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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **ACIN PEREZ, REBECA** **Referencia:** RYC-2011-07826

Area: Biomedicina

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Titulo:

Mitochondrial deficiency and cardiomyopathy: Role of Reactive Oxigen species.

Resumen de la Memoria:

Mitochondrial diseases are now considered to be among the most common forms of genetic disorders, with a minimum prevalence of 1 in 5000 individuals. They can be caused by mutations in either the nuclear or the mitochondrial DNA (mtDNA). One of the most well characterized clinical presentations is neuromuscular dysfunction, followed by cardiomyopathy, generally in the form of hypertrophic cardiomyopathy. Nowadays there are several clinical treatments approved for mitochondrial diseases. However true treatment is, with some exception, unavailable due to the complexity of the disease and the side effects observed. Several mutations involving mt-tRNA genes (mainly Leu1, Lys and Ile), mt-encoded protein and nuclear encoded protein genes have been associated with cardiomyopathy. Some of these mutations have been deeply studied in a cybrid cell culture model at the biochemistry level. However, very little is known about the signalling pathways that could lead to the development of cardiomyopathy. Mitochondrial physiology and biogenesis are deeply involved in the initiation and progression of the disease, through reactive oxygen species (ROS) production, energy deficiency and decrease in mitochondrial respirasome formation, as initial steps in the formation of the plaques. Recently, it as been demonstrated the role of some mitochondrial biogenesis-related genes, such as PGC1a, in mitochondrial fusion, pointing to the importance of the balance between mitochondrial fusion-fission in the progression of the disease. Interestingly, some of the mutations described in cardiomyopathy are very ROSgenic, strongly pointing to ROS and mitochondrial deficiency as an initial step in the onset of the cardiomyopathy.The aim of this project is to better understand the involvement of mitochondria in cardiomyopathies using different models of mitochondrial diseases that curse with increase ROS production. The role of ROS as the signalling molecule will be investigated and by controlling its levels I could establish the signalling pathway involved in the development of the disease. These results will provide an important overall picture, opening a new therapeutic field for mitochondrial pathology treatment that will be tested in animal models with mitochondrial dysfunction. Initially, the pathways will be studied in primary myoblasts or in induced pluripotent stem cells derived from patients (iPSC, that will be generated for this project). Then, their potential differentiation into cardiac cells will be investigated.

Resumen del Curriculum Vitae:

Licenciada en Bioquímica por la Universidad de Zaragoza (2000) y Doctora en Bioquímica por la Universidad de Zaragoza (2004). La tesis doctoral fue dirigida por el Dr. Enríquez y su estudio se centró en modelos celulares y animales de ratón con patologías en el DNA mitocondrial (mtDNA), donde se investigó la biología molecular y celular y la bioquímica de la mitocondria. Durante el período doctoral, realicé una estancia de 8 meses en el laboratorio del Dr. Lightowlers en NewCastle Upon Tyne en Inglaterra, donde generé a partir de células totipotenciales (ES), cíbridos ES trasmitocondriales. Estos cíbridos han sido usados posteriormente en la generación de ratones como modelos de patología mitocondrial in vivo y en estudios de diferenciación neuronal in vitro. Tras la lectura de la tesis doctoral, continué un año más bajo la supervisión del Dr. Enríquez como postdoc donde trabajé en la organización de los supercomplejos resporatorios o respirosomas y en la regulación de la función mitocondrial por fosforilación del complejo II de la cadena de transporte electrónico. En 2006 (y hasta la fecha) comienzo mi segundo postdoc en el laboratorio del Dr. Manfredi en Nueva York (USA). En este período centro mis investigaciones en la regulación de la función mitocondrial a través de modificaciones post-traduccionales. Continúo con el proyecto iniciado en Zaragoza y desarrollo un nuevo proyecto que dará como resultado la caracterización por primera vez de una ruta de señalización localizada íntegramente en la mitocondria y que regula la actividad respiratoria. En este trabajo se relaciona fosforilación oxidativa (OXPHOS) con la regulación del ciclo de Krebs, como sensor metabólico. Como continuación de este trabajo, surgen otros dos proyectos. En el primero de ellos, investigo como si esta ruta está regulada de la misma manera en condiciones patológicas vs normalidad. Fruto de este estudio, se propone una posible vía de terapia para paliar la deficiencia en modelos donde el complejo IV de la cadena respiratoria está alterado. Actualmente, y gracias a la financiación de dos proyectos en los que figuro como investigadora responsable, se están generando animales transgénicos para cruzar con modelos de patología mitocondrial para estudiar el mecanismo terapéutico in vivo. En el segundo proyecto, realizado en colaboración con el Dr. Gatti en la Universidad Wayne de Detroit (USA), he sido capaz de encontrar el residuo responsable de esta regulación en una de las proteínas del complejo IV. Este residuo ha evolucionado como adaptación metabólica para permitir que la célula coordine la producción o el almacenamiento de energía. Debido a mi formación en la biología y la bioquímica mitocondrial, he establecido diversas colaboraciones durante mi etapa postdoctoral. Dichas colaboraciones incluyen mi trabajo con Vitamina A y regulación OXPHOS (Dr. Hammerling, Sloan Kettering Institute, Nueva York); señalización intramitocondrial por PKA en modelos de ratón con deficiencias mitocondriales (Dr. Schon, Columbia University, Nueva York) o con problemas cardiovasculares (Dr. Basson, Cornell University, Nueva York); señalización intramitocondrial por PKA en levadura (Dr. Levin, Cornell University, Nueva York); mitocondria y Parkinson en modelos celulares y animales (Dr. Li, Cornell University, Nueva York); fosfodiesterasa mitocondrial (Dr. Steegborn, University of Bochum, Alemania).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **LI , HAN** **Referencia:** RYC-2011-08544

Area: Biomedicina

Correo electrónico: hli@cnio.es

Titulo:

The functional interplay between p27Kip1 and Sox2 in stem cells, develoment and tumorigenesis

Resumen de la Memoria:

Both mouse and human differentiated cells can be reprogrammed to an embryonic-like state, which is called induced pluripotent stem cells (iPS), by simply overexpression of three or four transcription factors. iPS cells can be produced from adult cells of any individual and largely behave like embryonic stem cells (ES): they are capable of self-renewing and forming all tissue types of the body. iPS are considered to be the substitution of ES in both basic research and clinical application in regenerative medicine. Despite their tremendous clinical potentials, little is known about the molecular mechanism of the reprogramming process at the molecular level. Poorly differentiated carcinomas or cancer stem cells have similar gene expression signatures to ES. The observed similarities between stem cell regulation and tumorigenesis in vivo suggested that tumour suppressors genes might play an important role during reprogramming. I have recently shown that the tumour suppressors encoded by Ink4/Arf locus (p16, p15 and ARF) and p53 are a barrier for reprogramming. Importantly, my data also gave rise to some relevant questions: are there any other tumour suppressors important for reprogramming?; why and how are they important for this process?; does the in vitro reprogramming process reflect in vivo tumorigenesis? My research line will focus on two well-known tumour suppressors: p27 and p53, and their respective roles in reprogramming and stemness regulation. It has been implied that cell cycle control is key for stemness maintenance. p27 is a potent tumour suppressor and major regulator of G1 phase. I will further explore the functions of the p53 isoforms in relation to stem cell, cancer and aging in vivo. Cancer results from an inappropriate expression of the programs governing stem cells. In vitro reprogramming processes to a certain extent mimic tumorigenesis. The ultimate goal of my research line is to unveil how tumour suppressors regulate in vitro reprogramming. Obtaining substantial insights into this spectacular process will place us in a position most advantageous and suitable to understand tumorigenesis initiated in vivo. Meanwhile, it is utterly important to dissect reprogramming at the molecular level; otherwise the development in regenerative medicine of risk-free applications of nuclear reprogramming will not be possible.

Resumen del Curriculum Vitae:

PhD and early Postdoctoral Research (2001-2007)I majored in Science from the University of Fudan in Shangai (China) and I obtained my PhD degree in Molecular Medicine from the University of Texas (USA) for research, carried out at the Health Science Center under the supervision of Prof. Paul Hasty, focused on the impact chromatin metabolism has on cancer and aging in genetically altered cells mice using embryonic stem cell/gene targeting technology. The Hasty lab studies proteins important for the repair of DNA double - strand breaks by two different pathways. The first pathway is called recombinational repair by virtue that it utilizes a homologous template usually provided by the sister chromatid. The second pathway is called non-homologous end joining (NHEJ) because it joins chromosomal ends without the use of a homologous template. Peer-reviewed articles- Marple, T., Li, H., Hasty, P. (2004). A Genotoxic Screen: Rapid Analysis of Cellular Dose-Response to a Wide-Range of Agents that either Damage DNA or Alter Genome Maintenance Pathways. Mut. Res. 554:253-266.- Yaneva, M.*, Li, H*., Marple, T., and Hasty, P. (2005) Non-homologous End Joining, But Not Homologous Recombination, Is Important for Cells Exposed to a Histone Deacetylase Inhibitor. Nucleic Acids Res. 33:5320-5330. (*Yaneva, M and Li, H* contribute equally to this paper.)- Li H, Vogel H, Holcomb VB, Gu Y, Hasty P. (2007). Deletion of Ku70, Ku80, or both causes early aging without substantially increased cancer. Mol Cell Biol. 23:8205-8214.- Li H, Mitchell JR, Hasty P. (2008). DNA double-strand breaks: a potential causative factor for mammalian aging?. Mech Ageing Dev. 129:416-424.- Li H, Choi YJ, Hanes MA, Marple T, Vogel H, Hasty P. (2009) Deleting Ku70 is milder than deleting Ku80 in p53-mutant mice and cells. Oncogene 28:1875-1878.Postdoctoral Research at the Tumour Suppressor Group -CNIO- (2007 - present)I joined the Tumour Suppression group headed by Dr. Manuel Serrano at CNIO in November 2007. Under his sponsorship I applied to the 2008 Call of ¿Programa Juan de la Cierva¿ and I was granted a contract to perform research focused on the role of stem cells in cancer and ageing and the impact of tumour suppressors on nuclear reprogramming, cancer and ageing. With a view to secure a more prolonged period of funding I successfully for a postdoctoral research contract from the Spanish Association Against Cancer (AECC) and in September 2010 I took up the said contract. My research during this time resulted in some landmark findings published in high-ranking journals (Nature, two papers; Cell Stem Cell, one paper). My recent achievement place me in a very good position to successfully address and develop the research lines that are the subject of this proposal.Peer-reviewed articles- Li H, Collado M, Villasante A, Strati K, Ortega S, Cañamero M, Blasco MA, Serrano M. (2009). The Ink4/Arf locus is a barrier for iPS cell reprogramming. Nature 460:1136-1139.- Marión RM, Strati K, Li H, Murga M, Blanco R, Ortega S, Fernandez-Capetillo O, Serrano M, Blasco MA. (2009). A p53-mediated DNA damage response limits reprogramming to ensure iPS cell genomic integrity. Nature 460:1149-1153.- Marión RM, Strati K, Li H, Tejera A, Schoeftner S, Ortega S, Serrano M, Blasco MA. (2009). Telomeres acquire embryonic stem cell characteristics in induced pluripotent stem cells. Cell Stem Cell 4:141-1454.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **BUENO UROZ, CLARA** **Referencia:** RYC-2011-08353

Area: Biomedicina

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Titulo:

Impact of MLL-AF4 fusion oncogene and its reciprocal AF4-MLL in human embryonic and somatic stem cell fate

Resumen de la Memoria:

Infant pro-B acute lymphoblastic leukemia (ALL) harbouring the fusion gene MLL-AF4 is associated with dismal prognosis and very brief latency. Several studies have sought to recapitulate human infant pro-B ALL MLL-AF4+ using mouse HSPCs. Unfortunately, however, in vivo leukemias do not faithfully recapitulate the actual human disease and the resultant phenotype/latency differs significantly from that seen in infant ALL. There are several potential reasons for this including: (i) inappropriate cell type is targeted; (ii) expression levels of the fusion gene may not be physiological; (iii) murine systems do not provide appropriate etiological content for essential secondary mutations; (iv) MLL-AF4 transforming ability is dependent upon a human cell context, (v) the reciprocal AF4-MLL fusion encoded protein may be necessary.We have just reported that the controlled lentiviral-mediated expression of MLL-AF4 has a phenotypic and functional impact in human stem cells at two developmental stages: neonatal (Cord Blood-derived CD34+ cells) and prenatal (human ESCs). In CB-CD34+ cells, the enforced expression of MLL-AF4 conveys a selective proliferation coupled to a survival advantage, resulting in an enhanced hematopoietic engraftment and clonogenic potential but is not sufficient for leukemogenesis. In human ESCs, expression of MLL-AF4 augments specification of hemogenic progenitors and skews their hematopoietic-endothelial potential but is not sufficient for leukemogenesis either. These data indicate that the inability to develop a MLL-AF4 infant ALL model is not due to the need of a human cell context or the expression level of MLL-AF4. Rather, it suggests that additional mutations or the AF4-MLL reciprocal product may be required to develop overt ALL. In this regard, Marschalek ¿s laboratory has shown that reciprocal AF4-MLL is sufficient to induce pro-B ALL in mouse stem cells. Besides, □15% of these patients have FLT3 activating mutations. Additionally, it is plausible that MLL-driven leukemias may require very few cooperating mutations as a result of epigenetic alterations that are in part driven by the altered functional activities of the MLL rearrangement. Thus, we propose to undertake 3 objectives devoted to elucidate potential key players contributing to MLL-AF4-mediated transformation and to establish a human-based MLL-AF4 model which is in high demand to understand the etiology and pathogenesis of this dismal infant leukemia and develop new therapeutic strategies:1. To study in vitro and in vivo whether the reciprocal AF4-MLL fusion and FLT3 activating mutations cooperate with MLL-AF4 in transforming CB-derived CD34+ hematopoietic progenitors.2. To study in vitro and in vivo whether the reciprocal AF4-MLL fusion and FLT3 activating mutations cooperate with MLL-AF4 in transforming human ESC-derived hematopoietic progenitors.3. To generate iPSCs from MLL-AF4-harbouring primary leukemic blasts in order to analyze (i) whether cell reprogramming affects the epigenetic alterations driven by the altered functional activities of the MLL rearrangement and (ii) whether the hematopoietic differentiation potential of MLL-AF4-harbouring iPSCs is impaired or skewed.

Resumen del Curriculum Vitae:

PERSONAL INFORMATION:NAME: Clara Bueno (November 9th, 1974)CURRENT POSITION: Research Associate at BACM (Andalusian Health Department)CONTACT INFO: Phone: 00 34 958 894672; E-mail: clara.bueno@juntadeandalucia.esEDUCATION & TRAINING:1992-1997 B. Sc. (Biology). University of Salamanca1997-2002 Ph.D. (Medicine). University of Salamanca (Mentors: Profs. Alberto Orfao and Jesús San Miguel)2002-2005 Post-doctoral Fellow in Quim Madrenas Lab. Immunology Department. Robarts Research Institute, University of Western Ontario, London, ON, Canada.2005-2007 Jose Carreras Trust Fellow. Section of Hemato-Oncology headed by Prof. Mel Greaves. Institute of Cancer Research, London, UK.2007-Present Research Associate at BACM (I.P. Pablo Menéndez), Granada, Spain.PUBLICATIONS:International peer-review publications: 41¿ Corresponding Author: 6 (Blood, Leukemia, Carcinigenesis, etc)¿ First Author: 17 (Leukemia, Immunity, Haematol, Eur J Immunol, etc)¿ Co-author: 18 (J Exp, Med, J Clin Invest, Leukemia, J Immunol, etc)¿ Accumulative Impact Factor: 258¿ H Factor: 13¿ Number of Citations: 424National invited publications: 2Book and Protocol Chapters: 5INVITED LECTURESNational: 14International: 5PATENTS AND TECHNOLOGY TRANSFER: 2 (immunology and stem cell biology)DOCTORAL THESIS SUPERVISION: 1 PhD will defend early 2012.PROFESSIONAL BREAKS: 6 months for maternity childcareLINES OF CURRENT RESEARCH:-Stem cells models for infant MLL-AF4+ and TEL-AML1+ acute lymphoblastic leukemia.-Human ESC and iPSC differentiation towards blood and endothelium.-Optimization of gene therapy strategies and ex vivo expansion of cord blood progenitors.SCIENTIFIC GRANTS (2007-2011): As Principal Investigator:Agency: Fundación Internacional Josep CarrerasReference: FIJC-05Period: 2007-2009Title: Developmental Impact of MLL fusion genes in human stem cell fateFunding: 150.000 USA $Agency: Consejería de Salud de la Junta de AndalucíaReference: TCyMR2006/0029Period: 2007-2009Title: Modelling MLL-AF4 leukemogenesis in human stem cellsFunding: 166.000 EurosAs Collaborator:Agency: Asociación Española Contra el cáncerReference: CI110023MENEPeriod: Awaiting final resolution Title: Infant MLL-AF4 pro-B ALL: towards the elucidation of the cellular and molecular mechanisms underlying MLLAF4-m,ediated transformation in human stem cellsFunding: 150.000 EurosAgency: FIS (ISCIII)Reference: PI10/00449Period: 2010-2012Title: Development of new cellular and molecular strategies for the generation of fully functional hematopoietic and mesenchymal stem cells from hESCs and iPSCs.Funding: 200.860 EurosAgency: Consejería de Economía, Ciencia y Empresa de la Junta de Andalucía.Reference: P08-CTS-3678Period: 2009-2012Title: Stem Cells and Cancer: mechanisms underlying pediatric mesenchymal cancerFunding: 213.600 EurosAgency: MICINN ¿ PLAN EReference: PLE2009-0111Period: 2009-2012Title: Towards the generation of functional hematopoietic stem cells from hESC: lessons from the mouseFunding: 347.000 EurosAgency: FIS (ISCIII)Reference: PI07/0029Period: 2007-2010Title: Development of a model for acute lymphoblastic leukemia pro-B MLL-AF4+ based on the use of human embryonic stem cells and umbilical cord bloodFunding: 80.000 Euros

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **VARELA EGOCHEAGA, IGNACIO ALEJANDRO** **Referencia:** RYC-2011-08320

Area: Biomedicina

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Titulo:

Identification of new tumor genes through the sequencing of cancer genomes.

Resumen de la Memoria:

Cancer is caused by somatically acquired changes in DNA sequence. These changes may be single base substitutions, copy number changes or rearrangements and may also be accompanied by epigenetic changes. Each of these classes of mutation may be "drivers" that confer clonal selective advantage and are therefore found in "cancer genes". Alternatively, these mutations may be "passengers" that have been carried along and have no selective advantage for the cancer cell. Over the last 25 years, there has been considerable progress in the identification of cancer genes altered by all these mechanisms and to date, about 400 genes altered in human cancer have been found (http://www.sanger.ac.uk/genetics/CGP/Census/).The big size of the human genome has made impossible, using traditional sequencing strategies, the complete characterization of somatic alterations present in a single sample, as well as the identification of the driver mutations among the big majority of passenger alterations. Nevertheless, the recent advent of new generation sequence technologies has provided new strategies for the systematic genome-wide identification of somatic mutations. There are several platforms which use massively parallel sequencing to generate high coverage sequencing information covering the whole human genome. During the last years I have contributed to the development of the protocols of experimentation and data analysis needed to identify somatic mutations in human cancer using new generation sequencing technologies, which has helped to the generation of the first complete catalogues of all somatic mutations present in individual cancer samples (Pleasance et al. Nature 463:184, Pleasance et al. Nature 463:191) and the identification of new tumour suppressor gene in renal cancer (Varela et al. Nature 469:539-542). Using this acquired experience and knowledge, I intend to continue using this technology to identify new cancer genes and to unravel the molecular mechanisms involved in the different aspects of human cancer like genetic predisposition, tumour progression, metastasis and development of treatment resistance.

Resumen del Curriculum Vitae:

My predoctoral research was focussed focused in the use of genetically modified mice to investigate the molecular mechanisms involved in human progeria syndromes. Thus, we identified that the accumulation of prenylated forms of lamin A in these illnesses produces alterations in the nuclear envelope and the associated chromatin, generating the constitutive activation of the p53 molecular pathway. This activation is associated with a senescence phenotype affecting specially the stem cells and compromising tissue regeneration. (Varela et al. Nature 437:564-568, Espada et al. 181:27-35). Subsequently we identified the prenylation of accumulated abnormal lamin A precursors as the primary cause of the abnormalities observed in progeria mice as the inactivation of this modification through the combined treatment with statins and aminobisphosphonates reduce dramatically the accelerated aging syndrome observed in the murine model (Varela et al. Nature Medicine 14:767-772).My postodoctoral studies were focussed in the identification of somatic mutations in cancer samples using next generation sequencing technologies. Thus, I participated in the generation of the first complete catalogues of somatic mutations in a cancer sample (Pleasance et al. Nature 463:184-190, Pleasance et al. Nature 463:191-196) which confirmed the potential of this new sequencing technologies for the study of cancer and increased the existing knowledge about the molecular mechanisms involved in the generation and repair of DNA mutations. Additionally, we developed a protocol of low coverage sequencing for the identification of the complete catalogue of genomic rearrangements in cancer samples. We performed this protocol in several samples of human and mouse cancer describing new mechanisms of formation of this rearrangements and identifying new fusion-genes that could be useful as targets for the development of specific antitumoral treatments (Stephens et al. Cell 144:27-40, Campbell et al. Nature 467:1109-1113, Stephens et al. Nature 462:1005-1010, Varela et al. Genome Biol. 11:R100).Finally, we performed a complete sequencing of the human exome in several samples of clear cell renal carcinoma. This project identified the PBRM1 gene recurrently mutated. Subsequently, a posterior analysis of this gene in a collection of around 400 renal cancer samples identified mutations in PBRM1 in more than one third of the cases. This converts PBRM1 in the most prevalently mutated gene in renal cancer of the ones identified in the last 20 years. Additionally, we found PBRM1 mutations in a mouse model of pancreatic cancer which suggest that this gene can be also involved in other types of tumours. Finally, we observed that the inactivation of PBRM1 produces an increase in proliferation and migration in renal carcinoma cell lines. These results encourage further investigation in the potential relevance of PBRM1 mutations in the diagnosis and treatment of patients with renal carcinoma. (Varela et al. Nature 469:539-542).

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CONVOCATORIA 2011

Nombre: **ROXIN , ALEXANDER CHARLES** **Referencia:** RYC-2011-08755

Area: Biomedicina

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Titulo:

Dynamics and cognition in neuronal systems

Resumen de la Memoria:

Computational modelling of the brain has grown from being highly speculative and under-constrained to being an essential tool in elucidating the functional role of neuronal assemblies. Two main approaches are usually taken in modelling studies of the brain: 1- abstract models incorporating essential biological constraints are studied to extract general dynamical principles of brain function and 2- a specific brain function is identified and a model is developed with the necessary level of detail to reproduce this function. I have, and will continue to undertake complementary work along both of these lines. 1- The use of simplified models has greatly improved our understanding of both single cell dynamics and the emergent dynamics in networks of large numbers of recurrently coupled neurons. The applicant envisions numerical and analytical work to explore the role of single-cell dynamics and network topology on the dynamical states of neuronal networks. Such work, while motivated by experimental findings and subject to biological constraints, seeks to provide a more general understanding of network dynamics and excitable media in general. This work requires both analytical and numerical theoretical tools as well as analysis of experimental data in order to confirm the theoretical findings and predictions.2- One of the great end-goals of neuroscience as a whole is to understand human cognition. Along the road to this worthy goal the neuroscience community has targeted simple cognitive tasks as being amenable to experimental study. Examples include simple decision making, and memory-guided tasks. Computational work along these lines attempts to pin down the physiological mechanisms underlying the animals' behavior during these tasks. The applicant intends to extend his work on the dynamics underlying simple perceptual decision making in the parietal cortex of monkeys and push forward his most recent work on memory formation and consolidation in the hippocampus and cortex. This work is directly motivated and constrained by behavioral and electrophysiological data as well as clinical studies in the case of lesion-induced memory impairment in humans.

Resumen del Curriculum Vitae:

Since receiving his PhD in Applied Mathematics at NorthwesternUniversity in 2003, the applicant has done postdoctoral work incomputational neuroscience at top research centers in Europe and theUnited States. While still a student, the applicant, who wasconducting research in fluid dynamics, sought out aninterdisciplinary collaboration with hippocampal electrophysiologistNelson Spruston. The applicant studied the interaction of the twomain excitatory input pathways onto CA1 pyramidal cells throughmorphologically realistic multi-compartmental models. This lead topredictions which were borne out in experiment (1). He subsequentlyreceived a prestigious NSF International Fellowship to work withNicolas Brunel at the CNRS in Paris. There he modelled spontaneousactivity in cortex, and showed that the complex spatio-temporalpatterns of activity which arise in biophysically realistic networkmodelling can, in fact, be captured in a simpler firing rate model.He also developed a model to quantitatively fit data on patterns of cortical up-and down state activity (2). In 2005 he received a Marie Curie Incoming Fellowship to workwith Gustavo Deco at the University Pompeu Fabra. There he studiedthe computational underpinnings of choice behavior in simple,two-choice preceptual decision making tasks. He showed that thedynamics of biophysically plausible networks of spiking neuronsunderlying the activity of parietal circuits implicated in two-choicedecision making behavior could be reduced rigorously to a simple,one-dimensional equation. The reduced equation fits non-human primateand human behavior exceedingly well (3). In 2008 he began work withStefano Fusi at the Center for Theoretical Neuroscience at ColumbiaUniversity in New York. Expaning on Stefano Fusi's earlier work, hedeveloped a model of memory encoding and transfer. The model, inwhich memories are encoded in the strength of recurrent synapticconnections, reproduces the phenomenology of so-called memoryconsolidation, whereby declarative memories are initially encoded inthe hippocampus and subsequently transferred to cortical areas viahigh frequency bursts or "ripples" during synchronous slow-waveactivity. The model allows one to show analytically that a spatiallydistributed consolidation process, such as one finds in the brain, iscomputationally superior to several alternatives in that the memorycapacity is higher. The model also reproduces clinical findings ongraded retrograde amnesia due to lesions of the hippocampus andmedial temporal lobe. A manuscript is currently in preparation. In April of 2010 the applicant began work as a Marie Curie Postdoctoral Fellow (through a training grant) at the Institut d'Investigacions Biomèdiques August Pi i Sunyer in Barcelona with Albert Compte. There, he is involved in implementing his memory consolidation model in a more biologically realistic network model which will include spike-timing dependent plasticity effects.The applicant has published 13 peer-reviewed articles, 10 as first author, most in top journals in their respective fields, with a total of 238 citations. (1) Jarsky*, Roxin* et al., Nat. Neurosci. 2005. (*) authors contributed equally(2) Roxin, Hakim and Brunel, J. Neurosci. 2008.(3) Roxin and Ledberg, PLoS Computational Biology, 2008.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **MEDINA VICO, PEDRO PBLO** **Referencia:** RYC-2011-07766

Area: Biomedicina

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Titulo:

MicroRNAs and SWI/SNF complex in cancer

Resumen de la Memoria:

Gene expression regulation is one of the most fascinating and intricate aspects of biology. MicroRNAs and chromatin structure both play important roles in this process and both have been found to be important in the development of human pathologies including cancer. Hence, they have been the main interests of my scientific career. The SWI/SNF complex is an ATP-dependent chromatin-remodeling complex that is known to regulate gene expression. Increasing evidence demonstrates that some components of the SWI/SNF complex are tumor suppressors and are involved in human cancer development. One subunit of this complex, SNF5, is inactivated in malignant rhabdoid tumors (MRTs) and heterozygous Snf5 knockout mice develop tumors that are histologically similar to human MRT. BRG1, one of the helicase/ATPase catalytic subunits of the SWI/SNF complex, is mutated in cancer cell lines. During my PhD work I discovered that around the 35% of non-small cell lung cancer (NSCLC) samples bear inactivated mutations of BRG1. This percentage of inactivation unveils to BRG1 as one of the most frequently mutated tumor-suppressor genes in lung cancer. However there are still many open questions that I would like to address (see detailed proposal): Is BRG1 expression inactivated by other methods than mutation?, Is BRG1 frequently mutated only in lung cancer? , Which is the primary function of BRG1 as tumor suppressor? MicroRNAs (miRNAs) are a recently discovered class of small RNA molecules that regulate gene expression at the post-transcriptional level. Aberrant biogenesis and/or expression of miRNAs have been linked to human diseases including cancer. Some miRNAs have been shown to affect cellular transformation, carcinogenesis and metastasis acting either as oncogenes or tumor suppressors. Pioneering reports have shown that miRNAs regulate the expression of chromatin remodeling complex proteins (Yoo et al., 2009). , which in turn have been shown to regulate miRNA transcription. During my posdoct I have been studying the role of microRNAs in cancer, with expertise in both fields (miRNAs and chromatin remodeling complexes) I propose to study the regulation of the SWI/SNF chromatin complex members by miRNAs and the biological repercussions of this regulation in the context of cancer (see detailed proposal). The contribution of these studies will shed light on the roles of the SWI/SNF complex and miRNAs in cancer. Ultimately this knowledge in cancer pathology may help us to develop new therapeutic strategies.

Resumen del Curriculum Vitae:

Bachelor degree in Biological Sciences in the University of Granada in 2001. I averaged a perfect GPA (4.00/4.00) in the last three seasons: 98/99, 99/00, 00/01 getting several academics prizes for this achievement. I joined to Lung Cancer Group (PhD advisor: Montse Sanchez-Cespedes) in the Spanish National Cancer Centre in Madrid in 2001. During my PhD studentship, I studied the molecular biology of the Lung tumors working in different projects including: I) The polymorphic variations in DNA repair genes and their relation with tumor susceptibility in human cancer II) The tumor suppressor BRG1: mutational analysis in cell lines and primary tumors, functional analysis and III) The tumor suppressor LKB1: mutational analysis in cell lines and biological function. I was visiting researcher to the worldwide known laboratory of Hans Clevers (Utrecht, The Netherlands). My thesis (Suma cum laude & European doctor Merit) got the prize for the best national thesis from the Royal Academy of Doctors of Spain (season 2006). After my PhD title I was working a year as Postdoctoral Researcher in the Lung Cancer Group (from Spanish National Cancer Centre, CNIO) to work in different projects including: I) Looking for oncogenes activated by amplification in lung cancer II) Genomic alteration and expression patterns in lung tumors and III) SOX4 role in human cancer. I moved to Frank¿s Slack Lab at Yale University funded by Postdoctoral Fellowship from ¿Ministerio de Educación y Ciencia¿ in 2007. I have been involved in several projects, including: I) let-7 microRNA family as tumor suppressor in vivo. II) Inhibition of microRNAs function in cell culture and mouse models. III) microRNAs as oncogenes in vivo.During my scientific career I have authored so far a total of 17 publications in reputed peer-reviewed international journals, including seven first-author original papers (Nature, Human Molecular Genetics (x2), Human mutation, Oncogene, Gene Chromosomes & Cancer, Cancer Epidemiology and Biomarkers) six collaborations and four first-author reviews. I have presented more than 37 communications in international meetings (some of them keynote talks or awarded). I have been recipient of several scientific research prizes, personal fellowships and honors for these achievements (see extended CV).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **RUIZ MACIAS, SERGIO** **Referencia:** RYC-2011-09242

Area: Biomedicina

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Titulo:

CELL CYCLE-DEPENDENT MECHANISMS INVOLVED IN THE MAINTENANCE AND ACQUISITION OF SELF-RENEWAL IN PLURIPOTENT AND TRANSFORMED CELLS.

Resumen de la Memoria:

Human embryonic stem (hES) cells show an atypical cell-cycle regulation characterized by a high proliferation rate and a short G1-phase. It has been suggested that self-renewal and pluripotency are intimately linked to cell-cycle regulation in ES cells although little was known about the overall importance of the cell-cycle machinery in maintaining ES cell identity. An appealing model to address whether the acquisition of stem cell properties are linked to cell-cycle regulation emerged with the ability to generate induced pluripotent stem (iPS) cells by expression of defined transcription factors. In my previous work, we observed that the characteristic cell-cycle signature of hES cells is acquired as an early event in cell reprogramming. We demonstrated that induction of cell proliferation increases reprogramming efficiency whereas cell-cycle arrest inhibits successful reprogramming. Furthermore, we showed that p21-dependent cell cycle-arrest is sufficient to drive hES cells towards irreversible differentiation. Our results established a link that intertwines the mechanisms of cell-cycle control to the mechanisms underlying the acquisition and maintenance of self-renewal and pluripotency in ES cells. Currently, my efforts are focused on understanding the molecular mechanisms of cell cycle regulation in the maintenance and acquisition of self-renewal in pluripotent cells. Epigenetic marks represent a layer of mitotically heritable information contained in the DNA that regulates the expression of the underlying genome sequences. The Polycomb group protein enhancer of Zeste hopmolog 2 (EZH2) is a methyltransferase responsible for histone 3 lysine trimethylation (H3K27me3). H3K27me3 plays an important role in the epigenetic silencing of master genes of differentiation and therefore, in the maintenance of the pluripotent state in ES cells. Recent reports have shown the existence of CDK-dependent phosphorylation of EZH2. This phosphorylation is important for recruitment of EZH2 and maintenance of H3K27me3 levels at EZH2-target loci. Interestingly, preliminary results using my hES cell-based models suggest that the p21-mediated cell cycle arrest in hES cells, which correlates with a decreased CDK activity, induces the up-regulation of master genes of differentiation in the first few days without changes in the expression of pluripotent markers. It is tempting to speculate that cell cycle arrest induces the release of EZH2 from promoters that regulate the expression of genes important to trigger differentiation in a CDK-dependent manner. These studies could be expanded to investigate whether similar mechanisms occur in transformed cells which also self-renew and provide information of new possible therapeutic targets in immortal cells.

Resumen del Curriculum Vitae:

This is a summarized CV (see attached file for complete CV).PERSONAL DATAName: Sergio Ruiz Macías. E-mail: sergioruiz76@gmail.comEDUCATION AND TRAINING:October 2007-Present Postdoctoral fellow with Dr. Juan Carlos Izpisúa BelmonteThe Salk Institute for Biological StudiesLa Jolla, CA, USA.October 2004-September 2007Postdoctoral fellow with Dr. Xosé R. García BusteloCentro de Investigación del CáncerSalamanca, SpainJuly 1999-June 2004 Ph.D., Summa cum LaudeDepartment of Biochemistry and Molecular BiologyUniversity Complutense, Madrid, SpainAdvisors: Dr. José Luis Jorcano Noval and Dr. Jesús Mª Paramio González1994-1999 Licenciado in Biological SciencesUniversity Complutense, Madrid, SpainMOST RELEVANT PUBLICATIONS:¿ Liu, G.H., Barkho, B., Ruiz, S., Diep, D., Qu, J., Yang, S.L., Panopoulos, A.D., Suzuki, K., Kurian, L., Walsh, C., Thompson, J., Boue, S., Fung, H.L., Sancho-Martinez, I., Zhang, K., John Yates III, Izpisua-Belmonte, J.C. (2011) Recapitulation of human premature aging by using iPSCs from Hutchinson-Gilford progeria syndrome. Nature, in press.¿ Gore, A., Li, Z., Fung, H.L., Young, J., Agarwal, S., Antosiewicz-Bourget, J., Canto, I., Giorgetti, A., Israel, M., Kiskinis, E., Lee, J.H., Loh, Y.H., Manos, P.D., Montserrat, N., Panopoulos, A.D., Ruiz, S., Wilbert, M., Yu, Y., Kirkness, E., Izpisua Belmonte, J.C., Rossi, D., Thomson, J., Eggan, K., Daley, G.Q., Goldstein, L.S.B. and Zhang, K. (2011) Somatic coding mutations in induced pluripotent stem cells. Nature, in press.¿ Ruiz, S., Panopoulos, A.D., Herrerías, A., Bissig, K.D., Lutz, M., Berggren, W.T., Verma, I. and Izpisua Belmonte, J.C. (2011) A high proliferation rate is required for somatic cell reprogramming and maintenance of human embryonic stem cell identity. Current Biology, 21: 45-52.¿ Ruiz, S., Brennand, K., Panopoulos, A.D., Herrerías, A., Gage, F.H. and Izpisua Belmonte, J.C. (2010) High efficient generation of induced pluripotent stem cells from astrocytes. Plos One, 5-12: 1-9. ¿ Ruiz, S., Santos, E. and Bustelo, X.R. (2007) RasGRF2, a guanosine nucleotide exchange factor for Ras GTPases, participates in T-cell signaling responses. Mol Cell Biol, 27: 8127-42.¿ Ruiz, S., Santos, M., Lara, M.F., Segrelles, C., Ballestin, C. and Paramio, J.M. (2005) Unexpected roles of pRb in mouse skin carcinogenesis. Cancer Res, 65: 9678-86.¿ Ruiz, S., Santos, M., Segrelles, C., Leis, H., Jorcano, J.L., Berns, A., Paramio, J.M. and Vooijs, M. (2004) Unique and overlapping functions of Rb and p107 in the control of proliferation and differentiation in epidermis. Development, 131: 2737-48.¿ Ruiz, S., Segrelles, C., Bravo, A., Santos, M., Perez, P., Leis, H., Jorcano, J.L. and Paramio, J.M. (2003) Abnormal epidermal differentiation and impaired epithelial-mesenchymal tissue interactions in mice lacking the retinoblastoma relatives p107 and p130. Development 130: 2341-53.PATENTS:INVENTORS: Xosé Ramón García Bustelo, Sergio Ruiz Macías and Eugenio Santos de Dios.TITLE: Modelos animales y células derivadas para su uso en la determinación de compuestos útiles en el tratamiento de linfomas de células T.APPLICATION FORM No: Publication number:2 341 213 File number: 200803543PRIORITY COUNTRY: Spain PRIORITY DATE: Filing date: 12/15/2008; Publication date: 6/16/2010

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **ALBERICH JORDA, MERITXELL** **Referencia:** RYC-2011-08940

Area: Biomedicina

Correo electrónico: malberi@bidmc.harvard.edu

Titulo:

Function of the transcription factor C/EBPg in hematopoiesis and leukemia

Resumen de la Memoria:

La leucemia mieloide aguda (LMA) es una enfermedad hematopoyética maligna que representa el 90% de las leucemias agudas en adultos, y se caracteriza por una acumulación de células sanguíneas inmaduras y no funcionales en la medula ósea y en la sangre. Un factor de transcripción esencial para la diferenciación mieloide es CCAAT/enhancer binding protein alpha (C/EBPa), el cual está afectado en un 10% de pacientes con LMA. El gen C/EBPa está situado en el cromosoma 19, y 70 kb upstream se encuentra otro miembro de la misma familia, C/EBPg. Se ha observado que C/EBPg actúa como un inhibidor dominante negativo de otros factores de transcripción, y aunque su función se ha descrito parcialmente en eritrocitos y en el linaje linfoide, poco se sabe sobre su papel en la diferenciación mieloide. Recientemente hemos observado que un subgrupo de LMA con defectos en C/EBPa presenta sobreexpresión de C/EBPg. A nivel clínico esta sobreexpresión coincide con un pronóstico desfavorable, y mi hipótesis es que altos niveles de C/EBPg contribuyen al desarrollo de LMA y están relacionados con un peor pronóstico. Datos preliminares demuestran que este cambio en los niveles de expresión de C/EBPg también está presente en células madre hematopoyéticas (HSC) de ratones knockout condicionales de C/EBPa. Hemos estudiado el patrón de expresión normal de C/EBPg en diferentes poblaciones hematopoyéticas de murinos, y observamos altos niveles de C/EBPg en las HSC de larga vida, y bajos niveles durante la diferenciación celular. En base a estas observaciones propongo investigar la función de C/EBPg en el mantenimiento de las HSC y en el desarrollo de la LMA. Para conseguir este objetivo 1) sobreexpresaremos y silenciaremos C/EBPg en líneas celulares hematopoyéticas para realizar experimentos in vitro de proliferación y diferenciación, y 2) estudiaremos dos modelos murinos que hemos generado: un ratón transgénico C/EBPg Tet inducible, y un ratón knockout condicional para C/EBPg. El trabajo aquí propuesto desvelará la importancia de C/EBPg en HSC y en células mieloides, y su relación con la LMA, abriendo las puertas a nuevas dianas terapéuticas para esta enfermedad.

Resumen del Curriculum Vitae:

Me licencié en biología por la Universidad de Barcelona (1994-1999), y durante el último año me trasladé al instituto IMP en Leiden (Holanda) con una beca Erasmus. El interés por la biomedicina me llevó; a cursar los estudios predoctorales en el Departamento de Hematología de la ErasmusMC, Universidad de Róterdam, Holanda (1999-2004). El título de mi tesis es ¿The peripheral cannabinoid receptor Cb2 in leukemia¿ y mis mentores fueron los Prof. B. Löwenberg y R. Delwel. El objetivo de este proyecto era estudiar la función de Cb2 en hematopoyesis e investigar la relación de esta proteína con en el desarrollo de la leucemia mieloide aguda. Este trabajo se publicó en 3 diferentes artículos en la revista Blood, donde mi participación se refleja con la primera posición de autoría (2002 15;99(8), 2003 15;101(4), 2004 104(2). Nuestras observaciones fueron destacadas en un comentario en esta misma revista y en relación con mi tema de investigación escribí una revisión (2003 Ann.N.Y.Acad.Sci. 996). Durante mi periodo predoctoral participé en el estudio y caracterización del modelo murino transgénico pSca-1/Cb2 y publicamos la predisposición leucémica de dicho modelo animal en Experimental Hematology (2002, 30). Además de las publicaciones derivadas de mi investigación, mi trabajo contribuyó a la obtención de una beca subvencionada por la fundación KNAW (2004-2009) en Holanda. Mi interés en la hematología, la leucemia mieloide y la biología de las células madre hematopoyéticas me llevó a realizar mi investigación posdoctoral bajo la dirección del Prof. D. Tenen en la Universidad de Harvard, en el Departamento de Hematología/Oncología del hospital BIDMC, Boston (2005-actualidad). Durante mi investigación posdoctoral, inicialmente subvencionada por una beca de la European Hematology Association (EHA), he contribuido a varios proyectos, siete de ellos publicados en revistas internacionales (4 en Blood, Genes and Development, Development and Journal Biol Chem), y seis de ellos actualmente bajo revisión (Nature Medicine, Nature Neuroscience, Cell, JCI y Journal Exp Hemat). Como primera co-autora he de destacar el estudio publicado en Blood, donde identificamos, aislamos y caracterizamos la célula cancerígena madre en la leucemia promielocítica mediante una nueva estrategia con citometría de flujo en modelos animales. Recientemente, también como primera co-autora en Blood, hemos publicado un artículo en el cual estudiamos los efectos de los cannabinoides en la hematopoyesis y en la movilización de células hematopoyéticas madre. En estos estudios, técnicas experimentales in vitro e in vivo, incluyendo transplantes de médula ósea en murinos, son llevadas a cabo. En otro artículo a destacar, actualmente bajo revisión en Nature Medicine y donde mi participación se refleja con la primera posición de autoría, estudiamos los factores de transcripción C/EBPa y C/EBPg en el desarrollo de leucemia. Paralelamente a mis proyectos de investigación colaboro con BIDMC y Harvard Stem Cell flow cytometry facilities, y en 2005-2008 formé parte del comité científico organizador de los congresos internacionales de la EHA. También he realizado tareas docentes en el laboratorio junto con la supervisión de estudiantes de medicina en sus proyectos.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **RODA NAVARRO, PEDRO** **Referencia:** RYC-2011-08664

Area: Biomedicina

Correo electrónico: rodanava@mpi-dortmund.mpg.de

Titulo:

Coordinated function of protein tyrosine phosphatases in cancer-related inflammation

Resumen de la Memoria:

Intracellular signalling operates in networks of biochemical reactions catalyzed and regulated by multiple molecular components. Extracellular stimuli induce posttranslational modifications (PTMs) that change the molecular/activation state of these components whose concerted activities reconfigure the signalling network to specify the cellular phenotype. Identify these components and probe their coordinated function in the living cell, the natural environment where they are under tightly spatial and temporal regulation, are still major challenges to predict cell fate decisions. Tyrosine phosphorylation plays a central role in signalling networks that specify the activation of leucocytes and tumour progression. Physiological levels of this reversible PTM are maintained by protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). Coordinated functions and regulatory mechanisms of PTPs have not been fully established yet, although functional disturbances of certain PTPs have been associated with cancer and chronic inflammation. The complexity arrives from the fact that the human genome encodes a large, structurally diverse family of PTPs, and certain cell types, like for example lymphocytes, express large PTP subsets. Thus, the motivation of this research proposal is to investigate the coordinated function of PTPs during leukocyte activation and tumour progression in cancer-related inflammation. More precisely, I propose two research lines: 1. Systematic screening of PTP gene function during leukocyte activation (1a) and tumour progression in response to cytokines (1b). This functional genomic discovery program will identify molecular components of signalling networks that regulate key cell functions for the pathogenesis of cancer and inflammation.2. Studying the molecular mechanisms that regulate the function of PTPs, including their intracellular dynamics. Quantitative fluorescence biosensors will be used with micro-spectroscopy techniques for measuring the molecular/activation state of PTPs in living cells. This approach, in combination with functional genomics, will allow determining the causality in the network.

Resumen del Curriculum Vitae:

My research career is backed up by a total of 23 peer-reviewed publications with an h-index of 10. The most outstanding publications have been obtained in research lines developed as postdoctoral researcher in prestigious European research institutions, like the University of Cambridge (UK) and the Max Planck society (Germany). I demonstrated research leadership in some of these research lines. Steps of my career are briefly explained:PhD. I did my PhD (January 2003) under the supervision of Dr. Elena Fernández-Ruiz (Molecular Biology Unit, ¿Hospital de la Princesa, Madrid, Spain¿), and funded by a fellowship of ¿Comunidad Autónoma de Madrid¿. In collaboration with Dr. Raju Kucherlapati (Yeshiva University, USA), we generated a high-resolution physical map of the natural killer (NK) gene complex (NKC) on the human chromosome 12 (Genomics, 2000). Genomic clones spanning the NKC were sequence by the human genome project. The main aim of our group was the identification and molecular characterization of new genes coding for lectin-like receptors. We obtained several publications among which I was first author in two (Roda-Navarro et al. Eur J Immunol, 2000 and Roda-Navarro et al. BBA, 2001). In 2002 I did a short stay at Dr. José María Casanovas¿s group (Karolinska Institute, Sweden), where we uncovered the functional significance of N-glycans in the lectin DC-SIGN (J Biol Chem 2005). Postdoctoral research.From January 2003 to May 2004, in collaboration with Dr. Francisco Sánchez-Madrid (¿Hospital de la Princesa¿), we studied the organization of the cytotoxic NK cell immune synapse (cNK-IS) (Roda-Navarro et al. J Immunol, 2004). We also contributed a review about NK cell biology to the journal Medicine (Roda-Navarro and Fernandez-Ruiz, 2005), an education program in medicine accredited by the Spanish national health system.From June 2004 to December 2006 I held a research associate position at the Dr. Hugh Reyburn¿s group (Department of Pathology, University of Cambridge, UK). Here, I was funded by a Spanish fellowship of the ¿Ministerio de Educación y Ciencia¿ and a full contract of the University. During this time I continued the research devised in Madrid about the cNK-IS. We designed an interdisciplinary research, which allowed me to share senior authorship with Dr. Reyburn in different publications (Roda-Navarro et al. PNAS 2006; Roda-Navarro and Reyburn FASEB J, 2007; and Roda-Navarro and Reyburn J Biol Chem 2009). Moreover, I was invited to write a review about the NK-IS (Roda-Navarro Front Biosci, 2009) and to edit an issue about the biology of NK cells in the Encyclopaedia of Biosciences organized by this journal.In January 2007 I moved to Proff. Dr. Philippe Bastiaens¿s group (Department of Systemic Cell Biology, Max Planck Institute of Molecular Physiology, Dortmund, Germany). Here, I¿ve been funded by several full contracts of the Max Planck Society and by a Marie Curie grant for career development of the European Union. Our research combines functional genomics and micro-spectroscopy techniques in order to characterize tyrosine phosphorylation networks that regulate the signalling by receptor tyrosine kinases. I am first equal contributor in two publications derived from this project (Nature Methods, 2010 and Methods in Enzymology, 2011 In press). The former has been evaluated as recommended in the Faculty of 1000 (FFa6).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **COZAR CASTELLANO, IRENE** **Referencia:** RYC-2011-08101

Area: Biomedicina

Correo electrónico: cozarirene@gmail.com

Titulo:

Role of beta-cell proliferation in the pathophysiology of insulin resistance and type 2 diabetes.

Resumen de la Memoria:

Diabetes has been declared the XXI century epidemic. It is estimated that its prevalence in Spain is 10-14%, which represents 15-20% of the total budget dedicated to Health Care. Therefore, it is urgent to define the factors contributing to diabetes onset and severity, and to identify new potential therapeutic approaches to prevent and treat diabetes and its complications.Type 2 diabetes develops through a multi-stage process. First, the body becomes unable to use insulin effectively, a condition known as insulin resistance. Then, the pancreatic beta-cells try to compensate secreting more insulin and maintaining normoglycemia. Eventually, beta-cells fail to produce enough insulin to overcome insulin resistance. This condition frequently progresses to diabetes. Two factors can contribute to beta-cell failure, decreased beta-cell mass and impaired beta-cell function.Others and I have shown that beta-cells can replicate by a variety of maneuvers (for decades it was accepted that beta-cells were terminally differentiated and unable to replicate), and that beta-cell replication plays a quantitatively significant role in maintaining adult pancreatic beta-cell mass and function. Our main research line is to determine the role of beta-cell proliferation in the pathophysiology of insulin resistance and type 2 diabetes:1) Identification of the molecular mechanisms that lead to impaired beta-cell proliferation in the pathophysiology of type 2 diabetes.2) Therapeutic role of beta-cell proliferation in the prevention and treatment of type 2 diabetes.3) Search for small molecules that induce beta-cell proliferation. (In collaboration with ¿Instituto de Productos Naturales y Agrobiologia-CSIC¿, La Laguna, Tenerife)Our working hypothesis is that in the transition from insulin resistance to diabetes, specific inhibitors involved in cell cycle control are upregulated in beta cells. This induces the cells to enter in quiescence preventing cell replication and eventually cell death. We hypothesize that maintaining compensatory beta-cell proliferation will prevent decreased insulin secretion and subsequent debut of diabetes.I have set up my independent lab, having two PhD students dedicated to the development of this research line; furthermore, we count with funding to develop this investigation (ISCIII, SAS and IRG-Marie Curie-FP7).

Resumen del Curriculum Vitae:

Undergraduate (1991-96): School of Chemistry, Univ. of La Laguna; and Biochemistry, Univ. of Salamanca.Graduate (1996-01): Department of Biochemistry, Univ. of La Laguna. I published one paper as first author (1).Postdoctoral training (2002-07): Dr. Andrew F. Stewart¿s lab, Division of Endocrinology, Univ. of Pittsburgh. 2007-09: Instructor of Medicine, Div. of Endocrinology, Univ. of Pittsburgh.From 2002-09 in Stewart¿s lab, I studied the cell cycle control in the pancreatic beta-cell. I published as first author four papers (2-5). I also published a revision in Endocrine Reviews (impact factor 22) (6). At the Univ. of Pittsburgh I established prolific collaborations which resulted in high quality publications (7-12).In 2009, I returned to Spain through the Miguel Servet Program (ISCIII) and since then, I am an independent researcher at the Research Unit of the ¿Puerta del Mar University Hospital¿ (Cádiz). I am the principal investigator of four funded projects (ISCIII, SAS and IRG Marie Curie Program FP7).(1) Cozar-Castellano et al. hIscA: a protein implicated in the biogenesis of iron-sulfur clusters. Biochim Biophys Acta. 1700:179-88. 2004.(2) Cozar-Castellano et al.Induction of Beta cell proliferation and retinoblastoma protein phosphorylation in rat and human islets using adenovirus-mediated transfer of cdk-4 and cyclin D1. Diabetes. 53:149-59. 2004.(3) Cozar-Castellano et al. Evaluation of Beta Cell Replication in Mice Transgenic for Both Hepatocyte Growth Factor and Placental Lactogen: Comprehensive Characterization of theG1/S Regulatory Proteins Reveals Unique involvement of p21. Diabetes 55:70-7.2006. (4) Cozar-Castellano et al. The Cell Cycle Inhibitory Protein, p21, is Not Essential for Maintaining Beta Cell Cycle Arrest or Beta Cell Function in Vivo. Diabetes 55: 3271-8. 2006.(5) Cozar-Castellano et al. Lessons from the first comprehensive molecular characterization of cell cycle control in rodent insulinoma cell lines. Diabetes 57:3056-68. 2008(6) Cozar-Castellano et al. Control of Cell Cycle Progression in the Pancreatic Beta Cell. Endoc. Rev. 27:356-70. 2006.(7) Lopez-Talavera et al. Hepatocyte growth factor gene therapy for pancreatic islets in diabetes: Reducing the minimal islet transplant mass required in a glucocorticoid-free rat model of allogeneic portal vein islet transplantation. Endocrinology. 145:467-74. 2004.(8) Fiaschi-Taesch et al. The Cellular Mechanism Which PTHrP Induces Proliferation in Arterial Smooth Muscle Cells: Definition of an Areterial Smooth Muscle PTHrP-p27 Axis. Circulation Research. 27;99:933-42. 2006(9) Vasavada et al. Tissue-specific deletion of the retinoblastoma protein: pRb is non-essential for maintaining beta cell arrest. Diabetes 56:57-64. 2007(10) Fiaschi-Taesch et al. Mutant Parathyroid Hormone-Related Protein, Devoid of the Nuclear Localization Signal, Markedly Inhibits Arterial Smooth Muscle Cell Cycle and Neointima Formation By Coordinate Upregulation of p15 and p27. Endocrinology 150:1429-39.2009(11) Fiaschi-Taesch et al. Survey of the Human Pancreatic Beta Cell G1/S Proteome Reveals a Potential Therapeutic Role for Cdk-6 and and Cyclin D1 in Enhancing Human Beta Cell Replication and Function in Vivo. Diabetes: 58:882-93. 2009(12) Fiaschi-Taesch et al. Induction of human b-cell proliferation and engraftment using a single G1/S regulatory molecule, cdk6.Diabetes:59:1926-36. 2010.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **BAYES PUIG, ALEJANDRO** **Referencia:** RYC-2011-08391

Area: Biomedicina

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Titulo:

Proteomic and Bioinformatic Studies of Synaptic Function in the Context of Human Mental and Behavioural Disorders.

Resumen de la Memoria:

Synapses of the central nervous system are the cellular structures mediating communication between neurons. Moreover, it is well accepted that synapses are key to the long-term neuronal changes underlying cognition and behaviour. Mouse mutations studies on synaptic proteins have shown how these molecules ultimately modulate animal cognition and behaviour. As in any other biological system, disruption of the normal molecular mechanisms within the synapse leads to disease and there is a growing body of data suggesting the central role of the synapse in neurodegenerative and mental and behavioural disorders.The line of research proposed aims at better understanding, at a molecular level, the physiological and pathological processes governed by the mammalian synapse, with particular attention on the proteins present in postsynaptic structures. The project will use human tissue and genetically modified mouse models of human mental and behavioural disorders (i.e. schizophrenia, mental retardation or mood disorders) to better understand the underlying molecular pathology of these diseases, and to deepen our basic knowledge of synaptic molecular biology. Most genetically modified animals have well-established cellular, behavioural and electrophysiological phenotypes, but the underlying molecular alterations are, in many cases, poorly understood. This project aims at filling this knowledge gap. Special attention will be given to cognitive disorders that have a well-established genetic cause, like nonsyndromic forms of mental retardations, particularly those caused by synaptic proteins (i e. GRIA3, GRIK2, SYNGAP1, SAP102 or CASK). Nevertheless, the study of psychiatric diseases, such as schizophrenia or autism, with a less well understood genetic background, will also be of importance to the project.The notion of proteins being elements of supra-molecular structures working in a coordinated fashion drives the experimental approach of the project. The objectives of this project will be addressed through the use of systems biology tools; particularly proteomics and bioinformatics. The synapse and the structures within (synaptic vesicles or postsynaptic density) can be biochemically isolated and are particularly amenable to proteomics tools since their number of components is in the range of the few thousands, a protein load which is within the resolution of actual proteomic methods.

Resumen del Curriculum Vitae:

My research career started during my bachelor's degree at the department of Biochemistry and Molecular Biology (Universitat Autònoma de Barcelona, UAB) where I then stayed for my Master (Biotechnology) and Ph.D. (Biochemistry) degrees. During this period I worked with two enzymes from the same family, one sensitive to natural inhibitors and an insensitive one. By comparing their structures I could see how the protein had changed to become insensitive to inhibitors. This project was done in collaboration with two laboratories, that of Dr. Jongsma in The Netherlands and that of the Nobel laureate Prof. Huber in Munich Germany. These stays were possible thanks to the awarding of several fellowships including a FEBS short-term fellowship. This research led to 3 first author publications, including a PNAS paper and a J Mol Biol as second author. In my Ph.D. I also worked with the human kallikrein-6, a protease with a role in cancer metastasis. Functional and structural studies allowed us to propose a new activation/inactivation mechanism of general applicability for the kallikrein family. This project produced two publications a first author paper and a second author (JBC) publication.After a short postdoc between the UAB and the laboratory of Dr FX Gomis-Rüth (IBMB-CSIC), from which I published the 3D structure of a protease-product complex, I moved to Prof. Seth Grant laboratory at The Wellcome Trust Sanger Institute (Cambridge, UK). Since then I've been working on the molecular biology of the synapse. During my postdoctoral stay I was awarded with an EMBO Long-Term Postdoctoral Fellowship and a Marie Curie Intra-European Fellowship, which together have funded four years of my research. Our main focus at the Grant laboratory has been the molecular study of the physiological and pathological processes governed by the synapse, particularly by the postsynaptic density (PSD). Our methodological approach is quite pioneer in the field of Neurosciences. We use systems biology tools, mainly proteomics and bioinformatics, an approach outlined in a review on neuroproteomics: Bayés A and Grant SG Nature Reviews Neurosciences Sep 2009. During my postdoctoral stay I have been involved in two projects: 1) the evolution of the synaptic proteome and 2) the characterization of the human cortical PSD and its role in disease. These have produced two papers: Emes RD et al. Nat Neurosci. Jul 2008 and Bayés A et al. Nat Neurosci. Jan 2011. Our findings show that there has been an increase in the molecular complexity of the postsynaptic proteome throughout animal evolution. We have also proven that within mammals the genes that constitute the PSD have been under a very strong evolutionary constraint. We have shown that the genes in the PSD are the most evolutionary conserved of the genes expressed in human neurons. We have also found that PSD genes cause more than 130 mendeleian neural diseases, that the human PSD is a neuronal structure with a disproportionately high neural disease susceptibility. Nevertheless, the PSD is relevant to some types of diseases, particularly cognitive and motor dysfunctions. Altogether I have 13 papers published or accepted for publication. According to ISI web of knowledge I have an average rate of citations per paper of 17-45 and an h-index of 8. I have also presented 14 posters and given 4 talks in international congresses.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **RICHLY , HOLGER** **Referencia:** RYC-2011-08098

Area: Biomedicina

Correo electrónico: holger.richly@crg.es

Titulo:

Molecular Epigenetics

Resumen de la Memoria:

A central question for the eukaryotic cell consists of the regulation of specific transcriptional programs. Cellular differentiation is subject to such a defined program and earmarked by a dramatic change in the epigenetic landscape. The deletion and writing of specific epigenetic modifications leads to a different pattern of gene expression and subsequently gives rise to diverse kinds of differentiated cells. Epigenetic factors involved in silencing and activation of genes as well as the occurrence of certain histone-tail modifications and methylation of DNA at CpG islands during differentiation have been studied in great detail in the last couple of years. Major progress in the understanding of cellular differentiation has been made dissecting the so-called Polycomb pathway. The molecular mechanism forming the basis of this pathway is comprised of at least two distinctive protein complexes, the Polycomb Repressive Complexes 1 and 2 (PRC1 and PRC2), that carry out successive enzymatic reactions. Firstly, PRC2 brings about the specific tri-methylation of histone 3 at lysine 27 (H3K27me3), which is thought to recruit PRC1 by binding one of its subunits. The last mentioned complex consecutively catalyzes the mono-ubiquitination of histone H2A at lysine 119 (H2Aub). More importantly are Polycomb proteins often found misregulated in cancer cells and so-called cancer stem cells. Especially the PRC1 subunit Bmi-1 has been shown to be a crucial player in the maintenance of self-renewal abilities of cancer stem. An understanding of the mechanisms underlying the differentiation or self-renewal abilities of stem cells and cancer stem cells is today one of the greatest challenges in cancer research and developmental biology. In order to achieve this aim molecular epigenetics are a very powerful tool. The purification of the histone H2A-ubiquitin binding protein ZRF1 and the discovery of its molecular action, as explained in more detail in the project proposal, provides a new insight into how eukaryotic cells mechanistically switch genes from a silenced to an activated state at the onset of cellular differentiation (Richly et al., 2010). The protein not only directs cell fate decisions during development and differentiation but has also been implicated in various cancers and can be regarded a major player at the crossroads of cancer, stem cell biology and development. The future research directions involve therefore partially the function of ZRF1 in stem cell biology, cancer and developmental processes. Molecular epigenetics are hence a very powerful tool that can be applied to cellular systems that involve a change in the gene expression pattern. Besides cellular differentiation the process of ageing will be of a great importance in the future. So far ageing research has mainly focussed on signalling pathways, as for example the insulin receptor pathway, that lead to a different pattern of gene expression and typical ageing phenotypes. However, the molecular mechanisms at the level of chromatin are not understood and it remains elusive which epigenetic marks cause the altered expression pattern in ageing cells or organisms, respectively. Another project will therefore be dedicated to elucidate the changes of the epigenetic landscape during ageing.

Resumen del Curriculum Vitae:

Curriculum VitaeName: Dr. Holger RichlyDate of birth: May 23rd 1974Place of birth: Willich, GermanySpoken languages: German, English, Spanish Current address: c/Mallorca 442, 6-208013 BarcelonaSpainTel: 0034-662341480Email: holger.richly@crg.esWorking place: Center for Genomic RegulationProgramme of Differentiation and Cancer08003 BarcelonaScientific Education:1995 -2000: Studies in Biochemistry at the Ruhr-Universität Bochum1998: ¿Vordiplom" in Biochemistry 2000: Degree in Biochemistry with Honours Diploma work with Prof. Benecke on the Function of a U6-snRNA specific Terminal Uridylyl Transferase2000 ¿ 2005: Graduate Studies with Prof. Stefan Jentsch at the Max-Planck-Institut of Biochemistry in Martinsried2005: PhD at the Ludwig-Maximilians Universität in Munich PhD-Thesis on the Function of CDC48 and Ubiquitin-binding proteins in Proteasomal Degradation 2005 ¿ present: Postdoctoral Fellow at the Center for Genomic Regulation with Dr. Luciano di CroceFellowships: FEBS-longtime FellowHonours and Prizes 1997 Gerd und Ruth Massenberg Prize2000 Prize of the Faculty of Chemistry (Best-of-the-year award)2001 ¿Preise für Studierende¿(Prize for diploma work)PublicationsRape M., Hoppe T., Gorr I., Kalocay M., Richly H., Jentsch S.Mobilization of processed, membrane-tethered SPT23 transcription factor by CDC48 (UFD1/NPL4), a ubiquitin-selective chaperone. Cell. 2001 Nov 30; 107(5): 667-77Trippe, R., Richly H., Benecke, B.J.Biochemical characterization of a U6 small nuclear RNA-specific terminal uridylyltransferaseEur J Biochem. 2003 Mar; 270(5): 971-80Schuberth C., Richly H., Rumpf S., Buchberger A.Shp1 and Ubx2 are adaptors of Cdc48 involved in ubiquitin-dependent protein degradationEMBO Rep. 2004 Aug; 5(8): 818-24.Richly H., Rape M., Braun S., Rumpf S., Hoege C., Jentsch S.A series of ubiquitin binding factors connects CDC48/p97 to substrate multiubiquitylation and proteasomal targetingCell. 2005 Jan 14;120(1):73-84Richly H., Lange M., Simboeck E., Di Croce L.Setting and resetting of epigenetic marks in malignant transformation and developmentBioEssays Volume 32, Issue 8, pages 669¿679, August 2010Richly H., Rocha-Viegas L., Ribeiro Domingues J., Demajo S., Gundem G., Lopez-Bigas N., Nakagawa T., Ito T., Rospert S., Di Croce L. (2010) Transcriptional Activation of Polycomb-repressed genes by ZRF1.Nature. 2010 Dec 23; 468 (7327): 1124-8.Holger Richly and Luciano Di CroceThe flip side of the coin: role of ZRF1 and histone H2A ubiquitination in transcriptional activationCell Cycle (2011) in pressContact details for three academic referencesProf. Dr. Stefan JentschDepartment of Molecular Cell Biology Max-Planck-Institut for BiochemistryAm Klopferspitz 18a82152 München/MartinsriedGermanyEmail: jentsch@biochem.mpg.deProf. Dr. Peter BeckerAdolf-Butenandt InstitutLudwig-Maximilians-Universität München (LMU)Schillerstr. 3380336 MünchenGermanyEmail: pbecker@med.uni-muenchen.deDr. Luciano di CroceCenter for Genomic RegulationC/ Dr. Aiguader, 8808003 BarcelonaSpainEmail: luciano.dicroce@crg.es

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **BERTONCINI , CARLOS WALTER** **Referencia:** RYC-2011-07873

Area: Biomedicina

Correo electrónico: carlos.bertoncini@irbbarcelona.org

Titulo:

DEVELOPMENT OF DRUG DISCOVERY STRATEGIES THAT TARGET AMYLOIDOGENIC INTRINSICALLY DISORDERED PROTEINS CAUSING NEURODEGENERATION IN PARKINSON¿S AND ALZHEIMER¿S DISEASES

Resumen de la Memoria:

A significant number of neurodegenerative disorders, including Alzheimer¿s (AD) and Parkinson¿s (PD) are intimately associated with the misfolding, self-assembly and aggregation of Intrinsically Disordered Proteins (IDPs) in the form of amyloid fibrils. Aggregation of the IDP alpha-Synuclein in the form of Lewy bodies is a hallmark of PD. Likewise, aggregation of the IDP Abeta peptide in the form of amyloid plaques characterizes patients with AD. An attractive approach to counteracting the tendencies for proteins to aggregate is to stabilize their native state by the means of small-molecule compounds, however, the structure-based rational design of small molecule ligands for IDPs has been so far a challenge. The conformational space natively populated by IDPs could only recently be characterized at high resolution employing NMR and computational tools. Instead of a single structure, IDPs populate an ensemble of structures, which is more accurately represented by hundreds of structures that, on average, fulfill all the NMR derived data. I propose to generate high-resolution structural ensembles of two amyloidogenic IDPs involved in neurodegenerative disorders, namely alpha-Synuclein and Abeta peptide, and to subject such ensembles to structure-based in silico screening methods, with the aim of discovering novel small molecule scaffolds that could stabilize the native state of these IDPs and counteract protein aggregation. In silico hits will be validated by a suite of in vitro and in vivo methodologies, and promising candidates will be subjected to hit to lead optimization strategies.I have applied such NMR methodologies and structure calculation protocols to characterize a low resolution structural ensemble of the IDP alpha-Synuclein during my PhD thesis, and during my postdoc have subjected this ensemble to in silico docking strategies. Docking results with known ligands of the protein fit very well with the binding regions probed by NMR, suggesting that in silico screening methods on a higher resolution structural ensemble could be highly successful. During my postdoc I also developed the NMR screening methodology as well as the in vitro and in vivo microscopy-based fluorescent assays that I plan to utilize in the validation of in silico hitsThis proposal embodies the first high resolution structure-based rational drug discovery approach targeting IDPs. Accomplishment of the present proposal will deliver a combination of basic science results and applied science results of high biomedical relevance. I expect to deliver the highest resolution structural ensemble up to date of two biomedically relevant IDPs, as well as novel protocols for performing docking on IDPs. Moreover, the identified small molecule ligands will be highly appealing to pharmaceutical companies that could further develop the lead compounds into pharmaceutically viable drugs.

Resumen del Curriculum Vitae:

Doctor en Ciencias Naturales por la Universidad de Göttingen, Alemania, con un trabajo doctoral realizado en el Departament of NMR-based Structural Biology del Max Planck Institute for Biophysical Chemistry bajo la dirección del Prof. Christian Griesinger (2002-2005). Investigador Postdoctoral en el Departament of Molecular Biology del Max Planck Institute for Biophysical Chemistry, Alemania, bajo la tutela del Prof. Thomas M. Jovin (2006). Investigador Postdoctoral asociado en el Department of Chemistry de la Universidad de Cambridge, Reino Unido, en el grupo del Prof. Christopher M. Dobson (2007-2009). Desde el 2010, investigador asociado al Laboratory of Molecular Biophysics, del Institute for Research in Biomedicine Barcelona, España.Mi area de interés se enmarca en la descripción de los mecanismos moleculares involucrados en el plegamiento incorrecto y agregación de proteínas amyloides, y su conexión con enfermedades neurodegenerativas como el Parkinson y el Alzheimer. Durante los últimos 10 años he desarrollado una variedad de ensayos bioquímicos y biofísicos para la determinación cuantitativa in vitro e in vivo de la agregación amyloide de proteínas, empleando fundamentalmente técnicas de espectroscopía de RMN y fluorescencia, así como microscopía multiparamétrica de fluorescencia. Aplicando estas herramientas estoy diseñando novedosas metodologías y plataformas de screening de compuestos químicos con actividad anti-amyloidogénica y potencial farmacológico para el tratamiento de enfermedades como el Parkinson y el Alzheimer.Poseo publicados un total de 21 artículos originales, 1 revisión, 1 capítulo de libro y 1 patente; de ellos, en 2 artículos he firmado como autor de correspondencia, en 10 como primer autor (3 de ellos compartido) y en otros 6 como segundo autor. 11 de los artículos han sido publicados en revistas del primer decil de su campo científico incluyendo PNAS, EMBO Journal, Nature Methods y JACS, y el resto en revistas dentro del primer cuartil tales como J. Biol. Chem, J. Mol. Biol. y Nucleic Acids Res. El índice de impacto promedio de los 22 artículos es de 6.8 puntos y estos han recibido un total de 632 citas. Como resultado de esto mi h index es de 12 puntos. He actuado como revisor en revistas como JACS, Biophysical Journal, PLoS One y Biopolymers, así como para entes financiadores como el Wellcome Trust y la US-Israeli Bi-national Foundation. He obtenido una EMBO postdoctoral fellowship (2007-2008), una CamBridgeSense innovation grant (2009), una personal development grant de ELAN Pharmaceuticals Inc. (2009) y una Marie Curie career development grant (2010-2011).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **CLIMENT BATALLER, JUAN** **Referencia:** RYC-2011-07843

Area: Biomedicina

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Titulo:

Genomic and Molecular approaches to predict response to breast cancer therapies: Role of the circadian clock in breast tumorogenesis

Resumen de la Memoria:

Breast cancer recurrence is a major cause of morbidity in patients who develop this disease. Although adjuvant systemic chemotherapy results in significant improvement of clinical outcome in breast cancer patients, it remains very difficult to predict individual responses to therapy. These data highlight the need for novel approaches to integration of large data sets including clinical and genetic information to predict individual treatment responses or survival. A related and equally important question is whether increased knowledge of molecular predictors of response could lead to improved methods for sensitization of resistant patients to the beneficial effects of these agents. We propose to develop predictors based on combinations of gene copy number changes in DNA isolated from tumor biopsies and paraffin sections. There are substantial practical advantages in using DNA in a clinical setting rather than RNA, because of its greater stability and the feasibility of isolating intact DNA from archival tissue blocks for validation of any predictors found. The main barriers to achieving these goals are a) the availability of sufficient numbers of well preserved breast cancer samples from patients with extended clinical outcome data, and b) development of analytical and computational tools that can handle the vast amounts of molecular data that can be generated from biological samples. We propose to circumvent these barriers by using a large set of breast tumor samples, for which outcome data on treatment responses are available. The computational issues will be addressed using novel algorithms that we have developed to construct genetic networks composed of combinations of clinical parameters and genetic information rather than lists of single genes. Candidate genes that may be involved in treatment resistance will be investigated using functional assays in a panel of 54 breast cancer cell lines that have been extensively characterized and profiled in our lab during the past years. In preliminary results recently published (Climent et al 2010) we found that circadian rhythm gene PER3 is directly related to tumor recurrence in patients with ER-positive breast cancers treated with Tamoxifen. These findings identify PER3 as a tumor suppressor gene in human breast cancers where copy number or expression level may serve as an indicator of probability of tumor recurrence in patients with ER positive tumors. Epidemiological evidence suggests that disruption of sleep patterns plays a significant role in increasing susceptibility to breast cancer, but whether coordinated functional deregulation of circadian clock family genes occurs in breast cancers remains to be determined. We propose further detailed studies to elucidate the relationship between control of sleep homeostasis and circadian rhythms, expression of circadian rhythm genes and DNA damage responses in order to understand the epidemiological data linking sleep disruption to breast cancer susceptibility and to elucidate the exact mechanisms involved.

Resumen del Curriculum Vitae:

I started my research training at the University of Valencia working with optical and electronic microscopy techniques in the Unit of Morphology Microscopy as an Undergraduate Student getting as result of this research my Bachelor Thesis in 1998. Later on I started to work in a private company, Sistemas Genomicos S.L., in collaboration with the Department of Genetics at University of Valencia (1999-2000). From May 2000 until June 2005 I did my PhD research program under the supervision of Dr Ana Lluch Hernández and Dr Jose Angel Martínez-Climent at the University of Valencia in the Department of Hematology and Clinical Oncology, Hospital Clinico Universitario. As a result of my PhD training I participated in eleven different projects that are published in scientific journals, three of them as a first author (Clin Cancer Res 8(12):3863-9 (2002), Blood 105(11):4445-54 (2005) and Cancer Research 67(2):818-26 (2007)), with a median Impact Factor of 10.5. One of them (Climent et al, 2007) was awarded with the American Association of Clinical Oncology (ASCO) Foundation Merit Award, and it is also the subject of a Patent Application (US 11/382,999). The results of my Doctoral Thesis were presented at the III Memorial Carlos Sogo in 2006 in La Coruña; and I was awarded with the II Maria Jose Jove National Award in Breast Cancer Research. During this period of five years I did several short term stays at the IDIBAPS (Institut d'Investigacions Biomediques August Pi i Sunyer), Barcelona (6months), at the CNIO (Centro Nacional de Investigaciones Oncologicas), Madrid (two months) and at the Laboratory of Medicine in the University of California San Francisco under the supervision of Dr Daniel Pinkel and Dr Donna Albertson, where I stayed for 9 months funded through a Fellowship of the "Sociedad Española de Oncologia Medica" (SEOM). I have been working as a Postdoctoral Fellow in Dr Allan Balmain laboratory at University of California San Francisco (UCSF) from 2005 until June 2010. Recently In July 2010 I was promoted to my current position of Assistant Research Scientist. Awards in this period include a Postdoctoral Fellowship from the Spanish Ministry of Education and Science and my last project, awarded by the Breast Cancer Research Program of the Department of Defense, the world's second-largest funding agency for breast cancer research, in which I have been the Principal Investigator ($398.000 / 2007-2010, W81XWH-07-1-0529). Both of these awards have covered my salary and the latter has also contributed to laboratory expenses, having under my supervision a technician, a bioinformatic expert and a graduate student. The total balance of work in my postdoctoral experience result in 6 different publications in scientific journals, two of them as a first author with a median impact factor of 12.4.(Biochem. Cell Biol. 85(4):497-508; Science 321(5895):1499-502; Oncogene 28(17):1892-903; Int J Cancer 1;127(5):1209-19; Topology and its Applications 157: 157¿164; J Clin Oncol. 10;28(23):3770-8) The last one (Climent et al 2010) it is also the subject of a Patent Application (SF2008-179). I recently (November 2010) did a short term stay of two months and established a new collaboration with the Institute for Cancer Research at Oslo University Hospital Radiumhospitalet, and the Nederlands Kanker Instituut - Antoni van Leeuwenhoek (NKI-AVL) at Amsterdam.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **RODRIGUEZ GONZALEZ, RENE** **Referencia:** RYC-2011-08705

Area: Biomedicina

Correo electrónico: rene.rodriguez@juntadeandalucia.es

Titulo:

Mesenchymal stem cells and cancer: tumor modelling and study of altered signalling

Resumen de la Memoria:

Mesenchymal Stem Cells (MSC) are among the most promising stem cells regarding their use in cell therapy. Moreover, due to their ability to home to tumor sites and inhibit tumor growth, MSCs could also be useful as anti-cancer therapy. Nevertheless, MSCs might also constitute a target cell for transforming mutations and constitute the initiating cell for sarcomas. To obtain tumor models from the cell type which transformation give rise to tumors represents a fundamental tool to know the tumor biology and to propose new therapies specifically targeted against the cell type at the origin of the tumor, therefore diminishing the chance of relapse. However, little is still known about the molecular mechanisms underlying MSCs transformation. In this memory, I propose research lines based on the study of the MSC biology and it¿s relation with tumorogenesis. First, we will try to establish a new model of mixoid liposarcoma based on expression of FUS-CHOP, a fusion protein believed to be essential in development of this disease, together with relevant secondary transforming hits, in human MSCs. Then, we will analyze the differential gene expression to discover pathways altered in transformed MSCs. In addition, we will study important signaling pathways that could be relevant in the transformation of MSCs. Thus, we will explore the basis of the MSC resistance to apoptotic agents as well as the Wnt pathway. The results of this work might be useful to find new specific therapeutic targets. In a second approach, regarding the use of MSCs as an antitumoral tool, we will explore the ability of normal and pro-apoptotic factors-overexpressing MSCs to inhibit tumor growth. We will also analyze which types of tumors could beneficiate in the future from this type of therapy. Finally, other proposed areas of research includes the development of new methods to generate induced pluripotent stem cells (iPS) from MSCs as well as other projects where my experience in cell signaling analysis (apoptosis, cell cycle or DNA repair pathways) and in different advanced techniques could be of interest.

Resumen del Curriculum Vitae:

I have two successive degrees in Organic Chemistry (1994) and Biochemistry (1996) at the University of Oviedo. Following this, I started my PhD in the laboratory of Prof. Pedro Sánchez Lazo at the University of Oviedo after having been granted with a pre-doctoral fellowship of the Spanish Science Ministry (FPI). This work finished with the successful defence in July 2002 of my thesis ¿Mitogenic and cytotoxic effects of TNF on murine fibroblasts¿ qualified with Sobresaliente ¿Cum Laude¿. Part of my thesis was carried out in the laboratory of Dr. David S. Ucker at the University of Illinois at Chicago (US) during a predoctoral stay of 3 months. Following my PhD, I joined in July 2003 Prof. Mark Meuth¿s laboratory at the Institute for Cancer Studies at the University of Sheffield (UK) as a Postdoctoral Research associate hired by the University of Sheffield. I worked here for nearly 4 years in a project designed to investigate genes controlling the commitment of cells to apoptosis in response to DNA damage. Then, I accepted my current position as a senior postdoctoral researcher in the Andalusian Stem Cell Bank (BACM) in July 2007. Here I specialized in Mesenchymal Stem Cell (MSCs) research, and I initiated projects mainly designed to unravel mechanisms leading to the tumoral transformation of MSCs. In 2009 I have been awarded a Post-Doctoral Grant from the Spanish Association for Cancer Research (AECC).During this scientific career I participated in 10 projects funded either by national or international programs. Worth noting, I am currently leading as Principal Investigator a 3-years project granted by the Andalusian Government. As a result of these projects, I have authored so far 2 book chapters as corresponding author and 20 publications in relevant international journals, 8 of them as main author [7 as first author (1 under revision) and other one as last and corresponding author]. 85% of papers contributed as main author and 60% of the total number of papers have been published in high impact factor (IF) journals ranked in the 1st quartile or 1st decile of their research fields including: Journal of Experimental Medicine (IF: 14.5), Stem Cells (IF:7.74), Cancer Research (IF: 7.54), Cell Death and Differentiation (IF: 8.25), Leukemia (8.29), Molecular Biology of the Cell (IF: 6.5), Clinical Cancer Research (IF: 6.75), PLOS genetics (IF: 9.5), Neoplasia (IF: 5.02) or J. Cell. Mol. Med. (IF:5.22). I was also selected or invited to present my research as oral presentations in several national and international conferences. Importantly, the clinical/industrial orientation of part of this work has made possible the development of 6 patents, 2 of them directly derived from the project I lead. In addition, I am currently supervising a PhD student and have already supervised the Master Thesis of two students. Other responsibilities include the supervision of BACM cytometer facilities. Finally, I have been reviewing research projects for Calls of the Andalusian Government as well as manuscripts submitted to different international journals from 2008 and I have been member of the Evaluation Committee of 2 PhD Thesis.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **MUÑOZ RISUEÑO, RUTH** **Referencia:** RYC-2011-07998

Area: Biomedicina

Correo electrónico: risueno@mcmaster.ca

Titulo:

Identification of differentiating agents for acute myeloid leukemic stem cells

Resumen de la Memoria:

Acute myeloid leukemia (AML) is a hematologic disorder characterized by the rapid expansion of immature myeloid progenitors in the bone marrow and blood. Remission rates with standard induction chemotherapy in patients with AML range from 50% to 85%; however, the majority of patients will relapse and succumb to the disease within 2 years. Unfortunately, survival rates for the majority of patients with AML have not dramatically changed in the last 30 years. As such, new therapeutic approaches are required. AML is organized in a hierarchy of distinct and functionally heterogeneous classes of cells that are ultimately sustained by a small number of leukemic stem cells (LSCs) with enhanced self-renewal capacity and drug resistance. These LSCs initiate AML and have been suggested to be responsible for relapse. Induction of terminal differentiation (and subsequently cell death) of LSCs is an attractive approach for AML therapy. Myeloid differentiation of AML cells can lead to the production of granulocytes, monocytes and/or dendritic cells; all of them with a limited life span and increased drug sensitivity compared to LSCs. Moreover, DCs are potent stimulators of the immune system and can induce auto- and allo-T-cell mediated anti-leukemic cytotoxic responses. We aim to identify agents able to induce directed differentiation to specific hematopoietic lineages. By comparing LSC gene expression profile and fully mature granulocytes, monocytes and DCs, we have identified the characteristic patterns of genes expression associated with the differentiation transition to specific lineages. Using in silico analysis, these gene signatures can be connected to bioactive small molecules that induce similar transcriptional regulation. Once candidates compounds are identified, we will test their cytotoxic and differentiation potential in AML cell lines in vitro and primary AML patient samples ex vivo. Also, T cell activation capacity will be studied with AML-derived DCs. In vivo anti-leukemic effect will be evaluated using xenotransplantation assays where AML patient samples are transplanted in immunodefient mice and treated with candidate compounds. Ultimately, an in-depth pre-clinical study will be performed to evaluate potential clinical application of the drug candidates.

Resumen del Curriculum Vitae:

As an undergraduate student, I worked in Dr. Isabel Guerrero¿s laboratory (CBMSO, Madrid, Spain) founded by CSIC (Introducción a la investigación 2001). After finishing my BSc in Biology (UAM, 2002), I started my PhD in Dr. Balbino Alarcón¿s laboratory (CBMSO, Madrid, Spain) founded by CSIC (Introducción a la investigación 2002) and MEC (FPU 2003-2006). My work as a graduate student focused on describing early events in T-cell activation. This study has led to the publication of 4 articles (Blood, PNAS, PLoSONE and Sci Signal), which I am the first author; 3 articles I have collaborated in (JEM, Clin Exp Immunol, Int Immunol) and 2 reviews (Trends Immunol, Adv Exp Med Biol). We described an in-house generated monoclonal antibody as a marker for TCR-engaged T cells (currently commercially available -Upstate, BD among other-). I obtained my PhD in Biology in June 2006 (UAM, Premio extraordinario). In October 2007, I joined Dr. Mick Bhatia¿s group (SCCRI, Hamilton, Canada), founded by the Canadian Cancer Society (TFF 2008-2011), where I have been working on human hematopoiesis and leukemogenesis in vivo. The projects I have been involved focused on xenotransplantation mouse models for human AML, screening anti-leukemia compounds and their pre-clinical validation, hematopoietic differentiation from human pluripotent stem cells and direct differentiation of human skin cells to blood. The work generated has been published in Nature and Stem Cells (first author), and 3 articles are under review, which I am the first author (Blood, Sci Trans Med, Nature). Additionally, I have collaborated in 2 reviews (Blood and Curr Opinion Hematol) and 2 patents are under evaluation. 12 communications in meetings have been presented. During my career, I have obtained 4 scientific awards (PINP-Fundación Severo Ochoa, Real Academia Nacional de Farmacia, Real Academia de Medicina y Cirugía de Cádiz, Grupo Joly-Caja Madrid).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **PALOMARES GRACIA, OSCAR** **Referencia:** RYC-2011-08734

Area: Biomedicina

Correo electrónico: oscarpalomares@hotmail.com

Titulo:

Identification of novel targets on human dendritic cells to develop alternative immunotherapy protocols of allergic diseases

Resumen de la Memoria:

The immune system is a complex interactive network with the capacity to protect the host from a broad range of pathogens while keeping a state of tolerance to self and non-self innocuous antigens. In these processes, dendritic cells (DCs) play a pivotal role. Immune tolerance-related diseases such as allergy arise as a direct consequence of dysregulated immune responses. Allergy is a Th2-mediated disease of increased prevalence leading to significant changes that negatively affect to the patients¿ quality of life. Currently, allergen-specific immunotherapy (allergen-SIT) is the single curative treatment of allergic diseases. The main drawbacks of allergen-SIT include inefficacy, risk to develop anaphylaxis and long duration. The rational design of vaccines specifically targeting DCs has emerged as a promising alternative to overcome these problems. However, a better understanding of the DC biology in the context of allergic diseases is required and two main aspects need further investigations: i) how allergenic proteins interact with DCs and ii) identification of novel molecules that modulate DC function. Recently, It has been suggested a potential anti-inflammatory role of the endocannabinoid system (ECS) in allergic diseases. In contrast, it has been shown that serotonin [5-hydroxytryptamine (5-HT)] receptors might contribute to exacerbate asthma in allergic patients. However, the mechanisms underlying such effects or how the innate and adaptive functional properties of DCs are altered remain unclear. In this context, my proposed research goal is to identify molecules on human dendritic cells that might play a role in the regulation of immune responses to allergens. To address this ambitious objective, I will undertake the following milestones: i) Study of the effect that allergens with enzymatic activity and chemical compounds targeting the ECS and 5-HT receptors exert on human DCs; ii) identification and structural and functional characterization of novel molecules modulating human DC function and iii) Study of the in vivo relevance of such molecules in animal models of allergic inflammation and human allergic patients. During my PhD and postdoctoral stay in Complutense University of Madrid under the guidance of Prof. Rosalía Rodríguez and Prof. Mayte Villalba I acquired expertise on methodologies related to molecular biology, protein chemistry and animal models of allergic diseases. Then, during my postdoctoral stay in the Swiss Institute of Allergy and Asthma Research (Davos, Switzerland) under the guidance of Prof. Cezmi A. Akdis I have acquired a proficient level in the field of cellular immunology and I have gained experience on the study of DC biology applied to the field of allergy, which has notably reinforced my previous scientific background. The proposed line of research is highly multidisciplinary and is aimed at the integration of areas such as Molecular Allergology, Clinical Allergology, Medicinal Chemistry and Cellular Immunology, taking as model the close relationship among these fields kept in other internationally recognized laboratories. The identification of molecules on human DCs playing a role in immune regulation of allergic diseases might well contribute to the rational design of novel drugs that would improve the current immunotherapy treatments of allergic diseases.

Resumen del Curriculum Vitae:

Degree in Biochemistry (Complutense University of Madrid (UCM), 2000). Collaboration grant MEC in the group of Dr. Rosalía Rodríguez (Dpt. Biochemistry and Molecular Biology I, UCM): master degree in Biochemistry, (Eur J Biochem 2002, 269:2538-45). Pre-doctoral Grant (MECD, 2001); PhD (2001-05) working on the identification, isolation, recombinant production and characterization of allergens from yellow mustard seeds and on the 1,3-beta-glucanase allergen Ole e 9 from olive pollen: (Biochem J 2003, 369:593-601; J Immunol 2004, 172:3644-5; Clin Exp Allergy 2005, 35:345-351; Int Arch Allergy Immunol 2006, 26:175-80; Int Arch Allergy Immunol 2006, 140:131-8; Ann Allergy Asth Immunol 2006, 97:61-5; Prot Sci, 2008 17:371-6; Ann Allergy Asth Immunol 2005, 94:586-92; Int Arch Allergy Immunol 2005, 137:18-26). Short stay (2002) in the group of MD Rudolf Valenta (AKH, University of Vienna, Austria): role of Ole e 1 in sensitization to Oleaceae (Int Arch Allergy Immunol 2006, 141:110-8). PhD with European mention (UCM, 2005); Supervisors: Dr. Rosalía Rodríguez and Dr. Mayte Villalba. Thesis awarded with ¿Premio Extraordinario de Doctorado¿. Post-doctoral fellowships (FIS and ALK-Abelló, 2005-06) to study allergenic proteins from yellow mustard seeds (J Allergy Clin Immunol 2007, 119:1189-96; Clin Exp Allergy 2009, 39:1929-36) and recombinant glucanosyltransferases (Gas1p): (J Biol Chem 2008, 283:18553-65). Assistant Professor (Dpt. of Biochemistry and Molecular Biology I, UCM, February 2006-March 2008); identification of etiological agents causing occupational allergies: (Allergy 2007, 62:1472-3; Allergy 2007, 63:784-5; N Engl J Med 2008, 358:1306-8). Post-doctoral fellowship (MEC-Fulbright, March 2008-April 2010) in the Swiss Institute of Allergy and Asthma Research (Davos, Switzerland), advisor: Dr. Cezmi A. Akdis. I was involved in 2 projects: i) mechanisms regulating the expression and maintenance of FOXP3 in Treg cells: (J Exp Med 2009, 206:2701-15) and ii) role of human palatine tonsils in the generation of oral tolerance to food and aeroallergens: (under revision in J Allergy Clin Immunol, 2011). I published as first author a review article discussing the role of Treg cells in allergic diseases (Eur J Immunol 2010, 40:1232-40) and as co-author a review article discussing the role of cytokines in diseases (J Allergy Clin Immunol 2011, in press). Currently, Assistant Professor in UCM (April 2010-continue). In this period I have published as last and corresponding author a paper that contributes to improve diagnosis and management of mustard allergy (J Allergy Clin Immunol 2011, in press). In summary, my work has generated a total of 27 scientific publications in peer-reviewed journals with a total accumulated impact factor of: 167.7 and total number of citations: 229. I attended to 5 national congresses (1 invited conference) and 16 international congresses (4 invited conferences & 4 oral presentations). My work has received 5 awards in international meetings. I am referee for J Allergy Clin Immunol (IF: 9.8) and Allergy (IF: 6.2). I participated in 7 research projects founded by public institutions and 4 by the pharmaceutical company ALK-Abelló. I received 5 fellowships from public national institutions and 1 from ALK-Abelló. From April 2010: Assistant Professor (Dpt. of Biochemistry and Molecular Biology I, UCM).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **JIMENEZ CHILLARON, JOSE CARLOS** **Referencia:** RYC-2011-08666

Area: Biomedicina

Correo electrónico: jjimenezc@fsjd.org

Titulo:

Origen Fetal de la Diabetes del Adulto: Papel Potencial de Mecanismos Epigenéticos

Resumen de la Memoria:

Epidemiological and experimental studies demonstrate that nutritional imbalances occurring during critical periods of development can have long-lasting metabolic effects. Specifically, foetal malnutrition or under-nutrition increases the risk for chronic adult diseases such as insulin resistance, dislipidemia, type 2 diabetes, obesity or cardiovascular disease. This is due, in part to permanent changes of gene expression in key tissues and cells. Genome integrates nutritional variation into permanent changes in gene expression through epigenetic modifications, including DNA methylation and histone modifications. Changes in epigenetic marks are very stable and can be inherited into the next generation if occurring in the germ line. DNA methylation is particularly relevant in the context of the present application because it is highly dependent on nutrients able to act as methyl donors: vitamin B12, folate and methionine.The applicant has developed a mouse model of foetal malnutrition that summarizes human metabolic physiology: Intrauterine food deprived mice develop obesity, glucose intolerance and diabetes with aging. Strikingly, glucose intolerance is inherited into the next generation offspring (F2), even in the absence of any nutritional alteration during second generation foetal development. Intergenerational inheritance of glucose intolerance through males suggests that there exist an epigenetic component in development of this particular phenotype. Main research line in our laboratory is based on the following hypothesis: Foetal malnutrition programs permanent changes in expression of genes that regulate key metabolic pathways. These changes are mediated, in part, by epigenetic modifications. In summary, we expect to gain insight on the molecular mechanisms underlying association between foetal under-nutrition, intrauterine growth restriction and increased risk for adult diabetes. Specifically, we propose the establishment of a causal relation between nutrition epigenetic mechanisms permanent changes in gene expression glucose intolerance and diabetes.

Resumen del Curriculum Vitae:

1. Datos personalesNombre: José Carlos Jiménez ChillarónOrganismo: Fundación San Juan de Dios, Esplugues, Barcelona.Departamento: Endocrinología.Email: jjimenezc@fsjd.org.2. Líneas de investigación¿Origen fetal¿ de la diabetes del adulto: Mecanismos epigenéticos.Nutrición postnatal, crecimiento infantil y ¿programación¿ de la obesidad infantil.3. Formación académicaLicenciado en Biología, Universitat de Barcelona (rama Fundamental): 1992Doctor en Biología, Universitat de Barcelona: 2000Research Fellow, Joslin Diabetes Center-Harvard Medical School: Sept. 2000- Dic. 2005.Instructor in Pediatrics, Children¿s Hospital Boston-Harvard Medical School: Enero 2006-agosto 2007.4. Publicaciones más relevantes.Pihlajamaki et al. Cell Metabolism, 2011 (in press); Wanzu et al. Journal of Clinical Investigation, 2011 (in press); Woo et al. Stem Cells Dev. 2011 Jan 19. PMID: 21247245; Pentinat et al. Endocrinology, 2010 Dec;151(12):5617-23.; Isganaitis et al. Diabetes. 2009 May;58(5):1192-200. Jimenez-Chillaton et al. Diabetes. 2009 Feb;58(2):460-8. Oge et al. Diabetologia, 2007, 50:1099-1108; Jimenez-Chillaron et al. Current Opinion in Endocrinology, Diabetes and Obesity, 2007, 14:23-29. Jimenez-Chillaron et al. Diabetologia, 2006, 49:1974-84; Goldfine et al. Diabetes, 2006, 55:640-650; Jimenez-Chillaron et al. Diabetes, 2005, 54:702-711; Ferrer-Martinez et al. Journal of Molecular Biology, 2004, 338:657-667; Combs et al. Diabetes, 2003, 52:268-276; Jimenez-Chillaron et al. Metabolism, 2002, 51:121-6; Jimenez-Chillaron et al. FASEB J, 1999, 13:2153-60; Novials et al. 1998, 17:182-6; Gomez-Foix et al. 1998, Biochem Soc Trans, 25:7-10.5. Premios y honores2000. Doctor ¿cum laude¿ en Biología por la Universidad de Barcelona.2000. Fulbright/Regional Government of Catalonia Award for Postdoctoral Research i the USA.2005. Finalista. New investigator award: 3rd International Congress of Developmental Origins of Health and Disease.2008. Premio mejor trabajo (presentación oral). 30 Congreso Sociedad Española de Endocrinología Pediátrica.2009. Premio mejor trabajo en alteraciones del crecimiento (presentación oral). 31 Congreso Sociedad Española de Endocrinología Pediátrica.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **GONZALEZ GALLEGO, TERESA** **Referencia:** RYC-2011-09423

Area: Biomedicina

Correo electrónico: tgonzalez@iib.uam.es

Titulo:

Endogenous and pharmacological modulation of ion channels

Resumen de la Memoria:

My main research line is ion channels pharmacology and electrophysiology. Voltage-gated K+ (Kv) channels play an essential role in mostly all physiological processes. In the heart, Kv channels control the repolarization process and they are targets for developing new anti-arrhythmic drugs. Kv1.5 channels generate the atrial specific IKur current, which is the main responsible of human cardiac atrial repolarization, and they are potential targets for new drugs useful in the treatment of supraventricular arrhythmias. My previous research had focused in the analysis of the drug-binding site of Kv1.5 channels, as well as in the binding site for their regulatory subunits (Kvb1.3). Traditionally, it was believed that drugs reached the central cavity of the channel from its intracellular side and blocked it after binding to residues in the pore. However, we have seen that some residues described as part of the drug-binding site point away from the pore. I am interested in the determination of the drug receptor-site on Kv1.5 to clarify if they bind to residues in the pore of the channel or if they insert between the α-helices of the channel. Another important feature of the IKur is its adrenergic modulation. We have seen that PKC activity, together with PIP2, fine-tunes the fast inactivation induced by Kvb1.3 subunit. Our recent findings point to the existence of a channelosome consisted by, at least, PKCbetaII-RACK1-Kv1.5 and Kvb1.3, therefore, I aim to analyze in deep the proteins involved in such channelosome, the effects of alfa and beta stimulation and the pharmacological consequences of the adrenergic stimulation. In addition, I plan to start a research in collaboration with clinical groups, which are describing new mutations on ion channels causing Long QT and Brugada Syndromes. My aim is to perform an electrophysiological and pharmacological characterization of these mutant channels. This will increase the knowledge about the molecular mechanisms of these diseases and, ultimately, will allow the developing of new treatments for each particular case in the future.

Resumen del Curriculum Vitae:

Bachelor degree in Biology (1998) by the Complutense University, Madrid, Spain. PhD in Pharmacology (2003) by the Complutense University, Extraordinary Award. Thesis title "Effects of local anaesthetics on potassium channels. Pharmacological consequences of the interaction between alfa (hKva1.5) and beta subunits (Kvb1.3 y Kvb2.1) of Kv1.5 channels¿. This period resulted in 12 publications (all in 1st quartile), 4 as first author (4 Br J Pharmacol, 2 JPET, 2 Mol Pharmacol, 3 Cardiovasc Res and 1 Circulation). 4 long term stays in internationally recognized centers (CVRTI University of Utah, USA; University of Marburg, Germany; Sanofi-Aventis GmbH, Germany; and Inst. Investigacines Biomedicas CSIC/UAM, Spain). 10 papers from the postdoctoral period (all in 1st quartile), 2 as first author and 1 as last author (1 J Physiol, 1 Am J Physiol-Cell Physiol, 2 Mol Pharmacol, 1 Anesthesiol, 1 BBRC, 1 EMBO J,1 MRMC, 1 Biochem Pharmacol and 1 J Mol Cell Cardiol). 45 contributions to national and internationally meetings (3 oral communications and 1 invited speaker). Participation in 11 Research Projects and 5 Research Contracts with Companies. 1 Doctoral Thesis supervised (Sobresaliente cum laude and Extraordinary Award) and 2 on progress. Accredited as Profesor titular (Assistant Professor) by ANECA. Teaching for 3 semesters in University of Marburg (Integrated Physiology and Anatomy, and Neurobiology for Medicine, Human Biology and Dentistry students). Experience in organization of meetings (2008). Currently, I have a JAE-Doc contract from CSIC in the Inst. Investigaciones Biomedicas Alberto Sols CSIC/UAM, Madrid.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **SANCHEZ-AGUILERA PEÑO, ABEL** **Referencia:** RYC-2011-09726

Area: Biomedicina

Correo electrónico: abelsanchezaguilera@gmail.com

Titulo:

Regulation of normal and leukaemic stem cells by the haematopoietic microenvironment

Resumen de la Memoria:

The presence of self-renewing ¿cancer stem cells¿ responsible for tumour initiation and maintenance has been well defined in multiple types of solid and haematologic tumours; however, our knowledge of their biology and how they differ from normal stem cells is very limited. While it is believed that leukaemia stem cells (LSC) ¿ like normal haematopoietic stem cells (HSC) ¿ depend on the interaction with a specialized microenvironment or ¿niche¿ for their self-renewal and maintenance, the identity and function of this leukaemic niche are essentially unknown. A better understanding of these processes is critical to the development of better therapies, because complete erradication of the tumour would require elimination of LSC. One of the best characterized models for the study of LSC are MLL-induced leukaemias, in which the presence of this self-renewing population has been well documented. Moreover, MLL-rearranged leukaemias represent a group of malignancies with particularly poor clinical outcome, underscoring the need for more effective therapies. Here I propose to investigate the contribution of the haematopoietic microenvironment to the development of MLL-induced leukaemias and its role in LSC maintenance and, at the same time, to expand our understanding of the normal HSC microenvironment. I will specifically characterize the role and requirement of nestin+ mesenchymal stem cells (MSC), previously shown to be essential for normal haematopoiesis, as a niche component for LSC. The role of specific extracellular signals (in particular the chemokine SDF), potentially mediating the interaction of MSC with normal and leukaemic HSC, will be investigated. Finally, I propose to study the effects of oestrogens and oestrogen receptor modulation on the proliferation, survival and self-renewal of HSC and their leukaemic counterparts, and their potential role in modifying leukaemic cell chemosensitivity. This project will ultimately attempt to establish the feasibility of targeting the haematopoietic microenvironment as a novel therapeutic approach, and to assess its efficacy in experimental models of MLL-induced leukaemias.

Resumen del Curriculum Vitae:

My research career has focused on the study of normal and malignant haematopoiesis. My predoctoral work (2001-2006) at the laboratory of Dr. Miguel A. Piris at the Centro Nacional de Investigaciones Oncológicas (CNIO, Madrid, Spain) aimed at investigating the biology of human B-cell lymphomas, and specifically two areas: the study of alterations in cell cycle regulatory genes and their involvement in the pathogenesis of human lymphomas, and identification of gene expression signatures associated with treatment response. We identified several novel alterations in cell cycle genes (p14ARF, MDM2, p18INK4c) in lymphomas, of biological and prognostic significance. We also defined molecular signatures correlating with treatment resistance in Hodgkin¿s lymphoma, suggesting that treatment response depends on alterations in both the malignant cell and its microenvironment. This predoctoral work culminated in the Ph.D. thesis ¿Alteraciones en las vías reguladoras del ciclo celular en neoplasias linfoides humanas¿ (2006).In September 2006 I joined the laboratories of Drs. David A. Williams and José A. Cancelas at Cincinnati Children¿s Hospital Medical Center (Cincinnati, USA) as a Research Fellow. This postdoctoral work was continued from June 2008 in Dr. David A. Williams¿ new laboratory at Children¿s Hospital Boston / Harvard Medical School (Boston, USA). The goal of my postdoctoral research has been to understand the role of Rho GTPases and their activators, the guanine nucleotide exchange factors (GEF) of the Vav family, in normal and leukaemic haematopoiesis. We have identified (1) an essential role of Vav1 in haematopoietic stem cell engraftment, retention, localization and response to SDF; (2) a role for Rac2 and Vav3 in mediating oncogenic signaling of p190/BCR-ABL in B-cell acute lymphoblastic leukaemia; (3) the involvement of the atypical GTPase RhoH in the development of B-cell chronic lymphocytic leukaemia.My research activity has resulted in 19 original papers (two of them currently under review) and two review articles. The total impact factor of these peer-reviewed publications is 158.947 (average = 8.366). I am first author of 6 of these papers (one of them under review; average impact factor = 8.861) and second author of 6. Since 2007 my work has resulted in 12 communications to congresses (11 international; 9 oral presentations; 7 as first author).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **SEGURA GINARD, MIGUEL FRANCISCO** **Referencia:** RYC-2011-07923

Area: Biomedicina

Correo electrónico: miguelsegu@gmail.com

Titulo:

Role of microRNA in Neural Crest tumor genesis and progression

Resumen de la Memoria:

MicroRNAs (miRNAs) are endogenous non-coding small RNAs that interfere with the translation of coding messenger RNAs (mRNAs) in a sequence-specific manner, controlling gene expression during development and tissue homeostasis. In recent years it has become apparent that miRNAs are dysregulated in a number of different human cancers and the over- or under- expression of specific miRNAs contributes to tumorigenesis and/or progression, as well as associates with patient outcomes. Neural crest derived-tumors, like neuroblastoma, or melanoma, exhibit highly metastatic and chemoresistant behaviour. Those tumors often contain cells that express developmental genes, have multidifferentiation potential and seem to evoke the migratory nature of neural crest stem cells. These observations suggest that alterations in developmental or differentiation programs within neural crest derived cells can critically contribute to tumor formation and progression. Moreover, the lack of effective treatments for advanced disease urgently calls for novel biomarkers able to accurately predict the possibility and timing of recurrence or metastasis, as well as improved therapy regimes. Currently, a number of studies have identified deregulated miRNAs in tumors but the functional role of these miRNA is still poorly characterized. The presence of functional redundancy in tumor cells likely buffers the impact of a single gene/target modification on the malignant process. miRNA-based cancer gene therapy offers the possibility of targeting multiple gene networks that are controlled by an individual miRNA. Notably, miRNAs show improved stability and maintain their expression profiles in archival formalin-fixed paraffin embedded (FFPE) samples, allowing retrospective studies in tumor banks. The overall goal of my research will be identifying differentially expressed miRNA between ¿low-risk¿ neuroblastomas (responsive to treatment) versus ¿high-risk¿ (unresponsive to conventional treatment) Once identified, I will analyze the impact of those miRNAs in the behaviour of tumor-derived cell lines in vitro and in vivo,and undifferentiated neural crest cells. I will focus in the characterization of miRNA that impact the pluripotency of neural crest cells and therefore maintaining the tumors in an undifferentiated state, which can be the reason for being more aggressive and resistant to therapy. Moreover, I will use miRNA as a novel therapeutic strategy in order to restore (mimic oligos) or block (anti-miRs) the deregulated miRNA found in the resistant tumors.These findings will have the potential to unravel molecular targets that could be exploited therapeutically, if identified at early stages of the disease.

Resumen del Curriculum Vitae:

Bachelor in Biochemistry, from Universitat Illes Balears (2000). PhD degree in Neuroscience, excellent cum laude and European Doctorate Award, Universitat de Lleida (2006). Thesis title: ¿Role of CD95/Fas/Apo-1 antagonists -FAIML and Lifeguard- in nervous system¿. Advisor Professor Joan X. Comella. This work resulted in 9 publications (1 as first author): Iglesias et al. (Neuropharmacology, 2003); Bayascas et al. (FEBS Letters, 2004); Sole et al. (Journal of Cell Biology, 2004); Simo et al (Cerebral Cortex, 2007); Gomez-Lazaro (Molecular Pharmacology, 2007); Fernandez et al (Journal of Neurochemistry, 2007); Segura et al (Journal of Neuroscience, 2007); Gomez-Lazaro et al. (Journal of Neurochemistry, 2008); Gozzelino et al. (Cell Research, 2008) and one review (Segura and Comella, 2008). It also resulted in one book chapter (Badiola et al 2008), 2 stays in internationally recognized centers, and 11 communications (9 oral and 2 posters). Intern student fellowship, Universitat Illes Balears (1999); undergraduate student from ¿Ministerio de Educación, Cultura y Deporte¿, Universitat Illes Balears (2000). Graduate student fellowship "Formación de personal universitario" from Ministerio de Educación, Cultura y Deporte, Universitat de Lleida (2001). Postdoctoral Fellowship Alfonso Martin Escudero, New York University (2007), Postdoctoral Fellowship National Cancer Center, New York University (2009). In March 2007, I joined Dr Eva Hernando¿s lab in New York University and so far it has been resulted in 6 publications so far: Segura et al. (PNAS, 2009); Segura et al. (Clinical Cancer Research, 2010); Moubarak et al. (Journal of Neuroscience, 2010); Huynh et al. (Oncogene, 2010), Kapoor et al. (Nature, 2010), Gaziel et al. (Cancer Cell, 2nd revision) and 1 review: Segura et al (Journal of Investigative Dermatology, accepted for revision). In addition to the publications, the results lead to the 1 Patent: ¿Compositions and Methods for diagnosing and treating melanoma (Application form No: 09723968.5-1223, USA US/24.03.08 /USP 38990). I have also participated in 5 communications (4 oral, 1 poster).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **LLAMAS LORENTE, MARIAN** **Referencia:** RYC-2011-08874

Area: Biomedicina

Correo electrónico: marian.llamas@eez.csic.es

Titulo:

Knowing the enemy: unravelling a novel regulatory system involved in bacterial virulence

Resumen de la Memoria:

The emergence and increasing prevalence of bacterial strains that are resistant to antibiotics demand the discovery of new therapeutic approaches. Inhibition of pathogenesis by targeting bacterial virulence represents a promising alternative for antimicrobial therapy. A central requirement of bacterial virulence is the ability to tightly regulate virulence genes in response to host signals. Next to the two-component regulatory system, cell-surface signaling (CSS) represents an important mechanism by which bacteria respond to the extracellular medium. However, whereas regulation by two-component systems has been studied in great detail, little emphasis has been on CSS regulation, although it offers great potential for the development of antimicrobial compounds. In this project I propose to characterize a novel and recently discovered CSS regulatory system, called PUMA3, that triggers the production of Pseudomonas aeruginosa virulence factors in response to a (human) host signal (Llamas et al., 2009). P. aeruginosa is a major human opportunistic pathogen causing infections in hospitalized patients. It is also the main cause of death of patients suffering from cystic fibrosis. Due to its natural resistance to antibiotics and its ability to acquire such resistance, P. aeruginosa infections are often difficult to treat. The P. aeruginosa PUMA3 system consists of three main proteins: an extracytoplasmic function (ECF) sigma factor (VreI), a sigma factor regulator in the cytoplasmic membrane (VreR), and a putative receptor (VreA). Presence of an (unknown) inducing signal results in the activation of the VreI sigma factor, which binds to the RNA polymerase and promotes the transcription of a specific set of virulence genes. Induction of the PUMA3 system (by overexpression of VreI) increases P. aeruginosa virulence (Llamas et al., 2009). In this project I will characterize this novel regulatory system in detail, by resolving the structure of its components, analyzing their functions, and identifying the conditions by which it is induced. Moreover, a high-throughput screen will be developed to target ECF sigma factors in order to find new drugs that prevent P. aeruginosa virulence. In addition to the fundamental interest of the description of any novel signal transduction system, PUMA3 represents the first CSS system dedicated to the transcriptional activation of virulence functions in a human pathogen in response to its mammalian host. Although PUMA3 will be mainly analyzed in P. aeruginosa, I will also broaden the scope of this research by studying the function of homologous systems in two other pathogens i.e. Burkholderia cepacia and Pseudomonas entomophila.A major reason for therapeutic failure in the treatment of bacterial infections is the high intrinsic resistance of bacteria such as P. aeruginosa to multiple classes of antibiotics and the paucity of new molecules being brought onto the market. We therefore need both new concepts and new techniques in knowledge-based drug discovery. In this project, I will use the knowledge of how pathogens interact with the host to identify molecules targeting crucial host-pathogen interaction pathways. Elucidation of the relationship between the PUMA3 system and virulence of P. aeruginosa will identify new targets for such drugs.

Resumen del Curriculum Vitae:

NAME: Marian Llamas Lorente; PLACE AND DATE OF BIRTH: Murcia, 13/11/1973. PRESENT PROFESIONAL POSITION: Researcher at Estación Experimental del Zaidín-CSIC (Granada, Spain). ACADEMIC BACKGROUND: Master in Biology 1997 (University Murcia); PhD in Biology 2002 (Summa cum laude) (University Granada). SCIENTIFIC EXPERIENCE AND STAYS IN FOREIGN CENTERS: Post-doctoral fellow/researcher in Dept. Medical Microbiology at VU University Medical Center (Amsterdam) (7,5 years, 2003/2010); PhD student at Estación Experimental del Zaidín-CSIC (Granada) (1998/2002); Short-term fellow at University British Columbia (Vancouver, Canada) (1999); 2-times Short-term fellow at Utrecht University (The Netherlands) (2000 and 2001); Research student at University of Murcia (4 years, 1994/1997)CURRENT RESEARCH TOPIC: Unravelling the molecular mechanism underlying cell-surface signaling regulation. PARTICIPATION IN RESEARCH PROJECTS: Participation in 7 research projects funded by international entities (as principal investigator in four of these).FELLOWSHIPS/GRANTS OBTAINED: (1) ECHO grant from The Netherlands Organisation for Scientific Research (NWO) (260,000 ¿) (December 2010-December 2014) (2) JAE-doc from Consejo Superior de Investigaciones Científicas (October 2010-October 2013) (3) Innovational Research Incentives Scheme VENI grant from The Netherlands Organisation for Scientific Research (NWO) at VU University Medical center (Amsterdam) (Individual subsidy, 200,000 ¿) (July 2005¿March 2009); (4) Postdoctoral Marie Curie (Individual) fellowship (EU) at VU University Medical center (Amsterdam) (140,800 ¿) (January 2003-December 2004); (5) European Molecular Biology Organization (EMBO) Short-term fellowship at Utrecht University (Utrecht) (May-July 2001); (6) Short-term fellowship from the Spanish Ministry of Education and Culture (MEC) at Utrecht University (Utrecht) (October-December 2000); (7) Short-term fellowship from the Spanish Ministry of Education and Culture (MEC) at University of British Columbia, (Vancouver, Canada) (July-September 1999); (8) FPI Predoctoral fellowship from the Spanish Ministery of Education and Culture (MEC) at Estación Experimental del Zaidín, CSIC (Granada) (January 1998-December 2001); (9) Studentship ¿Introduction to research¿ from the Spanish Ministery of Education and Culture (MEC) at University of Murcia (Murcia) (September 1996-August 1997).PUBLICATIONS: 10 peer-reviewed publications in Microbiology journals included in the ISI Journal Citation Reports (PLoS Pathogens (ranked 1st when excluding review Journals), Molecular Microbiology, Journal of Bacteriology, Microbiology, etc.), 7 of these signed as first author and 4 as corresponding author; three invited reviews in books (one as first and two as last author); 12 presentations in international congresses with oral presentations in 6 of them. ADDITIONAL EXPERIENCE: Collaboration with several international renowned groups. Reviewer of scientific manuscripts sent to Microbiology journals included in the ISI Journal Citation Reports (Journal of Bacteriology, Molecular Microbiology, Microbiology, etc.); Supervision of PhD students, research technicians, and of both bachelor and master students of the VU University (Amsterdam); Participation in the preparation and development of theoretical courses (teaching, grade exams, preparation of practical classes, etc.)

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **MORALES HERNANDEZ, MIGUEL ANGEL** **Referencia:** RYC-2011-07758

Area: Biomedicina

Correo electrónico: mamorales33@gmail.com

Titulo:

Dissecting drug resistance in pathogenic trypanosomatids

Resumen de la Memoria:

Leishmaniasis is a human protozoal disease caused by species of the trypanosomatid Leishmania with a wide range of clinical manifestations, from mild cutaneous forms to visceral syndromes. The disease is fatal if untreated and currently ranks second to malaria in terms of mortality and disability. Leishmaniasis is further compromised by the emergence of coinfection with human immunodeficiency virus (HIV) in endemic areas. Chemotherapy is the only way to control and treat the disease due to the lack of a human safe vaccine. However, this strategy is seriously threatened by rampant increase of resistance against standard clinical drugs, such as pentavalent antimonials, miltefosine and paromomycin. Moreover, the pipeline is nearly empty, as development of new leads from scratch is despised by the pharmaceutical industry upon economic grounds. Leishmania displays unique characteristics such as a strong posttranscriptional control, reducing the impact of transcriptomic studies, and most of the species lack RNAi activity and argonaute and dicer genes, making cumbersome the study of alternative strategies to fight resistance. Our plan is to unravel the contribution of the conserved MAPK transduction pathway both to avert resistance in Leishmania major and L .infantum, as well as to explore it as a target with new leads by: i) reverse genetics including gain and loss of function of protein kinases, conditional KOs, RNA interference in the closely related Trypanosoma brucei; ii) qualitative and quantitative gel-based and LC-based comparative phosphoproteomics; iii) using ceIl penetrating peptides (CPP) coupled to: a) drugs with faulty accumulation in the parasite, b) peptides and engineered antibody fragments (minibodies) competing or targeting essential MAPK sequences (activation loops, scaffold docking), otherwise unreachable as this class of inhibitors lack cognate transporters. The foreseeable outcome will be: 1) establishment of a minimalistic biological system linking drug resistance and MAPKs; 2) generation of conditional KOs by peptides and minibodies, due to the impossibility to use RNAi in Leishmania; 3) to exploit alternative inhibition sites in MAPK different from the classical ATP binding pocket, highly conserved throughout evolution. The project has a broad applicability to other vector-transmitted pathogens, including Plasmodium, Trypanosoma brucei, and Trypanosoma cruzi and will open new venues for the identification of new drug targets and the molecular surveillance of resistance.

Resumen del Curriculum Vitae:

During my PhD, my research on Leishmania/HIV co-infection significantly contributed to improve the molecular diagnosis of leishmaniasis, to evaluate proper therapeutic protocols for relapses versus re-infections, and to design preventive measures to eliminate transmission of the disease through needle-sharing. My Ph.D. Thesis in the Laboratory of Leishmaniasis, ISCIII, Madrid, Spain (supervisor Dr. Jorge Alvar) on ¿Molecular Epidemiology of Leishmania/HIV co-infection¿ received an score of ¿Magna Cum Laude¿. I was a Fellow of the Foundation for AIDS Research and Prevention in Spain. Aside my major involvement in the study on Leishmania molecular epidemiology I acquired significant knowledge in Bioinformatics, an interest that earned me the award to participate as the only Spanish representative together with twenty international scientists at the International Training Course on Bioinformatics (2001, Rio de Janeiro, Brazil) conducted and sponsored by NIH/NCBI, WHO/TDR, FIOCRUZ and Burroughs Wellcome Fund. I did my first post-doc at NYU School of Medicine, NY, USA. The scientific output was very productive for the future and I was able to mount the very first independent project of Dr. Spaeth¿s lab on Leishmania MAP kinases. My scientific impact is illustrated few years later by (i) three seminal first author papers, (ii) the focus of 5 Dr. Spaeth¿s lab members on Leishmania MAP kinase research, and (iii) a ¿3M fund from the EU targeting Leishmania MAP kinases for anti-parasitic drug development. Later on I accepted a research associate position at Institut Pasteur in Paris in 2005. Once again, I was instrumental for the fast and efficient deployment of the lab in France and the establishment of a second, cutting edge research project on quantitative Leishmania phosphoproteomics. I introduced quantitative 2D electrophoresis in the lab, which now represents a core technique that the lab applies on comparative analysis of Leishmania mutants and that is subject of many collaborations with teams in Germany, Switzerland, and Australia. This project resulted in three more first author papers. This work is ongoing and several manuscripts are currently under preparation. I was a Fellow of the INSERM Avenir program (Sept 2005-March 2008) and later I obtained the prestigious Fellowship Bourse Roux, Pasteur Institute, Paris, France (Sept. 2008- Feb. 2010).I have the abilities in all areas required to start a successful independent science career. I am a very hard worker, have an excellent scientific culture, and have shown productivity. The average IF of my first author papers is 8.30. My h-index is 10 and my normalized m-index is 1. In addition, I am a very good speaker, as documented at many international meetings and as a lecturer, and have shown very good management skills, being co-director of two PhD students and coordinating the efforts of three technicians in the lab. It is my purpose to continue making significant contributions to the scientific community, with emphasis on intracellular pathogens, while developing into an independent and innovative research scientist.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **SINDREU BALET, CARLOS** **Referencia:** RYC-2011-08026

Area: Biomedicina

Correo electrónico: bsindreu@uw.edu

Titulo:

Molecular mechanisms of memory and cognitive decline

Resumen de la Memoria:

Cognitive decline associated with normative aging is only expected to grow as the life expectancy of the population increases. Likewise, several disorders such as anxiety, depression or traumatic events are often accompanied by memory alterations, highlighting the importance of understanding the basic cellular and molecular mechanisms of cognition. Memories for salient events that occur during daily experience are generated as a result of biochemical signals triggered by synaptic activation. Activity-dependent post-translational modifications (such as protein phosphorylation) can not only modify the functional properties of neurons by acting on effector proteins, but also by stimulating changes in transcription and translation that are necessary for the long-term storage of memories. Although several neuronal signal transduction pathways have been implicated in memory formation, they are transiently activated and often targeted to multiple subcellular compartments, raising fundamental questions as to what specific mechanisms regulate their activation, cross-talk, and coupling to transcription/translation. I have begun to address these issues by studying the activation rules of the Erk/MAPK pathway, which has been strongly implicated in several forms of memory. We have found that the calcium-stimulated adenylyl cyclases AC1 and AC8 are indispensable for the co-activation of a linear cascade comprising PKA/MEK/Erk/MSK1/CREB in about 10% of CA1 neurons following fear conditioning (Sindreu et al., Neuron 2007). Interestingly, however, when Erk1/2 is targeted to the presynaptic terminals of hippocampal mossy fibers, it can be activated through synaptic zinc-dependent inhibition of tyrosine phosphatases (PTPs) independently of NMDARs and MEK, and support forms of memory different from those attributed to Erk1/2 in CA1 (Sindreu et al., PNAS 2011). This previous work has set the stage for the current proposal, where I aim to address candidate molecular mechanisms underlying memory formation, retrieval, and extinction, as well as to screen for signal transduction pathways which activation is impaired during learning in aged mice. Immediate aims include: (1) To clarify if different types of hippocampus-dependent memory (e.g. associative vs. spatial) are encoded by separate or overlapping neuronal ensembles. CrelacZ reporter mice will be used in combination with activity-dependent markers and viral delivery of life tracers. (2) To elucidate the role of calcium-stimulated adenylyl cyclases in memory retrieval and the associated activation of PI3K/Akt and Epac proteins. AC1/8 double KO mice will be used. (3) To assess the role of high-affinity zinc-inhibition of GluN2A-containing NMDARs in amygdala-dependent forms of memory extinction. Point mutants of GluN2A will be selectively restored in amygdala neurons of GluN2A KO mice. (4) To identify imbalances in the activity of kinases and phosphatases that may underlie memory deficits in aged mice, and to address the impact of increased neuronal oxidation in neuronal signaling in the aged brain.

Resumen del Curriculum Vitae:

Bachelor degree in Biology, Universitat de Barcelona, 1998. Masters degree (1999) and PhD degree in Cell biology (2004), Universitat de Barcelona. Thesis title ¿Anatomical and functional characterization of zinc-rich circuits in the CA1 region of the hippocampus¿, summa cum laude and ¿mencion europea¿, advisor Dr. J. Perez-Clausell, Gradute student fellowship: ¿Formacion de personal investigador¿ Ministerio de Ciencia y Tecnologia. Postdoctoral researcher in the laboratory of Prof. Daniel Storm, University of Washington, Seattle, since June 2004. Postdoctoral fellowships: two NIH Ruth L. Kirschtein National Research Service Awards (2006-2007 and 2008-2010). Four stays in internationally recognized centers (3 in foreign institutions). Five communications in international meetings, one as invited speaker. Relevant publications: 1) Phan T, Chan G, Sindreu C, Eckel-Mahan K, Storm DR Journal of Neuroscience 2011, pending minor revision for acceptance. 2) Sindreu C, Palmiter RD, Storm DR. Proc Natl Acad Sci USA Jan 18th 2011 Epub ahead of print. 3) DiRocco DP, Scheiner ZS, Sindreu C, Chan GC, Storm DR Journal of Neuroscience 2009, 29:2393-403. 4) Sindreu C, Storm DR Nature Neurosci 2008, 11:527-8. 5) Sindreu C, Scheiner ZS, Storm DR Neuron 2007, 53:79-89. 6) Wang Z, Sindreu C, Li V, Nudelman A, Chan GC, Storm DR Journal of Neuroscience 2006, 26:7375-9. 7) Sindreu C, Varoqui H, Erickson JD, Perez-Clausell J Cerebral Cortex 2003, 13:823-9. 8) Kokaia M, Asztely F, Olofsdotter K, Sindreu C, Kullmann DM, Lindvall O Journal of Neuroscience 1998, 18:8730-9.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **GRACIA SANCHO, JORGE SERGIO** **Referencia:** RYC-2011-08416

Area: Biomedicina

Correo electrónico: jsgracia@gmail.com

Titulo:

Protección endotelial durante la preservación de órganos para transplante: Mecanismos implicados y nuevas dianas terapéuticas.

Resumen de la Memoria:

Organ transplantation is the treatment of choice in several end-stage-organ diseases. Nowadays, early organ damage continues to be an important problem, representing up to 20% of early organ dysfunction, and remains a major focus of therapeutic attention. This is especially relevant when marginal organs (non-beating heart donors, elderly donors, etc) are used for transplantation. Early organ damage following transplantation has two main underlying mechanisms, alloantigen dependent events and vasculopathies. Vascular endothelial dysfunction, broadly defined as an impairment in the endothelial protective phenotype (vasodilator, anti-inflammatory and anti-thrombotic), has been shown to be a major contributor to early organ damage following transplantation but its characterization and possible modulation during organ procurement have been poorly investigated. In fact, a recent study from my postdoctoral stage firstly demonstrates that organ procurement conditions negatively affect endothelial phenotype. Thus, my research aims to 1- discover how different indispensable procedures occurring during organ procurement and transplantation affect endothelial function and organ protection (among others, I will evaluate cold storage using different preservation solutions, intermittent clamping, ischemic preconditioning and organ perfusion, both in vitro and in vivo), and 2- develop novel therapeutic strategies focused to maintain endothelial function during organ procurement for transplantation to ultimately ameliorate organ dysfunction in the post transplantation period.Considering that endothelial function maintenance during organ procurement is being defined as a key factor for a successful transplantation and patient recovery, the results derived from my research will provide important information describing the endothelial status during organ procurement periods, how this influences organ outcome upon reperfusion and, it will describe new therapeutic approaches to significantly improve organ procurement and to increase organ donor pool.

Resumen del Curriculum Vitae:

Undegraduate period. - Academic information: Bachelor in Sciences, degree in Biochemistry, Rovira i Virgili University (URV) 2003. - Research Experience: 1- Institute for Health Research and Policy ¿ London Metropolitan University, Feb-Jun 2003, supervisors Prof. C Branford-White and Dr KN White. 2- Department of Biochemistry and Biotechnology ¿ URV, July-Sept 2003, supervisor Prof. MJ Salvadó.Graduate period. - Academics: PhD by the University of Barcelona, Dec 2007. Extraordinary doctorate award from the University of Barcelona.- Research Experience: research developed at the Hepatic Hemodynamic Laboratory ¿ Hospital Clínic de Barcelona ¿ University of Barcelona. Nov 2003-Dec2007. Mentors, Prof. Jaime Bosch and Dr. JC García-Pagán. Research focused on molecular mechanisms underlying increased endothelial dysfunction in the cirrhotic liver.- Financing: Two successive fellowships, both competitive: from the Institut d¿Investigacions Biomediques August Pi i Sunyer and from the Spanish Health Ministry (PFIS, Insituto de Salud Carlos III). - Publications: 1) Gracia Sancho J et al, J Hepatology 2007; 47:220-227, 2) Gracia-Sancho J et al, Gastroenterology 2007; 133:959-966, 3) Gracia-Sancho J et al, Hepatology 2008; 47:1248-1256, 4) Angermayr B et al, J Hepatology 2006; 44:1033-1039 (3rd author), 5) Angermayr et al, Gut 2007; 56:560-564 (3rd author), and 6) Laviña B et al, Gut 2009; 58:118-125 (2nd author). - Periods at research centres: 1) April 2005, JW Goethe University (Frankfurt), Dr. RP Brandes laboratory. 2) October-December 2006, Harvard University (Boston), Dr. G García-Cardeña laboratory. - Participation in research projects: 1) Full time fellow, FIS PI 04/0655 from ISCIII, Spanish Health Ministry. 2) Full time researcher, SAF 2007/61298, Spanish Science and Innovation Ministry.Postdoctoral period. - Research Experience: 1-Postdoctoral Fellow at the laboratory of Dr. García-Cardeña, Center for Excellence in Vascular Biology, at Harvard Medical School and Brigham and Women¿s Hospital, Boston, USA. May 2008 - May 2010. Research on endothelial protection due to resveratrol administration and endothelial function characterization during preservation for transplantation. 2- Postdoctoral Researcher at CIBEREHD, Barcelona, June 2010-present. Research about endothelial characterization and protection in hepatic pathologies occurring with vascular damage.- Financing: USA: Two successive fellowships from the Spanish Association for the Study of the Liver and from the Department of Innovation, Universities and Enterprise (Government of Catalonia). Spain: Temporary contract from CIBEREHD.- Publications to date: 1) Gracia-Sancho J et al, Cardiovascular Res 2010; 85:514-519, 2) Gracia-Sancho J et al, Transplantation 2010; 90: 142-149, 3) Gracia-Sancho J et al, Gut 2010 (in press, DOI: 10.1136/gut.2010.220913), 4) García-Calderó H*, Rodríguez-Vilarrupla A*, Gracia-Sancho J* et al, J Hepatology 2010 (co-first author, in press, DOI: 10.1016/j.jhep.2010.07.034), 5) Adamo L et al, Nature 2009; 459:1131-1135 (5th author), 6) Villarreal G et al, Biochem and Biophys Res Comm 2010; 391:984-989 (4th author).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **LOPEZ GARCIA, LUIS CARLOS** **Referencia:** RYC-2011-07643

Area: Biomedicina

Correo electrónico: luisca@ugr.es

Titulo:

Exploring the biosynthesis and functions of coenzyme Q in health and disease

Resumen de la Memoria:

Coenzyme Q (CoQ) is an ubiquitous lipophilic molecule mainly synthesized in mitochondria in a complex biosynthetic pathway not completely characterized in mammals. CoQ is essential for ATP synthesis and for the scavinging of reactive oxygen species. However, it exists controversy regarding other funtions of CoQ, e.g. its role in the formation of mitochondrial active supercomplexes, its role in the activity of the mitochondrial permeability transition pore and uncoupling proteins, and its participation in the pirimidine metabolism through its involvement in the reaction catalyzed by dihydrooratate dehydrogenase. In humans, deficiencies of CoQ10 cause clinically heterogeneous mitochondrial diseases, but this heterogeneity is not understood. In the last years, we and others have identified the first mutations in CoQ10 biosynthetic or regulated genes: PDSS1, PDSS2, COQ2, COQ9 and ADCK3. Importantly, in some cases the patients respond positively to CoQ10 supplementation but in other cases the treatment fails. Specifically, only 4 of the 18 patients identified with molecular defect improved after oral supplementation with CoQ10. Based on previous in vitro studies I hypothesize that the clinical heterogeneity of CoQ10 deficiency and its unsuccessful treatment may be due to various factors: 1) different molecular defects; 2) different tissue-specific CoQ levels and tissue-specific CoQ functions; 3) different effects in the stability of the CoQ biosynthetic multiprotein complex; 4) different grade of bioenergetics defect and oxidative stress; and 5) poor absorption and bioavailability of the exogenous CoQ10, together with the different time of the diagnostic and intervention. To evaluate this hypothesis, identify the function and regulation of some functionally-unknown CoQ biosynthetic proteins, clarify the disputed function of CoQ, and evaluate alternative therapies, I propose: 1) to generate a series of CoQ deficient mouse models, i.e. Coq9 KI mice, Coq9 tissue-specific conditional KO mice and Fdrx tissue-specific conditional KO mice. We will also use the Pdss2 mutant mice (we have already generated KI and KO mice for Coq9 and have gotten Pdss2 mutant mice); 2) to identify the functions of Coq9 and Fdrx in the biosynthesis of CoQ, as well as to test if RORalpha could be involved in the regulation of CoQ biosynthesis; 3) to perform a complete behavioral, clinical, histological-morphological, physiological, bioquemical and genetical characterization of each strain, attending especially to the molecular-defect and tissue specificities and the controversial funtions of CoQ; 4) to test alternative and more effective therapies seeking to increase the bioavailability of CoQ10, increase its endogenous biosynthesis, increase the mitochondrial biogenesis, and increase the respiratory chain activities through static magnetic field application. The results of the project will be relevant to advance significantly in the understanding of CoQ biosynthesis in mammals, its multiple cellular functions and how CoQ deficiency cause heterogenic clinical phenotypes. Moreover, the proposed studies are not only of intellectual interest, but also of practical clinical importance for the treatment of primary and secondary CoQ10 deficiencies. Furthermore, our studies may be relevant to more common neurodegenerative diseases, aging and others mitochondrial disorders.

Resumen del Curriculum Vitae:

Bachelor in Biology at the University of Granada (2002). PhD in Biology at the University of Granada (2005). Directors of the Doctoral Thesis: Prof. Acuña Castroviejo and Prof. Escames. ¿Certificado de capacitación para supervisores de instalaciones radiactivas, especialidad medicina nuclear y laboratorio fuentes no encapsuladas¿ (2004). Postdoctoral stay at Columbia University, New York, USA (36 months: from 02/21/2006 to 02/28/2009), in the laboratories of Dr. Hirano y Dr. DiMauro, two world leaders in the research of mitochondrial disorders. Brief stay in the laboratory of Dr. Dikoma Shungu (Cornell University, New York, USA). Postdoctoral position at the Biomedical Research Center (Spain) (from 03/01/2009 to 03/31/2012). Active collaborations with National and International research groups and business companies. 29 original articles published in prestigious international journals (5 as fist author and 2 with the same contribution than the first author; 16 ranked in the Q1 and 10 in the Q2 of their subject categories). 8 reviews in international journals (2 as first and corresponding author). 3 chapter¿s book in international books. More than 590 articles (360 without self-citations) have referenced my articles with an average of 14.5 references by article. H Index: 16 (ISI Web of Science y Scopus). Accumulated Impact Factor: 151.284. 33 communications to international meetings (oral communication selected for the ¿5% highlight session¿ in the AAN 59th Annual Meeting). Invited speaker to the Department of Neurology Ground Rounds, Columbia University (New York, USA), the ¿51st Meeting of the Spanish Society of Geriatrics and Gerontology¿ (Bilbao, Spain) and the ¿176 European Neuromuscular Disorders Workshop: Diagnosis and treatment of Coenzyme Q10 deficiency¿ (Naarden, the Netherlands). Member of the organization committee (and co-chairman of the ¿rare diseases¿ session) of the XXXIII Annual Meeting of the Andalusia Society of Neurology (Melilla, Spain). Predoctoral fellowship from ¿Instituto de Salud Carlos III¿, Ministry of Health, Spain (length: 2 years and 6 months); Postdoctoral fellowship Ministry of Education and Science, Spain (length: 2 years); Postdoctoral contract ¿of excellence¿ from Andalusia Government (length: 3 years); Young Travel Award ¿XXXIII congress of the Spanish society of the physiological sciences¿; Young Travel Award ¿Mitochondria symposium 2008¿ (NIH, USA); Young Travel Award FASEB Summer Research Conference (Colorado, USA); 2010 Young Travel Award from the University of Granada. Principal Investigator of 3 active Grants: Marie Curie International Reintegration Grant Program, FP7 (COQMITMEL, 246691), ¿National Research Program¿ of the ¿Ministry of Science and Innovation¿, Spain (SAF2009-08315) and regional grant (CTS-6133) from the ¿Consejería de economía, innovación y ciencia¿ (Andalusia Government). Collaborator Investigator in other 14 Grants from Andalusia, Spain and USA Research Agencies. Referee of the ¿The Journal of Pharmacology and Experimental Therapeutics¿, ¿European Journal of Pharmacology¿, ¿Journal of Pediatric Biochemistry¿, ¿Pharmacological Reports¿ and ¿Recent Patents on Endocrine, Metabolic & Immune Drug Discovery¿. National Accreditation for ¿Profesor Contratado Doctor¿, ANECA. Educational role for the 2009/2010 and 2010/2011 academic years, University of Granada: 18 credits.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **GARCIA BUENO, BORJA** **Referencia:** RYC-2011-07955

Area: Biomedicina

Correo electrónico: bgbueno@med.ucm.es

Titulo:

¿Brain perivascular macrophages as new therapeutic target for the treatment of depression¿

Resumen de la Memoria:

Brain perivascular macrophages (PVMs) are derived from bone marrow precursors that populate the brain in the perivascular space (Thomas, 1999). Interestingly, PVMs are constitutively phagocytic and can serve as antigen-presenting cells (Hickey and Kimura, 1988), regulate the entry of HIV into the brain (Stoll and Jander, 1999) and participate in the immune surveillance of the nervous system (Bechmann et al., 2001). Recently, applicant¿s previous research group has found an antiinflammatory role of this elusive cell type in prostaglandin dependent neuroimmune-interactions (García-Bueno et al., 2009; Serrats et al., 2010). Two main candidates could fulfil this role: peroxisome proliferator activated receptor gamma (PPARgamma) and cannabinoid-2 receptor (CB-2). Both receptors are constitutively expressed in macrophages/microglia and have been identified as endogenous mediators of defence against excessive neuroinflammation PVMs phagocytic activity could be exploited to deplete them by central injection of the liposome-encapsulated proapoptotic drug clodronate. In addition, due to their hematopoietic origin, bone marrow transplants from WT or selective KO mice (PPARgamma, CB-2, i.e.) could be carried out to precisely define their role in CNS pathologies and the particular mediators involved. In this vein, a role for PVMs has been shown in animal models of multiple sclerosis (T-cell infiltration) and Alzheimer¿s disease (clearance of beta-amyloid) (Hawkes andMcLaurin, 2009; Polfliet et al., 2002).Increasing evidence demonstrates the importance of neuroendocrine and immune responses in the pathophysiology of depression (structural and functional abnormalities in selected brain areas, and motor and cognitive deficits). In this vein, recent studies show:1.-Increased translocation of LPS from gram-negative bacteria following external (psychological) and internal (organic) stressors (¿leaky gut¿) in depressed patients (Maes et al., 2008). This traslocation could de related, at least in part, with the chronic neuroinflammatory process and the ¿depressive-like behaviour¿ presented.2.-Trafficking of T-cells to the brain following stress reduces anxiety-like behaviour and down-regulates chronic inflammatory responses in depression (Miller, 2010).Taking into account all this background, my main research line will explore the antiinflammatory role of PVMs (PPARgamma and CB-2 related) in both neuro-immune interactions in an animal model of depression such as chronic mild stress, trying to regulate the neuroinflammatory process elicited and to normalize the behavioural alterations derived. In addition, I will extend my research to depressive patients (and other psychiatric diseases, as bipolar mania or schizophrenia in a close future) in a traslational study in collaboration with other members of CIBERSAM consortium.

Resumen del Curriculum Vitae:

En Junio de 2001 obtuve mi licenciatura en C.C. Biológicas en la UAM (nota media 2.05) y obtuve una beca predoctoral FPI en el Dept. de Farmacología de la Fac. de Medicina de la UCM. En Julio de 2006 defendí mi tesis doctoral: ¿Estudio de la ruta antiinflamatoria 15d-PGJ2 / PPARgamma; en cerebro y su modulación farmacológica en un modelo de estrés en rata¿, con calificación de Sobresaliente cum laude. En Octubre de 2006 conseguí un contrato como Research Associate en el Laboratory of Neuronal Structure and Function del Salk Institute for Biological Studies, en San Diego, USA, en el grupo del Dr. Paul E. Sawchenko. Tras un año, obtuve una contrato postdoctoral de la FECyT para estudiar el proyecto: ¿Prostaglandinas en la interacción entre los sistemas inmune y neuroendocrino: el papel de la vía antiinflamatoria 15d-PGJ2/PPARgamma¿.A lo largo de mi trayectoria investigadora he participado en múltiples proyectos de investigación nacionales e internacionales (17), consiguiendo 26 publicaciones (22 de ellas indexadas en PUBMED) en distintas revistas con una alta repercusión internacional en su campo (Factor de Impacto acumulado: 113.65; Factor de Impacto medio: 5.01; Índice h: 7). Dentro de estas publicaciones las 7 más relevantes son (4 de ellas como primer autor y 2 como autor de correspondencia): García-Bueno B et al., 2006. Biological Psychiatry; García-Bueno B et al., 2007. Neuropsychopharmacology; García-Bueno B et al., 2008. Neuroscience García-Bueno B et al., 2009. Journal of Neuroscience; Serrats J, Schiltz JC, García-Bueno B et al., 2010. Neuron; García-Bueno B et al., 2010. International Journal of Neuropsychopharmacology; Zoppi S et al., 2010. Neuropsychopharmacology).Complementando mi formación, he atendido a una veintena de congresos nacionales e internacionales en el campo de la Neurociencia. Además, he desarrollado actividad docente como Colaborador Honorífico de la asignatura: FARMACOLOGÍA (3º Medicina) en el Dept. de Farmacología de la Fac. Medicina de UCM en los años académicos 2003/2004, 2009/2010 y 2010/2011 y he sido tutor de un Diploma de Estudios Avanzados (DEA) y cotutor de una tesis sobre el papel del sistema endocannabinoide en la respuesta a estrés. Después de mi estancia postdoctoral de 25 meses en la que puse apunto un método inmunohistoquímico de la detección de mediadores lipídicos en vasculatura cerebral, obtuve conocimientos en técnicas de hibridación in situ de ARNm de genes de respuesta temprana (c-fos, ERK1-2, etc.), en la eliminación selectiva de microglía perivascular hematopoiética con liposomas y transplantes de médula ósea en ratones KO condicional para el receptor PPARgamma;, regresé a España como contratado Post-doctoral CIBERsam. ISCIII. MICINN, en el Grupo del Dr. Leza, donde mi investigación se centra en la evaluación de fármacos con perfil antiinflamatorio para el tratamiento de enfermedades neuropsiquiátricas como la depresión y esquizofrenia y en la búsqueda de marcadores inflamatorios en muestras plasmáticas de pacientes humanos con estas patologías.En la actualidad, el programa Ramón y Cajal me permitiría desarrollar las técnicas aprendidas durante mi formación para seguir estudiando el proceso neuroinflamatorio y descubrir nuevas estrategias terapéuticas derivadas para el tratamiento de enfermedades neuropsiquiátricas y neurológicas con base inflamatoria.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **RODRIGUEZ FERRON, SACRAMENTO** **Referencia:** RYC-2011-09169

Area: Biomedicina

Correo electrónico: sf380@cam.ac.uk

Titulo:

Epigenetic Control of Stem Cell Function: Implications in Adult Neurogenesis

Resumen de la Memoria:

The main goal of this proposal is the identification of epigenetic signatures associated to the decision switch between self-renewal and cell fate determination in stem cell populations. Stem cells are capable of extensive self-renewal while preserving the ability to generate cell progeny that can differentiate into different cell types. Intrinsic mediators as well as extrinsic cues provided by the niche (i.e. the microenvironment where stem cells reside in vivo) are important for stem cell self-renewal and differentiation. The balance between these two processes and the maintenance of the undifferentiated state are not likely to be controlled by single genes and emerging evidence suggests that, in stem cells, epigenetic mechanisms, such as changes in chromatin structure and function, provide a means for co-ordinately activating and repressing arrays of genes at specific steps in a differentiation pathway. Moreover, epigenetic mechanisms are usually associated with heritable changes in gene expression that are often reversible, a feature that may explain changes in stem-cell plasticity, such as the ability of a cell to transdifferentiate, dedifferentiate or become reprogrammed under various conditions. The work that I am proposing is aimed at characterizing specific epigenetic changes associated with the maintenance of pluripotency, like DNA methylation and histone modifications in specific stemness gene promoters (for example GFAP, Sox2 and Hes1) and studying the role and regulation of imprinted genes that could play important roles in stem cell maintenance (Igf2, Igfr2 and p57). I have described that absence of imprinting in NSCs by epigenetic modifications in the paternally expressed gene Dlk1, support stem cell maintenance in brain (Nature, in press). Disruption of imprinting can result in a number of human imprinting syndromes and has been reported to be also the most abundant alteration in cancer. Stem and cancer cells commonly share gene expression patterns, regulatory mechanisms, and signaling pathways suggesting that tumors arise from cell populations with deregulated self-renewal caused by epigenetic and/or genetic initiating events in the stem cell population. Therefore, another important goal of this proposal will be to analyze imprinting status in other somatic stem cells (skin stem cells and hematopoietic stem cells) to determine whether selective imprinting relaxation is a widespread strategy for controlling gene dosage in particular developmental contexts and its possible implication in neoplastic transformation. This type of analysis is important for the understanding of the normal epigenetic changes that are associated with stem cell growth and for the comprehensive analysis of the requirements for the establishment of a pluripotent cell state and of how these changes contribute to the formation of specialized cell types in multicellular organisms. This knowledge may help to clarify whether stem cell plasticity is mostly due to experimental manipulation or whether it actually represents in vivo biology with therapeutic potential. My knowledge on neural development and neurogenesis derived from my PhD work and my expertise in epigenetic regulation acquired during my postdoctoral training will allow me to develop my own independent research programme as outlined.

Resumen del Curriculum Vitae:

Bachelor degree in Biology, from the Universitat de València (1997). Undergraduate Project, Universitat de València (1999) with the title: ¿Análisis de la variación morfométrica y molecular en una población de Limonium dufourii¿. This work resulted in 1 publication: Rodríguez-Ferrón et al. (Conservations Genetics, 2003). PhD degree in Biology, excellent cum laude, Universitat de València (2007). Thesis title ¿Modulación de la proliferación/auto-renovación de células madrer neurales por factores celulares intrínsecos¿ advisor Isabel Fariñas. This work resulted in 6 publications, 5 of them as a first author: Ferrón et al. (Development, 2004); Seri et al. (Cerebral Cortex, 2006); Ramírez-Castillejo et al. (Nature Neuroscience, 2006, same contribution, resulted in a patent); Ferrón et al. (Nature Protocols, 2007); Ferrón et al. (Journal of Neuroscience, 2009); Ferrón et al. (Cell Stem Cell, 2010) and one review, García-Verdugo et al. (Brain Research Bulletin, 2002). One stay in internationally recognized center (National Neurological Institute, Milan). 10 communications to international meetings (6 posters and 4 oral presentations). Postdoctoral Research period in the Department of Physiology, Development and Neuroscience, University of Cambridge (England), in Prof. Anne Ferguson-Smith¿s lab leader in epigenetic regulation of stem cell maintenance: from 1-12-2007 until current date. Awarded with the ¿Herchel Smith Postdoctoral Research Fellowship in Stem Cell Biology¿ developing my own funded project as co-PI titled, ¿Role of epigenetic modifications of the imprinted chromosome 12 in neural stem cell (NSC) self-renewal and differentiation¿. This work has resulted in one publication: Ferron et al (Nature, in press) and one review: Radford et al. (FEBS Letter, in press) and other several manuscripts that are currently under preparation. I am currently developing one more year of research funded by ¿Welcome Trust Biomedical Science (UK)¿ to complete my postdoctoral training. Other functions during this period have been involvement in managerial duties, running project ideas and directing and instructing other members of the hosting lab. Collaboration with other members of the lab resulted in a publication that is under consideration in Cell Metabolism (in second review). The average Impact Factor (IF) of my publications is 12.81 being first author in 86% of them.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **PAGANS LISTA, SARA** **Referencia:** RYC-2011-08216

Area: Biomedicina

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Titulo:

Study of the molecular mechanisms that regulate scn5a expression

Resumen de la Memoria:

Many studies have demonstrated that alterations of the sodium currents in the heart can lead to cardiac arrhythmias, e.g. Brugada Syndrome (BrS). The scn5a gene encodes the alpha subunit of the cardiac sodium channel, which plays a key role in controlling the sodium currents during the action potential. To better understand the molecular basis of cardiac arrhythmias, I propose to study the molecular mechanisms that regulate the expression of the scn5a gene and their relevance to BrS.It is well known that posttranslational modifications of histones dictate transcriptional competence of gene promoters, and alterations of the histone modification patterns can be associated with disease. I will perform Chromatin Immunoprecipitation (ChIP) assays from cardiac biopsies to examine whether changes in histone modifications at the scn5a promoter lead to decreased scn5a expression in BrS patients compared to control subjects. Several evidences suggest that the transcription factor GATA-4 might play an important role in the regulation of the scn5a promoter. I will test this hypothesis in reporter experiments as well as EMSA and ChIP assays. Finally, I will assess the role of microRNAs with putative binding sites at the 3¿UTR of the regulatory region of scn5a in transient transfection experiments. Their effect will be validated in vivo via the introduction of specific antagomirs in mice.I anticipate that these studies will bring new insights and better understanding of promoter regulation and sodium channel expression. Because of the clinical relevance of this cardiac channel in many arrhythmias, I predict that these studies will have an impact for the future diagnosis and treatment of patients with cardiac arrhythmias and sudden cardiac death syndromes.

Resumen del Curriculum Vitae:

I obtained a BSc degree in Biochemistry from the University Autònoma of Barcelona in 1997 (graduating with honors). Then, I started my PhD studies at the Institut of Biologia Molecular de Barcelona (IBMB-CSIC) under the supervision of Dr. Ferran Azorín. To pursue my PhD project, I was awarded a 4-year predoctoral fellowship from the Catalan goverment (Generalitat de Catalunya). My thesis focus was devoted to the regulation of transcription during Drosophila melanogaster development. Specifically, I studied the roles of the transcription factors GAGA and TTK on the regulation of the pair-rule gene even-skipped. This project resulted in two first-author articles in Nucleic Acids Research (Pagans et al, 2002, Nucleic Acids Res.) and The Journal of Biological Chemistry (Pagans et al, 2004, J.Biol.Chem.). In addition, my contribution to other studies in the lab also led to two important publications (Garcia-Bassets et al, 1999, Nucleic Acids Res., Kosoy et al, 2002, J.Biol.Chem.). I continued my scientific career with a postdoctoral position in the Laboratory of Dr. Melanie Ott at the Gladstone Institute of Virology and Immunology, University of California, San Francisco (UCSF). During this period, I obtained funding from several grants: a postdoctoral fellowship from the Spanish Goverment (2003); fellowship grant from the American Foundation for AIDS Research (amfAR) (2006); a grant from the Universitywide AIDS Research Program (UARP) (2006); and a Basic Science award in HIV/AIDS from the Center for AIDS Research (CFAR) (2008). In 2009, I was promoted to Research Scientist at Gladstone. My research sought to understand the transcriptional regulation of the HIV-1 promoter as an important target for antiviral therapy. Specifically, I developed a strong interest in posttranslational modifications of the viral transactivator Tat as novel regulators of HIV transcription. My first studies led to the identification the class III deacetylase SIRT1 as a coactivator of HIV transcription and Tat deacetylase. This work, published in PLoS Biology, was the first in discovering the connection between SIRT1 and Tat and has been a reference for later studies in the field of HIV biology (Pagans et al, 2005, PloS Biol.). As a continuation and expansion of this line of research, I identified a novel posttranslational modification in Tat, lysine methylation. I found that the lysine methyltransferase methylates lysine 51 in Tat and activates HIV proviral gene expression. These studies have been published at Cell Host and Microbe (Pagans et al, 2010, Cell Host and Microbe). In addition, we have been invited to write a manuscript in which we have described the generation of methylated Tat specific antibodies (Pagans et al, 2011, Methods), as well as a review about HIV transcription in the context of chromatin (Kauder et al, Nat. Rev. Microb.). From these studies about Tat methylation, a patent application has been filed. As a result, we entered into a 3-year collaboration with JT-Pharmaceuticals, Inc.On Februrary 2010 I joined the Cardiovascular Genetics Center (University of Girona-IdIBGi), lead by Dr. Ramon Brugada, to study novel mechanisms that regulate cardiac sodium channel expression. On June 2010 I was awarded a Marie Curie International Reintegration Grant (IRG).