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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **HUARTE MARTINEZ, MAITE** **Referencia:** RYC-2011-08347

Area: Biología Fundamental y de Sistemas

Correo electrónico: mhuarte@gmail.com

Titulo:

Large Intergenic Non-coding RNAs as Regulators of Gene Expression in the p53 Pathway.

Resumen de la Memoria:

Mammalian cells encode thousands of RNA molecules structurally similar to protein coding genes ¿they are large, spliced, poly-adenylated, transcribed by RNA Pol II, with conserved promoters and exonic structures ¿ however lack coding capacity. Although thousands exist, only few of these large intergenic non-coding RNAs (lincRNAs) have been characterized. The few that have show powerful biological roles as regulators of gene expression by diverse epigenetic and non-epigenetic mechanisms. Significantly, their expression patterns suggest that some lincRNAs are involved in cellular pathways critical in cancer, like the p53 pathway. I explored this association demonstrating that p53 induces the expression of dozens of lincRNAs. My results, together with the emerging evidence in the field, suggest that lincRNAs may play key roles in numerous tumor-suppressor and oncogenic pathways, representing an unknown paradigm in cellular transformation. However, their mechanisms of function and biological roles remain largely unexplored.The goal of my research is to decipher the functional and biological roles of lincRNAs in the context of the p53 pathway to better understand the cellular mechanisms of gene regulation at the epigenetic and non- epigenetic levels, and to be able to implement lincRNA use for diagnostics and therapies. In order to approach these goals I will focus in the study lincRNAs that I previously identified as bona-fide p53 target genes. I will combine molecular and cell biology techniques with functional genomics approaches and in vivo studies. Importantly, I plan to perform the analysis of cancer patient samples, which will reveal the relevance of our findings in human disease. Altogether, the functional study of lincRNAs will not only be crucial for the development improved diagnostics and therapies, but also will help the better understanding of the mechanisms that govern cellular networks.

Resumen del Curriculum Vitae:

EDUCATION: 2003: PhD. UAM. CNB (CSIC), supervisor Dr. Amelia Nieto. 1997: B.S. Bilogical Sciences. University of Navarra.RESEARCH EXPERIENCE: Nov 2010-Present: Junior Group Leader, CIMA Research Institute, Pamplona. 2008-Nov 2010: Research fellow, Broad Institute of Harvard and MIT, Jonh Rinn's lab. 2004-2008: Postdoct, Pathology Dept, Harvard Medical School. Yang Shi's lab. 2003-2004: Postdoct, Molecular Biology Dept, CNB (CSIC), Amelia Nieto's lab. 2001: Mount Sinai School of Medicine, Adolfo Garcia-Sastre's lab. 1998-2002: Predoctoral fellow, Molecular Biology and Microbiology Dept., CNB (CSIC). Amelia Nieto's lab.PARTICIPATION IN PROJECTS AS PI:Selected as Associated Group in the ¿Young Investigator Program¿ of ¿Programa Consolider-Ingenio 2010 RNAREG¿ PUBLICATIONS: 1. Rinn J.L. and Huarte, M.* Review. Trends Cell Biology (Under Revision) *Corresponding author2. Huarte, M., Rinn J.L. (2010). Review. Hum Mol Gen (142) 409-419.3. Huarte, M*, Guttman, M., Feldser, D., Garber, M., et al. (2010). Cell 142, 409-419. *Corresponding author. Cover of August 6th Cell issue.4. Qi, H.H., Sarkissian, M., Hu, G.Q., Wang, Z., Bhattacharjee, A., Gordon, D.B., Gonzales, M., Lan, F., Ongusaha, P.P., Huarte, M., et al. (2010). Nature 466, 503-507.5. Honda, S., Lewis, Z.A., Huarte, M., Cho, L.Y., David, L.L., Shi, Y., and Selker, E.U. (2010). Genes Dev 24, 443-454.6. Huarte, M. (2009). Journal club. Nature 459, 487.7. Khalil, A.M., Huarte, M., Rinn J.L. (2009). Book Chapter. Imperial College Press, London Imperial College Press. Editor: Frank Slack, Yale University.8. Khalil, A.M*., Guttman, M*., Huarte, M., et al. (2009). Proc Natl Acad Sci U S A. 106(28) 11667-72 *equal contribution.9. Guttman, M., Amit, I., Garber, M., French, C., Lin, M.F., Feldser, D., Huarte, M., et al. (2009). Nature 458, 223-227.10. Li, F., Huarte, M., Zaratiegui, M., Vaughn, M.W., Shi, Y., Martienssen, R., and Cande, W.Z. (2008). Cell 135, 272-283.11. Huarte, M., F. Lan, T. Kim, M. W. Vaughn, M. Zaratiegui, R. A. Martienssen, S. Buratowski, and Y. Shi. J Biol Chem, (2007). 282(30): p. 21662-70.12. Iwase, S. ¿, F. Lan¿, M. Huarte*, P. Bayliss*, L. de la Torre-Ubieta*, H. Heng Qi, et al. Cell, 2007. 128(6): p. 1077-88. ¿* equal contribution.13. Lan, F., M. Zaratiegui, J. Villen, M. W. Vaughn, A. Verdel, M. Huarte, Y. Shi, S. P. Gygi, D. Moazed, and R. A. Martienssen. Mol Cell, 2007. 26(1): p. 89-101.14. Perez-Gonzalez, A., A. Rodriguez, M. Huarte, I. J. Salanueva, and A. Nieto. J Mol Biol, 2006. 362(5): p. 887-900.15. Whetstine, J. R., A. Nottke, F. Lan, M. Huarte, S. Smolikov, Z. Chen, E. Spooner, E. Li, et al. Cell, 2006. 125(3): p. 467-81.16. Affar el, B., F. Gay, Y. Shi, H. Liu, M. Huarte, S. Wu, et al., Mol Cell Biol, 2006. 26(9): p. 3565-81.17. Huarte, M, A Falcon, Y. Nakaya, J Ortin, A Garcia-Sastre, and A. Nieto., J Virol, 2003. 77(10): p. 6007-13.18. Huarte M, Sanz-Ezquerro JJ, Roncal F, Ortin J, Nieto A. J Virol, 2001. 75(18): p. 8597-604.FELOWSHIPS AND AWARDS:STEWART TRUST FOR CANCER RESEARCH AWARD 2007: $60000.POSTDOCTORAL FELLOWSHIP: Ramon Areces. 2004-2006.GRADUATE FELLOWSHIPS: CSIC, 2002-2003; Government of Madrid, 1998-2002.UNDERGRADUATE FELLOWSHIP: CSIC, 2007.ERASMUS FELLOWSHIP: EU, 1995-1996.DIRECTION OF RESEARCH WORK:2010 and 2009 Harvard and MIT graduate students; 2008 Harvard Summer Program.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **SAUER , MICHAEL** **Referencia:** RYC-2011-08995

Area: Biología Fundamental y de Sistemas

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Titulo:

THE ROOT CAP OF ARABIDOPSIS AS MODEL SYSTEM FOR FUNDAMENTAL CELLULAR PROCESSES

Resumen de la Memoria:

Cell biology of plants is a relatively new branch of research which is currently receiving more and more attention. Recent research revealed that plants have very interesting and unique cell biological properties different from animals or yeast. However, much of the machinery is conserved among eukaryotic systems and thus plant cell biology can also contribute to the understanding of other organisms.Here I propose a project which takes advantage of an organ comprised of highly specialized cells, the root cap of Arabidopsis thaliana to study three fundamental cell biological processes: Secretion, cell polarity and programmed cell death. The root cap is particularly well suited for these analyses because of high secretory activity, clearly defined cellular polarity and constant self renewal, which is counterbalanced by programmed cell death to maintain organ size. Consequently, all three processes can be studied in one model system with very simple organization and excellent experimental accessibility.The project will apply two main strategies in parallel: First, a systematic approach using established cell type sorting assays and subsequent transcriptomics and proteomics to identify genes and proteins unique to these cells. Once potential target genes are identified, biological function and interaction within a larger framework will be tested by reverse genetic analyses. Second, a comparative approach that aims to identify similarities and differences to other cell types in the root. For this, a combination of ultrastructure and advanced light microscopy of established markers for the processes under study will be employed. Once specific properties of root cap cells are defined, the behavior of known molecular components and pathways in these cells will be characterized by genetic and pharmaceutical approaches.Using an innovative model system, this project will identify novel components and mechanisms in secretion, polarity and cell death, thus increasing our knowledge of fundamental cellular processes in plants.

Resumen del Curriculum Vitae:

Resumen del curriculumI studied Biology at the University of Tübingen, Germany with specialization in plant molecular biology. There I was the first student ever to obtain the diplom (Masters equivalent) as cumulative work comprised of three research articles, two of which were published in Nature (1st author) and Cell, respectively, and are now among the most highly cited in the field. For my PhD, I joined the group of Dr. Jiri Friml at the Center for Plant Molecular Biology, where I specialized on cell biological aspects of hormone transport, specifically subcellular dynamics and polarity of plasma membrane residing hormone transporters. For a brief period of time, I worked at the institute of Plant Systems Biology in Ghent, Belgium, where I continued with research on plant cell polarity. I was awarded several prestigious postdoctoral fellowships (EMBO, Marie Curie, HFSPO) to join the group of Dr. Enrique Rojo at the CNB CSIC in Madrid, where I am studying subcellular protein trafficking, specifically trafficking to the vacuole and the underlying regulative mechanisms.Throughout my pre- and postdoctoral research, I have published a total of 25 articles, of these 9 as first and 6 as second author. 17 are original research articles published in high impact journals including Cell, Nature and Science. According to ISI Web of Science, these have been cited a total of 1255 times and score an average impact factor of 14.7. Moreover, I was several times selected speaker at international conferences and thus are well familiar with the scientific process of both generating significant scientific results as well as communicating them. I established and worked independently in many collaborative projects, often in other internationally recognized research institutes and therefore acquired an ample spectrum of experimental methods, namely advanced microscopy techniques, genomic and protein analyses, cell sorting and not the least bioinformatics skills to deal with large datasets as generated in high throughput --omics approaches. At the same time I established a wide network of contacts which will be very helpful for future research collaborations.During various stages of my career, I taught practical lab courses at both under- and graduate level. Additionally, I have supervised and tutored students at all levels as well as technical assistants in practical lab work.In summary, I have reached a solid understanding of plant molecular biology and plant cell biology in particular. The excellent training and the amount of independence and scientific freedom I enjoyed already early on in my scientific career have made me confident of my abilities to create and manage innovative projects. I am experienced in supervising people and have coordinated projects under both scientific and organizational aspects. Therefore, I feel well prepared for my next career step of becoming a creative and independent research group leader.

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CONVOCATORIA 2011

Nombre: **PASTOR PAREJA, JOSE CARLOS** **Referencia:** RYC-2011-08498

Area: Biología Fundamental y de Sistemas

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Titulo:

Biogenesis and secretion of basement membrane Collagen IV in Drosophila

Resumen de la Memoria:

Basement membranes (BMs) are polymers of extracellular matrix proteins that underlie epithelia and surround organs in all animals. In addition to providing structural support, BMs and their components are important regulators of morphogenesis, cell signaling, wound healing, immune responses and tumor progression. The major components of all BMs are Collagen IV, Laminin, Nidogen and the heparan-sulfate proteoglycan Perlecan, all conserved in Drosophila. Among them, Collagen IV is the most abundant, comprising 50% of the proteins of the BM. Multiple interactions among BM components have been mapped in vitro, but little evidence exists in vivo to show which of these interactions are crucial for BM assembly, maintenance and regeneration. I have determined already that Collagen IV, secreted by the fat body, is required for deposition of Perlecan (Pastor-Pareja & Xu, under review). I plan to extend this analysis to the mutual relations among all four major BM components. I will use RNAi and mutants to ask whether in the absence of a given component BM localization of the others is affected. Additionally, I plan to perform experiments in animals lacking these proteins, since I have observed already profound deformations in the absence of Collagen IV and Perlecan. I will therefore analyze effects on tissue architecture, intercellular signaling, cell proliferation, regeneration and tumor growth using appropriate fly models. Finally, I plan to investigate the biogenesis of Collagen IV, a very disease-relevant process. To do this, I will perform a genome-wide screening for genes involved in Collagen biogenesis in flies expressing Collagen IV-GFP. While Collagens comprise 30% of the protein mass of the human body, many steps of their synthesis are poorly understood. I expect to classify hits of the screening in terms of (1) subcellular/extracellular Collagen localization (2) monomeric/trimeric state of the Collagen chains and (3) specificity to Collagen (compared to other secreted proteins). My preliminary results argue for the potential of the approach to uncover genes involved in Collagen IV synthesis and general secretion (both ER-to-Golgi transport and Golgi-to-membrane). This screening may illuminate areas of the secretory pathway that remain controversial, such as the transport of large proteins, the specificity of cargo adaptors or the elusive players in transport from the Golgi-to-membrane.

Resumen del Curriculum Vitae:

I obtained my BS in Biology in 1999. After that, I started research as a PhD student in the laboratory of Antonio Garcia-Bellido (Centro de Biologia Molecular, 1999-2005), working on morphogenesis of the fruitfly Drosophila melanogaster. For my thesis work I studied the eversion of Drosophila imaginal discs, a tissue remodelling process during metamorphosis. This research produced a second-author (Martin-Blanco, Pastor-Pareja Pastor-Pareja, Wu Igaki, Pastor-Pareja et al., 2009, Dev Cell; Wu¿, Pastor-Pareja¿ & Xu, 2010, Nature). I am currently interested in the assembly, maintenance and regeneration of basement membranes, a topic on which I plan to focus my future research. My findings about the secretion and function of Collagen IV are the subject of a submitted manuscript (Pastor-Pareja & Xu, under review). The 7 original published articles I have authored to date (5 first author, 2 second author) have been cited a combined total of 170 times, none of them less than 7 times (H index=7). My work has been highlighted in Faculty of 1000 (three times), Nature Reviews Molecular and Cellular Biology (twice) and Nature Reviews Cancer. Given my training and past accomplishments, I feel fully able to lead a research line that uses genetic, cellular and molecular methodologies in Drosophila to further basic understanding of questions relevant to human health.

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CONVOCATORIA 2011

Nombre: **PEREZ JIMENEZ, RAUL** **Referencia:** RYC-2011-08808

Area: Biología Fundamental y de Sistemas

Correo electrónico: raulpjc@biology.columbia.edu

Titulo:

Single-Molecule Studies of Biological Systems: Mechanoenzymology and Mechanobiology

Resumen de la Memoria:

My research line mainly focuses on single-molecule biophysics using Atomic Force Microscopy (AFM). The study of chemical and enzymatic reactions at the single-molecule level as well as biological processes such us protein folding and molecular mechanotransduction in cellular systems, will be essential lines in my scientific career. Previous studies have demonstrated the capabilities of the single-molecule techniques to investigate biochemical and biophysical problems with an unprecedented level of details. I am interested in investigating the chemistry of enzymes such us thioredoxin, PDI or glutaredoxin. The atomistic details of these reactions can now be examined with sub-angstrom resolution. These enzymes are essential in all living organisms being implicated in numerous processes such as, redox regulation, protein folding, apoptosis or activation of ion channels. In addition, these enzymes are involved in diseases and molecular disorders like, cancer, viral attacking (HIV-1), inflammation, heart attack or asthma, among others. Therefore understanding the chemistry of these enzymes is a fundamental problem in modern biochemistry. I will concentrate my effort in studying the interaction of these enzymes with cell surface receptors such as CD4 or CD8. These receptors have important functions in the immune system but also they are associated to viral infections. CD4 is the primary receptor of HIV-1. I will study the mechanochemistry of these receptors with special attention to the role played by oxidoreductases enzymes in their regulation. I am also interested in elucidating the evolutionary aspects associated with the chemistry of enzymes and stability of proteins. Experimental paleogenetics and paleobiochemistry provide an opportunity to investigate in the laboratory the molecular history of modern organisms throughout the study of ancient proteins. The study of resurrected proteins can also reveal valuable information regarding the adaptation of extinct forms of life to climatic, ecological and physiological alterations. These reconstruction and resurrection studies have paved the way to formulate interesting questions about ancient organisms and the biomolecules supporting these ancient life forms. For instance, little is known about how the chemistry of primitive enzymes arose and how the environmental conditions affected the evolution of their chemistry. Another interesting case study is the emergence of mechanical stability in proteins and tissue resilience. This phenomenon may be certainly related with the Cambrian explosion (542 millions of years) that generated the vast majority of the animal phyla. Furthermore, it has been demonstrated that ancient proteins are highly stable to thermal denaturation and capable of working in harsh conditions such us low pH. These characteristics are likely to be related to the environmental conditions that supported early life. Therefore, protein resurrection techniques might be a powerful tool towards designing ultra stable and highly active proteins with biotechnological applications.

Resumen del Curriculum Vitae:

I started my scientific career after graduating in Chemistry from the University of Granada in 2000, majoring in Physical Chemistry. Late in 2000, I joined the laboratory of Professor Jose M. Sanchez-Ruiz in the department of Physical Chemistry at the same university, where I was awarded with a predoctoral fellowship from the Spanish Ministry of Education and Science to start the Ph.D. program in Chemistry. My research focused on the study of the effects of mutations in the stability and folding of proteins using the model protein thioredoxin, a reductase enzyme present in all organisms. As a student I became increasingly interested in the emerging field of single-molecule biophysics. The ability to manipulate individual protein molecules using an atomic force microscope fascinated me and I considered that the single-molecule approach was the perfect continuation in my career. After obtaining my Ph.D., I joined the laboratory of Prof. Julio Fernandez in the Department of Biological Sciences at Columbia University. Prof. Fernandez was one the pioneers in the single-molecule field. Here, I acquired training in single molecule force spectroscopy with special attention to the newly developed force-clamp technique that allows the application of well-calibrated forces to single proteins. I became part of the team that pioneered the first measurements of biochemical reactions under force. We carried out a number of exciting projects that have been published in prestigious journals such as Nature, Science and Nature Structural and Molecular Biology. Also, I have had the opportunity to conduct an exciting project that consisted in the resurrection of the oldest enzymes ever, going back in time more than 4000 million years. These enzymes belonged to some of the most primitive organisms that populated the planet and demonstrated aspect of ancient life that cannot be inferred solely from fossils records. Late in my postdoctoral period, I expanded my interests to biological and cellular systems. The versatility of the single-molecule techniques in studying mechanochemical processes is perfect to investigate numerous protein complexes that are exposed to mechanical forces in their cellular environments. In this vein, I initiated a project to investigate the role of mechanical forces in the entry of HIV-1 into T cells. Currently, I am focusing my research on the study of the mechanical properties of CD4, a cell surface receptor that serves as entry port for HIV-1.

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CONVOCATORIA 2011

Nombre: **MACHON SOBRADO, CRISTINA** **Referencia:** RYC-2011-09071

Area: Biología Fundamental y de Sistemas

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Titulo:

Role of PcrA helicase from Steptococcus pneumoniae in pMV158 replication.

Resumen de la Memoria:

The rolling-circle replication mechanism (RCR) is used by transposons, bacterial plasmids, bacteriophages and viruses, as they are the main genetic elements that spread the antibiotic resistance genes between pathogenic bacteria. RCR is initiated by a site-specific cleavage of one of the strands of the duplex, catalysed by the initiator protein, via a catalytic tyrosine and a divalent metal cation. Once the initiator protein is bound to the origin of replication, a helicase from the host bacteria is recruited, together with the rest of the replication machinery. I am interested in these initial steps of the recognition of the origin of replication by the initiator protein and the mechanism by which the helicase is loaded onto the DNA. The plasmid pMV158 is a promiscuous mobilizable plasmid from Streptococcus agalactiae that replicates by RCR. It has been described previously how the initiator protein RepB binds to the origin of replication and its three-dimensional structure. This protein is divided in two domains: The N-terminal domain responsible for the binding and processing of the origin of replication and the C-terminal domain responsible for the oligomerisation of the protein into a hexamer. The aim of this project is to study the interaction of RepB with the helicase PcrA from S. pneumoniae, through different approaches. This project involves the collaboration between two well established groups: Gloria del Solar Dongil¿s and Miquel Coll Capella¿s lab. First it will be established if there is any interaction between RepB and PcrA and if the presence or absence of a molecule of DNA (and what type of DNA) affects this interaction. We will also try to find out which domain of RepB is involved in the binding with PcrA and to detrmine the role of the oligomerisation domain in this process. All these conditions will be used afterwards as a reference for setting up some crystallization trials, in order to determine the three-dimensional structure of the entire complex. The knowledge of how this loading takes place will be useful in the design of putative compounds that may interfere in the binding of both proteins, with the result of the lost of the plasmid from the bacteria, as an impossibility of it to get replicated. The final consequence of this compound will be the blockage of the spreading of resistance to antibiotics between pathogenic bacteria.

Resumen del Curriculum Vitae:

PublicationsHerrikh, H.*, Machón, C.*, Grainger, W.H., Grossman, A.D., Soultanas, P. Nature, accepted for publication. *Both authors contributed equally to the manuscript. Agúndez, L., Machón, C., César, C.E.., Rosa-Garrido, M., Delgado, M.D., Llosa, M. Applied and Environmental Microbiology (2011) 77 (1).Grainger, W.H.*, Machón, C.*, Scott, D.J., Soultanas, P. Nucl. Acid Res. (2010) 38(9): 2851-64 *Both authors contributed equally to the manuscript.Machón, C., Lynch, G.P., Thomson, N.H., Thomas, C.D., Soultanas, P. Nucl. Acid Res. (2010) 38(6): 1874-88.Chintakayala, K., Machón, C., Haroniti, A., Larson, M.M., Hinrichs, S.H., Griep, M.A., Soultanas, P. Mol. Microbiol. (2009) vol 72 (2): 537-549. Zhang, W., Machón, C., Orta, A., Phillips, N., Roberts, C.J., Allen, S., Soultanas, P. J. Mol. Biol. (2008) vol 376 (5): 1237-1250.Machón, C., Fothergill, T.J., Barillà, D., Hayes, F. J. Mol. Biol. (2007) vol 374 (1): 1-8.Cesar, C.E., Machón, C., de la Cruz, F., Llosa, M. Mol. Microbiol. (2006) vol 62 (4): 984-996.Draper, O., Cesar, C.E., Machón, C., de la Cruz, F., Llosa, M. Proc. Natl. Acad. USA (2005) vol 102 (45): 16133-16140.Fernández-López, R.*, Machón, C.*, Longshaw, C.M., Martín, S., Molin, S., Zechner, E.L. Espinosa, M., Lanka, E., de la Cruz, F. Microbiology (2005) vol. 151 (11): 3517-3526. *Both authors contributed equally to the manuscriptMachón, C.*, Rivas S.*, Albert, A., Goñi, F.M., de la Cruz, F. Journal of Bact (2002) vol. 184 (6): 1661-1668. *Both authors contributed equally to the manuscript.Conference Communications:Machón, C. ¿UK Mobile Genetic Element Workshop¿. Organised by University of Birmingham, Birmingham (UK). 12th of May 2009. Title of the conference: ¿Interaction of RepD and PcrA with oriD sequence of pC221¿.Draper, O.; Elvira-Cesar, C.; Machón, C.; de la Cruz, F.; Llosa, M. ¿III Reunión de la Sociedad Española de Terapia Génica¿. Pamplona (Spain). 28-29th of January 2005. Title of the conference: ¿Nuevas herramientas para terapia génica: ¿Estudio del posible papel de una relaxasa conjugativa bacteriana como integrasa específica de ADN en el genoma humano¿. Draper, O.; Elvira-Cesar, C.; Machón, C.; de la Cruz, F.; Llosa, M. ¿Plasmid Biology 2004¿. Kanoni (Corfu, Greece). 15-21st of September 2004. Title of the conference: ¿Activities of a conjugative relaxase in the recipient cell¿. Machón, C.; Fernández-López, R.; Longshaw, C.; Martin, S.; Molin, S.; de la Cruz, F. ¿Biology of type IV secretion processes¿. Specific Support Action of the Sixth Framework Programme of the European commission. 2004. Las Navas del Marqués (Madrid). Title of the conference: ¿Unsaturated fatty acids are inhibitors of plasmid R388 conjugation, possibly targeting protein TrwD¿. Machón, C.; Fernández-López, R.; Longshaw, C.; Martin, S.; Molin, S.; de la Cruz, F. ¿Biology of type IV secretion processes¿. Organised by European Science Foundation, Giens (Francia). 12-17th of September 2003. Title of the poster: ¿Unsaturated fatty acids are inhibitors of plasmid R388 conjugation, possibly targeting protein TrwD¿. Machón, C.; Rivas, S.; Goñi, F.M.; de la Cruz, F. ¿Biology of type IV secretion processes¿.Organised by European Science Foundation, Castelvecchio Pascoli (Italia). 7-12nd of September 2001. Title of the poster: ¿Interactions of TrwD, a bacterial conjugation protein with model membranes¿.

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CONVOCATORIA 2011

Nombre: **MOREY RAMONELL, MARTA** **Referencia:** RYC-2011-09479

Area: Biología Fundamental y de Sistemas

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Titulo:

WHOLE GENOME APPROACH TO NEURAL NETWORK ASSEMBLY

Resumen de la Memoria:

A fundamental requirement in the assembly of any neural circuit is that neurons establish synaptic connections with their appropriate postsynaptic partners. Failure to do so results in inappropriate processing of information. Indeed, there is increasing evidence that neuropsychiatric disorders (e.g. autism, schizofrenia) reflect abnormal neural circuit assembly. The strategy to increase the processing capabilities of a neural system by diversifying classes of neurons into subclasses with distinct connectivity patterns is conserved through out evolution. In addition, so is the strategy used to segregate distinct neural circuits. This segregation is accomplished by specific neuronal subtypes establishing synaptic connections in particular layers of the neuropil. Drosophila melanogaster visual system shares these two developmental strategies with the vertebrate retina, spinal cord and cerebral cortex, suggesting that the mechanisms identified in the fly might be conserved in higher organisms.The goal of my research is to understand the regulatory programs that instruct the terminal identity of a neuron, and in particular, its synaptic specificity. To address this unsolved question, my approach is based on the study of closely related neuronal subtypes in the fly visual system. It is expected that a large fraction of the molecular differences between neuronal subtypes, with shared developmental origin and similar function, will be utilized to generate specific patterns of connectivity. The use of whole genome approaches (RNAseq) provides a handle to identify these molecular differences, the power of genetics allows for the identification of cell-type specific gene batteries determining synaptic specificity, and the study of cis-regulatory regions can offer an insight into the strategies that bring about specific connectivity patterns. I envision that performing these type of studies on synaptic pairs (i.e. both the pre- and post-synaptic neurons) will identify strategies that facilitate the process of cell-cell recognition. I anticipate that the identification of mechanisms controlling synaptic specificity in the fly will uncover general design principles regulating the precise wiring of neural circuits, and may provide insights into the molecular etiology of neurological and psychiatric diseases.

Resumen del Curriculum Vitae:

I obtained my BSc in Biology from the University of Barcelona in 1998 and was awarded the Premio Extraordinario de Carrera. With a Graduate Studies fellowship from CIRIT Generalitat de Catalunya I joined the laboratory of Dr. Florenci Serras and Dr. Montserrat Corominas. My work focused on the role of reactive oxygen species in development using Drosophila melanogaster as an in vivo model system, focusing on signaling pathways and apoptosis. I obtained my PhD with Honors, Excellent cum Laude May 30th 2003. This work resulted in the publication of 5 research articles: (1) Castellano, S., Morozova, N., Morey, M., Berry, M.J., Serras, F., Corominas, M., Guigo, R. In silico identification of novel selenoproteins in the Drosophila melanogaster genome. EMBO Reports, 2001; 2(8): 679-702, (2)(Serras, F., Morey, M., Alsina, B., Bagunya, J., Corominas, M. The Drosophila selenophosphate synthetase (selD) gene is required for development and cell proliferation. Biofactors 2001; 14(1-4): 143-149), (3) Morey, M., Serras, F., Hafen, E., Bagunya, J., Corominas, M. Modulation of the Ras/MAPK signaling pathway by selenoproteins in Drosophila Dev Biol, 2001; 238: 145-156, (4) Morey, M., Serras, F. 534: 111-114, (5) Morey, M., Corominas, M. 16(22): 4597- 4604. As a postdoctoral fellow and funded by a Howard Hughes Medical Institute Postdoctoral Fellowship (Oct 2003-Sept 2009), I moved on to study the molecular mechanisms regulating the assembly of neural circuits in the laboratory of Prof. Larry Zipursky at the University of California Los Angeles (UCLA). As a result of this work, I characterized and cloned several mutants with defects in synaptic specificity using the fly visual system as a model. This work has resulted in the publication of Morey, M.*, Yee, S.K.*, Herman, T., Nern, A., Blanco, E., Zipursky, S.L. Coordinate control of synaptic-layer specificity and rhodopsins in photoreceptor neurons. Nature 2008; 456(7223): 795-799) (*equal contribution) and Pappu, K. S., Morey, M., Nern, A., Spitzweck, B., Dickson, B.J., Zipursky, S.L. Robo-3 mediated repulsive interactions guide R8 axons during Drosophila visual system development. Under revision in PNAS, and two other pieces of work in preparation. I have designed an unbiased and whole-genome line of research to understand synaptic specificity in fly photoreceptors and since Oct 2009 I got hired as Research Assistant to pursue this project. During my career I have been actively engaged in teaching, training and mentoring at different educational levels. In addition, I have participated in a number international meetings (2 oral and 12 poster) and I have been invited to present my work in six different renowned international research centers and universities.

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CONVOCATORIA 2011

Nombre: **MARTINEZ BUEY, RUBEN** **Referencia:** RYC-2011-07602

Area: Biología Fundamental y de Sistemas

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Titulo:

Exploring protein interactions and their modulation through small-molecules

Resumen de la Memoria:

Microtubule plus-end tracking proteins (+TIPs) comprise a structurally and functionally diverse family of modular proteins that preferentially accumulate at microtubule (MT) growing ends. Here, their functions are to regulate MT dynamics and mediate the anchorage of MTs to many other different cellular structures in order to control fundamental cellular processes such as cell division, intracellular transport, cell adhesion and motility, and cell organization. +TIPs have a remarkable ability to form dynamic networks where most of the protein-protein interactions are mediated by End-Binding (EB) proteins. EBs are master regulators of all known +TIP networks; they are able to autonomously track MT tips independent of any binding partner, while the rest of +TIPs generally require EBs to efficiently track MT ends. A recent study has shown numerous +TIPs use a short linear sequence motif, known as SxIP, for localisation to MT ends in an EB-dependent manner. This motif has been proved to act as a ¿general MT-tip localization signal¿. My research line aims to obtain insights into the +TIP molecular recognition mechanisms and their modes of regulation, necessary to understand how the dynamic and transient +TIP interactions translate into cellular functions. A major focus of my research line involves the identification of small-molecules that modulate these interactions and serve as a biological tool that allows the dissection, with precise temporal control, of the functional interplay between EBs and the broad number of proteins carrying a SxIP MT-tip localization signal. Furthermore, given the crucial role of this interplay in essential cellular processes, most of them deregulated in neoplasia, such as mitosis or cell adhesion, this research might also spur development of new therapeutics. In fact, altered EB expression levels have been detected in several types of tumours. Thus, an exhaustive evaluation of EB proteins as potential new therapeutic targets is a priority of the proposed research line.The biochemical, biophysical, and structural methodologies I plan to use can be framed in the interdisciplinary fields of chemical and structural biology with strong emphasis on translational research. The employed methodology follows the typical scheme of a reverse chemical-genetics approach from a multidisciplinary point of view and can be readily used for different cellular targets of interest at the host institute.

Resumen del Curriculum Vitae:

SCIENTIFIC EXPERIENCE:01.11.2000-28.02.2001. Undergraduate research fellow. Instituto de Recursos Naturales y Agrobiología-CSIC. Salamanca. MSc Biochemistry. Universidad de Salamanca.16.07.2001-30.09.2001. Undergraduate research fellow. Universidad de Salamanca01.10.2001-30.03.2006. PN-FPU predoctoral fellowship. Centro de Investigaciones Biológicas- CSIC. Madrid. PhD Biochemistry. U Complutense de Madrid. Doctorate Extraordinary Prize.01.05.2006-31.07.2007. Alexander von Humboldt Foundation postdoctoral fellowship. Technical University Munich. Weihenstephan (Germany)01.09.2007-30.04.2010. FEBS postdoctoral fellowship. Paul Scherrer Institute. Villigen (Switzerland)01.05.2010-present. Juan de la Cierva postdoctoral contract. Instituto de Biología Molecular y Celular del Cáncer-CSIC/USAL. SalamancaRESEARCH PROFILE: During my PhD period, I acquired skills to characterize protein-ligand interactions and their effects on the respective cellular functions, focused on the regulation of microtubule dynamics by small molecules. The acquired skills included, among others, the thermodynamical characterization of the interaction, the development of methods for fast and robust assays -scalable to high-throughput- to measure binding affinities and the characterization of the ligand-induced effects both in vitro, by biochemical and biophysical methods, and in cultured cells, by cell biology methods. I also acquired skills on the ligand-induced effects on protein structure by using molecular dynamics computer simulations, electron microscopy and small-angle X-ray scattering (SAXS). Additionally, I actively participated in multiple collaborations, which introduced me in many other methodologies such as mass spectrometry, NMR, X-ray crystallography and organic chemistry. In my postdoctoral period, I am further improving and expanding these skills by studying protein interaction networks through the characterization of their molecular recognition mechanisms. As in my PhD, my research is mainly focused on the regulation of cytoskeletal structures, including microtubule plus end tracking proteins (+TIPs) and plakins (in my present position). The acquired skills include the functional dissection of complex cellular processes by in vitro reconstitution assays, using fluorescence microscopy and biochemical methods. They also include the structural and biochemical characterization of protein interactions using X-ray crystallography, electron microscopy, and small angle X-ray and neutron solution scattering (SAXS and SANS), in combination with classical biochemical and biophysical methodologies (CD, ITC, fluorescence, etc.).SELECTED PUBLICATIONS:Buey RM et al. 2004. Chem Biol 11, 225-236Gaitanaos T, Buey RM et al. 2004. Cancer Res 64, 5063-5067 (equal contribution)Buey RM et al. 2005. Chem Biol 12, 1269-1279Buey RM et al. 2006. Biochemistry-US 45, 5933-5938Buey RM et al. 2007. J Mol Biol 365, 411-424Buey RM et al. 2007. Nat Chem Biol 3, 117-125Honnappa S et al. 2009. Cell 38, 366-376Martin-Galiano AJ, Buey RM et al. 2010. J Biol Chem 285, 22554-22565Montenegro-Gouveia S et al. 2010. Curr Biol 20, 1717-1722.Ortega E, Buey RM et al. 2011. J Biol Chem in pressBalsera M, Buey RM et al. 2011. J Biol Chem in press (equal contribution)

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **ROIG NAVARRO, IGNASI** **Referencia:** RYC-2011-08803

Area: Biología Fundamental y de Sistemas

Correo electrónico: ignasi.roig@uab.es

Titulo:

Analysis of meiotic checkpoint in mammalian meiocytes

Resumen de la Memoria:

Meiosis is the special cell division by which the genome is reduced in half during gametegenesis. At meiotic prophase, double stranded breaks (DSBs) are created leading to synapsis and recombination of homologous chromosomes. These processes are carefully monitored in order to avoid possible deleterious effects that inefficient completion of these could cause to the integrity of the genome. When errors are produced, meiocytes arrest and apoptose. Recent studies suggest the existence of at least two mechanisms leading oocytes to death: one dependent on the repair of DSBs and another one independent of recombination. Similarly, studies in male mice have identified a mechanism that senses unsynapsed chromosome axes, independently of break formation, that can promote spermatocyte apoptosis. However, the mechanisms that control these processes are not well understood, neither identified. Moreover, because most mutant mice defective in meiosis display different phenotypes depending on the studied sex, it is commonly believed that different checkpoint mechanisms are active in male and female meiosis. My research goal is to identify the mechanisms that control meiotic progression and find out their key players. Based on my recent published and unpublished work, as well as, other groups work, I hypothesize that there are two major mechanisms controlling meiosis in both males and females: a DSB- dependent and a DSB-independent one. Moreover, previous data suggest that ATM plays a central role in the DSB-dependent one and ATR in the DSB-independent one. To accomplish this, my research plan will address the following objectives:1.-Define the involvement of ATM in a DSB-dependent checkpoint during mouse meiosis. 2.-Analyze the involvement of ATR in the DSB-independent silencing of unsynapsed regions of the genome leading to programmed cell death. The accomplishment of these objectives will provide new insights about which mechanisms control meiotic progression in mammals, a topic barely studied which has caused some debate in the field and misunderstanding of the phenotype of many mouse mutants. Understanding the mechanisms that control meiotic progression in mammals is thus important for understanding how gamete aneuploidy is prevented.

Resumen del Curriculum Vitae:

Education:1999 B.S. Biology, Universitat Autònoma de Barcelona, Spain2002 Master in Cell Biology, Universitat Autònoma de Barcelona, Spain2005 Ph.D. Cell Biology, Universitat Autònoma de Barcelona, SpainPositions and Appointments:09/99-02/01 Associate professor at the Cell Biology, Physiology and Immunology Department, UAB, Spain. 06/03-08/03 Postgraduate Researcher at Dr. Ashley Lab, Yale University, New Haven, USA.07/05-12/05 Postdoctoral Fellow at the Cell Biology, Physiology and Immunology Department, UAB, Spain.02/06-07/08 Postdoctoral Fellow, Molecular Biology Program, Memorial Sloan-Kettering Cancer Center, New York, USA.08/08-01/10 Research Fellow, Molecular Biology Program, Memorial Sloan-Kettering Cancer Center, New York, USA.09/09-present Lecturer, Cytology and Histology Unit, Dept. Cell Biology, Physiology 4(5):e1000076. (* Co-first authors).Roig I., Keeney S. Dev Cell. 2008 Sep;15(3):331-2. Wojtasz L., Daniel K., Roig I., Bolcun-Filas E., Xu H., Boonsanay V., Eckmann C., Cooke H.J., Jasin M., Keeney S., McKay M.J. and Toth A. PLoS Genet. 2009 Oct;5(10):e1000702. Roig I, Dowdle JA, Toth A, de Rooij DG, Jasin M, Keeney S. PLoS Genet. 2010 Aug 12;6(8). pii: e1001062.Lu WJ, Chapo J, Roig I, Abrams JM. Science. 2010 Jun 4;328(5983):1278-81.Daniel K, Lange J, Hached K, Fu J, Anastassiadis K, Roig I, Steward AF, Wassmann K, Jasin M, Keeney S, Toth A. Nature Cell Biology. In press.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **MORENO RISUENO, MIGUEL** **Referencia:** RYC-2011-09049

Area: Biología Fundamental y de Sistemas

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Titulo:

SPECIFICATION OF NEW STEM CELLS IN THE ARABIDOPSIS THALIANA ROOT

Resumen de la Memoria:

Stem cells underlie the formation of tissues and organs in multicellular organisms. Plants normally reprogram new stem cells from differentiated cells to form new organs and tissues postembryonically, while this is restricted to the embryo in animals. Thus, plants provide tractable systems to study cell reprogramming into stem cells. My research focuses on understanding this reprogramming process during lateral branching in the Arabidopsis root. This process requires that a subset of cells first acquire competency and then are specified as lateral root founder cells (LRFC). LRFC are cells pluripotent to form a new stem cell niche by stereotypic asymmetric divisions. I have shown that the selection of the subset of cells that first acquire competency is achieved by the periodic oscillation of genes at the root tip [1]. However, the molecular mechanisms determining how these cells acquire competency and then are specified as LRFC are largely unknown. To address these questions I will: (1) Characterize the function and targets of the oscillating transcription factors that I have identified (1) as important in establishing competence to form LRFC. Some experiments will include ChIP-ChIP/Seq, RNA profiling/microarrays and lineage analyses of the LRFC in the cognate mutants.(2) Perform a mutagenesis screen with a triple-marker line for competency (DR5), first asymmetric division of the LRFC (WOX5) and future organizing center of the subsequent stem cell niche (SCR) (Fig1).(2.1) Screen for and characterize mutants impaired in LRFC specification. These mutants should show competency to form LRFC (DR5 expression) but not be able to undergo further asymmetric divisions (neither WOX5 nor SCR expression).2.2) I will also characterize mutants that are not able to form new functional stem cell niches (WOX5 but no SCR expression).These approaches will help to unravel stem cell specification and reprogramming in Arabidopsis, and the knowledge gained could have applications in other species.1. M. A. Moreno-Risueno et al., Science 329, 1306 (Sep 10, 2010).

Resumen del Curriculum Vitae:

During my scientific career I have developed skills in different plant systems (Hordeum vulgare and Arabidopsis thaliana) and established a strong foundation in developmental and systems biology, genomics, genetics and molecular biology. My PhD research focused on transcriptional regulation during seed maturation and germination. I identified novel regulators of storage protein genes during seed maturation (Moreno-Risueno et al. (2007) Plant J 51: 352); and of hydrolase genes during germination (Moreno-Risueno et al. (2008) Plant J 53: 882). My postdoctoral research has significantly contributed to our understanding of transcriptional regulation during plant development. I identified a novel developmental regulatory mechanism, the root clock (Moreno-Risueno et al. (2010) Science 329: 1306), which is involved in selection of the subset of cells that become pluripotent to form a new lateral root. In a different project, I have identified root transcription factors involved in asymmetric cell division and cell identity. In addition, my work has helped to elucidate the role of cyclin CYCD6;1 during root tissue patterning (Sozzani et al. (2010) Nature 466: 128); and demonstrated the non-cell autonomous action of the master root regulator SHR to specify vasculature tissues from the endodermis (Carlsbecker et al. (2010), Nature 465: 316). I will use the skills and knowledge I have acquired to pursue research on cell reprogramming. I will investigate the molecular cues and regulators that determine how differentiated cells become competent and are specified as new stem cells during lateral root branching in Arabidopsis thaliana.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **DJOUDER ., NABIL** **Referencia:** RYC-2011-08901

Area: Biología Fundamental y de Sistemas

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Titulo:

Metabolic control of cell survival by nutrient and growth factor signalling pathways

Resumen de la Memoria:

Highly interconnected signal transduction pathways, such as the nutrient and growth factor cascades, regulate proliferation, growth, survival and metabolism of cells. The increasing knowledge of such cascades and their components is having a large impact on the delineation of molecular mechanisms underlying pathological states in human diseases such as cancer. Improper regulation of these circuitries can lead to the development of such diseases. By dissecting and delineating mechanisms of growth factor and nutrient signalling pathways, we are interested in a better understanding of the molecular circuitry underlying cancer development.In this regard, we have recently identified a novel downstream effector of the growth factor and nutrient-regulated mTOR-S6K1 circuitry, termed URI that acts at mitochondria to promote cell survival by binding and inhibiting PP1 phosphatase activity. We established URI/PP1 as new mitochondrial components dedicated to oppose sustained S6K1 survival signalling, ensuring that the mitochondrial threshold for apoptosis is set in accordance with nutrients and growth factors availability.Importantly, in several human cancer cell lines, over-expression of URI leads to increased S6K1 activity and cell proliferation. Moreover, recent work suggests, in several human carcinomas and leukaemias, URI is amplified and its protein expression correlates with tumour cell proliferation and reduced patient¿s survival. These observations support that URI expression promotes resistance to apoptosis and might have oncogenic activity.With a special focus on the Mitochondria-based URI Signal Transduction (MUST) complex, we aim to find new effectors of the growth factor and nutrient cascades, understand why cancer cells grow and proliferate in an unregulated manner and why they are resistant to apoptosis and how we could induce death in cancer cells. Using mouse genetics, in collaboration with Erwin Wagner, a master in developing mouse models, we aim at deciphering the contribution of URI in cancer development. In a long term goal, this work will lead to a better understanding of the molecular circuitry and mechanisms underlying cancer initiation and progression in response to growth factor and nutrient inputs.

Resumen del Curriculum Vitae:

I was born in France and obtained my PhD in Molecular Pharmacology from the University of Strasbourg (France) and the University of Freiburg (Germany), where I worked in the laboratory of Prof. Klaus Aktories. I studied the molecular mechanisms underlying the activation of mast cells by cross-linking of high affinity antigen receptors (Fcε-RI) and the involvement of small GTPases from the Rho family in this activation.In 2001 I moved to Basel as a postdoctoral research fellow and joined the laboratory of Prof. Wilhelm Krek at the Novartis Friedrich Miescher Institute. Since, I have been working in the field of growth control, cancer, and associated metabolic disorders. Most of my research focuses on the mTOR/S6K pathway and the integration of growth factors, nutrients, and energy homeostasis.In 2003 I moved with Prof. Wilhelm Krek to the Institute of Cell Biology at the Eidgenössische Technische Hochschule (ETH) in Zurich. I became a member of the Competence Centre for Systems Physiology and Metabolic Diseases (CCSPMD). In September 2009, I joined the CNIO as a Junior Group Leader, establishing my group in the field of Growth factors, Metabolism, and Cancer.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **JOHNSON , RORY** **Referencia:** RYC-2011-08851

Area: Biología Fundamental y de Sistemas

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Titulo:

Functional Analysis of Human Long Noncoding RNAs (LncRNAs) Using a New RNA Two Hybrid (R2H) Assay

Resumen de la Memoria:

The human genome contains tens of thousands of long non-coding RNA (lncRNA) molecules of unknown function. We have increasing evidence that these represent a major new class of gene regulators that are involved in diverse pathways of clinical relevance, including cancer, neurodevelopment and embryonic stem cell reprogramming. It is likely that only a small fraction of the true number of lncRNAs have so far been discovered, and many fewer (

Resumen del Curriculum Vitae:

Rory Johnson Email: rory.johnson@crg.euWebsite: www.roryjohnson.org Date of Birth: 9-2-79Nationality: IrishEmployment :2010-present: Staff Scientist, Centre for Genomic Regulation (Barcelona), Genomics and Bioinformatics Group.2009-2010: Research Associate, Genome Institute of Singapore, Stem Cell Laboratory. 2007-2009: Postdoctoral Fellow, Genome Institute of Singapore, Stem Cell Laboratory.Education:2002-2006: Wellcome Trust PhD in Neuronal Gene Regulation and Genomics, University of Leeds (UK).1996-2000: Msci Physics (1st Class), Imperial College London (UK). Specialisation: Biophysics and Structural Biology.Other Activities:2008-2010: Lecturer, University of Western Australia (Singapore Campus).2009-2101: Institute Representative to A*STAR Postdoc Committee.2008-2009: Chairman, Genome Institute of Singapore Postdoc Committee.Conference Presentations:2011: British Society for Neuroscience, Invited Oral Presentation.2010: Trends in Psychiatric Genetics and Neurobiology (USA), Invited Oral Presentation.2009: Abcam Regulatory Networks in Stem Cells (Singapore), Selected Oral Presentation.2009: Genome Informatics (Sanger Institute), Selected Oral Presentation.2006: Molecular Basis of Neurodegenerative Disease (University of Cork), Selected Oral Presentation.Review Duties:Invited to review manuscripts for: RNA, Nucleic Acids Research, Neurobiology of Disease, BBA.Invited to review grant requests: Ministry of Science and Biotechnology (Netherlands), Biological Sciences Research Council (UK).Courses:Animal Handling (Singapore 2008); Scientific Presentation (Singapore 2007); Statistics Masterclass (Singapore, 2007); Scientific Writing (Leeds, 2006); Bioinformatics and Genomics (Cambridge, 2005); Genome Access Course (Cambridge, 2004).

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **OLIVA BLANCO, MARIA ANGELA** **Referencia:** RYC-2011-07900

Area: Biología Fundamental y de Sistemas

Correo electrónico: marian@cib.csic.es

Titulo:

Structural and functional study of TubZRS DNA partitioning system from Clostridium botulinum C phage: molecular basis of phage segregation

Resumen de la Memoria:

TubZ was recently included in tubulin/FtsZ GTPase super-family and is involved in plasmid segregation. These GTPases differ from classical GTPases (ras, EF-Tu) in the nucleotide binding topology and GTP hydrolysis mechanism. Interestingly polymerizing GTPases assemble into single linear filaments whereas TubZ polymerize into double helical filaments similar to ParM, MreB or actin filaments. Bacterial partitioning systems constitute a minimalistic segregation system composed of three essential elements: two proteins (NTPase and a DNA-binding adaptor protein) and a centromer-like region on the DNA. Based on the nature of the protein responsible for the movement during segregation, these systems have been classified into type I (contains an NTPase with a variation of the Walker A type ATPase fold), type II (uses actin-like ATPases) and type III (uses the GTPase TubZ). Virulence plasmids from Bacillus (B. anthracis and B. cereus (pOX1), B. thuringiensis (pBtoxis)) that encode for lethal toxins also code for their segregation systems, which include TubZ (partitioning protein), TubR (DNA-binding protein) and tubS (centromer-like region). Genome sequence analysis of Clostridium botulinum C neurotoxin-converting phage showed up a putative partition system with an FtsZ-like protein, TubZ (ORF-189), a putative HTH-motif DNA binding protein, TubR (ORF-188) and two direct repeated DNA sequences, tubS, a typical feature of centromer-like region (upstream ORF-188). This is very interesting since from the seven types of botulism neurotoxins (A, B, C1, C-G) produced by C. botulinum, type C1 and D genes are carried by bacteriophages and C phage is one of them. The goal of my investigation is to unravel the phage C TubZRS segregation system mechanism of action. This project intends to open a new research line built up on my previous research career training and is focused in a new system that involves a polymerizing GTPase. I propose a holistic approach to carry out this study meaning I will use different techniques (structural, biophysical, biochemical and molecular biology) to solve these questions. Since the structure of the protein is directly linked to its function I intend to: (i) get the structure solution at atomic level of the components of the system: TubZ and TubR, (ii) perform a structural and biochemical analysis of the protein-protein and protein-DNA interactions, (iii) analyze the functional mechanism of TubZRS system in vitro by biophysical and biochemical experiments.

Resumen del Curriculum Vitae:

I graduated in Biology by the Universidad Complutense in Madrid (Spain) in 2000 in Bio-sanitary specialty. My thesis training was done at CIB-CSIC under Professor José Manuel Andreu supervision. I was supported by a CSIC contract and afterwards I was awarded with a FPI fellowship from the Spanish Ministry of Science and Technology. During 5 years I was involved in different projects financed by the Spanish Ministry of Science and Technology and Comunidad Autónoma de Madrid with the main purpose of studying the folding and assembly of the bacterial cell division GTPase FtsZ and the structural and functional relationship with eukaryothic tubulin. I gained my PhD in Biology from the Biochemistry and Molecular Biology program by the Complutense University in Madrid with the highest honors. In 2006 my thesis work was awarded with the Extraordinary Prize by the Complutense University. During my pre-doctoral training, I did a short stay of 5 months in the laboratory of Dr. Jan Löwe at the MRC-LMB (UK), which allowed me to get introduced into FtsZ structural studies. The results of my research were published in international recognized journals, with two first-authorships: Andreu JM, Oliva MA, Monasterio O. J. Biol. Chem. 2002; Oliva MA, et al. J. Biol. Chem. 2003; Oliva MA et al. Nat Struct. Mol. Biol. 2004; Bertrand S, Barthelemy I, Oliva MA, et al, J. Mol. Biol. 2005; Schlieper D, Oliva MA, et al. Proc. Natl, Acad. Sci. USA, 2005. Three of these publications have been revised and selected as ¿recommended¿ or ¿must read¿ in the scientific forum Faculty of 1000. During this time I also was involved in the writing of the book chapter ¿FtsZ folding, self-association, activation and assembly¿ in the book: ¿Molecules in time and space: bacterial shape, division and phylogeny¿ edited in Kluwer Academics Group. After my PhD I was awarded with an EMBO Long-Term Fellowship to work on Dr. Jan Löwe group (MRC-LMB, UK) and afterwards I was supported by two MRC contracts. Structural biology is a particularly important skill to the field of protein machineries since protein structure is directly linked to its biological function. Following my career development aim I worked on FtsZ related projects but also I was interested in the understanding of the complex machinery involved in the bacterial cell division process. From this period of time are two first-authorship papers: Oliva MA, Trambaiolo D, Löwe J. J. Mol. Biol. 2007 and Oliva MA, Halbedel S, et al. EMBO J. 2010. In 2008 I was awarded with a Juan de la Cierva contract to work in Dr. Fernando Díaz laboratory at CIB-CSIC and I started in my new position in May 2009. We work in collaboration with Dr. Andreu¿s group and want to combine my structural studies skills and the groups experience on tubulin and FtsZ drugs studies to the discovery and analysis of new antibacterial drugs. Furthermore we work on the biochemical characterization of TubZ, a new GTPase involved in the segregation of a bacteriophage. During my career I have participated in different workshops, talks and meetings through posters or oral presentations. I have attended international recognize courses to fulfill my formation in structural studies and scientific presentations skills. Finally I have been guide and trainer of PhD students and summer students and referee of different editorial groups since 2006.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **ESTELLA SAGRADO, CARLOS** **Referencia:** RYC-2011-08307

Area: Biología Fundamental y de Sistemas

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Titulo:

Genetic control of organ size and shape

Resumen de la Memoria:

In the last 30 years developmental biologists have identified many of the genes that control the architecture of our body plan, including those that specify the identities of specific organs such as the limbs. But little is known about the genetic control of organ size and, in particular, how the proportions within an organ are determined. The understanding of organ size is an important challenge in science since most of the genes that control this process will be relevant to tumorigenesis. Recent studies in this field place cell-cell interactions, involving cell adhesion molecules, as an important process that regulates many developmental events that lead to the specific control of organ size and patterned cell proliferation. In Drosophila, the protocadherin family (Fat (Ft), Fat-like, Flamingo and Dachsous (Ds)) mediates calcium-dependent cell-cell adhesion and is involved in different developmental processes including Proximo-Distal (PD) axis formation and growth regulation in the appendages. In the last years the important role of the Ds activity gradient in cell proliferation control has been described. Another signaling pathway implicated in the control of organ growth is the Notch pathway. The Notch genes encode for transmembrane receptors whose structure is maintained from worms to humans. Notch plays an important role in animal processes as diverse as proliferation, growth, differentiation and cell death. The project that I propose is based on the characterization of the role of Ds and Notch in the control of organ growth and shape using the formation of Drosophila legs as a model system. I will look for Notch and Ds target genes that are directly implicated in the control of appendage growth and shape. Recently I have described a new role for the Drosophila Sp family of transcription factors, Sp1 and buttonhead, in leg growth that could mediate Ds and Notch functions (Estella and Mann, 2010. PloS Genetics). The results that I will obtain would be of great significance to understand the role of these pathways (Notch and Ds) in human tumorigenesis.

Resumen del Curriculum Vitae:

I graduated in Biology in 1999 and during the last year of my studies I joined Ginés Morata's lab at the CBMSO in the Universidad Autónoma de Madrid. During this time, I experienced for the first time the dynamics of a Molecular Biology lab using Drosophila as a model organism to study pattern formation and growth. Shortly after that, I had the opportunity to stay in the lab and develop my thesis project, that was focused on the molecular and functional characterization of two sister genes of the Sp family of transcription factors, Sp1 and btd, during limb development. I also had the chance to collaborate with different groups within the CBMSO and abroad. A total of 3 publications, one of them as a first author, was the result of this period (Calleja et al, 2000; Suzanne et al, 2003; Estella et al, 2003). My first author paper was awarded with the Young Researchers Award for Best Publication in 2003 by the CBMSO. In 2004, I was granted with the postdoctoral fellowship of the Spanish Ministry to continue my research at Columbia University of NYC under the supervision of prof. Richard Mann. During this period I had the opportunity to study the molecular mechanisms that control proximo-distal axis formation. We have identified how two signalling pathways Wg (Wnt) and Dpp (TGFB) cooperate together to activate gene expression and how the Distalless (Dll) gene integrates the different levels of signalling activation. Moreover we have dissected the cis-regulatory elements of Dll that control its expression in a space and time dependent manner. Finally, we have functionally characterized the ventral selector gene for appendage formation in Drosophila, Sp1 and showed that vertebrate Sp8 can rescue many of the functions of the Drosophila gene, proving that these activities have been conserved, despite more than 500 million years of independent evolution. In the five-year period at Columbia University I had the chance to learn very diverse techniques (Molecular Biology, Biochemistry and Bioinformatics) that were critical to my training as a researcher. A total of 4 first author papers in prestigious journals such as Developmental Cell, PloS Genetics or Development were the result of this productive period (Estella and Mann, 2010; Mckay D, Estella et al, 2009; Estella et al, 2008, Estella and Mann, 2008). From 2007 till 2010 I was promoted as a research associate at Columbia University and in 2008 I started a collaboration with Gerry Rubin's lab at Janelia Farm Howard Hughes Medical Institute where I was characterizing the expression pattern of cis-regulatory elements of Drosophila genes. At Columbia University I was directly involved in supervising rotation students and a graduate Ph.D candidate. All this work has been presented as invited speaker at international conferences and prestigious research institutions. In 2010 I was hired by the Fundación IVI and temporally changed my research focus and system to become an independent researcher studying the decidualization process of the human endometrium at a molecular level. The acquisition of experience using primary cell lines and cell culture can be a unique quality not so common in developmental biologists. This turn in my research will lead me to acquire a translational point of view for the results I will obtain using a model organism as Drosophila to human biology and disease.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **NOVO LOPES HENRIQUES, ROSSANA ANDREA** **Referencia:** RYC-2011-09220

Area: Biología Fundamental y de Sistemas

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Titulo:

LIGHT AND CIRCADIAN REGULATION OF CELL GROWTH AND CELL DIVISION ¿ A ROLE FOR THE ARABIDOPSIS S6 KINASE (S6K)

Resumen de la Memoria:

Plants are sessile organisms that constantly adapt to a changing environment. Light perception is therefore a critical mechanism for plants to assess the number of neighbors, the time and length of the day and the season. Working in concert with light signals, the circadian clock anticipates rhythmical diurnal changes and prepares the adequate physiological responses. Several mutants defective in light perception and/or circadian function exhibit exaggerated hypocotyl length, petiole elongation, small leaves with a overall decrease in their biomass and fitness, a phenotype that strongly resembles shade-grown plants. I am interested in the mechanisms that, under light and circadian regulation, will account for these changes in plant architecture. Using the model plant Arabidopsis, I have studied the proteins involved in light perception and circadian regulation. Among those, the PIF (PHYTOCHROME INTERACTING FACTORS) family of transcription factors seems to be critical to the responses that characterize shade growing plants. PIFs are very unstable proteins that accumulate at the end of the night when they can bind to G-boxes sequences in the promoters of their target genes, most of which are required for cell expansion.My work with the 40S ribosomal protein S6 kinase revealed that this growth regulator, together with RBR1/E2FB, participates in a multi-protein complex that inhibits cell proliferation, especially when nutrient conditions are not optimal. I also found that S6K1 is co-expressed with a major component of the circadian clock, CCA1, which is a PIF target gene. Like CCA1, S6K1 transcript accumulates in the early morning, is under circadian regulation, and possesses G-Box element at its promoter/5¿UTR. This finding suggests a link between light, circadian clock, cell growth and cell division. My aim with this project is to establish this connection and extended it to other regulators of cell growth and cell division. I would like to generate a network where environmental signals can be connected to the proper intracellular mechanisms that underlie the adequate physiological response. Understanding the processes, leading to changes in plant the growth patterns and architecture that are set in motion by environmental changes, is critical to improve plant biomass under field conditions.

Resumen del Curriculum Vitae:

Rossana Andrea Novo Lopes Henriques, born in Moçâmedes, Angola, on the 14th of August, 1972.Education1997-2002 Ph.D. (Summa cum Laude) in Biology, specialty of Molecular Biology, Faculty of Sciences, University of Lisbon (in collaboration with the Koncz Laboratory, MPIZ, Cologne, Germany).1995-1997 MSc. (Excellent) in Cell Biology, University of Coimbra, Portugal.1990-1994 Degree in Biology, University of Coimbra, Portugal, with the final mark of 16/20. Research Experience October 2005- present Research Associate, Laboratory of Plant Molecular Biology, The Rockefeller University, USA.Research focus: Circadian clock function and light signaling. Post-translational regulation of circadian clock components, phytochrome A signaling network and phytochrome B post-translational regulation by the COP1 E3 ligase. Regulation of PIF protein stability by the different light signaling pathways. Epigenetic regulation of circadian clock function and identification of non-coding RNAs under circadian control.2002-2005 Postdoctoral Fellow, School of Biological Sciences, Royal Holloway, University of London, UK.Research focus: Growth signaling pathways involving the AGC kinase, PDK1, and its target proteins. Projects developed dealt with the identification of PDK1 targets such as AGC2-1 and the detailed study of the function of another AGC kinase ¿ S6K1. 1997-2002 PhD student at Faculty of Sciences, University of Lisbon, Portugal, and visiting student at the Koncz Laboratory, MPIZ, Cologne, Germany.PhD thesis: ¿Studies on Iron and Zinc transporter proteins (ZIP family) and on CYP90A2 (homolog of CYP90A1) in Arabidopsis thaliana and Camellia japonica¿.Research focus: Identification and characterization of Arabidopsis T-DNA insertion mutants for several members of the ZIP family of metal transporters. Optimization of tissue culture protocols for in vitro propagation of the woody plant, Camellia japonica, as well as the establishment of basic Molecular Biology protocols in this species, leading to the generation of a cDNA library. Isolation of C. japonica counterparts of the ZIP family of metal transporter genes and identification of CYP90A2, a protein involved in the Brassinosteroid synthesis pathway. Expression of this new P450 in heterologous systems and determination of protein function. Collaborating in the generation of the Koncz collection of Arabidopsis T-DNA insertion mutants.1995-1997 MSc. student, Department of Botany, University of Coimbra, Portugal.MSc. Thesis: ¿Genetic diversity studies in Anthurium scherzerianum Schott using RAPD markers: identification of two varieties¿.Research focus: Identification of different varieties of Anthurium scherzerianum using molecular biology techniques, and development of new tissue culture techniques for propagation of ornamental species.Publications2010Henriques R, et al., EMBO J. 29(17): 2979-93.Jang IC, et al., Plant Cell 22(7):2370-83.Baudry A, et al., Plant Cell 22(3):606-22. Nakamichi N, et al., Plant Cell 22(3):594-605. 2009Yang SW, et al., Plant Cell 21(5):1341-59.Henriques R*, Jang IC*, Chua NH. Curr. Opin. Plant Biol. 12(1):49-56.2007Kiba T, et al., Plant Cell 19(8):2516-30.Lin SS, et al., Plant Biotech. Rep. 1: 125-34.2006Zhang X, et al., Nature Prot. 1(2):641-6.2004Anthony RG, et al., EMBO J. 23(3): 572-81.2003Bögre L, et al., Trends Plant Sci. 8(9):424-31.2002Rios G, et al., Plant J. 32(2): 243-53.Henriques R, et al., P

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **MUNOZ FONTELA, CESAR** **Referencia:** RYC-2011-07845

Area: Biología Fundamental y de Sistemas

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Titulo:

Role of p53 in innate and adaptive immunity to influenza A virus.

Resumen de la Memoria:

Our research in recent years has revealed that in addition to its functions as a tumor suppressor gene, p53 also plays an important role in innate antiviral immunity. We have demonstrated that p53 enforces antiviral defense by two means: promoting apoptosis in infected cells to impair viral replication, and enhancing type I interferon (IFN) signaling by direct transcriptional activation of IRF9. We have generated evidence that loss of p53 impairs early inflammation in response to pulmonary influenza A virus (IAV) infection in mice. Thus, after IAV infection, p53-/- mice display reduced pulmonary monocyte infiltration and defective dendritic cell (DC) migration to the draining lymph nodes compared to wt mice, rendering p53-/- mice more sensitive to IAV-induced pathogenesis than their wt counterparts.We hypothesize that by promoting early expression of pro-inflammatory cytokines, p53 enforces pulmonary innate immunity to IAV, which ultimately, may influence the effectiveness of anti IAV-adaptive immunity. Thus, p53 modulation offers new possibilities of therapeutic intervention against pandemic IAV. To test such hypothesis we will:Aim 1: Elucidate the influence of p53 in anti-IAV pulmonary innate immunity.Rationale: In response to IAV infection, p53 promotes an early up-regulation of pro-inflammatory cytokines and infiltration of blood monocytes, which in the mouse, give rise to the two major pulmonary DC subsets, CD11bhigh DCs and CD103+ DCs. Whereas a strong inflammatory response has been shown to be essential for viral clearance, it is also associated to death induced by highly pathogenic IAV. By using mouse adapted IAV strains that reproduce the effects of low pathogenic and highly pathogenic IAV, in this aim we want to answer the following questions: 1) How does p53 promote pulmonary monocyte infiltration upon IAV infection? 2) How does this monocyte infiltration affect to the activation and migration kinetics of lung DCs? 3) What is the influence of p53-induced inflammation in the pathogenic response associated to mouse-adapted models of highly pathogenic vs. low pathogenic IAV?Aim 2: Investigate the contribution of p53 to anti-IAV cellular and humoral immunity. Rationale: DCs provide a bridge between innate and adaptive immunity due to their ability to capture and present antigens to T cells. Our preliminary studies indicate that after IAV infection, p53-/- mice show defective migration from lungs to lymph nodes. We hypothesize that p53 activity may influence cellular and humoral immunity to IAV. To test such hypothesis we will answer the following questions: 1) How does p53 loss affect to T cell immunity to IAV? 2) What is the effect of p53 in the generation of anti-IAV specific antibody responses?Aim 3: Evaluate the effectiveness of Mdm-2 inhibitors (p53 enhancers) as adjuvants of live attenuated IAV vaccines. Rationale: We hypothesize that modulation of p53 activity may be a novel host-targeted therapeutic strategy to influence anti-IAV inflammatory responses. Through our collaborators in this proposal, as well as through commercial sources, we have access to a panel of compounds that have been previously shown to enhance p53 activity. In this aim we will use such compounds to try to answer the following question: 1) Can we use p53 activators as live attenuated vaccine adjuvants to generate protective immunity to IAV?

Resumen del Curriculum Vitae:

Personal Statement.My research goal is to understand the pathobiology of viral infection from the point of view of the host (immune response, mechanisms of viral clearance) and the pathogen (mechanisms of immune evasion, modulation of cellular functions) and apply such knowledge to design more effective antiviral treatments and vaccines. As a graduate student, I uncovered several immune evasion mechanisms employed by Kaposi¿s sarcoma herpesvirus and by doing so, I realized that a significant number of cellular targets of KSHV were tumor suppressor genes, including p53 and PML. These findings led me to focus my research on the antiviral properties of type I interferon-inducible tumor suppressor genes, such as p53 and ARF. To pursue this line of research I joined Dr. Stuart Aaronson¿ lab at Mount Sinai School of Medicine for my postdoc, and I established a collaboration with Dr. Adolfo Garcia-Sastre who eventually, became also my co-mentor. I believe that our discoveries indicating that tumor suppressors such as p53 and ARF are able to prevent viral replication by different mechanisms changed the classic view about these genes as exclusively involved in preventing the emergence of cancer cells, and provided some insight into the reasons why they are so well conserved during evolution and so frequently targeted by viral proteins. I was honored to receive the ISICR Seymour and Vivian Milstein Young Investigator Award for these discoveries.Positions:2003-2006: Graduate Student. Dpt. Microbiology, Complutense University (Madrid, Spain)2004: Reseach Scholar. Imperial College, London (UK). 2006-2009: Post-Doctoral Fellow, Dpt. Oncological Sciences, Mount Sinai School of Medicine. NY (USA).2009-present: Instructor, Department of Oncological Sciences and Immunology Institute at Mount Sinai School of Medicine. Top Five Articles:Muñoz-Fontela, C., García, M. A., García-Cao, I., Collado, M., Arroyo, J., Esteban, M., Serrano, M., Rivas, C. (2005). Resistance to viral infection of `super p53¿ mice. Oncogene. 24, 3059-3062.Garcia, M. A., Collado, M., Munoz-Fontela, C., Matheu, A., Arroyo, J., Esteban, M., Serrano, M. & Rivas, C. (2006). Antiviral action of tumor suppressor ARF. EMBO J. 25(18), 4284-4292.Munoz-Fontela, C., Marcos-Villar, L., Gallego, P., Arroyo, J., Da Costa, M., Pomerantz, K. M., Lam, E W-F. & Rivas, C. (2007). The latent protein LANA2 from KSHV interacts with 14-3-3 and inhibits FOXO3a transcription factor. J Virol. 81(3), 1511-6.Munoz-Fontela, C., Marcos-Villar, L., Hernandez, F., Gallego, P., Rodríguez, E., Arroyo, J., Gao, SJ., Avila, J. and Rivas, C. (2008). Induction of paclitaxel resistance by the KSHV latent protein LANA2. J Virol. 82, 1518-25.Munoz-Fontela, C., Macip, S., Martinez-Sobrido, L., Brown, L., Ashour, J., Garcia-Sastre, A., Lee, S-W., Aaronson, SA. (2008). Transcriptional role of p53 in Interferon-mediated antiviral immunity. J. Exp. Med. 205, 1929-1938

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **GALLEGO MOLI, ORIOL** **Referencia:** RYC-2011-07967

Area: Biología Fundamental y de Sistemas

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Titulo:

Structural characterization of transient macromolecular complexes in living cells

Resumen de la Memoria:

Biological function emerges from the concerted action of numerous interacting biomolecules. Large and labile macromolecular assemblies mediate most of the cellular processes. In addition, proteins are frequently not folded in their functional form. In front of this scenario, it is evident that the characterization of protein complexes is frequently limited. Biochemical and structural methods (e.g. TAP-tag purification, EM, crystallography etc) have contributed immensely to our knowledge describing a broad panel of biomolecular complexes and transformed the understanding of protein function up to an atomic level. However, all of these approaches present serious restrictions (difficulty to isolate ephemeral complexes, lack of dynamic information, etc). Consequently, characterization of transient complexes and intrinsically disordered proteins remains as one of the major challenges for modern structural biology. This project aims to characterize large and dynamic protein complexes at the nanometer-scale there where high-resolution data (Å scale) is unlikely to be obtained, with special interest for short-lived binding phenomena. Using the model organism S. cerevisiae, cell biology and structural biology will be combined to achieve a better comprehension of evolutionary conserved complexes. For instance, the list of their individual components and a description of their binding dynamics is of major interest in order to understand the organization of the complex in ¿core¿ components and more transient ¿attachment¿ proteins, as well as to identify subcomplexes. Advanced microscopy techniques will reconstruct the organization of the assembly by mapping N and C-terminal positions of the proteins that make it up. When possible, X-ray crystallography and biophysical approaches will be employed to achieve more detailed information. It is expected that deciphering the architecture and motion of macromolecular complexes will significantly contribute to the understanding of molecular mechanisms that reside behind cellular processes.

Resumen del Curriculum Vitae:

As undergraduate student I developed keen interest in research. I joined the group of Prof. Dr. Xavier Parés to study the metabolism of retinoids, a class of lipids derived from vitamin A with powerful biological activity. I acquired experience in molecular biology, enzymology as well as protein expression and purification. Since I was highly motivated by the group¿s research I decided to embark on a Ph.D. in the same laboratory. During this period I was awarded a four years FPU fellowship. In the first half of my PhD I assessed the different human enzymatic families involved in retinoic acid synthesis: alcohol dehydrogenases (ADH), short chain dehydrogenases/reductases (SDR) as well as aldo-keto reductases (AKR). This study was done in collaboration with Dr. Natalia Kedishvili¿s group (School of Biological Sciences, UMKC, USA) where I worked during four months, and resulted in several publications in which I also participated. In one of them we proposed a novel model for the retinoic acid synthesis pathway (Gallego et al., Biochem. J. 2006). The second half of the project followed up the study of a human AKR involved in cancer development: AKR1B10. I used cell cultures to show, for the first time, that human AKRs reduce retinal in vivo. In addition, I addressed the structural understanding of AKR1B10 function together with the group of Dr. Ignacio Fita (Parc científic de Barcelona, IRBB) where I solved the structure of the AKR1B10-NADP+-tolrestat complex (PDB: 1ZUA). I identified the residues responsible for the substrate specificity of AKR1B10. Protein activity was successfully perturbed by adjusting the dynamics of enzyme-substrate assembly (Gallego et al., Proc. Natl. Acad. Sci. USA 2007). The Spanish Society of Biochemistry and Molecular Biology awarded me the José Tormo prize for young structural biologist for that work. After my Ph.D. I persisted in the study of biomolecular interactions and decided to move to the laboratory of Dr. Anne-Claude Gavin (SCB unit, EMBL, Germany), pioneer in systematic studies of protein complexes. For almost four years I studied protein-lipid interactions in the model organism S.cerevisiae. I combined different approaches (biochemistry, biophysics, live-cell imaging, genetics and X-ray) to achieve a deeper characterization and assessment of their biological relevance. A set of novel interactions with sphingolipids, a class of conserved bioactive lipids with an elusive mode of action, attracted my attention. Our work suggested that some PH domains have unanticipated ligands and also have a function in sphingolipid recognition. To follow up this line of research and understand the molecular mechanism that determine such specificity I solved the structure of one of these domains (PDB: 3NSU, Gallego et al., Mol. Syst. Biol. 2010 and F1000: Mayinger P: 2011. F1000.com/7616957). During this time I was awarded with a postdoctoral fellowship and I reviewed for the journal Proteomics. On April 2010 I moved to Dr. Marko Kaksonen¿s group (CBB unit, EMBL, Germany) to learn more sophisticated approaches that allow me to characterize biomolecular complexes. Currently, we are applying advanced light microscopy to characterize transient protein complexes in living cells. The goal of this project is the development of a new approach based in fluorescent microscopy to complement existing structural approaches like X-ray or EM, and that allow the analysis of more dynamic protein assemblies at the nanometer-scale.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **GIBLIN , JONATHAN PETER** **Referencia:** RYC-2011-08589

Area: Biología Fundamental y de Sistemas

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Titulo:

Molecular regulation of Type-I Myosins

Resumen de la Memoria:

El objetivo general de mi línea de investigación es el de entender los mecanismos moleculares que regulan la localización celular y la función de las miosinas de tipo I. Las miosinas de tipo I están involucradas en la remodelación de membranas dependiente de actina, necesaria en una amplia variedad de procesos celulares como la endocitosis, la exocitosis, la liberación de vesículas extracelulares y la regulación de la tensión de membranas, entre otros. La endocitosis es un proceso de remodelación de la membrana plasmática que requiere el reclutamiento de más de 50 proteinas a los sitios de invaginación de la membrana. Sin embargo, de los mecanismos que regulan este reclutamiento de la mayoría de estas proteinas no sabemos demasiado. Así, en la levadura Saccharomyces cerevisiae, una proteina de la familia de las miosinas de tipo I, Myo5p, es esencial para el proceso de endocitosis aunque no conocemos los mecanismos que regulan su localización en la membrana plasmática y su función. A lo largo de mi carrera científica he acumulado experiencia en técnicas de biología molecular y bioquímica que usaré para producir un modelo integrado del mecanismo molecular de la regulación de la localización y de la función de Myo5p, mediante la disección de interacciones proteina-proteina y proteina-lípido. La relevancia fisiológica de estas interacciones será determinada usando análisis genéticos y funcionales en levadura. En resumen, las tres líneas generales que conforman la base de este proyecto dilucidarán: (i) la base molecular de la regulación de la localización y función de Myo5p por calmodulina, (ii) la identidad del trigger fisiológico para el reclutamiento de Myo5p a los sitios de endocitosis y (iii) cómo la localización funcional de Myo5p a áreas de alta curvatura de la membrana plasmática se produce con una precisión tan exacta como la observada in vivo. En mi actual posición he adquirido los datos preliminares que me permitirán desarrollar las líneas (i) y (ii) y, a lo largo de este proyecto, tengo la intención de poner a punto nuevas metodologías para abordar mi último objetivo (iii) que representa una línea más ambiciosa a la vez que a más largo término. Es de esperar que los resultados obtenidos a lo largo de este proyecto de investigación, no sólo sean informativos de cómo funciona el proceso endocítico a nivel molecular, sino que también permitan un entendimiento más general de regulación de la familia de las miosinas de tipo I en otros procesos de remodelación de membranas dependientes de actina en levadura así como en otros organismos.

Resumen del Curriculum Vitae:

Datos personales:Jonathan Peter GiblinNacido en Sutton Coldfield, Reino Unido el 12 de Agosto de 1975.Pasaporte: 301013980NIE: X09696172QFormación académica:BSc. (Hons) Biochemistry Julio, 1996PhD Molecular Pharmacology Noviembre, 2001Posición actual:Investigador postdoctoral (contrato JAE Doc) en el Instituto de Biología Molecular de Barcelona (IBMB-CSIC), desde Abril de 2008.Palabras clave: Molecular Biology, Biochemistry, Type-I Myosins, Myo5p, Endocytosis, Phospholipids, PtdIns(4,5)P2, Calmodulin, Actin, Membrane curvature, Saccharomyces cerevisiae.Posiciones anteriores de carácter científico:Enero 1997-Enero 2002: PhD student, Department of Medicine, University College London, UK Febrero 2002-Febrero 2004: Junior Research Fellow, Department of Medicine, University College London, UKMarzo 2004-Febrero 2008: MRC Career Development Fellow, MRC National Institute for Medical Research, London, UKPublicaciones:Número de publicaciones en revistas internacionales: 9De las cuales primer autor: 5De las cuales entre el 25% de mayor índice de impacto de su área: 7 (para uno de los restantes dos todavía no se conoce su índice de impacto)Supervisión de estudiantes:Supervisión de tres alumnas internas del programa ¿Passa a l¿estiu al Parc¿Otros méritos:Reviewer para revistas internacionales: Molecular PharmacologyResumen:Mi interés general es el de entender los mecanismos moleculares que regulan la función de determinadas proteinas y el de entender cómo estos mecanismos permiten la coordinación de la multitud de funciones que una célula es capaz de llevar a cabo. A lo largo de mi carrera científica he estado involucrado en el desarrollo de tres áreas de investigación específicas que son: (i) la bioquímica y la regulación de los canales de potasio sensibles a ATP, (ii) el tráfico y secreción del Factor de von Willebrand y (iii) los mecanismos moleculares del proceso de endocitosis.En cada una de estas áreas de investigación he hecho contribuciones relevantes al campo, como queda reflejado por las publicaciones científicas en las que soy autor en revistas peer-reviewed de renombre internacional. A este punto de mi carrera, uniré la experiencia que he adquirido en los campos de la bioquímica y la biología molecular con la experiencia adquirida más recientemente en técnicas de genética y ensayos funcionales en levadura para entender cómo la actividad de las miosinas de tipo I se regula a nivel molecular y cómo se coordinan con sus funciones celulares.