressing B-cells	M van Zelm; JJM van Dongen; Alberto Orfao de Matos	01/2012
EP 11157001.6	Methods and means for monitoring disruption of tissue homeostasis in the total body	JJM van Dongen; JA Orfao de Matos Correia e Vale	01/2012
PCT/US2012/13557543	Methods and kit for the detection of cancer infiltration of the central nervous system	Alberto Orfao de Matos	07/2012
P201231170	Firma genética para el pronóstico del cáncer	Bustelo, X.R., Citterio, C., Menacho-Márquez, M., García-Escudero, R., Paramio, J.M.	20/07/2012
WO 2013053765	A new polynucleotide comprising a hematopoietic stem cell–specific transcriptional regulatory sequence, and mucosa-associated lymphoid tissue; useful for producing a transgenic nonhuman animal	Isidro Sánchez-García; José Ángel Martínez Climent; César José Cobaleda Hernández; Lorena Fontán Gabás; Carolina Vicente Dueñas	18/04/2013
Application number: 201330704	Polinucléotido que limita la expresión del oncogen humano TEL-AML1 a células madre hematopoyéticas y modelo animal que lo contiene	Isidro Sánchez-García; César José Cobaleda Hernández; Carolina Vicente Dueñas	17/05/2013
ES2388963	Desarrollo y uso de nanoparticulas lipídicas conteniendo edelfosina y otros éteres de fosfolípidos en la terapia antitumoral y antiparasitaria	María J. Blanco-Prieto, Ander Estella-Hermoso de Mendoza, Miguel Ángel Campanero, Janny Alexander Villa Pulgarín, Rubén Eduardo Varela Miranda, Faustino Mollinedo	09/2013
WO2013187765 (A2)	Methods, reagents and kits for detecting minimal residual disease	van Dongen Jacobus Johannes Maria; Orfao de Matos Correia e Vale Jose Alberto; Flores Montero Juan Alejandro; Almeida Parra Julia María; van der Velden Vincent Henricus Johannes; Boettcher Sebastian; Langerak Anthonie Willem; Mejstrikova Ester; Szczepanski Tomasz; Ritgen Matthias; Monteiro da Silva Lucio Paulo Jorge	19/12/2013

6.3 National & International Collaborations

CENTER	COUNTRY	RESEARCHER
Centro de Biología Molecular Severo Ochoa (CSIC)	Madrid / Spain	Balbino Alarcón
Universidad de Extremadura	Badajoz / Spain	Pedro Fernández-Salguero
Universidad de Cantabria	Santander / Spain	Piero Crespo
Universitat Pompeu Fabra	Barcelona / Spain	Luis A. Pérez-Jurado
University of Cincinatti	Cincinatti (OH) / USA	J. A. Cancelas
Harvard University	Boston (MA) / USA	David A Williams
CIEMAT	Madrid / Spain	Jesús M. Paramio
Hospital Universitario de La Princesa / CNIC	Madrid / Spain	Francisco Sánchez-Madrid
Universidade de Lisboa	Lisboa / Portugal	Pedro Simas
Universidade de Santiago de Compostela	Santiago de Compostela / Spain	Carlos Diéguez & Rubén Nogueiras
National Institutes of Health	Bethesda (MD) / USA	Silvio Gutkind
CABIMER	Sevilla / Spain	Andrés Aguilera
University of Newcastle	Newcastle / Australia	Keith Jones
Hospital Universitario de Salamanca	Salamanca / Spain	Ángeles Almeida
University of California	San Diego (CA) / USA	Kun-Liang Guan
Centro Nacional de Investigaciones Oncológicas (CNIO)	Madrid / Spain	Mariano Barbacid
Centro de Investigacion Médica Aplicada (CIMA)	Pamplona / Spain	José Ángel Martínez-Climent
Centro de Biología Molecular (CBM)	Madrid / Spain	César Cobaleda,
Universidad de Salamanca	Salamanca / Spain	Rafael Jiménez Fernández
Hospital Universitario Marques de Valdecilla- Fundación IFIMAV	Santander / Spain	Miguel A. Piris
Instituto de Biología Funcional y Genómica (IBFG)	Salamanca / Spain	Dionisio Martín-Zanca
UCSF	San Francisco / USA	Allan Balmain
University of Stanford	Standford / USA	Ash Alizadeh
Sanger Center	Cambridge / UK	Natalie Conte & Allan Bradley
Cornell Institute	New York / USA	Ari Melnick
University of Miami Sylvester Comprehensive Cancer Center	Florida / USA	Izidore Lossos
School of Clinical Sciences and Community Health	Edinburgh / UK	Robert Hardy
University of Washington	Washington / USA	Robert Rostomily
Fred Hutchinson Cancer Research Center	Seattle / USA	Larry R. Rohrschneider

CENTER	COUNTRY	RESEARCHER
Hospital Universitario de Salamanca	Salamanca / Spain	Mar Abad
Hospital Universitario de Albacete	Albacete / Spain	Alberto Ocaña
Universidad de Castilla La Mancha	Albacete / Spain	Ricardo Sánchez Prieto
Universidad de La Laguna	Santa Cruz de Tenerife / Spain	José Padrón
Hospital Vall de Hebrón	Barcelona / Spain	Santiago Ramón y Cajal
Harvard School of Public Health & University of Chile	Boston / USA & Santiago de Chile / Chile	Claudio Hetz
Centro de Investigacion Médica Aplicada (CIMA)	Pamplona / Spain	Fernando Lecanda
European Bioinformatics Institute (EBI)	Cambridge / UK	Paul Bertone
CCSB, Dana-Farber Cancer Institute & Harvard Medical School, Boston, USA	Boston / USA	Marc Vidal
IMDEA Food Institute	Madrid / Spain	Ana Ramírez-Molina
University of Calgary	Calgary / Canada	Vanina Zaremberg
Dalhousie University	Halifax / Canada	Christopher R. McMaster
University Medical Center	Mainz / Germany	Markus Munder
Universidad de Antioquia	Medellin / Colombia	Iván D. Vélez
University of Coimbra	Coimbra / Portugal	Paulo J. Oliveira
Imperial College London	London / United Kingdom	Ingrid Müller
Universidad de Salamanca	Salamanca / Spain	Antonio Muro
Universidad de Salamanca	Salamanca / Spain	José Luis Revuelta
Universidad de Salamanca	Salamanca / Spain	Manuel Medarde
Universidad de Salamanca	Salamanca / Spain	Isidro S. Marcos
Universidad de Salamanca	Salamanca / Spain	Pilar Basabe
Universidad de Pamplona	Pamplona / Spain	María J. Blanco-Prieto
Ecole Polytechnique Federale de Lausanne (EPFL)	Lausanne /Switzerland	Pierre Vogel
Universidad de Sevilla	Sevilla / Spain	Inmaculada Robina
CSIC	Madrid / Spain	A. Ulises Acuña

6.4 Spanish Cancer Network (RTICC)

Red Temática de Investigación Cooperativa en Cáncer

Thematic Networks of Cooperative Health Research (RETICS) are organizational structures, promoted by the Instituto de Salud Carlos III (ISCIII), composed by research groups in biomedicine, with multidisciplinary character, dependent on the different public administrations or private sector and belonging at least four autonomous regions aimed conducting cooperative research projects of general interest. They respond to the priorities of the National R+D (2008-2011) in the health sector and integrate the different types of research as a strategy to shorten the interval between the production of new knowledge and transfer and actual applicability medical practice.

The overall objective of the RETICS is to promote collaboration between the research groups of NHS working in related areas while facilitating the structuring of the research being done on it.

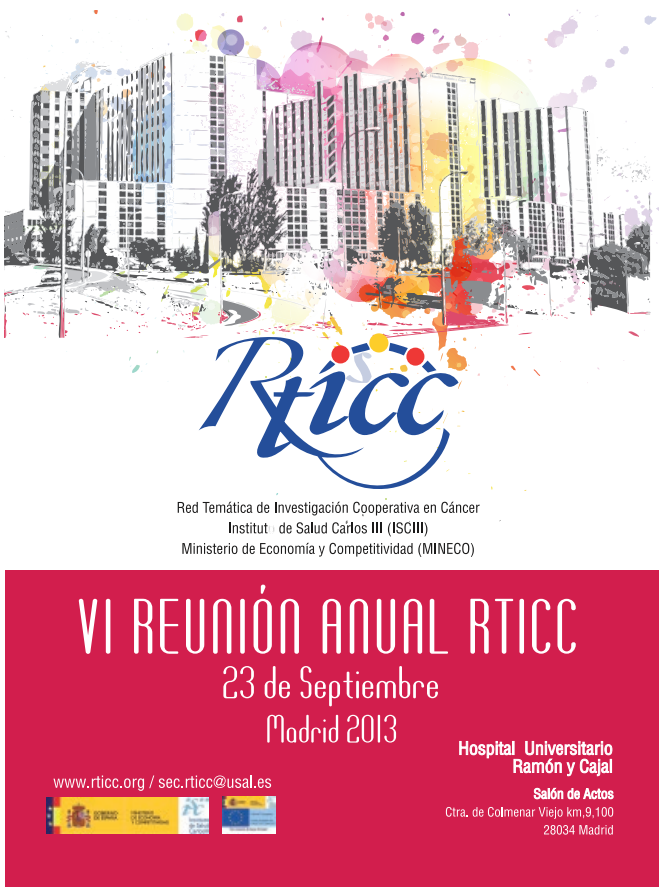
Until 2013 the Spanish Cancer Network 2007-2012 (RTICC) composed with 108 research groups (85 regular groups, and 21 clinical groups and 2 associate groups), with more than 1000 researchers from 52 institutions (universities, public research institutions and hospitals) and distributed in 13 autonomous communities, has been working in a structured form into 4 vertical lines of research and 6 horizontal service platforms, coordinated all of them by Dr. Eugenio Santos, director of the Cancer Research Center of Salamanca

In 2012, into The Strategic Action in Health 2012 of ISCIIII, was published a new call of RETICS program to finance a new network of cooperation in cancer research, in this occasion structured into seven 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 and finally (vii) Other Solid and pediatric tumors

The Application and Strategic Action Plan submitted jointly by 73 groups, to constitute a new RTICC, structured into the seven specific programs above mentioned and coordinated again by Dr. Eugenio Santos from Cancer Research Center of Salamanca, was evaluated positively, and since 2013 seven groups of the CIC, led by Drs Eugenio Santos, Xose Bustelo, Faustino Mollinedo, Alberto Orfao, Jesus San Miguel, Marcos Gonzalez, Atanasio Pandiella and Enrique de Alava are involved in five of the seven new programs of the new 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.



6.5 Award & Reconigtions

In 2012-2013 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.

Eugenio Santos

- National Prize FUNDALUCE 2012. Fundación de Asociaciones de Retinosis Pigmentaria de España FARPE. Salamanca, October 2013

Xosé Bustelo

- Gallego del Año. Grupo El Correo Gallego. Galicia (Spain) 2012

Jesús San Miguel

- Kyle Life achievement award. International Myeloma Foundation (IMF). Amsterdam 2012
- José Carreras Award. European Hematology Association- José Carreras Foundation Amsterdam 2012
- IV Edition Premio Sanitaria 2000 a la Sanidad de Castilla y León. Categoría Acción Investigadora. Grupo Empresarial Sanitaria 2.000 (editor de las publicaciones Revista Médica y Redacción Médica) & Janssen Laboratories Valladolid 2012
- Premio Rey Jaime I de Investigación médica 2013. Fundación Premios Rey Jaime I (Generalitat Valenciana & Fundación Valenciana de Estudios Avanzados) Valencia 2013

Alberto Orfao de Matos

- Premio Castilla y León de Investigación Científica y Técnica. Junta de Castilla y Leon. Valladolid 2012
- V Edition Premio Sanitaria 2000 a la Sanidad de Castilla y León. Categoría Acción Investigadora. Grupo Empresarial Sanitaria 2.000 (editor de las publicaciones Revista Médica y Redacción Médica) & Janssen Laboratories. Valladolid 2013

Samuel Seoane, Juan Carlos Montero, Alberto Ocaña & Atanasio Pandiella

- XIII Premio de Investigación Fundación Dr. Antonio Esteve al artículo: Effect of Multikinase Inhibitors on Caspase-Independent Cell Death and DNA Damage in Overexpressing Breast Cancer Cells (JNCI 2010; 102:1432-46).

7 Training Activities

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 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.

The average number of students enrolled per course has been about 30 and the total number of doctoral theses presented in this program exceeds 70.

STUDENTS PhD PROGRAM

2012-2013

Sara Aibar Santos
Vanesa Álvarez Álvarez
Laura Arango Duque
Patricia Ayala de la Roca
Cristina Sofía Baz Villoria
Elena Blanco Álvarez
Adrián Blanco Gómez
Ana Mª Carballido Vázquez
Diana Esther Castilla Perera
Ignacio Criado García
David Da Silva Moura
Rosete Sofía Das Dores Pais
Noelia Dasilva Freire
Paula Díez García
Conrad Friedrich Droste
Javier Fernández Mateos
Camilla Frattini
Idioa García Ramírez
María Hernández Sánchez
Carlos Jiménez Criado
Cristina Jiménez Sánchez
Mª Pilar Liceras Boillos
Teresa Da Conceiçao Lopes Ramos
Alberto Martín Lorenzo
Sara Ortiz Rivero
Irene Palacios Álvarez
Atenea Pascual Rodríguez
Jessica Pérez García
Juan Carlos Rama Merchán
Cristina Ramón Barros
Mª Florencia Re Louhau
Mª Luisa Rivera Reigada
Silvia Margarita Rojas Porras
Lucía Ruiz Roca
Beatriz Sáenz Narciso
Luis Carlos Sáez Martín
María Sánchez
Marta Tormos Pérez
Ricardo Usategui Martín
Teresa Usero Bárcena

2013-2014

Javier Acevedo Bouzas
Ruslan Alali
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
Iván 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

Master Degree in "Biology and Cancer Clinic"

The Master Biology and Cancer Clinic 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 Cancer Clinic 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

2011-2012

Vanesa Álvarez Álvarez
Pablo Alcón Hernández
Adrián Blanco Gómez
Alba Bosquet Agudo
Ignacio Criado García
Noelia Dasilva Freire
Paula Díez García
Javier Fernández Mateos
Ruth Maribel Forero Castro
Ester García-Casarrubios Pimentel
Idoia García Ramírez
María Hernández Sánchez
Carlos Jiménez Criado
Cristina Jiménez Sánchez
Mª Pilar Liceras Boillos
Jorge Maldonado Fernández de Gatta
Alberto Martín Lorenzo
Jorge Mata Garrido
Claudia Ollauri Ibáñez
Sara Ortiz Rivero
Jessica Pérez García
Catia Daniela Quintas Faria
Luis Ramírez Cebollero
Cristina Ramón Barros
Mª Florencia Ré Louhau
Lucía Ruiz Roca
Beatriz Sáenz Narciso
Ricardo Usategui Martín
Sara Villa Hernández

2012-2013

José Alejandro Aristizabal Castellanos
Juan Luis Blázquez Román
Jenny Lorena Brito Hoyos
María Campos Terrón
Mónica Patricia Cazar Cifuentes
Mauricio Andrés Chandía Cabas
Elia Henar Cornejo Muñoz
Beatriz Escudero Paniagua
Marta Fernández Prieto
Gema Fuerte Hortigón
Laura Gómez Hernández
Sara Gutiérrez Herrero
Leonor López Almeida
Marta Morte Corvinos
Blanca Nieto Bernáldez
María Isabel Prieto Conde
Vanessa Carolina Rivero Perdomo
Pablo Rodríguez Núñez
Sandra Ruiz García
Janine Wörthmüller Rodríguez
Miguel Zamora Porras

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

7.2 Doctoral Theses

PhD STUDENT	DIRECTOR	TITLE	DATE
Vera Susana Carneiro Maia	Carmen Guerrero Arroyo	**Mecanismos moleculares implicados en la regulación de la apoptosis y la adhesión celular por la ruta C3G/p38MAPK. Implicaciones en la patogénesis de la leucemia mieloide crónica**	24/02/2012
Esther Ortega Portero	José María de Pereda Vega	**Estudios estructurales y funcionales del dominicio plakina de plectina**	23/03/2012
Mª José Bernabé Barrios	Miguel Barrueco Ferrero / Rogelio González Sarmiento	**Valor de los polimorfismos de los genes CHRNA3A5B4 en la adicción al tabaco. Influencia de los mismos en el proceso de adicción**	30/03/2012
David Pescador Hernández	Juan Francisco Blanco Blanco / Jesús García Briñón / Fermín Sánchez Guijo	**Ingeniería tisular para el tratamiento de defectos osteocondrales**	27/04/2012
Alicia Ginel Picardo	Eugenio Santos	**Caracterización genómica y funcional de fibroblastos embrionarios derivados de ratones knockout para Sos1 y Sos2**	11/05/2012
Marta Vázquez Cedeira	Pedro Lazo-Zbikowski Taracena	**Sensibilidad a inhibidores de la familia de quinasas VRK y regulación de NFAT y COX-2 por la quinasa humana VRK2A**	18/05/2012
Lucía López Corral	Norma C. Gutiérrez / Jesús San Miguel Izquierdo	**Estudio del genoma y del transcriptoma en las fases evolutivas de las gammapatias monoclonales**	26/06/2012
Wendy Grey Nieto Pérez	Jose Alberto Orfao de Matos Correia e Vale	**Linfocitosis monoclonal de células B: Frecuencia de presentación en la población general de Salamanca y análisis de las características fenotípicas, genéticas del clon linfoide B**	29/06/2012
Ana Eugenia Rodríguez Vicente	Jesús Mª Hernández Rivas	**Identificación de nuevos subgrupos citogenéticos en Leucemia Linfática Crónica mediante el análisis combinado del genoma, exoma y transcriptoma**	23/07/2012
Itziar Fernández Martínez	Javier De Las Rivas Sanz / Agustín Mayo Íscar	**Desarrollo y aplicación de métodos estadísticos basados en recortes imparciales a datos de expresión génica de alta dimensionalidad**	24/07/2012
Filipa Bravo Lopes	Xosé R. García Bustelo	**Modulation of the immunological synapse of CD4+ helper T cells by gammaherpes viruses**	09/2012
Jesús García Gómez	Juan Jesús Cruz / Jesús García Mata	**Análisis de la supervivencia de las mujeres con cáncer de mama precoz diagnosticadas en Complejo Hospitalario de Orense. ¿La determinación inmunohistoquímica de Kli-67, bcl-2 y p53 en el tejido tumoral aporta información pronostica en estas pacientes?**	07/09/2012
Yurema Herran Santamaría	Alberto Martín Pendás / Elena Llano Cuadra	**Análisis funcional de las kleisinas meioticas de mamíferos**	14/09/2012

PhD STUDENT	DIRECTOR	TITLE	DATE
Lara Manyes i Font	Eugenio Santos	**Implicación de Pttg 1 en procesos celulares y fisiológicos mediados por RasGrf1**	20/09/2012
Cristina Gutiérrez Caballero	Alberto Martín Pendás / Elena Llano Cuadra	**Análisis funcional de proteínas implicadas en el mantenimiento de la estabilidad cromosómica en mamíferos**	21/09/2012
María del Pilar Ayuda Durán	José Arturo Calzada García / Andrés Avelino Bueno	**Inicio de replicación y estabilidad genómica en Saccharomyces cervisae**	01/10/2012
Stela Álvarez Fernández	Atanasio Pandiella Alonso	**La vía de ERK5-MEF2 en mieloma múltiple: implicaciones terapéuticas**	16/11/2012
Chen Xi	Atanasio Pandiella Alonso	**Targeting the mTOR and TRAIL pathways in multiple myeloma**	23/11/2012
Mónica López Bartolomé	Rogelio González Sarmiento / Clemente Muriel Villoria	**Estudio de variantes aléicas en genes asociados al dolor en pacientes con SDRC**	11/12/2012
Antonio García Gómez	Mercedes Garayoa / Jesús San Miguel Izquierdo / Fermín Martín Sánchez-Guijo	**Microambiente y lesión ósea en el mieloma múltiple: papel de las células "stem" mesenquimales y nuevos fármacos**	14/12/2012
Iria Barcia Sanjurjo	Ramiro Barcia / Pedro Lazo-Zbikowski Taracena	**Efecto de diferentes inhibidores y metales sobre las quinasas humanas VRK y la proteína viral B1R**	18/12/2012
Alberto Risueño Pérez	Javier De las Rivas Sanz	**Bioinformática aplicada a estudios del transcriptoma humano: análisis de expresión de genes, isoformas génicas y de ncRNAs en muestras sanas y en cáncer**	22/01/2013
Consolación Rosado Rubio	Rogelio González Sarmiento / Pilar Fraile Gómez	**Análisis clínico y genético del síndrome de Alport y la nefropatía del colágeno IV (alfa3/alfa4)**	07/02/2013
Rubén Eduardo Varela Miranda	Faustino Mollinedo / Antonio Muro	**Eficacia del análogo alquil-lisofosfolípido edelfosina en el tratamiento de la leishmaniosis, generación de resistencia y su utilidad potencial en terapia combinada**	12/02/2013
Mónica del Rey González	Jesús María Hernández Rivas	**Identificación de nuevas alteraciones genéticas y funcionales en los síndromes mielodisplásicos de bajo riesgo a través del estudio combinado del genoma, epigenoma y transcriptoma**	18/03/2013
Celia Fontanillo Fontanillo	Javier De las Rivas Sanz	**Desarrollo de algoritmos bioinformáticos para estudios de genómica funcional: aplicaciones en cáncer**	19/03/2013
Irene Rodríguez Hernández	Rogelio González Sarmiento	**Nuevas aportaciones a la caracterización molecular de los gliomas**	26/04/2013

PhD STUDENT	DIRECTOR	TITLE	DATE
María Sánchez Ledesma	Rogelio González Sarmiento / Ángel Sánchez Rodríguez / Ignacio Cruz González	**Hipertesión arterial e inflamación: análisis de polimorfismos genéticos y su correlación clínica y biologíca**	30/05/2013
Raquel Manso Calderón	Rogelio González Sarmiento	**Análisis de polimorfismos de genes relacionados con la función endotelial y la muerte celular en demencia vascular y enfermedad de Alzheimer**	05/07/2013
Mariana Reis Sobreiro	Faustino Mollinedo García	**Lipid rafts in cancer chemotherapy**	18/07/2013
Álvaro Cuesta Marban	Faustino Mollinedo García	**Mecanismos de toxicidad de lípidos antitumorales sintéticos en Saccharomyces cerevisiae**	26/07/2013
Laura Viñas de La Cruz	Andrés Avelino Bueno Nuñez	**Regulación de la desubiquitinación del PCNA en Schizosaccharomyces pombe**	30/07/2013
Sara Ciria Abad	Rogelio González Sarmiento	**Aproximación genética al estudio de las ictiosis**	06/09/2013
Ana Pastora Otero Motta	Enrique de Álava / María del Mar Abad Hernández / Jose Alberto Orfao de Matos / José Mª Sayagués Manzano	**Estudio de las alteraciones genéticas en Adenocarcinomas Gástricos mediante aCGH y FISH en su contexto clínico-patológico**	06/09/2013
Noemí Puig Morón	Jesús Fernando San Miguel Izquierdo / Ramón García Sanz / Marcos González Díaz	**Optimización y análisis crítico del estudio de la monitorización de enfermedad mínima residual mediante ASO RQ-PCR en pacientes con mieloma múltiple. Comparación con la citometría de flujo**	17/09/2013
Raquel Seijas Tamayo	Juan Jesús Cruz Hernández / Rogelio González Sarmiento	**Caracterización de variantes genéticas implicadas en la susceptibilidad a desarrollar carcinomas escamosos de cabeza y cuello. Correlación clínica**	18/09/2013
Daniel Fernández García	Rogelio González Sarmiento / Juan Jesús Cruz Hernández	**Nuevas aportaciones a la búsqueda de genes de predisposición al cáncer de mama hereditario**	27/09/2013
Clara Isabel Cieza Borrella	Rogelio González Sarmiento	**Caracterización de nuevos perfiles moleculares en carcinoma de endometrio esporádico**	28/09/2013
Noelia Alonso García	José Mª de Pereda Vega	**Estudios estructurales de las proteínas de hemidesmosomas: integrina a6b4 y tetraspanina CD151**	11/10/2013
Silvia Rojas Porras	Mª Consuelo del Cañizo Fernández-Roldán / María Díez Campelo / Sandra Mution Olave	**Lenalidomida y estroma en pacientes diagnosticados de síndrome mielodisplásico con deleción aislada del brazo largo del cromosoma 5**	25/11/2013
José Ángel Pérez Rivera	Pedro Pabón Osuna / Rogelio González Sarmiento	**Aplicación de la longitud telomérica y los polimorfismos de la telomerasa en el estudio de pacientes con síndrome coronario agudo**	17/12/2013

1 JORNADA TÉCNICA TRANSPOSICIÓN DE LA NUEVA DIRECTIVA UE: PROBLEMAS Y OPORTUNIDADES

Date 25/04/2012

Abstract

The new European directive (2010/63/EU) on the protection of animals used for experimental and other scientific purposes will oblige member States to introduce modifications in its own legal framework to adapt to this new framework.

Some of the changes to be introduced can significantly affect the development of research projects involving the use of animals. This meeting aims to provide an overview of the status of some relevant topics (training, definition of procedures, "reporting", etc.) and offer the possibility to discuss all these aspects.

Speakers

- Pilar León (Ministry of Agriculture, Food and Environment).
- Belén Pintado (Researcher, CNB-CSIC, Madrid; president of SECAL).
- Javier Guillén (AAALAC- International, Europe).

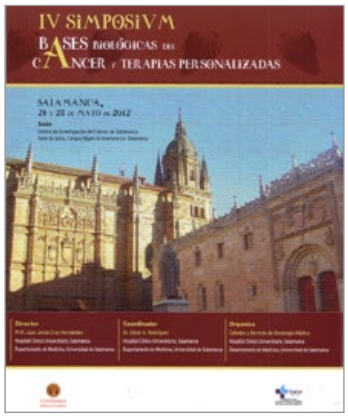
2 CURSO DE SEGURIDAD CRIOGÉNICA

Date 23/05/2012

3 IV SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER Y TERAPIAS PERSONALIZADAS

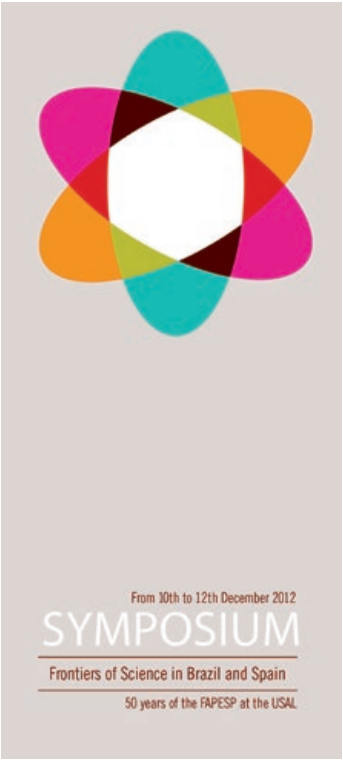
http://www.basesbiologicascancer.com/

Date 23/05/2012



4 TRATAMIENTO DEL DOLOR EN ASISTENCIA PRIMARIA. IESCYL

Date 04/06/2012



5 CURSO PROTEÓMICA CLÍNICA

Date 16/10/212

Program

- Self-assembled Protein Microarrays for Biomarker and Drug Discovery. / Joshua LaBaer, MD., PhD. (Director of Personalized Diagnostic Center. Biodesign Institute. Arizona State University. U.S.).
- Beads Suspension Arrays for Hematological Malignancies. / Fritdjof Lund-Johansen, MD., PhD. (Immunology Institute. University of Oslo. Oslo. Noruega)

6 SIMPOSIO: LAS FRONTERAS DE LA CIENCIA EN BRASIL Y ESPAÑA

Date 11/12/2012

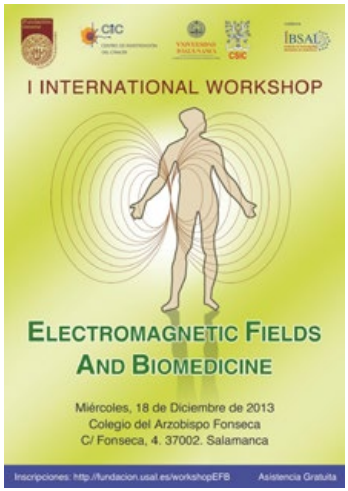
Program

- Cancer Epigenetics / Prof. Manel Esteller. (Director del Epigenetic Program del Instituto de Investigación Biomédica de Bellvitge, Barcelona)
- The genomic revolution and its impact on Cancer / Prof. Rogelio González-Sarmiento. Centro de Investigación del Cáncer, Universidad de Salamanca
- Head and Neck Cancer: from genes to personalized care / Dr. Luiz Paulo Kowalski, Hospital A.C.Camargo, National Institute for Oncogenomics Science and Technology
- The genome of chronic lymphocytic leukaemia: the International Cancer Genome Project / Prof. Marcos González. Departamento de Medicina, USAL
- Using Genomics to Improve Response to Neoadjuvant Therapy in Patients with Rectal Cancer / Anamaria A. Camargo. Ludwig Institute for Cancer Research
- The RAS GEFs as molecular targets. Therapeutic role of exchange factors of the Vav proto-oncogene family / Prof. Xosé Bustelo. Centro de Investigación del Cáncer, Universidad de Salamanca
- Improving experimental cancer therapy through a better understanding of tumor physiology / Roger Chamas. FM USP
- Design of new molecular targeted therapies for cancer / Prof. Atanasio Pandiella. CIC-USAL
- Nanotechnology and Heath / Dr. Antônio Claudio. Tedesco FFCL-USP-RP

7 V SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER Y TERAPIAS PERSONALIZADAS

Date 23-24/05/2013

8 I INTERNATIONAL WORKSHOP ELECTROMAGNETIC FIELDS AND BIOMEDICINE



http://fundacion.usal.es/workshopefb/

Date 18/12/2013

Program

Chair, Prof. Francisco J. García Criado

- What Electromagnetic Fields are? / Dr. Jesús Martín Martín Universidad de Salamanca
- Electromagnetic Fields and Disease. / Dr Rogelio González-Sarmiento. Universidad de Salamanca

Chair, Prof. Jesús Pérez-Losada

- Electromagnetic Fields and Health: What does Epidemiologyand IARC tell us? / Dr Martin Roosli (UNIBAS, Switzerland)

Chair: Isidro Sánchez-García

- Etiology and Biology of Human Childhood Leukemia. / Dra Carolina Vicente-Dueña Centro de Investigación del Cáncer: Salamanca
- The ARIMMORA European Project: Advanced Research on Interaction Mechanisms of Electromagnetic Exposures with Organisms for Risk Assessment. / Dr César Cobaleda Centro de Biología Molecular Severo Ochoa-CSIC. Madrid

7.4 Scientific Seminar Program

DATE	TITLE	SPEAKER	AFFILIATION
19/01/2012	**Challenging the basic paradigm in biomedical research: the role of variation in determining phenotype and disease**	John Quackenbush	Dana-Farber Cancer Institute Boston, Massachusetts, USA
24/01/2012	**Tumor suppressors beyond cancer**	Manuel Serrano	Spanish National Cancer Research Center (CNIO), Madrid
02/02/2012	**Papel multifuncional de la Annexin A6 en el tráfico intracelular y la señalización**	Carlos Enrich	Universidad de Barcelona, Barcelona
09/02/2012	**Role of the RRas2/TC21 GTPase in mammary gland development, breast tumorigenesis and lung metastasis**	Romain Larive	CIC-IBMCC (CSIC-USAL) Lab 02
16/02/2012	**Mecanismos de regulación de SIAH2 mediados por quinasas involucradas en la respuesta a estrés oncogénico**	Marco Calzado	Facultad de Medicina Universidad de Córdoba, Córdoba
23/02/2012	**Genetic and Physiological Analysis of Mitosis: Therapeutic implications**	Marcos Malumbres	Spanish National Cancer Research Center (CNIO), Madrid
01/03/2012	**The NIMA-family kinases Nek9, Nek6 and Nek7 as key regulators of the centrosome cycle during early mitosis**	Joan Roig	Institute for Research in Biomedicine (IRB), Barcelona
08/03/2012	**Uso de estudios de genómica funcional para la identificación de nuevas dianas y mecanismos de resistencia a terapia en cáncer**	Claudio Santos	Cancer Research UK, London Research Institute, Linncoln's Inn Fields, London, UK
15/03/2012	**New K-Ras signaling modulators: Calmodulin interaction and Ser181 phosphorylation**	Neus Agell	Universidad de Barcelona, Barcelona

DATE	TITLE	SPEAKER	AFFILIATION
22/03/2012	**Caracterización genómica y funcional de fibroblastos embrionarios derivados de ratones knockout para Sos1 y Sos2**	Alicia Ginel	CIC-IBMCC (CSIC-USAL) Lab 01
29/03/2012	**The trancription factor REST/NRSF, a master of neural cell differentiation and specificity, is an oncogene or a tumor suppressor?**	Jacopo Meldolesi	DIBIT San Raffaele Scientific Institute, Milano, Italy
12/04/2012	**Testing the Oxidative Stress Hypothesis in Drosophila: Structural Damage, Redox State and Aging**	William Orr	Department of Biological Sciences, Southern Methodist University, Texas, USA
19/04/2012	**lincRNAs: novel componets of the p53 network**	Maite Huarte	Centro de Investigación Médica Aplicada (CIMA), Pamplona
26/04/2012	**Clinical impact of flow cytometry analysis of cerebrospinal fluid in NHL patients: future perspectives**	Alberto Orfao	CIC-IBMCC (CSIC-USAL) Lab 11
03/05/2012	**La importancia de las modificaciones post-traduccionales en el control del proceso de migración celular**	Sonia Castillo Lluva	CIC-IBMCC (CSIC-USAL) Lab 07
08/05/2012	**Prediction of the effectors of the anti-inflammatory response by ChIP-seq and RNA-seq analysis**	Diego Miranda-Saavedra	WPI Immunology Frontier Research Centre (IFReC) Osaka University, Japan
10/05/2012	**RNA regulation in X chromosome dosage compensation**	Fatima Gebauer	Centro de Regulación Genómica (CRG), Barcelona
17/05/2012	**Transición epitelio-mesénquima y metástasis: Nuevos mecanismos de regulación**	Amparo Cano	Instituto de Investigaciones Biomédicas "Alberto Sols" – IIB-UAM-CSIC, Madrid
23/05/2012	**Inhibición de la vía PI3K/Akt en lipid rafts es crucial para la inducción de apoptosis en células de linfoma de manto**	Mariana Reis Sobreiro	CIC-IBMCC (CSIC-USAL) Lab 06
07/06/2012	**Análisis de la Desubiquitinación de PCNA en Schizosaccharomyces pombe**	Laura Viñas	CIC-IBMCC (CSIC-USAL) Lab 05
14/06/2012	**Functional analysis of the meiotic kleisins in the mice**	Elena Llano	CIC-IBMCC (CSIC-USAL) Lab 09
19/06/2012	**Early detection of colorectal cancer using microRNA biomarkers in patient blood sample**	Michael Hansen	Senior Scientist, Exiqon, Denmark
27/06/2012	**High-Resolution In Vivo Micro-Imaging for Small Animal Research**	Philippe Davault	VisualSonics
28/06/2012	**Mining the hematopoietic stem cell niche for novel therapeutic targets in leukemia**	Dorothy Sipkins	Dept. of Medicine, Section of Hematology/Oncology The University of Chicago, Chicago, USA
12/07/2012	**Distinct patterns of intratumoral clonal evolution at diagnosis and progression of Follicular Lymphoma**	Ash Alizadeh	Stanford Comprehensive Cancer Center, Standford, USA
19/07/2012	**Lessons learned from the clinical trials with TK inhibitors on the biology of human leukemias**	Giuseppe Saglio	Department of Clinical and Biological Sciences, University of Turin, Italy
24/07/2012	**Cytogenetics as a Diagnostic Tool for Renal Tumours: Clues and Pitfalls**	Paola Dal Cin	Harvard University; Cytogeneticist CAMD; Department of Pathology, Brigham and Women's Hospital, Boston

DATE	TITLE	SPEAKER	AFFILIATION
27/09/2012	**Caracterización de células B clonales en linfocitosis B monoclonal y leucemia linfática crónica**	Arancha Rodríguez Caballero	CIC-IBMCC (CSIC-USAL) Lab 11
04/10/2012	**Tumor suppressor genes in cancer, development and reprogramming**	Manuel Collado	Research Institute of Santiago de Compostela (IDIS) /Clinical University Hospital (CHUS), Santiago de Compostela
11/10/2012	**Estudio transcriptómico del estroma de la médula ósea inducido por interacción con las células de mieloma: implicaciones en la fisiopatología del mieloma múltiple. Eficacia de dos nuevos inhibidores del proteasoma para el tratamiento de la enfermedad**	Mercedes Garayoa	CIC-IBMCC (CSIC-USAL) Lab 12
16/10/2012	**Self-assembled Protein Microarrays for Biomarker and Drug Discovery**	Joshua LaBaer & Fritdjof Lund-Johansen	Immunology Institute. University of Oslo. Oslo. Noruega
18/10/2012	**Problems in translational research and drug development**	Alberto Ocaña	Hospital Universitario de Albacete, Albacete
25/10/2012	**Caracterización molecular de tumores de endometrio**	Clara Cieza Borrella	CIC-IBMCC (CSIC-USAL) Lab 14
08/11/2012	**Cancer associated inflammation facilitates metastatic breast cancer and counteracts chemo-responsiveness**	Karin de Visser	The Netherlands Cancer Institute, Amsterdam, Netherlands
15/11/2012	**La proteína del centro germinal HGAL incrementa la activación de Syk dando lugar a hiperplasia linfoide y amiloidosis**	Isabel Romero-Camarero	CIC-IBMCC (CSIC-USAL) Lab 13
22/11/2012	**Structural and numerical chromosomal aberrations in childhood leukaemia's unravelled by massive parallel sequencing**	Arndt Borkhardt	Düsseldorf University Hospital, Düsseldorf, Germany
29/11/2012	**Regulation of the cytoskeleton in angiogenesis**	Harry Mellor	University Walk , Bristol, UK
13/12/2012	**Targeting oncogene-induced replication stress for cancer therapy**	Óscar Fernández Capetillo	Spanish National Cancer Research Center (CNIO), Madrid
20/12/2012	**Estudio de la deficiencia de Snai2/Slug en el desarrollo del cáncer de mama ErbB2/Neu positivo**	Lourdes Hontecillas Prieto	CIC-IBMCC (CSIC-USAL) Lab 07
10/01/2013	**Resistencia a terapias anti-ERBB2/HER2 en cáncer de mama**	Elena Vela Sarrión	CIC-IBMCC (CSIC-USAL) Lab 15
17/01/2013	**PERP-ing into p53 apoptosis: insights from uveal melanoma**	Luminita Paraoan	University of Liverpool, Liverpool, UK
24/01/2013	**Modulación de la invasión celular por la quinasa humana VRK2 a través de la regulación de NFAT y COX-2**	Marta Vázquez-Cedeira	CIC-IBMCC (CSIC-USAL) Lab 04
31/01/2013	**The genetics of individuals: why would a mutation kill me, but not you?**	Ben Lehner	Centro de Regulación Genómica (CRG), Barcelona
07/02/2013	**Specific targeting of Caspase-9/PP2A interaction in tumor cells without effect on healthy cells as a new anti-tumor strategy**	Angelita Rebollo	Hôpital Pitié Salpêtrière, Paris, France

DATE	TITLE	SPEAKER	AFFILIATION
14/02/2013	**Anticuerpos monoclonales inmunoestimuladores: nuevas herramientas terapéuticas**	Ignacio Melero	Centro de Investigación Médica Aplicada (CIMA), Pamplona
21/02/2013	**Spatiotemporal regulation of epidermal stem cells during homeostasis, aging and cancer**	Salvador Aznar Benitah	Centro de Regulación Genómica (CRG), Barcelona
28/02/2013	**Caracterización de una nueva ruta molecular de intercomunicación entre autofagia y apoptosis mediada por BAK**	Michal Letek	CIC-IBMCC (CSIC-USAL) Lab 18
07/03/2013	**ERKs nuclear and cytoplasmic processes and their use in antineoplastic therapy**	Piero Crespo	Instituto de Biomedicina y Biotecnología de Cantabria (IBBTEC), Santander
15/03/2013	**Caracterización del transcriptoma de células madre mesenquimales (MSCs) humanas utilizando RNAseq**	Beatriz Rosón	CIC-IBMCC (CSIC-USAL) Lab 19
21/03/2013	**How studying mammary development gives us insights into breast cancer**	Zena Werb	University of California, San Francisco, USA
11/04/2013	**Inhibición de las rutas de ubiquitinación de proteínas dependientes de complejos cullin-ring ligasa en sarcoma de Ewing**	Daniel J. García	CIC-IBMCC (CSIC-USAL) Lab 20
18/04/2013	**The role of SIRT2 in cell cycle and genome stability**	Alejandro Vaquero	Cancer Epigenetics and Biology Program (PEBC) Bellvitge Biomedical Research Institute (IDIBELL), Barcelona
25/04/2013	**Functional redundancy of Sos1 and Sos2 in double knockout mice: Impact on lymphopoiesis and overall survival**	Fernando Calvo Baltanás	CIC-IBMCC (CSIC-USAL) Lab 01
02/05/2013	**Ribosome biogenesis, Cell Cycle Checkpoints and Cancer Progression**	George Thomas	Vontz Cancer Center, COM, University of Cincinnati, USA & ICO-IDIBELL, Barcelona
09/05/2013	**Vav family exchange factors are regulated by concurrent inhibitory inputs from N- and C-terminal domains**	María Barreira	CIC-IBMCC (CSIC-USAL) Lab 02
10/05/2013	**Structural Biology of RNA-mediated Gene Regulation and Methylation-mediated Epigenetic Regulation**	Dinshaw J. Patel	Memorial Sloan-Kettering Cancer Center, New York, USA
13/05/2013	**Using cloned mouse stromal cell lines as models to study mesenchymal stromal cell biology**	Rhodri Ceredig	Regenerative Medicine Institute-Department of Physiology (School of Medicine), National University of Ireland, Galway, Ireland
16/05/2013	**A new function for CPEB1 coordinates alternative 3 UTR processing with translational regulation in cell cycle and cancer**	Raúl Méndez	Institute for Research in Biomedicine (IRB), Barcelona
30/05/2013	**Apoptosis and inflammation induced by the granule exocytosis pathway of killer cells: an alternative to overcome multidrug resistance of tumor cells to apoptosis**	Julián Pardo	Centro de Investigaciones Biomédicas de Aragón (CIBA), Universidad de Zaragoza, Zaragoza
06/06/2013	**Oportunidades de financiación de la carrera investigadora en las Acciones Marie Curie (Programa PEOPLE, VII Programa Marco)**	Jorge Izquierdo Zubiate	Junta de Castilla y León (ADE) Agencia de Innovación, Financiación e Internacionalización empresarial de Castilla y León

DATE	TITLE	SPEAKER	AFFILIATION
13/06/2013	**Noncanonical IKK kinases in cancer**	Lienhard Schmitz	Justus-Liebig-University, Giessen, Germany
20/06/2013	**Organización estructural del factor de intercambio de nucleótido de guanina C3G**	María Gómez Hernández	CIC-IBMCC (CSIC-USAL) Lab 17
27/06/2013	**Novel insights into the nuclear functions of the DYRK1A protein kinase**	Susana de la Luna	Centro de Regulación Genómica (CRG), Barcelona
04/07/2013	**Diferencias en el mecanismo de toxicidad de dos alquilfosfolípidos en Saccharomyces cerevisiae**	Álvaro Cuesta Marbán	CIC-IBMCC (CSIC-USAL) Lab 06
11/07/2013	**Mecanismos de regulación de la entrada en mitosis por la fosfatasa Cdc14A en células humanas**	Sara Ovejero	CIC-IBMCC (CSIC-USAL) Lab 05
03/10/2013	**Coronin proteins and Rac1 GTPase: in the activation and in transduction, till the end of the signal do them apart**	Virginia Ojeda Seijas	CIC-IBMCC (CSIC-USAL) Lab 02
10/10/2013	**Functional Analysis of REX-1 in early embryo development and in stem cells: association with polycomb function**	Ignacio García-Tuñon Llanio	CIC-IBMCC (CSIC-USAL) Lab 09
17/10/2013	**The International Child Cancer Cohort Consortium, enhancing the search for preventable causes of childhood cancer**	Terry Dwyer	Murdoch Childrens Research Institute, International Agency for Research on Cancer (IARC), Lyon, France
24/10/2013	**El papel fundamental de N-ras en el desarrollo de la memoria inmunológica frente a las infecciones**	Margarita del Val	Centro de Biología Molecular "Severo Ochoa", Madrid
31/10/2013	**Tumour suppressor mechanisms in the control of chromosome stability**	Ashok Venkitaraman	Hutchison/MRC Research Centre, Cambridge, UK
07/11/2013	**Nuevas dianas terapéuticas en el tratamiento de las lesiones osteolíticas del mieloma múltiple**	Antonio García Gómez	CIC-IBMCC (CSIC-USAL) Lab 12
14/11/2013	**Nuevas aproximaciones traslacionales al cáncer de vejiga: Genómica, epigenética y modelos animales modificados genéticamente**	Jesús Paramio	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Madrid
21/11/2013	**Molecular Switches controlling Growth and Adhesion Signals**	Daniel Lietha	Spanish National Cancer Research Center (CNIO), Madrid
28/11/2013	**Análisis de la heterogeneidad genética de los Adenocarcinomas ductales de pancreas y su relación con las características de la enfermedad**	María Laura Gutiérrez	CIC-IBMCC (CSIC-USAL) Lab 11
05/12/2013	**Characterization of the role of chromatin remodelling genes in cancer through the use of NGS**	Ignacio Varela	Instituto de Biomedicina y Biotecnología de Cantabria (IBBTEC), Santander
12/12/2013	**Efecto de la variación genética natural sobre la reprogramación stem tumoral**	Lucía Ruiz Roca	CIC-IBMCC (CSIC-USAL) Lab 13
19/12/2013	**AhR regulates cell differentiation through the control of transposon-containing pluripotency genes**	Pedro M. Fernández Salguero	Universidad de Extremadura, Badajoz

8 Science Outreach


Ensino Médio
Ensino Médio

During 2012 the area of communication have developed various outreach activities framed within public relations aimed at different sectors of society, of which include:

- Guided visits. In 2012-2013 they have treated more 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. In addition, they were received to the university students not only of Biomedicine, but also with profiles of Ethics and Fine Arts.
- Participation in Empírika 2012: "Empírika, the Ibero-American Exhibition of Science, Technology and Innovation" is an international event and itinerant biennial, which took place for the first time in 2010 in Salamanca (Spain), anticipating eight years to VIII Centenary celebrations of the University of Salamanca in 2018. The second edition was held in October in São Paulo (Brazil) with academic activities such as seminars and conferences as well as workshops and cultural activities with high content of popular science. The Cancer Research Center participated in the stand of the University of Salamanca in 2012 to promote services of the University of Salamanca, including the National DNA Bank.
- On February 16th 2012 Cadena Ser ("La Ventana de Castilla y León") visited the Cancer Research Center to record a live program to highlight their outstanding research lines.
- At the request of Mr. Alfredo Pérez Rubalcaba, IBMCC researchers participated in a working meeting at the CIC on April 30.
  http://www.flickr.com/photos/psoe/sets/72157629931600017/with/6982367380/
- Social networking services: In 2012-2013, 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.
  Example: On February 2012, CIC supported the social awareness campaign #tengocáncer and comprehensive cancer care.

Stand of the CIC in Empirika Fair, held in São Paulo, Brazil

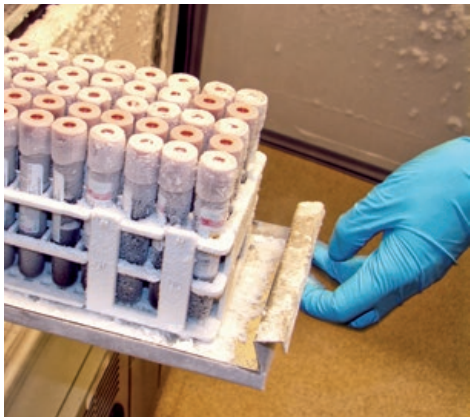
Moreover, in 2012-2013 several researchers have received various awards or appointments.

- April 12th 2013: Prof. Alberto Orfao has received the Award Castilla and León of Scientific and Technical Research in their respective edition to 2012.
- June 6th 2013: Prof. San Miguel received the Prize King Jaime I of medical research 2013.
- July 6th 2013: The authors of the paper Effect of Multikinase Inhibitors on Caspase-Independent Cell Death and DNA Damage in -Overexpressing Breast Cancer Cells (JNCI 2010; 102:1432-46) have received the prize "XIII Premio Dr. Antonio Esteve" as the most relevant paper in pharmacology signed by a Spanish researcher between 2010 and 2011. The article demonstrates that the combination of trastuzumab and dasatinib inhibits tumor growth in animal experiments.
- September 22th 2013: Prof. Alberto Orfao received the main award of the health awards of Castilla y León driven by the publishing company health 2000. The award recognizes his work in molecular diagnosis of neoplastic diseases.
- November 6th 2013: Researcher Javier de las Rivas named President of the Iberoamerican society of bioinformatics.

Press Conference delivery
"XIII award Dr. Antonio Esteve"

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

- June 2012: New therapeutic target for the treatment of pancreatic cancer.
- September 2012: Discovered new signaling route in breast cancer metastasis to lung.
- November 2012: The National DNA Bank collects and processes 7% of the samples for the 1000 genomes project.
- January 2013: National DNA Bank participates in the RD-Connect research project. Multiple entities and researchers from around the world participate in the RD-Connect project. The ultimate goal is to promote cooperation that allows better diagnosis and treatment of rare diseases.
- January 2013: Presentation at a press conference of advances in research on breast cancer. The study showed that the mTOR activation is a common target of the leading breast cancer triple negative.
- February 2013: TMEM59 defines a novel ATG16L1-binding motif that promotes local activation of LC3. The research describes a molecular mechanism that can target conventional endosomes for autophagic degradation.
- July 2013: Dr. Isidro Sánchez-García has been selected to be part of the Halifax Project. More than three hundred and fifty researchers from more than thirty countries work together in this international consortium.
- July 2013: Researchers of the CIC describes the function of the Vav proteins in the skin cancer. Vav proteins can provide drug targets for this tumor and other skin diseases such as psoriasis.
- August 2013: Researchers at CIC clarified, for the first time, interconnections existing between stress, nervous system, obesity, and healthy diets and high in fat.
- October 2013: The "Fundación contra la ceguera" funded studies, which will be developed in the CIC, to explain how the retinal degeneration occurs.



Samples of the National Bank DNA

Press conference
CIC-Foundation against blindness

In 2012 and 2013 they have carried out various activities related to fundraising:

- National Award in Cancer Research "Drs. Diz Pintado"
  – January 2012: the FICUS celebrated the delivery of the prize National Award in Cancer Research "Drs. Diz Pintado", which was awarded to Manel Esteller.
  – January 2013: the II National Award in Cancer Research "Drs. Diz Pintado" was awarded to Óscar Fernández-Capetillo.
  – December 2013: Dissemination of the III National Award in Cancer Research "Drs. Diz Pintado".
- February 2012: "Van Dyck" cinemas and World Cancer Day: "Van Dyck" cinemas held the pre-premiere in favor of the FICUS.
- September 2012: Benefit concert to fund research on breast cancer drug resistance:
  On 22th September 2012, the "Young Orchestra and Choir of the community of Madrid" (JORCAM) played Beethoven's Ninth Symphony at the National Auditorium in a benefit concert to fund three cancer research projects. One of these projects is being developed by research groups led by Dr. Pandiella (of the CIC) and Dr. Ocaña (of the CHUA) for drugs that combat the current resistance in breast cancer. The key to these works is to identify biological differences in resistant cells and design compounds that attack them and eliminate.
- November 2012: Rottary Club of Salamanca:
  Cancer Research Center and the Rotary Club of Salamanca presented, on 27th November 2012, the collaboration between the two organizations, which is to disseminate diagnostic tests on hereditary cancer through the 34,000 club Rotarians of the world and of the associations of cancer.
- January 2013: The Roscón Race.
  Paradinas San Juan hosted the Roscón Race in January 2013. The money raised was earmarked research grants for CIC staff.
- January 2013: XIII Trade Gala:
  The trade Gala closed the XXV campaign activities of Christmas animation organized by the Chamber of Commerce and industry of Salamanca. The money raised was donated to the CIC.

Delivery II National Award in Cancer Research "Drs. Diz Pintado"

Presentation at a press conference of Trade Gala

Poster concert "Tribute Moisés Ferreras (1971-2011)"

Poster: The 5th solidarity Readers Challenge

- March 2013: Benefit concert "Tribute to Moisés Ferreras (1971-2011)" held in the principal theatre of Burgos:
  Moisés Ferreras was treated in the service of Hematology of the University Hospital of Salamanca. All the money raised has been donated to the Foundation for Cancer Research at the University of Salamanca and is designed entirely in research into new treatments for patients with hematologic malignancies. The concert was organized by his widow Marta Hernández.
- March 2013: VII beneficent contest of elegance:
  Salamanca was from 15 to 17 March one of the centres of international interest thanks to the celebration of the VII beneficent contest of elegance. The competition was organized by the Ferrari Club of Spain, and the Rotary Club Salamanca Plaza Mayor in collaboration with Automotive Museum and the Salamanca City Hall. The Cancer Research Center received the money raised from the auction included in the program of activities.
- March 2013: Ocean Club of Salamanca:
  Ocean Club of Salamanca celebrated its anniversary distributing 2,000 coupons worth 5 €, which included awards. The money raised went to the FICUS through the AECC.
- August 2013: The 5th solidarity Readers Challenge.
  The Centre for Socio-Cultural Development of "Germán Sánchez Ruipérez Foundation" launched the 5th solidarity Readers Challenge. The event raised funds for CIC researchers working on the development of new drugs for the treatment of patients with triple-negative breast cancer.
- November 2013: Benefit concert:
  On November 30th was held in the theater "Juan del Enzina", a benefit concert for the Center for Cancer Research, within the cultural program of the University of Salamanca. The concert was a particularly emotive, because the initiative has come from David Muñoz, teacher professional Gijón Conservatory of Music, who was treated in the Hematology Department of the University of Salamanca Complex.
- December 2013: Christmas Campaign:
  Commercial establishments of Prior Street Salamanca donated the profits from his Christmas campaign (5th December-6th January 2014) at the Cancer Research Center of Salamanca.

9
Press Clippings

INICIATIVA | PROYECCIÓN DE "DECLARACIÓN DE GUERRA"

Van Dyck acoge hoy un preestreno solidario en favor del Centro del Cáncer

- Se donarán los cinco euros de la entrada
- En colaboración con LA GACETA

La Gaceta de Salamanca (enero)

AVANCE ESPAÑOL

Halladas seis proteínas clave en la extensión del cáncer de mama

ABC
MADRID

Un grupo de investigadores, con participación española, ha identificado seis proteínas claves que actúan de forma coordinada para favorecer el crecimiento de tumores de mama y su propagación hacia el pulmón. Los resultados de este trabajo, que cuenta con la participación de investigadores españoles, se publican en la revista «Science».

ABC (septiembre)

División de células cancerígenas durante el proceso de proliferación de un tumor de mama, vista bajo un microscopio. / SCIENCE PHOTO LIBRARY

ONCOLOGÍA

Demuestran que algunas células de los tumores de mama 'navegan' por la sangre y sirven para diagnosticar la enfermedad en su fase inicial con un simple análisis

Cómo detectar el cáncer en la sangre

El Mundo (junio)

Atanasio Pandiella, subdirector del Centro de Investigación del Cáncer de Salamanca (CIC)

El centro del cáncer de Salamanca reducirá un tercio de su personal

- El CSIC necesita 173 millones adicionales para cuadrar sus cuentas de 2012

UN AÑO DIFÍCIL

ABC (mayo)

INVESTIGACIÓN SON UNA BUENA FUENTE DE FINANCIACIÓN QUE NUESTRO PAÍS NO EXPLO...

Patentes: prestigio e ingresos extras para la ciencia españ...

Los investigadores están sufriendo los recortes como el resto de colectivos de este país, pero ...

Diario Médico (septiembre)

Diario Médico (junio)

ONCOLOGÍA LA INVESTIGACIÓN SE ENCUENTRA EN LAS PRIMERAS FASES Y SE PIDE CAUTELA

El retículo endoplásmico, diana prometedora en páncreas

→ Faustino Mollinedo y Consuelo Gajate, del Centro de Investigación del Cáncer de Salamanca, han demostrado que la molécula sintética éter fosfolípido es capaz de provocar la muerte de la célula tumoral. Por el momento, el trabajo se ha hecho en cultivos celulares y en animales.

Consuelo Gajate y Faustino Mollinedo.

URGEN SOLUCIONES

ABC (octubre)

El primer mapa de la diversidad genética humana

▸ Secuencian 1.092 genomas humanos de habitantes de cuatro continentes

El Mundo de Castilla y León (octubre)

INNOVADORES DE EL MUNDO

Un sistema 'pasa revista' continua a las placas solares

Cerco al cáncer de mama más agresivo

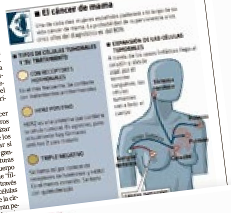
'Interiorista' del GPS que mejora la localización sin cobertura

Laboratorio que vigila las nucleares y la red eléctrica

> EL EXPERTO

Características de los tumores mamarios

Por Atanasio Pandiella



El Periódico de Catalunya (octubre)

INVESTIGACIÓN CIENTÍFICA INTERNACIONAL

Un gran mapa genético explora la relación entre mutaciones y salud

- El estudio secuencia el genoma de 1.092 personas de cuatro continentes
- Las variantes raras pueden explicar la contribución genética a las enfermedades

los datos

LIBRE ACCESO A LOS RESULTADOS


Saber Vivir (abril)
Todos los retos de la lucha contra el cáncer
Terapias a medida en función de la genética
Los médicos saben qué es lo que causa el cáncer pero no logran detenerlo. Por ello la investigación coordinada entre hospitales y laboratorios es clave en este sentido
ABC (mayo)
Premios Castilla y León
Girbés y Santos reclaman más peso a la investigación
Los científicos Tomás Girbés y Eugenio Santos, Premios Castilla y León de Investigación Científica y Técnica, reclamaron ayer más atención de las administraciones, y en especial del Gobierno para la investigación y evitar con los recortes retroceder un cuarto de siglo. Santos y Girbés participaron ayer en Soria, en los arcos de San Juan de Duero, en el séptimo de los encuentros «Los mejores de los nuestros. Conversaciones», al que asistióel consejero de Sanidad, Antonio Sáez. «La investigación es una actividad a medio o largo plazo y si no la atendemos como está ocurriendo ahora se producirá un agujero y vamos a perder lo que habíamos avanzado en los últimos veinticinco años», reivindicó Santos.
INNOVADORES DE EL MUNDO
Avance contra un cáncer infantil
Científicos de Salamanca hallan el modo de bloquear tumores de piel
Un equipo del Centro de Investigación del Cáncer consigue frenar el crecimiento de las células que producen esta enfermedad
Considera que es sólo «la punta del iceberg» de este programa biológico
Contra la obesidad
El Mundo de Castilla y León (junio)
Ensayo de un medicamento contra un cáncer de huesos infantil
El Mundo de Castilla y León (abril)
Enfermedad rara
un 'cóctel' de ra el agua potable
ESPECIALIZADA / Investigación/ El CiC trabaja con la diana mTOR en este subtipo de tumor mamario
BEZ235 y QT frenan el avance del cáncer de mama triple negativo en ratón
Gaceta Médica (enero)
>>SALAMANCA
Un paciente organiza un concierto benéfico para el Centro de Investigación del Cáncer
El Norte de Castilla (junio)

9.2 2013


>PERSONAJES ÚNICOS / ISIDRO SÁNCHEZ

Lidera el grupo de Oncología Experimental y Traslacional del CIC y no comparte muchas de las creencias generalizadas sobre la enfermedad. Investiga un nuevo enfoque que permita atacarla desprogramando las células cancerígenas. Por José Manuel Blanco

El cáncer desde otro ángulo

«El patólogo es imprescindible para que el Centro del Cáncer funcione bien»

Carmen García Macías Directora del Laboratorio de Patología Molecular

La nueva directora explica que este profesional ofrece al investigador un diagnóstico «más rápido y eficaz»

Limitaciones económicas

CASTILLA Y LEÓN

>UNA DÉCADA DEL CONSEJO GENÉTICO EN CÁNCER HEREDITARIO

Nuevos equipamientos y criterios para acortar la espera del programa de cáncer hereditario

La unidades de consejo genético revisarán los «laxos criterios de selección» para realizar el test / En enero reciben equipamiento de secuenciación que multiplica la velocidad de análisis / Están situadas en las provincias de Burgos, Salamanca y Valladolid y han estudiado a más de 3.000 familias

La espera para primera consulta supera el año y para resultados 9 meses

Con los equipos que irán al CIC y al IBGM el resultado pasa de 4 y 6 meses a 2 semanas

Una trabajadora del Centro del Cáncer donde se analizan las muestras extraídas en Salamanca.

Programa de consejo genético de cáncer hereditario

EL MUNDO. LUNES 25 DE NOVIEMBRE DE 2013

>UNA DÉCADA DEL CONSEJO GENÉTICO EN CÁNCER HEREDITARIO

«Opto por extirparme los senos porque sólo me preocupa vivir y evitar que aparezca»

Cuando los estudios revelan una mutación genética y por ello predisposición al cáncer de mama, ovario o colon el paciente se enfrenta a dos opciones: seguimiento o cirugía

Juan Jesús Cruz (d) conversa con personal médico y técnicos de la Unidad de Salamanca que coordina con Rogelio González Sarmiento.

Los test genéticos dan positivo en el 20 y 25% de los casos estudiados

Con el gen BRCA1 hay 60% de posibilidades de tener cáncer de mama y 40% de ovario

«Hay quien prefiere no saberlo, pero al saberlo previenes»

El Mundo de Castilla y León (junio)

El Norte de Castilla Ed. Salamanca (junio)

El Norte de Castilla (junio)

Scientific Report

2012 | 2013

CIC

CENTRO DE INVESTIGACIÓN DEL CÁNCER

iBMCC

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

CSIC

CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

VNiVERSiDAD D SALAMANCA

CAMPUS DE EXCELENCIA INTERNACIONAL

Unión Europea

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