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AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **EFEYAN , ALEJO**
Referencia: RYC-2013-13546
Área Científica: Biomedicina
Correo Electrónico: efeyan@wi.mit.edu

Título:

Nutrient sensing by mTOR in mammals

Resumen de la Memoria:

Since my early steps in scientific research, I have been interested in master regulators of fundamental biological processes. During my Ph.D., I studied how the tumor suppressor protein p53 exerts its cancer protection. In particular, by means of genetic engineered mice, I aimed to dissect the relative contribution of different inputs that activate p53 (DNA damage response and oncogenic signaling) to its ability to exert tumor suppression functions. Our results unequivocally showed the dramatic importance of oncogenic signaling, compared to that of the DNA damage response (Efeyan et al., Nature 2006; Efeyan et al., Cancer Research 2007; Efeyan and Murga et al., PLoS 2009) I also performed a similar genetic approach to dissect the relevance of certain targets of p53 in p53-specific protection, which showed a moderate contribution of the cell cycle regulator p21 (Efeyan et al., Oncogene 2007).

For my postdoctoral studies, I switched to the study of a master regulator of cell growth: the mechanistic target of rapamycin (mTOR), involved in the pathogenesis of cancer and diabetes. When part of mTOR complex 1 (mTORC1), this kinase drives cell growth by regulating every anabolic pathway in the cell, and is. MTOR integrates signaling cues from the organismal nutritional state, elicited by growth factors and other hormones, and cues from local nutrient abundance. Unlike the growth factor signal transduction, our understanding of the nutrient signaling pathway has just begun, triggered by the discovery of the family of Rag GTPases. Before my postdoctoral research, work on nutrient sensing by mTORC1 was restricted to cell culture studies, and whether this pathway had any function in the context of a mammalian organism was obscure. By means of generating novel genetically-engineered mouse models to study the function of the Rag GTPases, my postdoctoral work pushed forward this field by: 1) demonstrating that this nutrient sensing signaling pathway is essential for embryonic development and for adult life, being RagA more important than RagB (Efeyan et al., submitted); 2) showing that the regulation of RagA activity is key for coordinating fasting responses, for the regulation of autophagy, and for enduring the neonatal starvation period (Efeyan et al., Nature 2013). This work also demonstrated that the Rag GTPases work as multi-node nutrient sensors, signaling both amino acid and glucose sufficiency to mTORC1. I am currently investigating the impact of the nutrient sensing signaling pathway in adult mammalian physiology, in particular, in cancer and aging.

Resumen del Currículum Vitae:

In brief, I obtained my grade from the University of Buenos Aires, and my undergraduate Thesis was focused in experimental mouse models of breast cancer. From this work, I published three papers, on of them as a first author.

I obtained my Ph.D. degree from the Autonomous University of Madrid, and my Ph.D. Thesis was performed under the supervision of Manuel Serrano at the CNIO, on the regulation of tumor suppression by p53. My Thesis work obtained Outstanding Cum Laude grade and the Extraordinary Thesis Award. From my Ph.D. work, I published 9 papers (4 first-author papers including one in Nature, and additional papers in Nature and Cell Metabolism) plus one first-author review.

For my postdoctoral experience, I joined David M. Sabatini lab at the Whitehead Institute at MIT, where I currently study the mTOR kinase and nutrient sensing signaling pathway in mice. During my postdoctoral work, I published one first-author paper in Nature, and an additional first-author paper pending to be resubmitted after first revision. I also published two papers in Science and Cell Metabolism. In addition, I wrote four reviews as first-author, including one in Nature Reviews in Molecular Cell Biology, for which I am also corresponding author.

I obtained five fellowships (3 Ph.D. fellowships: FPI, CNIO Predoctoral and FPU; and 2 Postdoctoral Fellowships: Long Term Human Frontiers Science Program Organization and Charles King's Trust).

I provide a selected list of publications:

-Selected articles from my Postdoctoral work:

1. RagA, but not RagB, is essential for development and adult life. Efeyan A, Schweitzer LD, Bilate AM, Chang S, Kirak O, Lamming DW, Sabatini DM. Re-submission in preparation after first revision.
2. Rag GTPase-mediated regulation of mTORC1 by nutrients is necessary for neonatal autophagy and survival. Efeyan A, Zoncu R, Chang S, Gumper I, Snitkin H, Wolfson R, Kirak O, Sabatini DD, Sabatini DM. Nature. 2013 Jan 31;493(7434):679-83

-Selected Articles from my Ph.D. Thesis:

3. Limited evidence for the in vivo role of ATM in the response to oncogenic stress. Efeyan A*, Murga M*, Martinez-Pastor B, Ortega-Molina A, Soria R, Collado M, Fernandez-Capetillo O, Serrano M. PLoS One. 2009;4(5):e5475.(*: equally contribution)
4. Induction of p53-dependent senescence by the MDM2 antagonist nutlin-3a in mouse cells of fibroblast origin. Efeyan A, Ortega-

Molina A, Velasco-Miguel S, Herranz D, Vassilev LT, Serrano M. Cancer Res. 2007 Aug 1;67(15):7350-7.

5. Tumour biology: Policing of oncogene activity by p53. Efeyan A, Garcia-Cao I, Herranz D, Velasco-Miguel S, Serrano M. Nature. 2006 Sep 14;443(7108):159.

6. Genetic dissection of the role of p21Cip1/Waf1 in p53-mediated tumour suppression. Efeyan A, Collado M, Velasco-Miguel S, Serrano M. Oncogene. 2007 Mar 8;26(11):1645-9.

-Selected articles from my undergraduate Thesis:

7. Establishment of two hormone responsive mouse mammary carcinoma cell lines derived from a metastatic mammary tumor line. Efeyan A, Fabris V, Merani S, Lanari C, Molinolo AA. Breast Cancer Res Treat. 2004 Feb;83(3):233-44.

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AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **DOS SANTOS BENEDITO, RUI MIGUEL**
Referencia: RYC-2013-13209
Área Científica: Biomedicina
Correo Electrónico: Rui.benedito@cnic.es

Título:

Regulation of the biology of blood vessels by Notch and its downstream gene regulatory networks in development, homeostasis and disease

Resumen de la Memoria:

Blood vessels are an important therapeutic target in cancer and cardiovascular diseases where their microstructure can change locally in response to diverse stimuli. The knowledge accumulated during the last years in the field of vascular biology allowed the use of VEGF and its major endothelial receptors as targets in numerous therapies designed to stimulate or inhibit the growth of blood vessels. This led to a significant improvement in the treatment of many vascular related diseases and cancer. But VEGFs and their receptors do not work alone and their different functions can also be controlled by other mechanisms which compensate or overrule the VEGF function. One such mechanism is the Notch cell-to-cell and membrane-to-nucleus signaling pathway, which we found to be a key regulator of the initial arterial-venous differentiation programme and also plays a fundamental role during developmental (Benedito et al., 2009, Cell) and pathological angiogenesis. Contrary to the previous understanding of the Notch function, we recently found that Notch can regulate angiogenesis independently of VEGF signaling (Benedito et al., 2012, Nature) which will be relevant for the design of future anti-angiogenesis therapies, specially in situations of known resistance to anti-VEGF, which occur frequently in cancer and age-related macular degeneration. The overall aim of my future career is to define with high spatial and temporal detail how Notch controls different processes related with endothelial proliferation or maturation, and characterize some of the molecular mechanisms underlying this VEGF-independent role of Notch, in different endothelial contexts, as a way of gaining further understanding of the biology of blood vessels in order to improve current angiogenesis-related therapies. Based on our preliminary data, we will characterize the distinct Notch functions in angiogenic versus quiescent vasculatures by using advanced genetic tools that will enable us to modify and interrogate gene function with single-cell resolution and in a high-throughput manner. Despite the advances in the knowledge of the Notch function during vascular development, there are still many open questions that in order to be answered require a more integrated approach and new technologies.

In the future, we will pursue the following key objectives :
1) To understand how the Notch signaling pathway regulates different processes related with endothelial proliferation and differentiation during angiogenesis and in quiescent vessels.
2) To identify novel and key downstream targets of Notch, and understand their function in vascular development, homeostasis and disease.
My research project has the potential to increase significantly our understanding of key molecular mechanisms involved in important aspects of the biology of blood vessels. Millions of people around the world already benefited with therapies that modulate vascular function during tumor development or metastasis, cardiovascular diseases or in age related macular degeneration. We will generate several unique genetic tools and use complementary independent approaches that will differentiate our research and have a high potential to unveil new biological mechanisms with therapeutic relevance.

Resumen del Currículum Vitae:

My scientific career started in October 2002, in Portugal, where I did my PhD in the vascular biology and Notch signaling fields under the supervision of Dr. António Duarte. My main project involved the phenotypic characterization of mutant mice lacking the function of the Notch ligand Dll4. In collaboration with Janet Rossant's group in Toronto, we discovered that Dll4KO embryos succumb at very early stages of development due to defects in the genesis and differentiation of the first embryonic arteries (Duarte et al. Genes and Dev. 2004 and Benedito et al. BMC Dev. Biol. 2008). Later on we also found that the mutant endothelial cells do not form a stable basement membrane, continue to proliferate, and migrate excessively towards other areas of the embryo, leading to the reduction of the arterial calibre, a phenomenon also observed in zebrafish embryos (Benedito et al. BMC Dev. Biol. 2008 and Benedito and Adams, Science 2009). After finishing my PhD work, at the end of 2006, I decided to move abroad and I started my postdoctoral studies in the laboratory of Dr. Ralf Adams, at the renowned London Research Institute - CRUK. With the knowledge acquired during my PhD and the access to more advanced genetic tools and equipment, we studied the role of the different Notch ligands and modulators during developmental angiogenesis by using a wide range of techniques and genetically modified mice. Through this methodology we were able to find that the canonical Notch ligand Jagged1 is a potent pro-angiogenic regulator that antagonizes Dll4-Notch signaling in angiogenic endothelial cells that express the Fringe family Notch glycosyltransferases (Benedito et al. Cell, 2009, PHH-MP Prize 2009). Later I started a second post-doc project, while supervising a technician and master students. By using inducible loss-of-function genetics in combination with blocking antibodies and chemical inhibitors in vivo we were able to dissect the expression and functional interactions between Notch and the two

most important VEGF ligands and receptors. We found that Notch can control angiogenesis independently of VEGFR2 and VEGF signaling. In contrast, VEGFR3, the main receptor for VEGF-C, is strongly modulated by Notch, and VEGFR3 kinase inhibition but not ligand blocking antibodies can suppress the sprouting of endothelial cells with low Notch signaling (Benedito et al. Nature, 2012). I was also corresponding author in this work and I received the Werner Risau Prize 2013 for outstanding studies in vascular biology. These latest results raise many other questions in the field and suggest that successful therapeutic targeting of VEGF receptors or their ligands will depend on the status of endothelial Notch signaling (Benedito and Hellstrom, Exp. Cell Res. 2013). During the last period of my postdoctoral studies, I also had time to supervise two PhD students that gave important contributions to the vascular biology and Notch signalling fields. The student Lin Wang used advanced genetic tools to show that there is an endothelial compartment in the bone marrow closely associated with hematopoietic stem cells and that influences their clonal expansion (Wang et al. Embo J., 2013). The student Manuel Ehling showed that Notch is essential for the remodeling of veins and the perivenous capillary plexus during vascular maturation (Ehling et al., Development 2013).

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AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **LUJAMBIO GOIZUETA, AMAYA**
Referencia: RYC-2013-14331
Área Científica: Biomedicina
Correo Electrónico: lujambia@mskcc.org

Título:

Functional dissection of liver cancer

Resumen de la Memoria:

Cancer cells are characterized by broad epigenetic and genetic alterations. These alteration can affect oncogenes or tumor suppressor genes, leading to their activation or inactivation, respectively, and to the development of cancer. During my PhD, I studied the epigenetic regulation of microRNAs and other non-coding RNAs in cancer. MicroRNAs (miRNAs) are small, evolutionary conserved, non-coding RNAs of 18-25 nucleotides in length that have a function in gene regulation. By undertaking different approaches, I identified several microRNAs specifically methylated in cancer and metastasis, demonstrating, for the first time, that miRNAs can be regulated by epigenetic mechanisms in these pathologies (Lujambio et al. Cancer Res. 2007;Lujambio et al. PNAS. 2008). Moreover, I also demonstrated that other non-coding RNAs, such as transcribed ultra-conserved RNAs (UCRs) can be deregulated by epigenetic mechanisms in cancer (Lujambio A et al, Oncogene. 2010). In theory, this aberrant methylation could be reversed by epigenetic drugs, restoring the expression of tumor suppressor non-coding RNAs and reverting the tumor phenotype (Lujambio et al. Nature. 2012).

During my postdoctoral research, I have shown that p53 acts non-cell-autonomously to suppress tumorigenesis by promoting an anti-tumor microenvironment, in part, through secreted factors that modulate macrophage function (Lujambio et al, 2013, Cell). More recently, we have uncovered a potential therapeutic target for c-Myc overexpressing liver tumors. Briefly, by screening a custom library of small hairpin RNAs (shRNAs) targeting known drug targets in a c-Myc-driven murine liver cancer model, we have identified a candidate gene as required for disease maintenance (manuscript in preparation).

For my independent scientific career, I plan to exploit the use of shRNA libraries (and to a lesser extent, the use of mouse models of cancer) to dissect the involvement of cellular senescence in liver cancer initiation.

Resumen del Currículum Vitae:

I studied Biology at the University of Navarra, and was awarded with the Premio Extraordinario Fin de Carrera by the same university and with the 2nd Premio Extraordinario Fin de Carrera by the Ministerio de Edudación y Ciencia. As an undergraduate, I gained research experience in several laboratories, including the laboratories of Gines Morata (CBMSO) and Manel Esteller (CNIO). These early experiences provided me with excellent training in molecular biology techniques. In 2005, I started my PhD at the Cancer Epigenetics Lab at CNIO (Madrid, Spain), under the supervision of Dr. Manel Esteller, and supported by an FPU Fellowship. During my PhD, I identified several tumor-suppressor and metastasis-suppressor microRNAs (Cancer Research, PNAS), and described, for the first time, the epigenetic regulation of other non-coding RNAs in cancer (Oncogene). Moreover, I visited the lab of Reuven Agami, at NKI (Nederlands), where I studied the impact of different microRNAs in the epigenetic landscape of cancer cells. For these studies, I was awarded with an Embo Short-Term Fellowship. My expertise in the epigenetic and non-coding RNA field is reflected by the publication of three reviews (2 in Cell Cycle and 1 in Nature), and by the "Premio Eduardo Gallego" from the "Fundación Francisco Cobos".

In October 2009, seeking to expand my expertise in cancer and attracted by the cutting-edge technology developed in the laboratory of Dr. Scott Lowe, I moved to Cold Spring Harbor Laboratory (CSHL) as a postdoctoral scientist. I decided to focus my research on liver cancer, a very aggressive disease that lacks effective treatment. First, I studied the role of p53 and cellular senescence of hepatic stellate cells in limiting liver damage and hepatocellular carcinoma. This work was published in Cell (April 2013) and was highlighted by Nature Medicine, Cancer Discovery, Nature Cell Biology, and discussed in a review in Current Biology. Moreover, I have devoted my efforts, not only to better understand liver cancer biology, but also to identify potential therapeutic targets for liver cancer. For that, I have combined the use of RNA interference and mosaic mouse models of cancer, and identified a promising target for c-Myc overexpressing liver tumors (manuscript in preparation). For my postdoctoral research, I was awarded an "EMBO Long-Term Fellowship". In addition, my work has been selected for presentation as oral communications at several prestigious meetings. Taking advantage of my new expertise in the RNA interference (RNAi) field acquired while training in Dr. Lowe's lab, I have been actively involved in the inception of the RNAi Core at MSKCC. This task has endowed me with a valuable experience that will be very useful when setting up and leading my laboratory. Finally, my academic training has allowed me to obtain extensive theoretical and practical knowledge in the fields of cancer, senescence and RNAi screens, and has facilitated my development into an independent, highly motivated and hard-working scientist with a strong desire to continue to study the role of senescence in tumor suppression and to exploit senescence with therapeutic purposes.

The average impact factor of my first-author papers is 15, and each has been cited 155 times.

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AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **GIORGETTI , ALESSANDRA**
Referencia: RYC-2013-13221
Área Científica: Biomedicina
Correo Electrónico: agiorgetti@carrerasresearch.org

Título:

Implications of master transcriptional regulators in blood emergence and differentiation during hematopoietic development from iPSCs

Resumen de la Memoria:

I became interested in haematopoiesis and stem cells during my bachelor thesis and PhD training. I completed my PhD with Dr. Lazzari (GMP facility at the Ospedale Maggiore Policlinico Milano) in 2004. During my PhD I set-up a comparative gene expression analysis of CD34+ and CD133+ progenitor cells derived from cord blood (CB) by DNA microarray technology. During my first postdoctoral training, I was involved in several clinical trials. The most relevant one was focused on the clinical-grade ex vivo expansion of CB CD34+ cells for allogenic transplantation of pediatric patients. This experience allowed me to obtain the qualification of GMP operator and strengthen my interest in translational research. Moreover, during this period I cultivated interest in studying the influence of physiological and pathological factors on the mobilization of circulating endothelial progenitor cells. I continued this work in Dr. Rafii's Laboratory, at Weill Cornell Medical College in New York. There, I was involved in the search of biomarkers through analyses of circulating endothelial progenitor cells in peripheral blood of patients with lung cancer. We identified the existence of a unique population of circulating hemogenic cells with a specific Id1/Id3 molecular signature (American Journal of Hematology 2005, Curr Neurovasc Res. 2006; Am J Cardiol. 2007). In 2008 I moved to the Center of Regenerative Medicine of Barcelona (CMRB), as research associate. There, I participated in developing protocols for the generation and banking of new lines induced pluripotent stem cells (hiPSC). Then, based on my previous knowledge on the biology of hematopoietic cells I reasoned that CB cells could be an ideal source of hiPSC for allogeneic therapies. Not only I succeeded at demonstrating that CB cell could be reprogrammed to iPSC, but I also found that these cells could be reprogrammed with only 2 of the 4 factors necessary to reprogram other types of somatic cells, thereby providing new mechanistic insights into the process of nuclear reprogramming. The work resulted in two high-impact publications (CellStemCell 2009; Nature Protocol 2010), a chapter book (Springer Protocol Handbook Series, 2011) and a patent (WO 12/819.059). I also collaborated in two projects aimed to characterize the genomic integrity of human iPSCs as well as in the differentiation of iPSCs toward germ cells, studies that were published in Nature 2011; Stem Cells 2011; PNAS 2012 and Nature Communications 2013. Moreover, my interest on CB stem cells incited me into exploring the transdifferentiation potential of these cells toward other lineages. I have recently demonstrated that these can be converted directly into functional neurons by the overexpression of SOX2 and c-MYC (PNAS 2012). This work described for the first time the possibility to convert human blood cells directly into neuronal-like progenitor cells that can be expanded and further differentiated into functional neurons. Currently, I am working at Josep Carreras Leukaemia Research Institute as staff investigator. My long-term goal is to develop new strategies for the in vitro generation of specific blood cells for cell replacement therapies in hematological disorders. My initial approach is based on temporal regulation of specific transcription factors to improve the differentiation of blood lineages from hiPSC.

Resumen del Currículum Vitae:

Starting my career as a stem cell biologist during my first postdoctoral training I focused my research on gene expression analysis, transcriptional regulation and the biology of hematopoietic stem cells and their clinical application, with a particular interest on cord blood stem cells (CBSC). In 2008 I joined Stem Cell Bank of CMRB (Barcelona) where I actively participated in the generation (and banking) of several human induced pluripotent stem cell (iPSC) lines derived from healthy volunteers and patients, acquiring invaluable knowledge in reprogramming technologies. Then, I combined my previous experience in CBSC biology with my knowledge of reprogramming technology to demonstrate that CBSC can be reprogrammed to pluripotency faster than fibroblasts and keratinocytes by overexpressing only two transcription factors; OCT4 and SOX2. These data resulted in two high-impact publications (Giorgetti et al., Cell Stem Cell 2009 and Giorgetti et al., Nat Protocols 2010), a book chapter (Spring Protocol Handbook Series, 2011) and a patent (Patent title: Generation of induced pluripotent stem cells from cord blood. 06-18-2010. WO 12/819.059) and support the use of CB as an alternative, safe source of iPSCs amenable to worldwide banking and distribution. My expertise in reprogramming was also instrumental in finalizing two projects aimed to characterize the genomic integrity of human iPSCs derived from fibroblasts and other somatic cell types. The results of these studies demonstrate that epigenetic aberrations are a general feature of the hiPSCs state and are independent of the somatic cell source (Nature, 2011; PNAS, 2012, Nature Communications, 2013). Following my long-standing interest on CB stem cells I have recently demonstrated that these cells can be converted directly into functional neurons by the forced expression of two transcription factors SOX2 and c-MYC (Giorgetti et al., PNAS 2012; 109:12556-12561; Patent title: Cord blood-derived neurons by expression of SOX2; 15-06-2012; WO US2012/042). In 2011, I joined as head of Laboratory of Hematopoiesis and Blood disorders at Inbiomed Foundation. In September 2013 I moved to Josep Carreras Leukemia Research Institute in Barcelona as a staff junior investigator. Currently, my main interest is to study the role of lineage-specific transcription factors during hematopoiesis development from hiPSCs in order to develop new strategies for the in vitro generation of specific blood cells for cell replacement therapies.

AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **GARCIA CAO, ISABEL**
Referencia: RYC-2013-12775
Área Científica: Biomedicina
Correo Electrónico: igcao@yahoo.com

Título:

Study of the mechanisms underlying tumor suppression by using genetically engineered mouse models

Resumen de la Memoria:

My research line is focused on understanding the mechanisms underlying tumor suppression and developing informative cancer mouse models. I started my scientific career as assistant student in the Complutense University of Madrid, and then joined Dr. Manuel Serrano¿s group at the National Centre of Biotechnology (CNB, Madrid). Since then, my research focus is on cancer biology and mouse genetics. In particular, the generation of mice with increased gene dosage of p53 (�Super p53� mice) represents a very useful mouse model to test several hypotheses related to cancer and aging. �Super p53� mice exhibit an enhanced response to DNA damage, are protected to cancer compared with wild-type mice and do not show premature aging. The main contribution of this work was the demonstration that it is possible to enhance cancer resistance in a mammalian organism without secondary effects, such as aging. To further challenge the role of p53 in aging, we collaborated with Maria A. Blasco (CNIO) to study the effect of an extra copy of p53 in telomere-driven aging. The analysis of the aging process in telomerase-deficient mice carrying two or three functional copies of the p53 gene revealed that moderately increased levels of p53 do not affect telomere-driven aging. I have also tested the relevance of the tumor suppressor p19ARF for p53-mediated cancer protection (�Super p53� in a p19ARF-null background). We have previously observed that �Super p53� are resistant to develop cancer. This resistance is lost in the absence of p19ARF, a p53 activator, indicating that p19ARF is essential for p53-mediated tumor suppression. During my research at Dr. Manuel Serrano¿s lab I have also generated a classical knockout mouse for the pro-apoptotic gene Par4 (prostate apoptosis response 4). Par4-null mice show a decrease in their survival compared with wild-type mice and are prone to develop endometrial adenocarcinomas and prostate hyperplasia. This mouse model was useful to reveal the tumor suppressor role of Par4, with a particular impact in the endometrium and prostate.
I continued my research in Dr. Pier Paolo Pandolfi¿s laboratory at the Sloan Kettering Institute (New York) and subsequently at Beth Israel Deaconess Medical Center (Harvard Medical School, Boston). The lab has well-known expertise in molecular biology and cancer genetics methodologies, and has been able to develop a number of informative murine models of cancer to investigate in vivo the function of several genes important in tumorigenesis. My research at Pandolfi¿s lab was focused in the tumor suppressor PTEN and the consequences of its elevation. I have recently generated transgenic mice with increased PTEN levels using large genomic BAC clones (>100Kb) containing the complete PTEN genomic locus and therefore recapitulating the regulation and expression of the endogenous copy. Mice with increased PTEN dose are viable and show reduced body size due to decreased cell number, with no effect on cell size. Interestingly, PTEN elevation at the organism level results in increased energy expenditure and reduced body fat accumulation, revealing PTEN as a key metabolic modulator that shifts cellular energy metabolism towards mitochondrial respiration. This study shows that PTEN promotes a metabolic switch towards tumor suppression, with broad implications to the fields of cancer development and metabolism.

Resumen del Currículum Vitae:

I started my scientific career during my BSc education in Biochemistry. I joined Dr. Rosalia Rodriguez¿s lab as Assistant Student at the Complutense University, where I studied the biochemical properties of allergens with the final aim of improving allergy diagnosis and treatment. My research was supported by the Last Term Student Fellowship from the Education and Science Ministry of Spain (MEC). In 1998 I received my BSc in Biochemistry (Complutense University, Madrid), obtaining the Degree¿s Extraordinary Prize of the Faculty of Chemistry. After my graduation, I joined Dr. Manuel Serrano¿s lab at the National Centre of Biotechnology (CNB) to start my thesis project on tumor suppression. During my PhD, I have developed several genetically modified mouse models to study cancer. In particular, the generation of �Super p53� mice proved that it is possible to increase cancer resistance without accelerating aging. �Super p53� mice have been very useful to test several hypotheses on tumor suppression, stress and aging. I received funding support from the MEC Predoctoral Fellowship. In 2003 I defended my PhD Thesis entitled "New mouse models for the study of cancer: increased gene dosage of p53 and elimination of Par4 ", obtaining the maximum qualification of Cum laude by unanimity and the Doctoral Extraordinary Prize of the Faculty of Chemistry (Autonoma University, Madrid). My thesis project led to 4 publications in prestigious scientific journals, 3 of them as first-author. After obtaining my PhD, I continued my research focused on cancer biology and mouse genetics as Postdoctoral Researcher at Dr. Serrano¿s lab at the Spanish National Cancer Research Centre (CNIO). One of my projects was the generation and characterization of Par4-null mice. This mouse model was useful to reveal the tumor suppressor role of Par4, with particular impact in the endometrium and prostate. My research led to 3 first-author and several co-author articles in prestigious cancer journals. During these years, I acquired a solid background in cell biology and cancer mouse models, which led me to join Dr. Pier Paolo Pandolfi¿s lab initially at the Sloan Kettering Institute (New York), and subsequently at Beth Israel Deaconess Medical Center (Harvard Medical School, Boston). When I joined Dr. Pandolfi¿s lab I was interested in studying the consequences and potential benefits of elevating PTEN. Our study revealed PTEN as a key

metabolic modulator that shifts cellular energy metabolism towards tumor suppression. PTEN elevation can offer a therapeutic approach to prevent cancer and obesity. The findings of this study have been published as an article in Cell. During my research at Pandolfi¿s lab I received funding from the MEC Postdoctoral Fellowship and the HFSP Long Term Fellowship. During this time I had the opportunity to interact on a daily basis with experts on the field of cancer, and establish successful collaborative relationships with groups at Harvard Medical School -Dr. Lew Cantley and Dr. Marcia Haigis- as well as international collaborations abroad. The interaction with scientific collaborators working at the forefront of cancer research gave me the opportunity to broaden my knowledge on cancer biology and metabolism.

AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **GOICOECHEA DE JORGE, ELENA**
Referencia: RYC-2013-13395
Área Científica: Biomedicina
Correo Electrónico: e.goicoechea-de-jorge@imperial.ac.uk

Título:

Complement system dysregulation in disease

Resumen de la Memoria:

I am a complement biologist whose main research interest is the study of the complement system and its association with disease. Complement is an essential component of innate immunity with crucial roles in microbial killing, apoptotic cell clearance, immune complex handling and modulation of adaptive immune responses.

My interest in complement began with my doctoral training in Prof. Santiago Rodríguez de Córdoba's group. My thesis focussed on the study of the molecular basis of atypical haemolytic uremic syndrome (aHUS), a paradigm of complement-mediated renal disease. I was the first one to demonstrate that, in addition to loss-of-function mutations in complement regulators, gain-of-function mutations in complement activators are associated with aHUS (Goicoechea de Jorge et al. PNAS, 2007). I also demonstrated that confluence of multiple inherited risk factors in complement genes is required for aHUS to develop. During my thesis, I also performed work with in collaboration with Prof. Matthew Pickering in London that led to the development of the first animal model of aHUS (Goicoechea de Jorge et al. J. Exp. Med. 2007).

Once completed my PhD training and motivated by the idea of studying complement dysregulation in vivo, I moved to Imperial College London and joined Prof. Pickering's group as a postdoctoral researcher. During this time I completed a program of work demonstrating that complement C5 is critical for renal injury to develop in our aHUS model (Goicoechea de Jorge et al. JASN, 2011). I also expanded my expertise in complement dysregulation to the study of other complement-mediated renal diseases such as C3 glomerulopathies. In collaboration with Prof. Patrick Maxwell (University College London), I identified a mutation in complement factor H-related 5 gene (CFHR5) associated with familial C3-glomerulopathy, describing for the first time a mutant CFHR5 protein associated with disease. This work led to a Lancet publication (Goicoechea de Jorge, et al., 2010). This finding opened a new avenue of research in the complement field and gave me the opportunity to outline a program of work and secure a Junior Research Fellowship (JRF) from Imperial College, which allowed me to become established as an independent investigator.

Since then, I have focussed my research in understanding the biology of the CFHR gene family and its association with disease. Recently, my major finding has been the discovery of the dimerization status for some of the CFHR proteins and its functional implications. This work was published last year (Goicoechea de Jorge et al. PNAS, 2013) and led to the recent generation of a patent.

Throughout six years of scientific research abroad, I got to know different research environments that have giving me the opportunity to know different ways of thinking and to learn diverse experimental techniques. I have been involved in several fruitful collaborations and I have succeeded in becoming established as an independent investigator and recognised complement biologist, as reflected in the invitations received to present in international conferences and seminars.

In summary, my scientific contribution to date is reflected in 26 publications (7 peer-review first author articles in high profile journals), 19 international conference communications, being an invited speaker in 4 occasions, and one patent.

Resumen del Currículum Vitae:

I am a complement biologist interested in understanding how dysregulation of complement system, a major component of innate immunity, leads to diverse pathologies. Funded by a FPI fellowship form Spanish Ministry of Science and Technology, I completed my doctoral thesis (Suma Cum Laude) at the University Autónoma of Madrid (Spain) under the supervision of Prof. Santiago Rodríguez de Córdoba. My PhD focused on the study of the molecular basis of atypical haemolytic uremic syndrome (aHUS), a paradigm of complement-mediated renal disease. My work led to several publications having a major contribution on the genetics of aHUS (Goicoechea et al. Proc Natl Acad Sci USA, 2007, 104:240-245; Esparza-Gordillo et al. Hum Mol Gen. 2005, 14(5):703-712), and on the generation of the first animal model of the disease (Goicoechea et al. J Exp Med, 2007, 204(6)1249-1256). Overall, during this period my work led to 16 publications, including 3 first authorships, 5 second authorships, 3 reviews and one book chapter. I also had 9 international conference communications, being awarded in two occasions for best oral communication.

In 2008, I moved to Prof. Matthew Pickering's group (Imperial College London) as a postdoctoral researcher. During this time I investigated the role of complement in different animal models of renal disease, providing me the opportunity to deepen into the knowledge of complement dysregulation in vivo and to explore possible therapeutic interventions. The results of this postdoctoral phase led to 7 publications, including one invited commentary and 3 first authorships (Lancet 2010, 376(9743):794-801; J Am Soc Nephrol. 2011, 22(1):137-145; and PloS Pathog. 2012, 8(10): e1002981). Moreover, I participated in 5 international meetings as a speaker, in one of which I was an invited speaker.

Importantly, during my postdoctoral I developed a new research avenue that allowed me to secure a Junior Research Fellowship (JRF, Imperial College London) in 2011, to work at the Centre for Complement and Inflammation Research. This prestigious award launched me towards the first steps of scientific independence. Since then, my main research interest has focused on elucidating the biology of the complement factor H family and its association with disease. My scientific contribution as a Junior Research Fellow to date includes 3 publications, one of them a first author publication (Proc Natl Acad Sci USA, 2013, 110(12):4685-4690). Importantly, my work led to the recent creation of a patent (PTC/GB2014/050258) where we provide novel biological targets associated with the modulation of the complement system.

Throughout six years of scientific career abroad, firstly as a postdoctoral and subsequently as a Junior Research Fellow, I have been actively engaged with the scientific community by attending regular meetings and by participating in either teaching or supervising activities. I established key international collaborations with experts in the complement field, I served as a reviewer for PloS Genetics and I have been invited to present my work in several conferences and seminars. My scientific contribution to date encompass one patent, 26 publications, including 7 peer-review first authorship articles, and 19 communications in conferences (most of them international) and seminars, being an invited speaker in 4 occasions.

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AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **MARIÑO GARCIA, GUILLERMO**
Referencia: RYC-2013-12751
Área Científica: Biomedicina
Correo Electrónico: gmg.marino@gmail.com

Título:

Metabolic links between autophagy, aging and other human pathologies

Resumen de la Memoria:

My first contact with scientific research was at Prof. Carlos López-Otín laboratory in 2001, while studying my last year of Biochemistry Degree at Oviedo University, Spain. Just after graduating, I joined López-Otín lab as a pre-doctoral student under Spanish Government FPU grants program. During this period, I started a new line of research focused on the study of human autophagins (Atg4s), the only proteases specifically involved in autophagy. Initially, my work was focused on the cloning and biochemical characterization of these enzymes. Later on, I was able to get insights into the actual physiological roles of autophagins-1 and -3 through the generation and characterization of mice deficient for each of these two genes. This approach led to the description of a new protective function for autophagin-3 in tumour progression, and to the establishment of an essential and novel role for autophagy in balance perception and inner ear development.

In parallel, I got involved in the study of premature aging, an ongoing line of research at López-Otín laboratory. My participation in this project led to the finding that premature aging in mice activates a pro-survival metabolic response involving autophagy induction. Rather than being just an epiphenomenon, this metabolic reprogramming turned out to be essential for the development of progeroid features. In fact, restoration of somatotroph axis was sufficient to significantly improve health and enhance the lifespan of progeroid mice.

Once I got my PhD, and given my interest in the links of metabolic pathways and longevity, I moved to Prof. Guido Kroemer lab in Paris, funded by an EMBO Long Term fellowship. There, I developed and coordinated a new line of research focused on the study of autophagy regulation at the metabolic level. Through the use automated microscopy and metabolomics platforms, I was first able to describe the preponderant role for acetylation reactions in autophagy regulation and very recently, I showed for the first time that cytoplasmic Acetyl-CoA is a master regulator of autophagy, thus integrating this catabolic pathway in general metabolic regulation.

In summary, my research career has been focused on the study of autophagy, a catabolic pathway with essential homeostatic functions in eukaryotic cells, and in the elucidation of autophagy links with metabolic alterations underlying aging and a variety of human pathologies.

Resumen del Currículum Vitae:

I started in scientific research while I was still studying my Bachelor in Biochemistry and Molecular Biology at University of Oviedo (Spain) in 2001, at Carlos López-Otín laboratory, funded by a Collaboration Grant (Beca de colaboración), from the Spanish Ministry of Education (MEC).

Once I finished my Biochemistry degree, I obtained a FPU (Formación del Profesorado Universitario) pre-doctoral grant (2002) from the MEC, which funded me during my pre-doctoral studies. During this period, I was awarded with a mobility grant (MEC) that allowed me to perform a two-month stage at Prof Noboru Mizushima laboratory in Tokyo, Japan. There, I learned the latest methods in autophagy research and established ties with the prominent Japanese autophagy research community.

In July 2007, I obtained my PhD. with the qualification 'Summa cum Laude' at the University of Oviedo. Then, I continued working at López-Otín lab as a hired postdoc until december 2009, and finished some of the projects that I had started during my PhD studies.

In January 2010, and given my interests in autophagy and in the mechanisms underlying physiological and pathological aging, I moved to the lab of Prof. Guido Kroemer in Paris, funded by an EMBO post-doctoral Long-Term Fellowship. Since 2012, I am working as a hired senior postdoc at Guido Kroemer lab where also I help to coordinate autophagy-related projects.

During my research career, I have mastered a large variety of techniques and I have acquired the capacity to design and coordinate research projects, as well as writing scientific manuscripts and handle revision processes. To date, I have authored 45 scientific articles (19 of them as first or co-first author) in top-ranked international journals (including Cell, Science, Nature Rev. Mol. Cell. Biol., Molecular Cell (x4), Cell Metabolism, JCB, JCI, PNAS, EMBO J (x2) or EMBO Molecular Medicine). According to ISI web of knowledge, my work has been cited 1687 times, with an average rate of citations per paper of 40 and an h-index of 18. I have also presented 14 communications in international meetings and participated in a variety of research projects of both national and international scope.

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Nombre: **PENAGARIKANO AHEDO, OLGA**
Referencia: RYC-2013-12558
Área Científica: Biomedicina
Correo Electrónico: openaga@ucla.edu

Título:

Translational Research on Neuropsychiatric Disorders

Resumen de la Memoria:

The focus of my research is on neuropsychiatric disorders and, specifically, Autism Spectrum Disorders (ASD). My research has a translational focus, studying the molecular pathways and circuits that lead to abnormal behavior with the purpose of restoring normal behavior. Autism is a neuropsychiatric disorder characterized by deficits in two behavioral domains: social behavior/communication and repetitive/restricted interests. It has a prevalence of 1 in 88 children according to the latest estimates from the Center for Disease Control (CDC, 2012), being one of the primary health issues worldwide. Animal models that faithfully replicate autism-related behaviors are essential to study the disorder at the molecular level, gain insight into disease mechanisms and test potential pharmacological interventions. For the last years I have been leading a multi-faceted work, involving anatomy, development, physiology and behavior of the Cntnap2 mouse model of ASD, a model that has proven to have high construct, face and predictive validity, which is critical for translational research. This work has been recently published in Cell (Peñagarikano et al., 2011).

Thus, this mouse model provides a new tool for mechanistic and therapeutic research in ASD. In autism, no drug has yet been proven to consistently improve social behaviors. Current pharmacotherapy is used to mostly reduce stereotypic behaviors and noncore associated phenotypes. We have performed an in vivo drug screening in Cntnap2 mutant mice targeting affected social behaviors and found that intranasal administration of the neuropeptide oxytocin dramatically improves social deficits in this mouse model. Strikingly, the same treatment in wild-type littermates did not show any behavioral response, suggesting a hyper-reactivity to oxytocin in Cntnap2 mice. Interestingly, we found that oxytocin levels are reduced in the brains of Cntnap2 mutant mice. Several lines of evidence suggest an association of the oxytocin system and ASD, and clinical trials with oxytocin in autistic patients show promising results. Currently I am exploring the neurobiological basis for the oxytocin signaling deficits in the Cntnap2 mouse model of autism and the mechanism whereby oxytocin exerts its behavioral effects.

My work includes mouse behavioral characterization, in vivo drug screenings, molecular biology, neuroanatomy, in vivo stereotaxic virus injections for gene delivery, and microdialysis to study the relationship betwee neurons, brain circuits and behavior, with a translational focus. The ultimate goal of my research is to apply findings in mouse models of neuropsychiatric disorders towards human interventions.

Resumen del Currículum Vitae:

I received my PhD in 2003 from the Department of Genetics in the School of Sciences of the University of the Basque Country, Bilbao, Spain. The focus of my Thesis was Fragile X syndrome, a neurodevelopmental disorder which is the most common form of inherited intellectual disability, and one of the most common genetic causes of Autism. I studied the stability of the FMR1 gene in Basques, a very ancient isolated population very well suited to study the origin of unstable genes. Our results were in agreement with the hypothesis of different mutational pathways leading toward Fragile X syndrome (Peñagarikano et al., American Journal of Medical Genetics, 2004). Before starting my postdoctoral training I conducted some clinical work screening DNA samples of intellectually disabled cases who were negative for Fragile X syndrome for mutations in the MecP2 gene. This gene is responsible for Rett syndrome, another neurodevelopmental disorder characterized by intellectual disability and autism-like features. I found a predicted deleterious and yet undescribed mutation in one of our samples (Peñagarikano et al., Human Genetics, 2005; Tejada, Peñagarikano et al., Clinical Genetics, 2006).

After completing my PhD I became a postdoctoral researcher in the Department of Human Genetics at Emory University, Atlanta, USA, where I continued my work on Fragile X syndrome focusing on its molecular basis (Peñagarikano et al., Annual Review of Genomics and Human Genetics,2007). In 2008, to deepen my knowledge on the neuronal basis of autistic behavior, I joined Dr. Daniel Geschwind's laboratory, a leading researcher in this field, in the Department of Neurology at the University of California at Los Angeles (UCLA). Autism is a neuropsychiatric disorder characterized by deficits in two behavioral domains: social behavior/communication and repetitive/restricted behavior. It has a prevalence of 1 in 88 children according to the latest estimates from the Center for Disease Control (CDC, 2012), being one of the primary health issues worldwide. One of the primary reasons for the absence of effective treatments for ASD is the lack of animal models that faithfully replicate autism-related behavior. During my late postdoctoral work I led a multi-faceted work, involving neuro-anatomy, brain development, neuronal physiology and behavioral characterization of the Cntnap2 mouse model of ASD

(Peñagarikano et al., Cell, 2011). This work was awarded the "Top10 achievements in autism research in 2011" by Autism Speaks, one of the leading Foundations on Autism research. As a result of this work, I was invited to write a review on Autism in Trends in Molecular Medicine (Penagarikano and Geschwind, 2012) a book chapter on the subject (Peñagarikano and Geschwind, 2013), and as a speaker at international neuroscience meetings.

Currently, I continue to use this mouse model to study their deficits in social behavior, since there is currently no treatment indicated for this devastating aspect of the disease. For this purpose I was awarded a Training grant in Translational Research by Autism Speaks, as well as a Voucher Award from the UCLA Clinical and Translational Science Institute (CTSI). The initial results of these studies have been presented as peer selected oral presentations at Society for Neuroscience 2012 and International Meeting for Autism Research 2013 and will be published shortly.

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Nombre: **SIERRA SAAVEDRA, AMANDA**
Referencia: RYC-2013-12817
Área Científica: Biomedicina
Correo Electrónico: amanda.sierra@ehu.es

Título:

Microglial phagocytosis in health and disease

Resumen de la Memoria:

Microglia are the brain professional phagocytes, a more beneficial and less explored role than its traditional implication in the neuroinflammatory response. Despite the central role of phagocytosis in maintaining tissue homeostasis in all the widespread conditions in which apoptosis is known to occur, from brain development to brain diseases such as epilepsy, stroke, Alzheimer s or Parkinson s, our current knowledge on the receptors involved its mechanisms of execution, and its functional consequences remains poor. During my postdoctoral training, I discovered that contrary to the assumptions in the literature, microglial phagocytosis in physiological conditions in the adult brain is fast and efficient, and is tightly coupled to apoptosis (Sierra et al., Cell Stem Cell 2010). Using as a model the adult hippocampal neurogenic cascade, where newborn cells undergo apoptosis, I established a series of parameters that quantify phagocytosis dynamics in vivo and allow us for the first time to illuminate the intricate interaction between apoptosis and phagocytosis. In my lab at the Achucarro Basque Center for Neuroscience as Ikerbasque Research Professor, we currently use a multidisciplinary approach involving experiments in vivo and in vitro (organotypics, primary cultures) in mice and human tissue, as well as confocal and electron microscopy, flow cytometry, genomic and proteomic analysis, and multivariate statistics to expand these findings in two directions: 1,The role of microglia in controlling adult neurogenesis and hippocampal-dependent learning and memory; 2, The pathological impairment of microglial phagocytosis in brain diseases that leads to delayed clearance and inflammation. With 22 peer-reviewed manuscripts, over 1900 citations, a fully equipped lab with 3 PhD students, and funding from a National Research Plan from Mineco, I have demonstrated my capacity to integrate previous knowledge and technical approaches into a coherent, integrated, long-term research plan, and build up a consolidated trajectory as a young leader in Neuroscience in Spain and Europe.

Resumen del Currículum Vitae:

BSc in Biology 1995-2000 (U. Complutense, Madrid): Best College Report in Biology 2001; Fellowship for Technicians 1999-2001 (Comunidad de Madrid). PhD in Neuroscience 2000-2003 (Cajal Institute and U. Complutense): PhD Thesis Extraordinary Award 2003; Fellowship for PhD students 2000-2004 (Carlos III); 12 papers published summing 1236 citations, 3 as first author; Young Investigator Award (Workshop on Steroid Hormones, CO). Postdoctoral fellow at Rockefeller University, NY 2004-2006; Postdoc Fellowship (Ministry of Education); 4 papers published, 2 as first autor: Glia 2007 (136 citations) and Glia 2008 (94 citations) Postdoctoral associate at Stony Brook University, NY and Baylor College of Medicine, TX, 2006-2011; 3 papers published, 2 as first autor, including Cell Stem Cell 2010 (174 citations, impact factor 25); Keystone Symposia Scholarship 2011. Ikerbasque Research Professor at Achucarro Basque Center for Neuroscience and University of the Basque Country, and Head of the Laboratory of Glial Cell Biology since 09/2011; 3 papers published, 1 submitted, 1 in preparation; funding from Ikerbasque Foundation (144.000€, 2011-2013, as PI), Basque Government (50.000€, 2012-2013, as co-PI), and Mineco (125.000€, 2012-2015, as PI); fully equipped lab with 3 PhD students (Basque Government PhD and University of the Basque Country fellowships); teaching in two Master courses; elected member of the board of directors of the Spanish Glial Network; member of the Euroglia meeting 2015 (Bilbao) organizing committee; co-editor of Springer book "Microglia in Health and Disease"; Marie-Curie Fellow 2011-2014 (Co-Fund Program).

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Nombre: **CANUDAS PUIG, SILVIA**
Referencia: RYC-2013-12598
Área Científica: Biomedicina
Correo Electrónico: silvia.canudas@gmail.com

Título:

Role of Telomere maintenance during tumor progression

Resumen de la Memoria:

Telomeres, specialized structures at the end of chromosomes, are essentials for genome integrity and maintenance. Mammalian Telomeres consist of TTAGGG DNA tandem repeats and shelterin, a six-subunit complex (TRF1, TRF2, TIN2, TPP1, POT1, Rap1). Due to the "end replication problem", in most somatic cells, telomere shortening acts as a molecular clock leading to senescence/apoptosis. However, embryonic, tumor and stem cells normally maintain telomeres by expressing Telomerase, a reverse transcriptase that adds telomeric repeats to the ends of chromosomes. The human stem cell disease Dyskeratosis congenita (DC) is caused by mutations in Telomerase complex. Recently the shelterin subunit TIN2, was found to be mutated in individuals with DC. The lack of TIN2 function cause telomeres to shorten dramatically and stem cells to die early. How these mutations result in very short telomeres is unknown. My studies have shown that TIN2 is required to establish or maintain cohesion at telomeres and that this cohesion is essential for telomere stability and genome integrity. Cells lacking TIN2 were unable to repair double stranded DNA breaks and were also prone to completely losing their telomeres. Both phenotypes could be caused by a failure to keep sister chromatids close enough for them to undergo homologous recombination, preventing the cells from repairing damaged DNA or lengthening telomeres via the replication pathway called ALT. Strikingly I have identified that DC mutation cluster in TIN2 harbors a binding site for heterochromatin 1 (HP1γ). Mutations in this site lead to a loss in sister telomere cohesion and interfere with telomere length maintenance by telomerase. My data suggest a unique requirement for HP1 at replicating telomeres, and further provide insight into the severe telomere dysfunction typical of TIN2 DC patients and the importance of telomere maintenance for stem cell function. Thereby, my future research aim is to elucidate the mechanisms of sister telomere cohesin as well as the importance of telomere maintenance in genomic integrity in tumorigenesis and stem cell biology, especially in Ephithelial tumors.

Epithelial tumors are the most common neoplasic alteration in humans. Lethality is mostly associated to the presence of distant metastasis; This process happens in the late phases of tumorigenesis and is normally associated to the previous loss of epithelial characteristics by tumor cells and the acquisition of mesenchymal traits, a process known as epithelial-mesenchymal transition (EMT). Snail 1 transcription factor is the key inductor of EMT. My preliminary, unpublished results showed that during EMT Snail1 transcription factor repress telomerase and regulates telomere integrity important for tumor progression. Understanding Snail1 mechanism in stem cells and telomere maintenance could interfere with cancer treatment efficacy and should prove useful for the understanding of particular cancers and for the development of specific therapeutic strategies.

Resumen del Currículum Vitae:

BS in Biology from Universitat de Barcelona (1998). PhD degree in Biology from the department of Biochemistry and molecular Biology, excellent cum laude (2004). Suported by FPI fellowship from Ministerio de Educación cultura y Deportes, I conducted my graduate studies in the laboratory of Dr. Fernando Azorín Marín at the Institut de Biologia Molecular de Barcelona (IBMB-CSIC). My PhD work was focused on the study of homeotic gene regulation and expression, with particular emphasis on the GAGA protein using Drosophila melanogaster as a model. This work resulted in 4 publications: Espinas et al. (JCB, 1999), Espinas et al. (EMBO Rep.,2000), Canudas et al. (NAR, 2005), Costa et al. (Chomosoma Research, 2006). My interest in Genome integrity and maintenace led me join to Susan Smith laboratory at the Skirball Institute of Biomolecular Medicine (New York University) in New York as a Postdoctoral Research Fellow in 2004. I was specially interested in Telomere maintenance and genome integrity. This work resulted in 3 first author publications: Canudas et al. (EMBO J. 2007), Canudas et al. (Journal of Cell Biology, 2009), Canudas et al. (Gens & Dev, 2011) and 1 second author, Benjamin R. Houghtaling,Silvia Canudas (Cell Cycle, 2012). 3 stays in internationally recognized centers (2 in foreigners institutions). 7 comunications to international meetings (3 oral presentations, 4 posters) 5 national meetings, . During My postdoctoral studies I obtained fundings from HRSB Breast cancer research, New York State Department of Health (2006). In 2010 I was selected to receive the Helen L. and Martin S. Kimmel Stem Cell Fellow award. Since September 2011 I am working as postdoctoral fellow at IMIM (Barcelona, Spain).

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Nombre: **RODRIGUEZ LARREA, DAVID**
Referencia: RYC-2013-12799
Área Científica: Biomedicina
Correo Electrónico: david.rodriguez-larrea@chem.ox.ac.uk

Título:

Protein Biophysics

Resumen de la Memoria:

The candidate initiated his research career in the Department of Biochemistry, University of Salamanca after cursing the degrees of Biology (2003) and Biochemistry (2004). He conducted research on the study of erythrocite membrane proteins by micro-calorimetry under supervision of Dr. Valery Shnyrov and Professor Enrique Villar, obtaining the Tesina (equivalent to Masters degree). Further, coursed the Doctorate courses on the Molecular Mechanisms of Biological Processes on the same University (equivalent to Masters degree). Although he was awarded a fellowship from Junta de Castilla y Leon (competitive fellowship) he moved to the Department of Physical-Chemistry at University of Granada to carry on his PhD under supervision of Professor Jose Manuel Sanchez-Ruiz (2005-2009) with a fellowship from Junta de Andalucia (competitive).

During his PhD he has been involved in the study of the biophysical properties of proteins using several techniques such as Differential Scanning Calorimetry (DSC), Isothermal Titration Calorimetry, Circular Dichroism, Fluorescence, Dynamic Light Scattering and the design of proteins with increased stability and catalysis using evolutionary information obtained with bioinformatic analysis of sequence alignments and by using genetic algorithms for charge distribution optimization. Further, he has also been involved in computational studies for the design of new catalytic activities and in Molecular Dynamics simulations. From this period he published several articles in international peer-reviewed journals (out of a total of 19), 4 of them as first author and 5 as second author

The candidate obtained his PhD with "suma cum laude" in 2008, with the thesis "Energetics, kinetics and evolution of proteins: implications in molecular design". After this he obtained a post-doctoral contract in order to finish several research projects while applying for the EMBO Long Term fellowship.

The candidate obtained the EMBO Long Term fellowship in 2010. This fellowship is granted by the European Molecular Biology Organization and is considered one of the most prestigious fellowships in the world. It is highly competitive with a success rate of 13% in the last round (source EMBO). The candidate proposed a project for the use of single-molecule approaches that allow the study of protein co-translocational unfolding. The candidate developed his proposal in Professor Hagan Bayley lab at Oxford University (U.K.). Professor Hagan Bayley is one of the world leaders in the use of single-molecule approaches using nanopores. Remarkably, the candidate succesfully acomplished his proposal, resulting in publications in Nature Nanotechnology (first author), Science and Nature Biotechnology (first and corresponding author). Further, he has patented a methodology for the single-molecule detection of post-translational modifications.

Finally, I have held collaborations with industrial companies such as Novozymes and Oxford Nanopore Technologies. I have been directing students in the lab and have gave lectures in the University of Granada. I am member of several scientific societies, acted as referee and I frequently present my research at both national and international meetings.

Resumen del Currículum Vitae:

The candidate has 19 publications in well recognized international peer-reviewed journals, including 1 Science, 1 Nat. Biotech (both first and corresponding author), 1 Nat. Nanotech, 1 Nat. Struct. Mol. Biol, 1 JACS, 3 JMB, 3 JBC, 2 Biophys. J,... Out of them, 6 are as first author, 5 as second author and 1 as corresponding author. These publications cover most of the fields in protein research (their biophysical properties [Rodriguez-Larrea D et al, JMB 2006], their design for improved catalysis and stability [Rodriguez-Larrea D et al, Biochem. J, 2010], their action mechanism [Ousden N. et al, Science, 2013], their study at the single molecule level [Rodriguez-Larrea D & Bayley H, Nat. Nanotech, 2013] and the development of biotechnological applications [Rosen* CB, Rodriguez-Larrea*# D and Bayley# H, Nat. Biotech, 2014], aswell their study by molecular dynamics and designing new catalytic activities by computational approaches). Some of them result from collaboration with leading companies in the biotechnological sector such as Novozymes [Rodriguez-Larrea D et al, JMB, 2006] and Oxford Nanopore Technologies [Rosen* CB, Rodriguez-Larrea*# D and Bayley# H, Nat. Biotech, 2014] (which has lead to US patent 61/896,933 and UK patent 1316849.7). The candidate presents frequently his work at both international and national meetings (Biophysical Society, Protein Society,..), and has been invited for talks at SEBBM, Jacobs University, Oxford University, EMBL and Aarhus University.

The candidate has been awarded with national fellowships Junta de Castilla-Leon (rejected) and Junta de Andalucia (for his PhD). Has been recipient of the highly competitive European Molecular Biology Organization (EMBO) Long Term fellowship for his post-doctoral research. In this period the candidate has been involved as researcher in grants from the US government (NHGRI) and in an Advanced Grant from the ERC.

Further the candidate took part in courses from the University of Zaragoza and the Spanish Chemical Society, collaborates in open projects such as Wikipedia (entry "proteina", methods for denaturing proteins) and is member of scientific societies SEBBM and SCUK. In addition, has given lectures at the University of Granada, both for first year students and master students. The candidate frequently directs students in the laboratory (Toby Guram, master student at Oxford University, Christian B. Rosen, PhD student at Aarhus University, Sussane Bomke and Sussane Dammers, undergraduate students at Munchster University).

The candidate is corresponding author on Rosen* CB, Rodriguez-Larrea*# D and Bayley# H, Nat. Biotech, 2014 and shares 33% of the patent US 61/896,933. Has held collaborations with several groups, leading to two supervisor-independent publications [Halskau O, JBC, 2009] and [Rodriguez-Almazan C, JBC, 2008]. Has been invited to give talks at Oxford University, Aarhus University, EMBL, SEBBM,... and has been granted with several competitive fellowships (EMBO Long Term between others). Has been at Oxford University since May 2010, with 3 works in high impact journals: [Rodriguez-Larrea D & Bayley H, Nat. Nanotech, 2013], [Ousden N. et al, Science, 2013] and [Rosen* CB, Rodriguez-Larrea*# D and Bayley# H, Nat. Biotech, 2014]. Further, broadened his experience with research periods at Bergen University (Norway) and Cape Town University (South Africa).

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AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **PASQUALI , LORENZO**
Referencia: RYC-2013-12864
Área Científica: Biomedicina
Correo Electrónico: pasquali@clinic.ub.es

Título:

Genetic and epigenetic susceptibility to the development of diabetes.

Resumen de la Memoria:

My line of research and my scientific interested is centered on understanding the molecular mechanisms that underlay diabetes, in particular throughout my scientific career I could mature and combine different expertise in the clinical, human genetics, molecular biology and bioinformatics fields with the goal of understanding the genetic and epigenetic susceptibility to the development of diabetes.

I centered my efforts in exploring the epigenetic landscape of the insulin producing pancreatic islet tissue in human cells. I could integrate genome-wide epigenetic marks, including histone modifications and open chromatin profiles with transcription factor binding and expression maps in human pancreatic islets to build a pancreatic islet-cell cis-regulome map. The integration of such map with Genome Wide Association Studies (GWAS) uncovered an enrichment of Type 2 Diabetes (T2D) associated genetic variation in islet enhancers, linking islet cis-regulatory networks to the mechanisms underlying T2D.

Overall the outcome of this line of research opened the path to understand the genomic regulation of the islets of Langerhans, shed light on the molecular mechanisms that underlay T2D and provided a reference cis-regulatory map for ongoing efforts to dissect the transcriptional program of pancreatic beta-cells

My current aim is to combine my clinical, human genetics and bioinformatic knowledge to unmask the physiopathogenesis of diabetes. My specific research interest is in understanding genomic regulation of the pancreatic islets of Langerhans and to use this information to gain new insights into the molecular defects that cause different forms of diabetes. I would like to use the support of the Ramón y Cajal subprogram to transition to an independent investigator career in this field.

Resumen del Currículum Vitae:

I trained as a medical doctor and specialized in pediatrics at the Gaslini Institute in Genoa, Italy. I soon got interested in pediatric endocrinology and dedicated a large part of my clinical residency at the Regional Center for Diabetes held in this university hospital and worked in strict contact with the molecular biology lab connected to this center.

I built up my molecular biology research skills at the University of Pittsburgh (USA) where I had the opportunity to work for two years at the Rangos Research Center for Diabetes with Prof. M. Trucco, acquiring both expertise in molecular biology techniques and scientific project leading capacities. During this experience my focus on the susceptibility to the development of diabetes and its complications led to several first authorship publications in high impact factor journals.

Back at the Gaslini Institute in Italy, I obtained my PhD in human genetics combining my basic research capacities with my clinical knowledge to study the human molecular genetics of monogenic diabetes.

Throughout these experiences I published 11 between papers and reviews, holding the first authorship of 7 of them.

In 2009 I moved to Prof. J. Ferrer&#65533;s lab at IDIBAPS, my current institute, as a CIBERDEM investigator. I here developed a focused interest and training in computational regulatory genomics. I soon could integrate this knowledge with molecular biology bench work to explore the epigenetic landscape of the insulin producing pancreatic islet cells. The outcome of this line of investigation opened the path to understand the genomic regulation of the islets of Langerhans and shed light on the molecular mechanisms that underlay type 2 diabetes. This effort led to two first authorships in Nature Genetics, one coauthorship in Cell Metabolism and another in a manuscript currently under review. I had an unquestionable leading role in both of my first-author papers that have been highlighted by "News and Views" editorials as well as press releases.

Throughout my career I played an active role as investigator in several international collaborative projects, including EU (DIRECT, CEED3, EPIMETAB) and NIH (LINKBETA) consortia. I was also awarded a fellowship from the European Fundation for Diabetes.

My current aim is to combine my clinical, human genetics and bioinformatic knowledge to understand the physiopathogenesis of diabetes.

My specific research interest is in unrevealing the genomic regulation of the pancreatic islets of Langerhans and using such notions to gain new insights into the molecular defects that cause different forms of diabetes.

Throughout my training in an international environment, I have gained the maturity, technical excellence, and experience to now direct my own research group. The support of the Ramón y Cajal subprogram together with the framework provided by the CIBERDEM, would enable the launching of my independent investigator career.

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Nombre: **VALIENTE CORTES, MANUEL**
Referencia: RYC-2013-13365
Área Científica: Biomedicina
Correo Electrónico: valientm@mskcc.org

Título:

CELLULAR AND MOLECULAR MECHANISMS OF BRAIN METASTASIS

Resumen de la Memoria:

It is becoming widely accepted that the main caveat to manage cancer is the ability of this disease to spread throughout the body in a process termed metastasis. This is the main reason why cancer is still associated with death; in fact 90% of cancer-associated deaths are directly linked to metastasis. Among secondary organs commonly affected during cancer progression, the brain is of outstanding interest given the rising incidence, extremely poor prognosis and understudied biology. Up to date epidemiological data indicates that by number of cases, brain metastasis constitutes the most common neurological complication of cancer, being ten times more common that all brain primary tumors combined and currently affecting 200.000 patients only in the U.S. Metastasis is a highly complex process given its multiple and consecutive steps which makes it extremely inefficient, yet lethal when developed. Most of the cancer cells leaving from a primary tumor will perish and never take over. Much of this attrition is associated with the last step of metastasis, the colonization of secondary organs. However what limits the colonization of cancer cells, and what are the mechanisms required to establish a metastatic lesion remained unknown. Understanding this an other limiting steps of metastasis will allow to expose the "Achilles" heel" of cancer, allowing to rationalize future therapeutic development to target the disease more efficiently. By combining experimental models of brain metastasis, clinical samples and analysis of the host brain microenvironment I have identified the mechanism by which brain metastatic cells could survive in the brain during the initial steps of colonization (Valiente et al., 2014, Cell). My research has identified natural defenses produced by the reactive brain to the presence of metastatic cells. Astrocytes get immediately activated when sensing cancer cells and produce a protease activity lethal for cancer cells in the brain. A very limited number of metastatic cells however will succeed and colonize the brain. When these brain metastatic cells were analyzed we discovered that they avoid the lethal action of this protease by overexpressing serine protease inhibitors specific for this activity. The approach followed lead to identify genetic determinants required to fulfill critical bottlenecks in the early steps of brain colonization. In a broader view the implications and technical innovations of this work have settled the bases to understand the biology of disseminated disease in the brain. My future interest is to develop a research program with the main goal of identify and characterize the limiting steps of brain metastasis colonization and dissect the molecular regulation.

Resumen del Currículum Vitae:

I did the bachelor in Veterinary Science at the University of Zaragoza (1998-2003). During the last year of my studies I joined the Department of Genetics (2002-2003). Under the supervision of Pilar Zaragoza I developed a PCR based diagnostic method for a tick-borne disease of dogs, named Ehrlichiosis. During 2003 I started to take part in an ongoing research line at the same laboratory studying Amyotrophic Lateral Esclerosis (ALS) in a mouse model for this disease. Under the supervision of Rosario Osta I became familiar with mice manipulations, biopsies protocols from different tissues, sensory-motor behavior tests, quantitative PCR, cloning and immunohistochemistry. Since I liked the project I decided to join the laboratory and started a PhD in Anatomy, Embriology and Genetics at the University of Zaragoza (2004). However the year after I realized the laboratory had very important limitations that will narrow down significantly my choices in the future if I was going to continue the scientific career. I finally took the decision to explore other laboratories given that I was determined to pursue a PhD in life sciences. Among different interviews I did, the laboratory of Oscar Marín at the Institute of Neurosciences (Alicante, Spain) was the one that I was looking for. As I joined the lab I decided to study the molecular regulation of neuronal migration during the development of the cerebral cortex as the main aim of my PhD studies (2005-2009). I was involved in two main projects. In collaboration with the laboratory of Miguel Valdeolmillos, we characterized the migration of interneurons at a cellular level for the first time, identifying the RhoGTPase ROCK as a critical regulator for the steering navigation of this neuronal precursor (Martini, F, Valiente, M, et al., 2009, Development). In parallel I studied the intracellular regulation of the two migratory modes in the cerebral cortex, radial and tangential migrations. This work dissected the role of Focal Adhesion Kinase (FAK) as a critical regulator of glial-guided migration of projection neurons given its interaction with connexin26 (Cx26). This was the first report linking focal adhesions and gap junctions in the migration of neuronal precursors (Valiente et al., 2010, Journal of Neuroscience). During the PhD and funded by EMBO, I decided to travel abroad (2007) to do a short stay of three months at the Sandford-Burnham Medical Research Institute (San Diego, CA, US), where I joined the laboratory of Pedro Aza-Blanc, Director of the Functional Genomics Core Facility, to use lentiviral vectors in migrating neurons in 3D matrices. I participated in the publication of three reviews at the end of the PhD. I also participated in successful collaborations with other laboratories (Fazzari et al., 2010, Nature; Martin-Ibanez et al., 2010, Journal of Comparative Neurology). After completing the PhD I decided to change the main subject of my research, and even the scientific field. Given my interest in the ability of neuronal precursors to navigate through the brain, I found the phenomena of cancer cells colonizing a secondary organ fascinating. The unique opportunity to study metastasis in the brain was available at the laboratory of Dr. Massagué. During my postdoctoral training

(2010-present) I succeeded to establish the methodology

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Nombre: **GARCIA GONZALO, FRANCESC**
Referencia: RYC-2013-14887
Área Científica: Biomedicina
Correo Electrónico: fgarciagonzalo@gmail.com

Título:

Molecular Mechanisms of Primary Cilia Function

Resumen de la Memoria:

After having worked in the fields of membrane trafficking (1999-2006) and stem cell biology (2006-2008), I have become an expert in ciliary biology, the field in which I plan to stay in the future. Thus, the main goal of my current and future research is to achieve a deeper understanding of the mechanisms underlying primary cilia function.

Primary cilia are microtubule-based membrane protrusions of the cell surface that function as cellular antennae. In humans, primary cilia are essential for us to sense our environment (we see, smell and hear through cilia) but they also regulate critical aspects of our developent and homeostasis, including brain and limb patterning or feeding behavior. Failure of primary cilia to function properly leads to ciliary diseases, also known as ciliopathies, which include polycystic kidney disease (PKD), Bardet-Biedl syndrome (BBS), Meckel syndrome (MKS) and Joubert syndrome (JS), among others.

During my postdoctoral research at UCSF (2008-2014) I have made major advances in our understanding of two ciliopathies, MKS and JS. When I joined this laboratory, most causative genes for MKS and JS had been identified, yet their functions were unknown. I established that most MKS and JS gene products physically interact with each other and are part of a multiprotein complex. Furthermore, I found that this complex localizes to the base of primary cilia, in a region known as the transition zone. I also created and analyzed mouse mutants lacking some of these genes. These studies showed that complete loss of function of this MKS/JS complex causes a mouse phenotype that closely resembles human MKS, whereas partial loss of complex function leads to a mouse version of human JS. I also defined the function of this complex at the molecular and cellular levels: the complex plays a supportive role in primary cilia formation, but its main function is to allow
membrane proteins to localize inside cilia.

Since I made these important discoveries, I have focused on the question of how ciliary composition is regulated. This has led me to study the functional relationship of the MKS/JS complex that I characterized and another ciliopathy complex, the nephronophthisis or NPHP complex, which also controls ciliary membrane composition. This study will be submitted for publication in the next few months. Additionally, I am now very interested in the role specific lipids (such as phosphoinositides) play in the control of ciliary membrane composition and ciliary signaling.

Resumen del Currículum Vitae:

Dear Members of the Search Committee:

I am currently a postdoctoral researcher in the laboratory of Dr. Jeremy Reiter at the University of California, San Francisco (UCSF), where I have been since 2008. I am extremely interested in obtaining a Ramon y Cajal fellowship, as this would allow me to become an independent researcher and participate in the teaching of future generations of scientists.

I would not be applying for this position if I did not feel prepared for it. My preparedness derives from fifteen years of experience working as a scientist in five different labs, three different countries, and in multiple areas of biomedicine, including biochemistry, cell biology, developmental biology and mouse genetics.

After graduating in biochemistry with highest honors in 1998, I performed my PhD at the University of Barcelona, including a three-month stay at the University of Giessen, Germany. I completed my PhD in 2005 after publishing my work as the lead author in four peer-reviewed articles (Garcia-Gonzalo et al. 2002, 2003, 2004 & 2005). After 2005, some of my PhD work was published in three additional articles (Chong-Kopera et al. 2006, Casas-Terradellas et al. 2006, Hadjebi et al. 2008) and one patent (Casas-Terradellas et al. 2006). During my PhD years I was also actively involved as a teacher at the School of Medicine and Dentistry of the University of Barcelona.

Upon completion of my PhD I moved to the United States of America. I first spent three years at the University of California San Diego (2005-2006) and The Salk Institute for Biological Studies (2006-2008), in which I published a study on the role of lipids in keeping human

embryonic stem cell pluripotency (Garcia-Gonzalo & Izpisúa-Belmonte 2008). In 2007, I also attended the Molecular Embryology of the Mouse course at Cold Spring Harbor Lab, New York, where I became familiar with mouse developmental genetics and disease models. I applied this knowledge when I joined my current lab at UCSF, where my biochemical, cell biological, developmental and mouse genetics background all came together to study primary cilia and the ciliopathies caused by their malfunction. My recent article in Nature Genetics is a great example of this seamless integration of disciplines (Garcia-Gonzalo et al. 2011). In addition to this, I also published some of my ciliopathy work as a coauthor in a Cell paper (Sang et al. 2011). More recently, I have reviewed the cilia field in the Journal of Cell Biology (Garcia-Gonzalo & Reiter 2012). Besides my research, I have also mentored three graduate students at UCSF during their trimestral rotations in our lab, two of whom decided to join the lab afterwards.

Thank you very much for your consideration.

Sincerely,

Francesc R. Garcia-Gonzalo

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Nombre: **ROJAS GONZALEZ, ANA ISABEL**
Referencia: RYC-2013-14533
Área Científica: Biomedicina
Correo Electrónico: anabel.rojas@cabimer.es

Título:

GATA factors in Liver and Pancreas: From Development to Disease

Resumen de la Memoria:

I completed my predoctoral training at the department of Plant Molecular Biology of IRNAS (CSIC) Seville, Spain under the supervision of Dr. Juan Jordano in 2001. During my predoctoral formation I acquired expertise in molecular biology techniques, incluiding generation of transgenic plants, and gained a strong background in developmental gene regulation in plants.

I did my posdoctoral stay at the Cardiovascular Research Institute at the University of California San Francisco, California, USA, under the supervision of Dr. Brian Black during a period of 6 years. The project I developed in Dr. Black lab centered on the study of the transcriptional regulation of cardiovascular development and more
specifically, the role and regulation of the zinc finger transcription factor Gata4 during cardiac vertebrate development. During this period, I gain expertise in developmental biology in general, mammalian gene regulation and manipulation of mice as animal model. I also acquired strong expertise in generation of transgenic mice and conditional knockout mice.

Currently, I am working at ¿Centro Andaluz de Biología Molecular y Medicina Regenerativa¿ (CABIMER), in Sevilla. I have a contract from the ¿Miguel Servet¿ program of ISCIII, which ends by April 2014. In CABIMER, I have been established as an independent research group and I have develop news research lines.My current research lines focus on the study of the molecular and genetic processes that occur during pancreatic and liver embryonic development with emphasis on transcriptional factors. We are also interested to understand how these transcriptional factors are involved in the development of diseases associated to these organs, such as diabetes and hepatic fibrosis. With special attention to GATA transcription factors, our lines of research are the following.

1. Molecular and cellular mechanisms in pancreas formation and in beta cell function.
2. Molecular basis for hepatic fibrosis induction and progression

The develop of these research lines requires the knowledge, professional skils and expertise I believe I have been acquired during my posdoctoral trainning.

Resumen del Currículum Vitae:

Degree in Biology at the University of Sevilla (1996). Ph.D. in Biology at the University of Sevilla (2001). My thesis research was focused on the transcriptional regulation of small heat shock proteins during embryogenesis in plants. My work during my PhD resulted in the publication of 5 papers, two of them as a first author (Prieto-Dapena et al., Plant Molecular Biology, 1999), (Rojas et al., Development, 1999), (Almoguera et al., Plant Physiology, 2002), (Rojas et al., Plant Physiology, 2002), (Almoguera et al., Journal of Biological Chemistry, 2002) and in the invention of two patents. I did my postdoctoral training in the laboratory of Dr. Brian Black at the Cardiovascular Research Institute at University of California San Francisco, USA, for 6 years. During this time my research focused on the transcriptional regulation during cardiac development. I was awarded with a Spanish postdoctoral fellowship from Ministry of Education and Science from 2003 to 2005 and an American postdoctoral fellowship from American Heart Association (AHA) Western Affiliates from 2005 to 2007. My work during my postdoctoral stay resulted in 5 papers, 3 of them as first author (Rojas et al., Development, 2005); (Rojas et al., Molecular and Cellular Biology, 2008); (Rojas et al., Developmental Dynamics, 2009) and two of them as a second (Heidt et al., Molecular and Cellular Biology, 2007) (Schachterle et al., Developmental Biology, 2011). I am also the first author of a review in a book chapter about cardiac transcriptional regulation (Rojas et al., Transcriptional control of cardiac boundaries, in Advances in Developmental Biology, 2007). In 2008, I was awarded with a ¿Miguel Servet¿ contract and I started to form my own group in ¿Centro Andaluz de Biología Molecular y Medicina Regenerativa¿ (CABIMER) in Sevilla. In our current lab we have developed innovative research lines focused on the study of the molecular and genetic processes that occur in pancreas and liver development and how these molecular factors are also involved in the development of diseases associated to this organ such as diabetes and hepatic fibrosis. Since I joined CABIMER I have obtained three competitive grants as principal investigator (two from the Subprograma de Proyectos de Investigación en Salud del Instituto de Salud Carlos III, 2008 and 2011, and 1 from the Andalusian Regional Government, 2009). This funding allowed us to acquire all the equipment and reagents necessary for the new laboratory as well as to hire personnel. Our lab is currently composed of two predoctoral students (of whom I am the Thesis Director). The work from my lab has resulted so far in the publication of three papers of high impact factor

(Developmental Biology, 2010; Journal of Clinical Investigation, 2012, and Hepatology, 2014) and one invited review (Molecular Cell Life Science, 2013), of which I am the corresponding author. I have also established several collaborations that resulted in the publication of two papers and 2 book chapters. Part of the data generated in my lab have been objected to the application of patent.

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Nombre: **CAMPOS PRIETO, LUIS ALBERTO**
Referencia: RYC-2013-13197
Área Científica: Biomedicina
Correo Electrónico: l_a_campos_p@yahoo.es

Título:

Métodos biofísicos aplicados al plegamiento y a la unión de proteínas: técnicas espectroscópicas y de molécula única

Resumen de la Memoria:

El factor común en la trayectoria investigadora del candidato es el empleo de técnicas biofísicas para estudiar el plegamiento y unión de proteínas.

Durante el periodo pre-doctoral, en colaboración con el prof. Javier Sancho, se desarrollaron las siguientes líneas de investigación:
-Obtención de la estructura a baja resolución del intermediario en equilibrio de apoflavodoxina. Para ello, se diseñaron 25 mutantes que fueron analizados experimentalmente para obtener información sobre el efecto de las mutaciones en los equilibrios nativo-intermedio e intermedio-desnaturalizado. Mediante un análisis energético adecuado se obtuvo una estructura donde el intermediario presentaba la zona de unión al cofactor FMN desestructurada.
-Estabilización dirigida de apoflavodoxina mediante mutaciones estabilizantes localizadas. Mediante la optimización de la superficie electrostática de la proteína, se diseñaron 8 mutantes en los que se pudo seleccionar entre estabilización "relevante" o estabilización "residual" dependiendo de la posición de la mutación.
-Estudio de la unión entre apoflavodoxina y FMN y efecto en el mecanismo de plegamiento de la proteína. Se confirmó que el FMN se une preferentemente al estado nativo.
-Cálculo del incremento de energía de unión de un puente de hidrógeno. Mediante un análisis de un ciclo de doble mutante de un puente de hidrógeno aislado cuidadosamente seleccionado se observa que no contribuye a la estabilidad de la proteína, y que sólo cuando los grupos que forman el puente están cercanos, se convierte en energéticamente favorable.
-Estudio del intermedio en equilibrio de la pepsina. Las conclusiones de este estudio permiten descubrir el mecanismo de funcionamiento de la pepsina en el interior del estomago.

Durante el periodo postdoctoral, en colaboración con el Dr. Victor Muñoz, se han desarrollado otras líneas de investigación, en este caso relacionadas con técnicas de molécula única:
-Descubrimiento de un coctel foto-protector para poder trabajar con técnicas de molécula única FRET a altas intensidades de láser sin foto-desactivación de las etiquetas fluorescentes. De esta forma, se obtiene un mayor número de fotones que permiten trabajar con una resolución temporal de unas decenas de microsegundos.
-Análisis de los histogramas provenientes de experimentos de molécula única FRET obtenidos para una proteína "downhill", BBL, a diferentes concentraciones de desnaturalizante químico. Dicho análisis confirma el comportamiento "downhill" de la proteína.
-Análisis de los histogramas provenientes de experimentos de molécula única FRET con una proteína de dos estados, SH3, a diferentes concentraciones de desnaturalizante químico. Se observa compactación del estado desnaturalizado a bajas concentraciones y expansión del estado nativo conforme aumenta la concentración de desnaturalizante, indicando un grado alto de flexibilidad acorde con la teoría de paisajes energéticos.
-Perfeccionamiento de técnicas de inmovilización en superficie para obtener trayectorias de molécula única de mayor longitud. Una estancia en el laboratorio del Dr. Gilad Haran ha permitido obtener los conocimientos necesarios. En desarrollo.
-Conversión de una proteína dos estados en una proteína "downhill" mediante mutaciones seleccionadas. Trabajo en desarrollo donde se han obtenido mutantes con menor barrera energética y sin cambio estructural.

Resumen del Currículum Vitae:

El candidato está contratado actualmente en el Centro Nacional de Biotecnología en Madrid, donde aplica técnicas biofísicas, incluyendo espectroscopía y técnicas de molécula única, a problemas relacionados con el plegamiento y la interacción entre proteínas.

Concluyó la carrera de Ciencias Químicas en 1998 en la Universidad de Zaragoza, con premio fin de carrera incluido, y decidió comenzar su carrera científica en el laboratorio del profesor Javier Sancho, con una beca FPU como soporte económico. Bajo su tutela, completó en 2004 el doctorado en ciencias por la Universidad de Zaragoza defendiendo la tesis doctoral "análisis energético y estructural de una proteína modelo con un equilibrio de tres estados: la flavodoxina de Anabaena PCC7119" y recibiendo una calificación de sobresaliente cum laude. Durante dicho periodo finalizó estudios científicos que generaron 14 artículos, 5 como primer autor, y realizó en 2001 una estancia pre-doctoral de 3 meses en la Universidad de Maryland, EEUU.

Tras la defensa de la tesis, decidió realizar una estancia postdoctoral de 3 años (2004-2008) con el grupo del Dr. Victor Muñoz, en la Universidad de Maryland (EEUU), sufragada en parte por una beca postdoctoral del gobierno español, donde completó el aprendizaje de técnicas biofísicas, entre las que se incluyen medidas cinéticas y técnicas de molécula única. Tras estos años residiendo en EEUU, el candidato se trasladó al Centro de Investigaciones Biológicas en Madrid junto con el resto del grupo, disfrutando de una beca postdoctoral Marie Curie (2008-2011), donde montó un laboratorio de técnicas de molécula única para continuar con su trabajo. Durante este periodo de tiempo en colaboración con el Dr. Victor Muñoz ha publicado 6 artículos, 4 como primer autor.

Finalmente, el grupo al completo se ha trasladado el año pasado al Centro Nacional de Biotecnología. El candidato ha colaborado activamente en ambos cambios de localización del grupo de trabajo, incluyendo el traslado de instrumental y la organización y puesta en funcionamiento de material y personal en la nueva ubicación. Además, está a cargo de la gestión de la unidad de técnicas de molécula única dentro del laboratorio del Dr. Victor Muñoz.

El candidato posee en su currículum 22 publicaciones, entre las que se incluyen 20 artículos publicados en revistas de medio-alto impacto (9 como primer autor, incluyendo un Nature Methods y varios PNAS) y un capítulo del libro "Estructura de proteínas" de la editorial Ariel Ciencia. Además, ha presentado su trabajo en numerosos congresos científicos, incluyendo varias presentaciones orales en congresos internacionales. Con respecto a la docencia, ha colaborado en dos cursos oficiales de la Universidad de Zaragoza durante 2 años.

Finalmente, en el currículum se incluyen varias becas de las que el candidato ha disfrutado, incluyendo una beca de colaboración con grupo de investigación durante la carrera, una beca pre-doctoral FPU, una beca postdoctoral del gobierno español y una beca postdoctoral Marie Curie. Posee un buen dominio del inglés, reforzado primero por la estancia de 3 años en EEUU y después por el continuado uso de este idioma durante los años trabajando en un grupo de trabajo de carácter netamente internacional, donde el inglés es utilizado siempre. Además, está colaborando con varios grupos científicos externos, incluyendo alguno extranjero.

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Nombre: **GONZALEZ PEREZ, ABEL**
Referencia: RYC-2013-14554
Área Científica: Biomedicina
Correo Electrónico: abeldavidgp@gmail.com

Título:

Cancer Genomics

Resumen de la Memoria:

The main challenge I would like to address is the integration of data on driver and actionable alterations from primary tumors with the information of response to drugs from cell lines, xenografts and clinical trials. (The former should allow us to stratify, or even individualize, cancer patients based on their molecular profiles, whereas the latter will help us determine the treatments that are better suited for each profile.) The first step would be to develop a knowledgebase of genomic and epigenomic alterations detected across thousands of tumors. This database will also collect all information available on the pattern of response to drugs by primary or secondary tumors (from clinical trials), cancer cell lines and xenografts. Then, I plan to develop metrics ﷺusing machine learning approachesﷺ to retrieve from this database the most similar primary tumors, cell lines or xenografts to a patient's tumor, given its genetic and epigenetic alterations profile. (These metrics will take into account the clonal architecture of the tumor under analysis.) Retrieving all available clinical information on this cluster of 'proximal' tumors would then allow to make predictions on the clinical evolution of the patient's tumor. Similarly, it would be possible to determine which drug or combination of drugs would better target its specific profile of molecular alterations.

The main goal of the project I would like to pursue consists in identifying biomarkers of resistance and sensitivity of tumors to targeted drugs, based on the set of genomic, transcriptomic and epigenomic alterations observed in the tumor. The project ultimately aims to contribute to make accurate predictions of the putative response of patients' tumors to targeted drugs across major cancer types. This project will be broken down into four major parts:

A) Collect a database of response of tumors to targeted drugs
The main output of this first part of the project will be a knowledgebase of genomic and epigenomic alterations detected across thousands of tumors, as well as information on the pattern of response to drugs by primary or secondary tumors (from clinical trials), cancer cell lines and xenografts.

B) Identify biomarkers of resistance and sensitivity to targeted drugs
The main output of this second part of the project will be a set of alterations (biomarkers) that predispose groups of tumors towards sensitivity or resistance to several targeted drugs. They will be accompanied by mechanistic hypotheses.

C) Design metrics to classify new tumors
The main output of this part of the project will be a set of metrics, rules and/or methods to retrieve from the database of genomics alterations in tumor samples and their response to targeted drugs.

D) A system to automatically predict the effect of targeted cancer drugs
The fourth and final part of the project will consist in developing a bioinformatics systems to automatically predict the effect of targeted drugs on new tumor samples. One first key part of this system will be the information on functional interactions network developed in the course of over two decades of high-throughput biology. It will also build upon the set of mechanistic hypotheses on the determinants of sensitivity and resistance to targeted drugs constructed in the second part of the project.

Resumen del Currículum Vitae:

After obtaining my degree in Biochemistry, I did my PhD in Bioinformatics at the National Bioinformatics Center, in Cuba with a project focused on the transcriptional regulatory network of gamma-proteobacteria. I developed computational methods to identify transcription factors binding sites across the genomes of these organisms. Then, I designed and implemented a web-based database with the results of applying these methods to 30 bacteria to make them easily accessible to the microbiological research community. Furthermore, I used this data to produce sound hypotheses on the evolution and dynamics of the gamma-proteobacteria transcriptional regulatory machinery.

I then moved to the field of cancer genomics at the Biomedical Genomics Group of the University Pompeu Fabra in Barcelona. I started working in the development of an automated platform for the analysis of next generation sequencing data from patients samples developed in collaboration with a Spanish genomics medicine company. I specifically participated in the development of a system to analyze the functional impact of single nucleotide variants and small indels. I then developed two methods aimed at improving the

assessment of this functional impact both for germline variants (Condel) and somatic mutations (TransFIC). I then moved on to develop bioinformatics methods to identify genes responsible for the initiation of tumorigenesis across cohorts of cancer patients. I looked both on somatic single nucleotide variants and copy number variants. Eventually, these methods, were assembled within a complex computational pipeline available to cancer genomics researchers to analyze their own cohorts of somatic mutations in cancer patients looking for specific driver genes acting in them. We also used this pipeline in-house to analyze most publicly available cohorts of tumor samples. With the results of this analysis we finally set up a web-discovery tool (IntOGen-mutations) aimed at supporting researchers in the analysis of cancer genomics datasets.

I possess both a broad biological knowledge allowing me to ask meaningful questions, and the statistical and informatics skills to find their answers through the analysis of big datasets. In recent years, I have focused mainly on the development of bioinformatics methods to analyze large cancer genomics datasets. I have a good grasp of the biology of tumors and a solid comprehension of the types of data generated by the most common high-throughput cancer genomics platforms, and the bioinformatics tools and approaches to analyze them.

On the informatics side, I am fluent in the two programming languages that are most commonly used in bioinformatics, PERL and Python and I have experience using HTML, CSS, and PHP for web-oriented programming. I also have solid experience working with relational databases, mostly in MySQL, and have worked on most currently existing Linux distributions, thus acquiring good administration skills. I have some knowledge of software engineering, mostly oriented towards design and implementation of workflows. During my roughly twelve years of bioinformatics fiddling, I have come across several dozens of programs, which I have tested, on top of which I have done scripting, most commonly to connect their input and output together to form pipelines. Finally, I have experience using comp

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Nombre: **SENOVILLA GONZALEZ, LAURA**
Referencia: RYC-2013-14285
Área Científica: Biomedicina
Correo Electrónico: laurasenovilla@hotmail.com

Título:

Ploidy and Immunosurveillance

Resumen de la Memoria:

Dr. Laura Senovilla is a scientist with more than 12 years of experience in research. She has a multidisciplinary background in endocrine physiology, cancer biology and immunology as well as broad experience in animal models.
Starting from her last year of university (2001/2002), as a collaboration between SEK University (Segovia) and the Insituto de Biología y Génetica Molecular (IBGM, Valladolid), to the four years as PhD Student (2002 – 2006, FPI fellowship, IBGM, Valladolid) she was studying the characterization of multifunctional pituitary cells under the supervision of Prof. Javier García-Sancho and Dr. Carlos Villalobos. She defended her thesis entitled "Phenotypical and functional characterization of multifunctional pituitary cells" in July 2006 (summa cum laude), receiving the PhD Prize for the best thesis from the Medical School of the University of Valladolid.
Since 2007, Dr. Laura Senovilla is working in the laboratory of Prof. Guido Kroemer at the Insitut Gustave Roussy (Villejuif, France) as a postdoctoral fellowship (2007-2009, Marie Curie stipend; 2009-2011, Fondation pour la Recherche Médical fellow) and as associated researcher (2012 – present). Her scientific success is reflected by her list of publications which covers more than 50 papers (more than a half as first, second or last author) in peer review journals, including Science, Aging, Trends Immunology, Nature Review Drug Discovery, Cell Reports, EMBO J. Her main scientific interest focused on the relationship between cancer cell ploidy and its effect on the immune system. Part of this work has been published in Science in 2012 and has been honored by the Institut Necker – Fondation Tourre Prize 2013 (Paris, France). At present, Dr. Laura Senovilla is the head of the "Ploidy and Immunity" team in Guido Kroemer's laboratory, and is supervising the work of Dr. José Manuel Bravo – San Pedro, Dr. Fernando Aranda and Dr. Michaela Semeraro. She is also responsible for the scientific PhD training of Mrs. Norma Bloy.

Dr. Laura Senovilla recently discovered a new control mechanism of tumor proliferation by the immune system, which recognizes and eliminates cells that bear more chromosomes than usual (Science, 2012). This work highlighted for the first time the existence of a link between hyperploidy, stress of the endoplasmic reticulum (ER) and immunosurveillance. Dr. Laura Senovilla found that the increase in the number of chromosomes causes ER stress which subsequently leads to the translocation of calreticulin (CRT) to the cytoplasmic membrane. Surface exposed CRT serves as a signaling entity that stimulates an immune response which in turn eliminates these cells and establishes a long term anti-tumoral immunity. To investigate the translational relevance of these findings, the ploidy status and the ER stress response were monitored using tissue biopsies obtained from 60 women affected by locally advanced breast cancer. The results correlated local immune responses with reduced nuclear size (in responders to chemotherapy) and the absence of such an immune response with increased nuclear size (in non-responders to chemotherapy).

Resumen del Currículum Vitae:

1. EDUCATION

1.1 UNIVERSITY DEGREES AND DIPLOMAS
PhD by the University of Valladolid. School of Medicine, University of Valladolid (Spain) 04/07/2006 Director: Prof. J. GARCIA-SANCHO. Co-director: Dr. C. VILLALOBOS. Distinction Cum laude.
BS, Biology (Molecular Biology speciality). University SEK of Segovia (Spain) 22/02/2002.

1.2. SPECIALIST, ONGOING, TECHNICAL, PROFESSIONAL TRAINING
Special training in animal experimentation for senior biologists, Level I. Ministère de l'alimentation, Paris (France). Date of end of training: 01/06/2012, 80 hours.
International Advanced ICAS/ApopTrain Training Course on "Advances in cell death research – from basic principles to new therapeutic concepts". Schloss Reisensburg, Günzburg (Germany). Date of end of training: 20/07/2008, 40 hours.
Seminar of computer optimized microscopy. University of Valencia (Spain). Date of end of training: 02/07/2004, 50 hours.
Course of modern microscopy applied to biomedicine. National Center for Biotechnology (CNB). Madrid (Spain). Date of end of training: 16/10/2003, 30 hours.

2. RESEARCH EXPERIENCE

2.1. CURRENT POSITION
01/02/2013 – Present: Associated Researcher in the INSERM Unit U848 "Apoptose, Cancer, Immunité". Gustave Roussy Campus Cancer (GR, Villejuif (France) under supervision of Pro. G. KROEMER. Project "Study of the immunogenicity of tetraploid cells and comprehension of their regulation".
More than 60 first and co-authored publications in Science, Trends Immunol, Mol Cell, Cell Rep, Nat Rev Drug Discov, Oncogene, EMBO J, Cancer Res and others (please refer to the "Publications" list).
2.2. PREVIOUS LABORATORIES
01/02/2007 – 31/12/2012: Postdoctoral Researcher in the INSERM Unit U848 "Apoptose, Cancer, Immunité". Institut Gustave Roussy (IGR, Villejuif (France)) under supervision of Pr. G. KROEMER.
01/07/2002 – 31/01/2007: PhD student in the group "Calcium and cellular function". Institute of Biology and Molecular Genetics (IBGM, University of Valladolid (Spain)) under supervision of Pr. J. GARCIA-SANCHO and Dr. C. VILLALOBOS in the project "Phenotypic and functional characterization of multifunctional anterior pituitary cells"
7 publications in some of the most considered journals of endocrinology including 2 first-authored Endocrinology and 1 first-authored J Clin Endocrinol Metab.
04/2005 – 06/2005: Doctorate stay. School of Medicine. Catholic University of Leuven (Belgium) under supervision of Pr. C. DENEF.
07/2003 – 09/2003: Doctorate stay. Department of Physiology. University of Liverpool. Liverpool (United Kingdom) under supervision of Pr. O.H. PETERSEN.

3. TEACHING EXPERIENCE
Present: Supervisor of 1 PhD student (Norma BLOY) and 3 postdocs (Dr. Fernando ARANDA, Dr. Jose Manuel BRAVO-SAN PEDRO and Dr. Michaela SEMERARO).
Course 2012/2013: Supervisor of 2 works leading to a Master (students: Chloé BORDENAVE, Pauline GARCIA and Julien PESQUET) in the unit of Pr. KROEMER (INSERM U848)
Course 2009/2010: Supervisor of a work leading to a Master (student: Claire PAILLERET) in the unit of Pr. KROEMER (INSERM U848)
4. SCIENTIFIC PRIZES AND AWARDS
2013 Prix Institut Necker – Fondation Tourre. Paris, France.
2007 Extraordinary Doctoral Award to the bests thesis of the course 2005-2006 from the Valladolid University Medical School. Valladolid, Spain.

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Nombre: **ABAD MENDEZ, MARIA**
Referencia: RYC-2013-14747
Área Científica: Biomedicina
Correo Electrónico: mabadmendez@hotmail.com

Título:

From celular senescence to cell reprogramming in living organisms.

Resumen de la Memoria:

I majored in Biological Sciences at Universidad Autónoma de Madrid in 2003. I carried out my PhD at Instituto de Investigaciones Biomédicas "Alberto Sols" (Madrid), under the supervision of Dr. Ignacio Palmero. My doctoral research focused on the field of tumour suppressors and senescence; my main achievement during this period was the identification of the chromatin remodelling protein ING1b as a novel and critical regulator of the cellular senescence response. My doctoral research led to three research articles published in peer-reviewed journals (two of which I first-authored) and one review article.

I moved in 2009 to the Tumour Suppresor group headed by Dr. Manuel Serrano at CNIO. My research has since then centred on cellular reprogramming, stem cells and their relationship to tumorigenesis. I have pioneeringly generated a "reprogrammable" mouse strain that allowed me to demonstrate for the first time ever that cellular reprogramming in living organisms is indeed feasible: somatic adult cells from multiple tissues can be converted into induced pluripotent stem cells (iPS cells). In addition, I was able to stablish that in vivo-reprogramming triggers the acquisition of totipotency features; the in vivo reprogrammed cells reach a more primitive and plastic stage than those reprogrammed in vitro. I recently published my work as a full research article in the high-ranking journal Nature in which I am first author. My results bear very important implications for regenerative medicine, opening up new venues for in situ tissue regeneration. Accordingly, my work was named "most notable advance of 2013" by Nature Medicine, and has had a great impact, meriting comments and analyses in several scientific journals and world-wide lay media coverage. Additionally, my postdoctoral research has also contributed to some other projects developed in the Serrano lab in the stem cells and cancer field, some of them already published (Palla AR et al., Oncogene 2013, Epub ahead of print). My current investigations focus in exploring the relationship among in vivo reprogramming, cancer, and tissue regeneration.

Resumen del Currículum Vitae:

EDUCATION

December 2008 — Ph.D. in Biochemistry, Molecular Biology and Biomedicine.
Universidad Autónoma de Madrid, Spain.

September 2003 — Bachelor Degree in Molecular Biology and Biochemistry
Universidad Autónoma de Madrid, Spain

SCIENTIFIC EXPERIENCE

May 2009-Date — Postdoctoral Fellow
Spanish National Cancer Research Centre (CNIO), Madrid, Spain.
Supervisor: Manuel Serrano, PhD.

Sept 2003-May 2009 — Ph.D. student
Instituto de Investigaciones Biológicas "Alberto Sols", Madrid, Spain.
Supervisor: Ignacio Palmero, PhD.

June-Sept 2002 — Undergraduate student
University of Cambridge, Department of Genetics, UK.
Supervisor: Alfonso Martinez Arias

PUBLICATIONS

- Abad M, Mosteiro L, Pantoja C, Cañamero M, Rayon T, Ors I, Graña O, Megías D, Domínguez O, Martínez D, Manzanares M, Ortega S, Serrano M.
Reprogramming in vivo produces teratomas and iPS cells with totipotency features.
Nature. 2013 Oct 17;502(7471):340-5.

- Palla A.R., Piazzolla D., Abad M., Li H., Dominguez O., Schönthaler H.B., Wagner E.F. and Serrano M.
Reprogramming activity of NANOGP8, a NANOG family member widely expressed in cancer. Oncogene. 2013 Jun 10. [Epub ahead of print]

- Abad M, Moreno A, Palacios A, Narita M, Blanco F, Moreno-Bueno G, Narita M and Palmero I.
The tumor suppressor ING1 contributes to epigenetic control of cellular senescence. Aging Cell. 2011 Feb; 10:158-71.

- Menéndez C, Abad M, Gómez-Cabello D, Moreno A and Palmero I.
ING proteins in cellular senescence. Curr Drug Targets. 2009 May;10:406-1. Review.

- Abad M, Menéndez C, Fuchtabuer A, Serrano M, Fuchtbauer E-M and Palmero I.
Ing1 mediates p53 accumulation and chromatin modification in response to oncogenic stress.
J Biol Chem. 2007 Oct 19;282:31060-7

- Goeman F.,Thormeyer D., Abad M., Serrano M., Schmidt O., Palmero I. and Baniahmad A.
Growth inibition by the tumor suppressor p33ING1 in immortalized and primary cells: Involvement of two silencing domains and effect of Ras. Mol Cell Biol. 2005 Jan;25:422-31.

PATENTS AND UTILITY MODELS

Inventors: Serrano Marugán, M., Abad Méndez, M., Mosteiro Carretero, M. Ll.
Title: Novel induced pluripotent stem cells and method of preparation thereof.

Application Form No: EP13382187.6
Priority Country: Europe
Priority Date: 21/05/2013
Holder Entity: Fundación Centro Nacional de Investigaciones Oncológicas Carlos III

MAIN CONTRIBUTIONS TO CONGRESSES

- Abad M., et al.
Reprogramming in vivo and beyond.
Invited talk.
NESCI Research Day
Newcastle University, UK

- Abad M., et al.
Reprogramming in vivo produces teratomas and iPS cells with totipotency features.
Poster
Nature-CNIO Cancer Symposium: Frontiers in tumor heterogeneity and plasticity.
Madrid, Spain

- Abad, M., et al.
Active demethylation in non-CG context during differentiation of mouse Embryonic Stem cells.
Poster
CNIO Frontiers Meeting 2011
Recapturing Pluripotency: Links between cellular reprogramming and cancer.

CNIO, Madrid.

- Abad, M., et al.
Role of the Ing1 locus in responses to stress through p53 acetylation and chromatin modification.
Poster
Mechanisms and Models of Cancer.
Cold Spring Harbor Laboratory, New York.

HONOURS AND AWARDS

"Notable Advance of 2013"
Nature Medicine 19, 1564"1565 (2013)

"Mejores Ideas 2013" (The Best Ideas 2013) Prize
Category of Research and Pharmacology
Diario Médico, November 2013

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SUBDIRECCIÓN GENERAL
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Nombre: **CASTILLO LLUVA, SONIA**
Referencia: RYC-2013-14308
Área Científica: Biomedicina
Correo Electrónico: scastillolluva@usal.es

Título:

Cellular Migration and Tumourigenesis

Resumen de la Memoria:

My PhD and postdoctoral research career has allowed me to analyze the responsible mechanisms of cell polarity (PhD student with professor José Pérez-Martín at CNB, Spain) and cell migration (postdoctoral position with Dra Angeliki Malliri at Paterson Institute for Cancer Research, UK), both necessary processes for the epithelial-mesenchymal transition (EMT). The EMT is a highly conserved cellular program that allows polarized, immotile epithelial cells to convert to motile mesenchymal cells. This important process has been implicated not only in physiological migration of cells, but also in the pathogenic program leading to carcinoma invasion and metastasis by giving rise to the dissemination of single carcinoma cells from primary epithelial tumors. My second postdoctoral position (Dr Jesús Pérez-Losada, CIC, Spain) allowed me to analyze the implication of EMT in metastasis using mouse models of breast cancer.

During my PhD student stage, I worked on how developmental decisions leading to differentiation often require resetting of the cell cycle and induction of new morphogenetic programs. Furthermore, I analyzed the polarity growth required during the pathogenic program, a conserve process in mammalian cells required for cell migration and invasion. This work allowed me to publish seven papers, three of them as first-author papers and two second-author papers.

After obtaining my PhD I decided to direct my efforts into biomedical research focusing my research on studying the role of Rho GTPases in tumourigenesis.I joined Dr Angeliki Malliri's group at the Paterson Institute for Cancer Research, and I focused my research on studying the role of Rho GTPases in migration and invasion. This work has made an important contribution to the understanding of how the GTPase Rac is regulated to promote cell migration and invasion. This work allowed me to publish, four papers, two of them as first-author.

Almost two years ago, I decided to continue working in the migration-invasion processes, but from a more clinical prospective. I joined Dr Jesús Pérez-Losada¿s group trying to understand the implication of cancer dissemination and prognosis using mouse models of breast cancer. This work will allowed me to publish this year a first author paper (manuscript in preparation) and a second author paper (submitted).

Resumen del Currículum Vitae:

Postdoctoral positions

March 2012-Present	Post-doctoral Scientist	
	Instituto de Biología Molecular y Celular del Cáncer	Salamanca (Spain)
Jan 2006-March 2012	Post-doctoral Scientist	
	Paterson Institute for Cancer Research (PICR)	
	Manchester (UK)	
Jan 2005-2006	Post-doctoral Scientist	
	Centro Nacional de Biotecnología (CNB)	
	Madrid (Spain)	

FELLOWSHIPS

March 2012-Present	JAEDOC. CSIC
Aug 2006-2008	EMBO Long term Individual Fellowship
Jul-2000-2004	Pre-doctoral Fellowship Ministerio de Ciencia y Tecnología
Dec 1998-2000	Comunidad Autónoma de Madrid

Relevants publications

M. Daugaard; Roberto Nitsch; Babak Razaghi; Lindsay McDonald; Ameer Jarrar; Stéphanie Torrino; Sonia Castillo-Lluva; et al.,; P. H. B.

Sorensen. Hace1 controls ROS generation of vertebrate Rac1-dependent NADPH oxidase complexes. NATURE COMMUNICATION. 4 - 2180, 17/07/2013.

Sonia Castillo-Lluva; Chong Tan; M Daugaard; Poul Sorensen; Angeliki Malliri; Ronald T. Hay; Angeliki Malliri.The tumour suppressor HACE1 controls cell migration by regulating Rac1 degradation.migration. ONCOGEN.32 -13,pp. 1735 - 1742.03/2013

Sonia Castillo-Lluva; Michael H. Tatham; Richard C. Jones; Ellis G. Jaffray; Ricky D. Edmondson; Ronald T. Hay; Angeliki Malliri.SUMOylation of the GTPase Rac1 is required for optimal cell migration. NATURE CELL BIOLOGY.12 - 11,pp. 1078 - U70.11/2010

Ignacio Flor-Parra; Sonia Castillo-Lluva; Jose Perez-Martin .Polar growth in the infectious hyphae of the phytopathogen Ustilago maydis depends on a virulence-specific cyclin. PLANT CELL.19 - 10,pp. 3280 -3296.10/2007

Sonia Castillo-Lluva; Isabel Alvarez-Tabares; Isabella Weber; Gero Steinberg; Jose Perez-Martin Sustained cell polarity and virulence in the phytopathogenic fungus Ustilago maydis depends on an essential cyclin-dependent kinase from the Cdk5/Pho85 family. JOURNAL OF CELL SCIENCE.120 - 9,pp.1584 - 1595.05/2007

S Castillo-Lluva; J Perez-Martin .The induction of the mating program in the phytopathogen Ustilago maydis is controlled by a G1 cyclin. PLANT CELL.17 - 12,pp. 3544 - 3560.12/2005

E Garrido; U Voss; P Muller; S Castillo-Lluva; R Kahmann; J Perez-Martin .The induction of sexual Development and virulence in the smut fungus Ustilago maydis depends on Crk1, a novel MAPK protein. GENES & DEVELOPMENT.18 - 24,pp. 3117 - 3130.12/2004

S Castillo-Lluva; T Garcia-Muse; J Perez-Martin .A member of the fizzy-related family of APC activators is regulated by cAMP and is required at different stages of plant infection by Ustilago maydis. JOURNAL OF CELL SCIENCE.117 - 18,pp. 4143 - 4156.08/2004

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Nombre: **CALON , ALEXANDRE**
Referencia: RYC-2013-14657
Área Científica: Biomedicina
Correo Electrónico: alexandre.calon@gmail.com

Título:

Mechanisms driving colorectal cancer initiation and progression

Resumen de la Memoria:

I am finishing my postdoctoral period in the laboratory of Eduard Batlle, at the IRB Barcelona where I discovered that metastasis depends on a gene program expressed by the tumor microenvironment upon TGF-beta stimulation. These results were recently published in the journal Cancer Cell (Calon et al. 2012; Impact Factor 26.6).
This work has led to three patent requests protecting the use of the TGF-beta response signature for diagnosis and prognosis of CRC as well as its use as a companion diagnostic kit for the selection of patients likely to benefit from therapies based on TGF-beta inhibitors. In addition, we have obtained competitive funds to validate the technology and develop a diagnosis tool for the clinical setting.
I am currently preparing a second manuscript unraveling the origin of high TGF-beta in CRC and its connection with tumor hypoxia (Calon et al., to be submitted to Cancer Cell).
During my stay in Eduard Batlle's laboratory, I helped supervise one PhD student, Elisa Espinet, with whom I am currently preparing a manuscript describing the TGF-beta signaling in Cancer Associated Fibroblasts mediating colon cancer progression. The lab technician and the anatomopathologist that participate to my project, Sergio Palomo and Mar Iglesias are now both preparing with my help their PhD related to our research on cancer stroma. Finally, we very recently published a review on CAF-supported tumor growth and metastasis where I am acting as corresponding autor (Calon et al., 2013).
As a PhD student, I studied the functions of the transcription factors CDX1 and CDX2 in the laboratory of Jean-Noël Freund in Strasbourg. I studied the differential activities of CDX1 and CDX2 proteins during intestinal homeostasis and focused on their involvement in the transcriptional machinery and their link with the TGF-beta pathway. My work was granted a Jean and Madeleine Schaeverbeke research award and gave rise to six publications in peer-reviewed journals, three of them as a first author.

Resumen del Currículum Vitae:

Academic Background
2007-present: Postdoctoral researcher. IRB
2003-2006: PhD INSERM (French Institute of Health and medical Research)
2002-2003: Master Research Degree in Molecular and Cellular Biology

Awards
2008 Juan de la Cierva postdoctoral fellowship.
2007 Schaeverbeke research award
2007 Ministerio de educación y ciencia postdoctoral fellowship.
2003 INSERM/Alsace doctoral fellowship

Research and Development
Colostage. A new test for the prediction of recurrence in CRC
Small animal imaging using X-ray micro-CT

Patents
EP13382204
EP12192291
EP11382368; worldwide PCT/EP2012/072425

Publications
Differential gene expression profile between carcinoma-associated fibroblasts and their paired normal colonic fibroblasts in colorectal cancer.
BERDIEL-ACER M.; CUADRAS D.; CALON A.; BERENGUER A. ET AL. in Revision, Molecular Oncology. 2014

GeneX loss impedes Wnt dependent tumorigenesis through aberrant activation of the BMP signaling pathway.

WHISSEL G., MONTAGNI E., CALON A., HERNANDO MOBLONA X.ET AL. in Revision Nature Cell Biology 2014

Origin of TGF-beta in CRC and its connection with tumor hypoxia.
CALON A; LONARDO E.; TAURIELLO DV.; PALOMO PONCE S.ET AL. in Preparation 2014

TGF-beta signaling in Cancer Associated Fibroblasts mediates colon cancer progression.
CALON A.; ESPINET E.; TAURIELLO DV; PALOMO PONCE S.ET AL. in Preparation 2014

TGF-beta in CAF-mediated tumor growth and metastasis.
*Corresponding authors
CALON A.*, TAURIELLO DT., BATLLE E*. In Press, Sem Can Biol., 2013.

Dependency of Colorectal Cancer on a TGF-Beta-Driven Program in Stromal Cells for Metastasis Initiation.
CALON A., ESPINET E., PALOMO-PONCE S., TAURIELLO D.V.F. ET AL. Cancer Cell 2012

Cdx1, a dispensable homeobox gene for gut development with limited effect in intestinal cancer.
*Calon A. and Bonhomme C. contributed equally to this work
BONHOMME C*, CALON A*., MARTIN E, ROBINE S ET AL. Oncogene 2008

Intestine-specific homeobox gene Cdx2 decreases mobility and antagonizes dissemination of colon cancer cells.
GROSS I., DULUC I., BENAMEUR T., CALON A. ET AL. Oncogene 2008

Different effects of the Cdx1 and Cdx2 homeobox genes in a murine model of intestinal inflammation.
CALON A., GROSS I., LHERMITTE B., MARTIN E. et al. GUT 2007

Functional interaction between the homeoprotein CDX1 and the transcriptional machinery containing the TATA-binding protein.
CALON A., GROSS I., DAVIDSON I., KEDINGER M. ET AL. Nucleic Acids Res 2007

Multiple-contrast X-ray micro-CT visualization of colon malformations and tumors in living mice.
CHOQUET P., CALON A., BRETON E., BECK F. et al. C R biol. 2007

Differential regulation of the glucose-6-phosphatase TATA box by intestine-specific homeodomain proteins CDX1 and CDX2.
GAUTIER A., DOMON C., CALON A., FREUND JN. ET AL. Nucleic Acids Res. 2003

International Meetings
Stromal TGF-b Signals in Colon Cancer Metastasis 2013 speaker
A Stromal TGF-Beta-Driven Program promotes Metastasis Initiation in Colorectal Cancer 2013 speaker
Dependency of Colorectal Cancer on a TGF-beta-driven program in stromal cells for metastasis initiation 2012 speaker
CDX2 in Inflamed Bowel Disease and Associated Colorectal Cancer 2006 speaker
CDX2 in a Murine Model of Inflammatory Bowel Disease and in Associated Colorectal Cancers 2006 speaker
Differential interactions between CDX Homeotic proteins and specific partners 2005 speaker

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DESARROLLO E INNOVACIÓN

SECRETARÍA GENERAL
DE CIENCIA, TECNOLOGÍA
E INNOVACIÓN

DIRECCIÓN GENERAL
DE INVESTIGACIÓN
CIENTÍFICA Y TÉCNICA

SUBDIRECCIÓN GENERAL
DE RECURSOS HUMANOS
PARA LA INVESTIGACIÓN

AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **FORMENTINI , LAURA**
Referencia: RYC-2013-13693
Área Científica: Biomedicina
Correo Electrónico: lformentini@cbm.uam.es

Título:

The H+-ATP synthase: a critical hub deciding bioenergetics and cell fate.

Resumen de la Memoria:

I started my research career in 2005 in Italy, under the supervision of Professors F. Moroni and A. Chiarugi in the School of Medicine of the University of Firenze. Since the beginning my investigation was focused on energy metabolism and its implication in cell death. Nowadays it is known that mitochondria play key roles not only in energy provision but also in cell death regulation and in ROS and Ca2+ signaling. Modern trends are concerned with the identification of the structural and molecular links between mitochondrial functions. An example of this integration is the connection existing between oxidative phosphorylation and cell death. These two master tasks of mitochondria are molecularly and functionally integrated despite the many forms and shapes of cell death. A great deal of effort during my PhD was directed at understanding the mechanisms contributing to NAD and mitochondrial ATP loss once the nuclear enzyme polyADPribose polymerase 1 (PARP-1) gets hyperactivated. In particular, we demonstrated that PARP-1 indirectly interacts with mitochondrial function causing energetic derangement and necrosis, highlighting the nucleus-mitochondria cross talk involved in cell death (Formentini et al, J.Biol.Chem., 2009)
In 2009 I moved to Spain where I joined the laboratory of Professor J.M. Cuezva due to his interest in the bioenergetics of cancer cells. A key transducer in energy conservation is the H+-ATP synthase, an enzyme complex that we recently demonstrated to be a master regulator of cell death (Formentini* et al., Antiox.Red.Signal., 2012). The expression of the catalytic subunit of the H+-ATP synthase is repressed in human tumors providing a signature of disease progression and response to therapy. We have described that the ATPase Inhibitory Factor 1 (IF1) of the H+-ATP synthase also plays a prominent role in human carcinogenesis. IF1 expression is negligible in normal colon, lung and breast epithelial cells but highly increased in all carcinomas derived from these tissues (Formentini* et al., Oncogenesis, 2013). Accordingly, the over-expression of IF1 in colon cancer cells triggers a metabolic reprogramming to an enhanced aerobic glycolysis also promoting a retrograde ROS signal to the nucleus that activates cellular proliferation and resistance to apoptosis (Formentini et al., Mol Cell, 2012). Hence, IF1 emerges as a most relevant mitochondrial protein in defining energy metabolism and cell death programs needed to support tumor development. The study of the role of IF1 in cancer has been the main field of my postdoctoral investigation during the last 5 years. For this purpose I have developed conditional and tissue specific mouse models able to express the human IF1 or a mutant version of the protein (Formentini et al., EMBO J, 2014). A main objective of my research line (now supported by a competitive fellowship by the AECC) is to deepen into the knowledge of the cell biology of IF1 and its implication in colon inflammation, cancer onset and progression. With this purpose we started an international collaboration with Prof. Smits from the University of Rotterdam with the aim of generating a mouse expressing IF1 in colon. This model will allow to understand the relevance of the inhibition of the H+-ATP synthase in colon in vivo, providing knowledge based on a new pathway for prevention, diagnosis and therapy of colon cancer

Resumen del Currículum Vitae:

Personal information:
Laura Formentini
27/02/1980, Firenze,Italy
Address:c/ S.Nicolas 8,28013,Madrid,Spain
Mail:lformentini@cbm.uam.es

Position:
-October 2012-Today:
UAM-AECC post-doc position in J.M.Cuezva group, CBMSO, UAM University, Madrid
-October 2009-September 2012:
Juan de la Cierva post-doc position in J.M.Cuezva group, CBMSO, UAM University,Madrid
-April 2009-December 2010:
Post-doc position in J.M.Cuezva group, CBMSO, UAM University, Madrid

Formation:
-April 8th 2009:
PhD title in Pharmacology and Toxicology. University of Florence.
Grading: Cum laude (Spanish homologation: 2012)

-Nov 4° 2005:
Specialistic Degree in Pharmaceutical Chemistry and Technology, University of Florence.
Grading: 110/110. ﷺCum laude﷾ (Spanish homologation: 2011)

Languages: Italian, Spanish, English

Research Proyects:
1-Ministero italiano della Salute; 2007-2009; IP: A. Nistri, A. Chiarugi
2-Comunidad de Madrid; 2006-2010; IP: Dr. J.M.Cuezva
3-CIBERER; 2007-2009; IP: Dr. J.M.Cuezva
4-BFU2007-65253/BMC; 2008-2010; IP: Dr. J.M.Cuezva
5-BFU2010-18903; 2011-2013; IP: Dr. J.M.Cuezva
6-Comunidad de Madrid, S2011/31MD-2402; 2012-2016; IP: Dr. J.M.Cuezva

Papers: Number of papers: 20; First name papers: 8; Total Impact Factor: 104,9

20)Formentini L et al., EMBO J (in press). CLAVE: A. IF:9,8
19)Buonvicino D, Formentini L et al., J Biol Chem. 2013 Dec 20;288(51):36530-7 IF:4,6
18)Formentini L*, Sánchez-Aragó M* et al., Oncogenesis 2013 Apr 22;2:e46. (*,igual contribución)
17)Formentini L*, Sanchez Aragó M* et al., Antioxidants & Redox Signaling, 2013 Jul 20;19(3):285-98. IF:8,2. (*, igual contribución).
16)Sánchez-Aragó M, Formentini L et al., Cell Cycle, 2012 Aug 15;11(16):2963-4. IF:4,9.
15)Gerace E et al, Eur J Neurosci. 2012 Jul;36(1):1993-2005. IF:3.6
14)Formentini L et al., Mol Cell. 2012 Mar 30;45(6):731-42. IF:15,2.
13)Moroni, F et al., Br. J. Pharmacol, 2012 Mar;165(5):1487-500. IF:4,9.
12)Pittelli M, Formentini L et al., J.Biol.Chem, 2010 Oct 29;285(44):34106-14. IF:5,3.
11)Sánchez-Cenizo L, Formentini L et al., J.Biol.Chem, 2010 Aug 13;285(33):25308-13. IF:5,3.
10)Formentini L et al., IUBMB Life, 2010 Jul;62(7):554-60. IF:4,2.
9)Moroni F, Formentini L et al., Br J. Pharmacol, 2009 Jul;157(5):854-62. IF:5,2
8)Formentini L et al., J. Biol Chem, 2009 Jun 26;284(26):17668-76. IF:5,3.
7)Formentini L et al., Biochem Pharmacol, 2009 May 15;77(10):1612-20. IF:4,8
6)Formentini L et al., Br J. Pharmacol, 2008 Dec;155(8):1235-49. IF:5,2
5)Pellicciari R et al., ChemMedChem, 2008 Jun;3(6):914-23. IF:3,3
4)Porcu M et al., Cornea, 2007 Jan;26(1):73-9. IF:2,1
3)Faraco G et al., Mol Pharmacol, 2006 Dec;70(6):1876-84. IF:4,7
2)Fossati S, Formentini L et al., Biochem Cell Biol, 2006 Oct;84(5):703-12. IF:2,9
1)Cozzi A et al., J Cereb Blood Flow Metab, 2006 May;26(5):684-95. IF:5,4

Teaching duties:
2006-2009:
- Assistant at Faculty of Medicine, University of Florence (50 hours/year; 3 years):
Graduate Courses: Motor Sciences; Science and Technology of Sport; Management of Sport and Motor Activities
-Seminars and verbal communications

2009-Today:
-Professor at Department of Molecular Biology, UAM University (50 hours/year; 4 years):
Graduate Courses:Biochemistry; Chemistry and biochemistry of food and nutrition
-Seminars and verbal communications
-Direction of ﷺBioquimica Exp Avanzada﷾ final projects, UAM University, Madrid

ANECA title: ﷺProfesor Contratado Doctor﷾, 2012

MINISTERIO
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AYUDAS RAMÓN Y CAJAL
CONVOCATORIA 2013

Nombre: **PINEDA MARTI, JOSE RAMON**
Referencia: RYC-2013-13450
Área Científica: Biomedicina
Correo Electrónico: jr.pineda.marti@gmail.com

Título:

Study of neurotrophic factors and huntingtin in Huntington's disease and irradiation on neural and cancer stem cells niches.

Resumen de la Memoria:

My specialization is Neuroscience first and foremost. I started my career in the laboratory of Dr. Jordi Alberch (University of Barcelona, Spain). Alberch's laboratory research is well reputed in Huntington's disease (HD), a fatal neurodegenerative disorder whose symptoms include severe cognitive and motor impairments with a life expectancy varying from 10 to 15 years after diagnosis. The neurodegeneration is caused by the mutation of huntingtin gene. I received a pre-doctoral grant from the Spanish "Ministry of Education and Science", and my thesis work was oriented around two main axes in the development of different models of genetic and cellular therapies for HD. With 7 published papers and the involvement in 8 financed projects I obtained my doctoral degree with distinction. Then I moved to the Curie Institute in France with a post-doctoral grant from the Spanish "Ministry of Education and Science" (posteriorly reconverted to FECYT contract) to work in the laboratory of Dr. Frédéric Saudou. Saudou's laboratory is a European reference in the HD field situated in the "Institut Curie", one of the most well stablished private center of international research. There I demonstrated that pharmacological inhibition of calcineurin by FK506 is able to restore the transport of BDNF vesicles on primary cultures. I also unravelled a new role of huntingtin on the microtubule-dependent traffic of non-vesicular PCM1 protein. Being that PCM1 is responsible for ciliogenesis, we characterised that mechanism could play a role in several uncharacterised external (long known) side-effects of HD patients. I completed my first post-doc with two first author papers, "Molecular Brain" and "The Journal of Clinical Investigation" (JCI cover November 2011)) and several collaborations with USA and European labs. Then I decided to broaden my scientific background to new areas, and I joined the laboratory of Radiopathology led by François Boussin in the core of the R&D center of the "Atomic Energy Commission" (C.E.A), an civil and military organisation that leads technological research in Europe and ensures that the nuclear deterrent remains effective in the future. During my second postdoc, I worked on neural stem cells and cancer stem cells, publishing at the moment 3 papers and one review mainly focused on the mechanisms that impair adult neurogenesis after ionising irradiation exposure. In collaboration with Garcia-Verdugo, recognised internationally in ultrastructural studies of neurogenic niches, I found that irradiation increases TGF-beta 1 levels and its blockage in vivo by administration of TGF-beta neutralizing antibodies or an inhibitor of its receptor makes possible induced cell cycle reentry of of neurogenic niches of irradiated mice.

I am completing my postdoc with a 55K" grant that I obtained from "Fondation de France" to finish the part of the project focused in glioma stem cells. TGF-beta and neurogenesis is known to be altered in HD. I would like to return to Spain to join a leading lab to put to good use all my acquired expertise in the HD field. My credentials include an overall H-index 10, 13 papers, 427 citations in peer-reviewed journals and participation in numerous national and international congresses.

Resumen del Currículum Vitae:

I received a formation in Biological Sciences with undergraduate research experience (1997-2000) as student under the supervision of Professor Carlos López-Garcia, head of the department of Cell Biology of University of Valencia. I joined several labs, including Jordi Alberch"s laboratory as a PhD student in Barcelona (5 years). As postdoctoral experience I had two stages in Frédéric Saudou"s lab at Curie institut (2 year and 10 month) and François Boussin"s lab at "French Alternative Energies and Atomic Energy Commission" (3/11/2009 to present).

I obtained several grants including a "FPU pre-doctoral grant" and "Postdoctoral" grant both from Spanish "Ministry of Education and Science" both reconverted to "associate professor" from UB and "FECYT contract" respectively. Currently I have 55K" from a project that I submitted to "Fondation de France" but I also participated in 8 Spanish research projects from my stay in Jordi Alberch"s lab.

As the FPU grant allowed me to be a lecturer in the Medicine School, I lectured on "Structure and function of the digestive and renal system" for a total of 400h in all my thesis period. I also lectured in work"practices "Animal models for the study of neurological diseases: histological , biochemical and molecular characteristics" of the European Network " DiMI Network of Excellence" as part of the "Technology Platforms and Training" (TTP 's)). I got my PhD with distinction (01/12/2006), and I obtained the prize for best doctoral student (2008).

I have the credentials from the "National Agency for Quality Assessment and Accreditation" (ANECA) as "Trainee lecturer PhD" (2012) and from the French "Ministry of Higher Education and Research" the "Maître de Conférences" (MdC) for the Section 65, Cell Biology

and Section 69, Neurosciences (2013), both equivalents to Spanish ANECA "Contracted Lecturer PhD".

My scientific production includes 13 papers (which 2 I am first author and 2 second author from my PhD stage, and 3 I am first author and 1 second author from my Postdocs). Globally I have an H-index of 10 and I have published in international journals as "The Journal of Clinical Investigation" (twice), "EMBO Mol. Med", "Stem Cells" or the "Journal of Neuroscience" among others. Overall, my works were refered and citated 427 times in peer-reviewed journals (source ISI-Web of Knowledgement January 2014).

I participated in 20 national and international congresses (FENS, ASCB, Society for Neuroscience) 4 times as a speaker including "40th Annual Meeting of the European Radiation Research Society" (2013, Dublin, Ireland) and "Spanish Society for Neuroscience" (2005, Torremolinos, Spain). I also presented the research to naive audiences, including a conference in "Colegio de España " at the "Cité Internationale Universitaire de Paris" (2008, Paris, France).

I am a formal member of the "American Society of Cell Biology" (ASCB), and "European Huntington"s Disease Network". In the past I formed part of the SENC association, but then I moved to the French equivalent "Société des Neurosciences".

Recently I was a finalist of "I Premio Talento Joven CV" organized by Bankia-Levante EMT (2013). I also was selected and audited for evaluation to join the corps of CNRS and Inserm researchers (2012 and 2013). I have skills in French, English, Spanish and Catalonian/Valencian languages.