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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **SABATE LAGUNAS, RAIMON** **Referencia:** RYC-2011-07987

Area: Ganadería y Pesca

Correo electrónico: raimon.sabate@uab.cat

Titulo:

PROTEINA PRION (PrP) Y NUEVOS PRIONES DE MAMÍFEROS CON INTERÉS GANADERO: ANALISIS COMPUTACIONALES, IN-VITRO, IN-VIVO Y EN MODELOS ANIMALES

Resumen de la Memoria:

Los priones, proteínas con capacidad para agregarse in-vivo en estructuras amiloides auto-perdurables consideradas como elemento fundamental de la capacidad infectiva, han tenido y tienen importante repercusión en el mundo de la ganadería. Así pues, la proteína prion (PrP) se manifiesta en forma de encefalopatía espongiforme subaguda transmisible (ESST); enfermedad neurodegenerativa letal que afecta desde ovejas (¿scrapie¿) y vacas (encefalopatía espongiforme bovina popularmente conocida como mal de las ¿vacas locas¿) hasta humanos (Creutzfeldt-Jakob). La línea principal de investigación se ha dividido en:1. Cribado de nuevos priones potencialmente infecciosos en mamíferos con interés ganadero. 1.1. Predicción in-silico de nuevos priones en mamíferos con interés ganadero. Recientemente, se han aplicado estudios bio-informáticos a la detección de nuevos priones de levadura (Alberti et al., Science 2009). Nuestro grupo ha también desarrollado un nuevo y potente algoritmo capaz de cribar posibles nuevos priones en S.cerevisiae. Este algoritmo puede ser utilizado para analizar el proteoma de mamíferos de interés ganadero (vaca, oveja, cabra, etc.) en búsqueda de nuevos priones de mamíferos aún no conocidos. 1.2. Caracterización in-vitro de los mejores candidatos. Estudio de las propiedades cinéticas, fisicoquímicas y estructurales. Similitudes con el mecanismo de PrP. 1.3. Cribado in-vivo de nuevos posibles priones en mamíferos con interés ganadero. Tal y como previamente se ha realizado para el estudio del péptido amiloide beta (Abeta), causante de la enfermedad de Alzheimer, (Bagriantsev et al., BMC Biol. 2006) la fusión de nuestros candidatos a priones con Sup35 (prion de levadura) proporcionará un sistema rápido de cribado de éstos.2. Capacidad infectiva de la PrP. 2.1. Predicción in-silico de mutaciones sobre PrP (PrPx). La aplicación de algoritmos de predicción de regiones amiloides como Waltz o Aggrescan (creado por nuestro grupo) junto con nuestro nuevo algoritmo para la detección de priones nos permitirá analizar el efecto de mutaciones puntuales en la secuencia de PrP, así como la realización de cribados alanina y prolina. 2.2. Caracterización in-vitro de las mutaciones representativas. Estudio de las propiedades cinéticas, fisicoquímicas y estructurales. 2.3. Cribado in-vivo de la capacidad infectiva de agregados obtenidos in-vitro. El modelo PrP-Sup35 será utilizado para testar la capacidad prion de las mutaciones más representativas. 2.4. Cribado in-vivo del efecto de mutaciones en PrP. Estudios de agregación utilizando el sistema PrPx-Sup35. 2.5. Cribado in-vivo de sustancias anti-prion. Aplicación del modelo PrP-Sup35 en presencia de posibles sustancias anti-prion.3. Ensayos in-vivo en animales transgénicos y tests de PMCA. En colaboración con los grupos del Dr. Joaquín Castilla (Unidad de Proteómica, CIC bioGUNE) y del Dr. Juan María Torres del Centro de Investigación en Sanidad Animal (INIA-CISA). 3.1. Ensayos in-vivo de los nuevos priones detectados in-vivo en levadura. 3.2. Ensayos in-vivo de los mutantes PrP más representativos elegidos en el apartado 2.4.3.3. Ensayos in-vivo

Resumen del Curriculum Vitae:

A modo de resumen de mi trayectoria científica, cabría destacar que en la actualidad he publicado cerca de 40 artículos en revistas indexadas en JCR®. Estas publicaciones, de las cuales soy el primer autor de 25 y el autor de correspondencia de 6, tienen un factor de impacto (IF) acumulado (sumatorio de IFs de los artículos obtenido de JCR 2009) de alrededor de 150 y el número de citaciones recibidas se ha distribuido de manera que proporcionan un índice h de 13. De estos artículos, 17 se han publicado en revistas del primer cuartil (Q1) de sus respectivas áreas temáticas, 17 en revistas del segundo cuartil (Q2), y 3 y 2 en revistas del tercer (Q3) y cuarto cuartil (Q4) respectivamente. De entre estos cabría destacar 1 (Trends in Biochemical Sciences) , 2 (Andgewantde Chemie Internacional Edition), 1 (Cellular and Molecular Life Science), 1 (Journal Biological Chemistry), 2 (PLOS One), 3 (Journal Molecular Biology), 2 (Langmuir), 2 (Journal Physical Chemistry B), 1 (ChemBioChem), 1 (Electrophoresis) y 1 (Microbial Cell Factories) sólo por citar algunos. Además, en estos momentos hay 8 artículos más que están en proceso de revisión en diferentes revistas del primer (5) i segundo (3) cuartil de sus respectivas áreas y de los cuales soy el primer autor y autor de correspondencia de 5. Durante este periodo he participado en 14 congresos nacionales e internacionales incluso como ponencia invitada y moderador (¿chairman¿), y he participado en 8 proyectos de investigación nacionales e internacionales.Durante mi trayectoria científica, realizada principalmente en la en la Facultad de Farmacia de la Universidad de Barcelona (UB-Barcelona), el Institut du Biochimie et Génétique Cellulaires perteneciente al Centre National de la Recherche Scientifique (CNRS-Bordeaux), y la Facultad de Biociencias y el Instituto de Biotecnología y Biomedicina (IBB) de la Universidad Autónoma de Barcelona (UAB-Bellaterra), he recibido diversas becas pre- y post-doctorales y premios de los que cabría destacar una beca predoctoral FPI/FIAP de la Generalidad de Cataluña y dos becas post-doctorales, una Fulbright/MEC del Ministerio de Educación y Ciencia y una Beatriu de Pinós (B1) de la Generalidad de Cataluña (ICREA), así como el premio extraordinario de doctorado de la Universidad de Barcelona el año 2005.En estos años he sido miembro de diferentes grupos consolidados de investigación (SGR), he participado en diversos proyectos de investigación, tanto nacionales como internacionales y pertenezco a la Red de Referencia en Biotecnología de Cataluña (XRB). Además, la posibilidad de compaginar mi tarea como investigador con la de docente, como profesor asociado en la Facultad de Farmacia en al Universidad de Barcelona (UB) y actualmente con un contrato de intensificación de la investigación en la Facultad de Biociencias de la Universidad Autónoma de Barcelona (UAB) me ha permitido complementar mi faceta de investigador permitiéndome obtener las acreditaciones de profesor lector, profesor Agregado y de investigación de la Generalidad de Cataluña. Además en la actualidad estoy co-dirigiendo dos tesis doctorales.

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CONVOCATORIA 2011

Nombre: **SALINAS REMIRO, IRENE** **Referencia:** RYC-2011-08834

Area: Ganadería y Pesca

Correo electrónico: isalinas@um.es

Titulo:

MUCOSAL VACCINES IN AQUACULTURE: INTEGRATION OF ADAPTIVE MUCOSAL IMMUNE RESPONSES

Resumen de la Memoria:

Mucosal surfaces are the first portals of entry for bacteria, viruses and parasites in fish. Mucosal vaccines are of great advantge in fish farming, where great numbers of juveniles can be vaccinated via the water without the need to handle and stress them. Moreover, protection of mucosal sites is only achieved when mucosal lymphoid tissues are stimulated.The mucosal immune system is known to be more complex than the systemic immune system. Vertebrates, including teleost fish, possess a common mucosal immune compartment (CMIC) which means that the stimulation of one mucosal site results in the protection of distant mucosal tissues. How this happens in fish is to date unknown, but in mammals it is possible thanks to the presence of specific mucosal integrins and receptors (i.e. alpha4beta7) that home lymphocytes back to the mucosal site where they encountered antigen. The CMIC concept has huge implications for the design of effective vaccines since protection at mucosal surfaces is only achieved when adequate stimulation of local mucosal defenses takes place. Understanding the CMIC and its degree of compartimentalization has led to great advances in other fields, for instance nasal immunisation against HIV results in protection in the urogenital and respiratory tract. This knowledge is currently lacking in fish and therefore I would like to dedicate my research to this purpose.Recently, early vertebrates such as teleost fish were found to posses a dedicated adaptive mucosal immunity. Thus, as in mammals and IgA, teleost fish also have a special immunoglobulin that orchestrates the homeostasis in the gut. IgT, as IgA, also controls the relationship with the commensal microorganisms that live in the gut lumen. The proposed project will be carried out in gilthead seabream and rainbow trout due to their importance in fish farming, the fact they are marine and freshwater species (respectively) and that they are both established immunological models. Specific aims of the project are:i) identification of cell markers that are mucosal imprints and therefore enable the integration of MALT responses such as receptors and chemokines, ii) the study of IgM and IgT, B cells and plasma cells during different viral and parasitic infections and the effect on commensal microbial populations and immune exclusion processes, iii) the elaboration of a map or flow chart that describes the relationships and compartimentalization of all fish MALT.The ultimate goal of this Ramon y Cajal application is to gain deeper knowledge on the cross-talk among fish MALT. Understanding fish mucosal immune system in a holistic manner will ensure the development of novel mucosal vaccines that protect fish at all mucosal sites.

Resumen del Curriculum Vitae:

I started my scientific career as an undergraduate student at the University of Plymouth. I spent one summer helping with different aquaculture research projects including tilapia and salmon vitamin E diets. After finishing my BsC at the University of Alicante, where I did a Marine Biology degree, I spent 5 months in France as part of te European program Leonardo da Vinci., I did a Masters of Research in Applied Fish Biology at the University of Plymouth with funding from a British Council-CAM fellowship. My research project was conducted at the Freshwater Marine Laboratory in Aberdeen under Dr. A.E. Ellis supervision. Dr. Ellis was the father of fish vaccinology and one of the pioneers in the field in Europe. My Masters thesis resulted in one publication in Fish and Shellfish Immunology and important findings that revealed the activation of Mx (antiviral) responses by different immunostimulants and the importance of temperature in the kinetics and duration of the Mx response in salmon. I finished my project at the University of Plymouth under Dr. J.E. Harris and M. Gilpin supervision during the next 8 months and obtained my Master degree with distinction.I joined the Department of Cell Biology at the University of Murcia in Novemeber 2003. I obtained a Predoctoral fellowship from Fundacion Seneca to work on the gut immune responses of different fish species and their modulation by probiotic bacteria. my PhD thesis resulted in 8 first author publications plus 9 other papers where I am mostly second author. Papers got published in the most recognised international journals within the field. Moreover, during my PhD I visited three other research laboratorios, one in Spain (IRTA), one in Norway (University of Bergen and Institute of Marine Research) and one in the USA (University of Pennsylvania). I obtained my PhD in October 2007 and by then I had already participated in ten national and international congresses.My first postdoctoral appointment was in Dr. JO Sunyer¿s laboratory at the School of Veterinary Medicine, University of Pennsylvania. My postdoctoral work led to the discovery of the function of IgT, the latest Ig class from vertebrales. Our groundbreaking findings were published in Nature Immunology, and I am first autor of this paper with Dr. YA Zhang. One of my IHC images was selected for the cover of the journal (September issue). I have also written another two review papers on mucosal immunoglobulins in fish. I supervised two summer students, one working on the ontogeny of IgT and the second on the role of B cells in gut inflammation.During my second postdoctoral position, funded by Fundacion Seneca, I worked 24 months at the Nacional Institute of Water and Atmospheric Research in Wellington, New Zealand at the Biotechnology and Aquaculture group. During this period I obtained my first grant as a principal investigator to study the immune response of New Zealand groper during scuticociliate parasite infections. This work has resulted in one published paper and two more about to be submitted.In March 2011 I will be hosting the the First New Zealand and Australia Fish Immunology workshop. As the main organizer of this event to which I invited two international speakers, Dr. B Nowak (University of Tasmania) and Dr. K Cain (University of Idaho). The theoretical and practical workshop has participants from all over the world.

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CONVOCATORIA 2011

Nombre: **CLOP PONTE, ALEJANDRO** **Referencia:** RYC-2011-07763

Area: Ganadería y Pesca

Correo electrónico: mafkess@hotmail.com

Titulo:

CUTTING EDGE GENOMICS FOR THE IDENTIFICATION OF THE GENETIC VARIATION UNDERLYING TRAITS OF INTEREST IN DOMESTIC ANIMALS.

Resumen de la Memoria:

Although currently, tens of genetic tests are being incorporated in animal breeding schemes, the pace at which relevant DNA polymorphisms are being discovered and implemented could be improved. In the last years we have dramatically increased our understanding in the biology of genomes and how gene function and regulation can affect phenotypes in animals. In parallel, cutting edge technologies and resources to study structural and functional aspects of genomes are very powerful tools to identify a proportion of the functional variation that is responsible of phenotypic diversity. I have extensive expertise on the genetic analysis of complex traits in domestic animals. Moreover, I have demonstrated experience on the biology and analysis of microRNA polymorphisms and its impact on phenotypes and I am currently performing ChIP-seq (chromatin immunoprecipitation followed by high throughput sequencing) in heterozygous samples to identify, via the analysis of allelic imbalance, functional polymorphisms in the human genome that could play a role in the pathogenesis of psoriasis.The research I want to undertake aims at the identification of genetic polymorphisms underlying complex phenotypic variation of relevance in animal breeding and animal health. I will analyse available commercial and experimental populations of domestic animals with phenotypic data on traits related to: i) carcass and meat quality in pig, sheep, beef and poultry such as growth and fatness; ii) milk yield and composition in dairy cattle, sheep, and goat; iii) health as for example the host ¿ pathogen interaction in viral diseases in pigs, mastitis in dairy animals, and resistance / susceptibility to viral and bacterial infections in poultry.To this aim, I plan to implement state-of-the-art genomics knowledge, technologies and resources ranging from large- and small-scale genomic association studies (Illumina DNA chips), to the analysis of the transcriptome (RNA-seq) and the interaction of the genome with histones, histone modifications, polymerases and transcription factors (ChIP-seq) to interrogate the functional landscape of genomic candidate regions. By combining these approaches together with bioinformatics-based sequence analysis, I expect to narrow down the list of candidate polymorphisms to a manageable number of variants for which targeted functional studies could be performed.Within the aim explained above, I believe that a significant proportion of the functional genetic variation resides in the miroRNA regulatory pathway. For this reason, I have particular interest on how DNA polymorphisms in the microRNA pathway affect complex traits in animals and I will focus part of my research towards deciphering the impact of this mechanism in phenotypic variation.My plan is to identify the functional genetic variation that can contribute improving the wealth and sustainability of the livestock production sector at the same time that it sheds light towards the understanding of the biological basis of these phenotypes, making a significant contribution to basic biology and ultimately human health.

Resumen del Curriculum Vitae:

After obtaining my degree in Veterinary Medicine (Universitat Autònoma de Barcelona - UAB, 1991-6) I started my career in livestock molecular genetics and genomics. I did my PhD (1997¿2001) at the Unit of Molecular Genetics leaded by Prof. Armand Sanchez within the Department of Animal and food sciences at UAB. My PhD project aimed at identifying QTL of economic interest in an outbred pedigree made by intercrossing Iberian and Landrace pigs. During 2002, I was a research scientist at the same group and worked in several projects including collaboration with a porcine feeding company. In 2003, I joined Prof. Michel Georges¿ Animal Genomics group at University of Liège (Belgium), and in 2004 and 2005 I was awarded a Marie-Curie post-doctoral fellowship within the same group. During this 3-year period I worked on the positional cloning of the mutation causing muscular hypertrophy in the Texel sheep. We identified a functional variant affecting a miRNA target site, and thus were the first to describe this novel source of functional genetic variation. This was published in Nature Genetics, the most prestigious journal in the field of genetics, and had big impact in the life sciences community (2009 Impact Factor: 34). From 2006 to 2008 I worked in the scientific interface of Genesis Faraday (Roslin, Scotland), a non-profit organization aimed at the technology transfer of research in livestock genetics.I have been a senior post-doctoral research fellow in the group led by Professor Richard Trembath at the Division of Genetics & Molecular Medicine at King¿s College London (KCL), UK, since July 2008. My current research aims to identify the polymorphism responsible for the effect of the human PSORS1 locus in psoriasis. We are implementing high throughput sequencing, bioinformatics, and functional genomics with the aim to find the PSORS1 causal variant/s. Currently, I am initiating my own project on Chromatin ImmunoPrecipitation followed by high throughput sequencing (ChIP-seq) and the subsequent analysis of allelic imbalances on heterozygous locations to improve our understanding of the functional basis of psoriasis. This cutting edge research which I am pioneering within our department.I am first author of 7 and co-author of another 16 indexed articles. Moreover, we have several articles that are now awaiting for a decision from the editors of the Journal of Animal Sciences and the Journal of Investigative Dermatology. I have participated in two book chapters: "Origin and genetic variation of pig breeds" (ELS) and MicroRNA as a source of Genetic Variation in Animals, of which I am the corresponding author. I am contributing a review on the genetic diversity among African pig breeds for the Archeological African Reviews journal. Worth mentioning is the article published in Nature Genetics, cited 273 times and chosen in the Editor¿s choice Highlights in the journal Science. Altogether, articles in which I am co-author has been cited 670 times. Moreover, my h-index is 11.Finally I am co-applicant of the sucsessful 8M EUR 2008 EU FP7 Large Collaborative Project Quantomics and principal investigator of a KCL-BRC young investigators award to perform Functional Genomics in the context of psoriasis. I am co-supervising the PhD thesis of Ms. XXX at the Dept of Animal Sciences at the UAB.

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CONVOCATORIA 2011

Nombre: **SILVESTRE CAMPS, MIGUEL ANGEL** **Referencia:** RYC-2011-08750

Area: Ganadería y Pesca

Correo electrónico: silvestre_mig@gva.es

Titulo:

Producción in vitro de embriones en mamíferos domésticos

Resumen de la Memoria:

Actualmente la predeterminación del sexo de los animales es un elemento clave para incrementar la eficiencia de los sistemas productivos ganaderos. Si añadimos a ello el potencial de producir embriones in vitro (PIVE) a partir de oocitos procedentes de la punción ecoguiada (OPU) en vacuno lechero y de criopreservarlos eficientemente, dispondremos de una tecnología sumamente interesante tanto a nivel de investigación básica como aplicada. Se pueden obtener embriones sexados por diferentes vías, la más inmediata se basa en el uso de semen sexado, sin embargo actualmente su uso no está muy extendido y no es muy aconsejable con tratamientos de superovulación. Todavía son necesarios más estudios para mejorar la calidad de este tipo de semen y la eficiencia del proceso de sexaje y además que esté disponible de la mayor parte de machos de alto valor genético. Independientemente, el uso de semen sexado en la PIVE no parece que pueda darse de forma inmediata (distintas concentraciones de heparina por macho para la capacitación, baja concentración y mala calidad del semen sexado). Así, se ha observado que el proceso de sexaje de espermatozoides inducía cambios en la membrana del espermatozoide acelerando los procesos de capacitación y reacción acrosómica tras la congelación e incubación. También se ha observado que tras 33 horas de incubación, se incrementaba dramáticamente el fraccionamiento del ADN en los espermatozoides sexados en comparación con los no sexados. La inyección intracitoplasmática del espermatozoide (ICSI) podría ser una alternativa a la fecundación in vitro (FIV) convencional pero su eficacia es aún baja, existiendo pocas investigaciones utilizando semen sexado. El objetivo de la línea de investigación es la optimización de la producción de embriones in vitro con semen sexado fundamentalmente mediante FIV en vacuno. Igualmente, se estudiarán los factores que podrían incrementar la eficacia de la ICSI con semen sexado, como método alternativo. Para ello es necesario alcanzar una serie de objetivos parciales centrados en: (1) Optimización de la FIV de embriones con semen sexado comercial: para ello se estudiará el efecto de la eliminación de la zona pelúcida de los oocitos MII en la fecundación in vitro con semen sexado y el efecto de diferentes concentraciones de antioxidantes en el medio de descongelación del semen sexado sobre la producción y calidad de embriones PIV. (2) Optimización de la ICSI con semen no sexado: en especial por el estudio del efecto de distintos protocolos de activación artificial oocitaria que en vacuno, a diferencia de otras especies, resultan esenciales por su impacto tanto en la producción como en la calidad embrionaria. Tanto mediante la OPU, como mediante la ICSI, el nº de efectivos disponibles suele ser bajo, lo cual afecta a la eficiencia global del sistema de producción. (3) En este sentido y debido a la baja eficacia de la PIVE individualizada o con un nº reducido de efectivos a cultivar, se plantea el estudio del efecto de factores de crecimiento u otros suplementos en el cultivo reducido de embriones PIV con semen no sexado, tanto sobre su producción como su calidad. Independientemente del uso de semen sexado, esta línea aportaría conocimientos relativos a la PIV de embriones de vacuno, en especial los relativos a la interacción entre gametos, activación oocitaria y cultivo de embriones.

Resumen del Curriculum Vitae:

El Dr. Silvestre obtuvo el título de I. Agrónomo en 1998 en la Universidad Politécnica de Valencia (UPV) y su doctorado en el Dpto de Ciencia Animal de la UPV en junio de 2001. Después disfrutó de una beca de investigación de la Conselleria de Agricultura, Pesca y Alimentación en la Unidad de Mejora Genética del Dpto de Ciencia Animal de la UPV (Dic.2001-Mar.2004). Posteriormente fue contratado como Profesor Ayudante Doctor en la Universidad de Zaragoza (Mar.2004-Dic.2004), como Colaborador Científico Adjunto (2005-2009) y como Técnico titulado (mar.2010-nov.2010) en el Centro de Tecnología Animal del Instituto Valenciano de Investigaciones Agrarias (CITA-IVIA). Actualmente, está contratado como Colaborador Científico Adjunto en el CITA-IVIA). Formación: Ha dirigido dos Tesis Doctorales. Ha dirigido 1 Trabajo experimental para la obtención del Diploma de Estudios Avanzados y 3 Tesis de Master. Ha participado como profesor en las 2 ediciones en el Master Interuniversitario de la UPV-UAB ¿Mejora Genética y Biotecnología de la Reproducción¿. Ha sido tutor de prácticas de empresa de 6 alumnos (U. Valencia, UPV y U.Cardenal Herrera CEU). Proyectos: Ha participado con EDP en 4 proyectos de investigación (3 nacionales y 1 autonómico), en dos de ellos como Investigador Principal (IP; financiado por el INIA y la Conselleria de Educación de la GV) y en el resto como miembro del equipo investigador. También ha sido IP de una Ayuda Complementaria a Proyectos de Investigación. También ha participado en 4 convenios y contratos con empresas de los cuales en 2 ha sido IP. Publicaciones: 23 artículos en revistas científicas, de las cuales 20 están incluidos en el JCR con índice de impacto [Theriogenology(5), Reproduction in Domestic Animals(5), Animal Reproduction Science(2), Cryobiology(2), Zygote(2), Journal of Animal Science(2), Livestock Production Science(1), Reproduction Nutrition Development(1)]. Del total de artículos, el solicitante es primero o último firmante en 15. Ha publicado 9 artículos en revistas de divulgación. El solicitante ha participado en 35 contribuciones a congresos. Formó parte del comité de expertos de la primera edición del Master Inter-universitario de Mejora Genética y Biotecnología de la Reproducción (UPV-UAB, 2007-2008). También ha sido el coordinador de 1 jornada de transferencia de tecnología. Ha participado como ponente en 11 jornadas, cursos de divulgación o seminarios. Fue finalista en el Student Competition del 16th Meeting of the European Embryo Transfer Association, 2000. Y obtuvieron el premio al Mejor poster en la 10th Conference of the European Society for Domestic Animal Reproduction. Salvador et al., 2006. Ha codirigido la Tesis de I. Salvador (2007), premiada con el Premio Extraordinario de Tesis. Ha realizado estancias cortas en el INRA de Nouzilly (A. Caraty / L.A. Zarazaga), Facultad de Agronomía-Universidad de Buenos Aires (D.F. Salamone) y University of Massachusetts - Amherst - Veterinary and Animal Sciences (R.A. Fissore). Ha sido ¿referee¿ de proyectos de investigación de instituciones regionales, nacionales y extranjeras y de revistas internacionales. Acreditación de la figuras de Profesor Contratado Doctor, Profesor Ayudante Doctor, Profesor Colaborador y Profesor de Universidad Privada.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **TOIVONEN , JANNE MARKUS** **Referencia:** RYC-2011-08363

Area: Ganadería y Pesca

Correo electrónico: jtoivonen.iacs@aragon.es

Titulo:

Characterization of MicroRNAs and their targets in skeletal muscle and muscle stem cells in motor neuron disease models for potential use in diagnostics and therapeutics.

Resumen de la Memoria:

A primary feature of motor neuron diseases (MNDs) such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) is muscle weakness that derives from the loss of neuromuscular communication. Both humans and domestic animals suffer from MNDs, but the insight into pathological features is most often gained from rodent models of diseases. Research on MNDs has primarily focused on neuronal tissue but this ¿neurocentric¿ view has been challenged by work demonstrating direct contribution skeletal muscle tissue to the disease pathology. In mouse model of ALS, toxic signals from the muscle compromise the neuromuscular connection and this connectivity is at least partially controlled by muscle-specific microRNAs (miRNAs), small non-coding RNAs involved in post-transcriptional gene silencing. In the last 10 years, microRNA research has gained tremendous attention from the research community. Recently, a single muscle-specific miRNA has been shown to suppress ALS progression and promote maintenance of neuromuscular junctions. Although several muscle-specific or muscle-enriched miRNAs are known, their potential role in motor neuron disease has not been systematically studied in animal models or in humans. The proposed research line firstly investigates the miRNAs in ALS and SMA mice by determining: 1) spatiotemporal expression pattern of miRNAs in fast-twitch and slow-twitch muscles during the course of the disease; 2) microRNA alterations in cultured satellite cells derived from these muscles; 3) predicted miRNA target genes for the affected miRNAs; 4) the effects of manipulation by miRNA mimics and stem-loop inhibitors on cell growth and differentiation; 5) the potential of MND-regulated miRNAs as diagnostic markers from the animal blood plasma. Secondly, the applicability of these candidate markers will be evaluated in human MND patient-derived plasma samples as well those dericed from domestic animals, such as muscular atrophy cats and hereditary muscle diseases in horse.It is becoming clear that the role of muscle is important, yet overlooked aspect in maintenance of neuromuscular connectivity in motorneuron disease. Muscle-expressed miRNAs are novel group of post-transcriptional regulators that can mediate important aspects of MND pathophysiology. Therefore, systematic characterization miRNA-mediated gene regulation in affected muscles and stem cells derived from those will deepen our understanding on progression of motorneuron disease and potentially indicate cost-effective diagnostic markers useful for monitoring disease progression and to predict treatment outcomes in animals and in human patients.

Resumen del Curriculum Vitae:

I conducted my Masters degree and PhD work in Finland, in a Centre of Excellence in Research on Mitochondrial Disease and Ageing, lead by Prof Howard T Jacobs. In my research I modelled mitochodrial diseases, particularly mutations targeting mitochondrial translation machinery, using bacteria and flies as model organisms. I also investigated transcriptional and post-transcriptional gene regulation in cultured human cells. My PhD work resulted in five publications (three of which first author) and a review article, and gave me strong skills for molecular cloning, DNA, RNA and protein techniques, in vivo and in vitro work, as well as techniques on studies of gene regulation.To gain strong knowledge on genetics of ageing and fluent language skills, I spent next five years as a postdoc in the United Kingdom. The work was carried out in the University College London (UCL) Institute of Healthy Ageing in the laboratory of Professor Dame Linda Partridge. Using Drosophila flies as a model organism, I studied how mutations on mitochondrial translation machinery, Krebs Cycle intermediate transporter, uncoupling proteins, and nuclear hormone receptors. Additionally, we described genes and pharmacological agents involved in autophagy and protein translation that affect normal ageing. This postdoc resulted in 3 research articles (2 of which first author), as well as a review and PNAS communication. As ageing is slow to study, we are currently in a process of finalizing a further manuscript describing new ageing gene in Drosophila.Since June 2009 I have been working as a postdoc in the University of Zaragoza, in the laboratory of Professor Rosario Osta, part of the Centre of excellence LAGENBIO, and funded by Instituto Aragones de Ciencias de la Salud (I+CS). The laboratory works on various aspects of motor neuron disease, including search for disease biomarkers, therapeutic molecules and characterization of adult stem cells. This has given me a strong knowledge on work with adult stem cells, such as those derived from muscle, fat and bone marrow. It has also resulted in two accepted publications, two submitted articles and a review. More specifically related to the proposed research line, I have recently optimized a protocol to initiate work on microRNAs using muscle and serum samples from mice.I communicate with ease in English language and have given invited talks in international conferences such as Gordon Reasearch Conference and European meeting on Mitochondrial Pathology. I get along with people well and, starting from my PhD studies have had a pleasure to co-supervise several undergraduates in their studies leading to Mres, BSc and MSc titles. During my last 3-year postdoctoral project in London, I was leading the project independently with the help of a research technician. I have been collaborating internationally and nationally with many research groups, including those studying ageing and mitochondrial research, and therefore created a network of colleagues on whose expertise and help I can count on when necessary. I¿m hard working, competent at laboratory work, creative and, importantly, rigorous in my interpretation of experimental data. I do not fear to apply my knowledge and skills with originality in new directions, but instead see new situations inspiring.

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SUBPROGRAMA RAMON Y CAJAL

CONVOCATORIA 2011

Nombre: **LORENZO MORALES, JACOB** **Referencia:** RYC-2011-08863

Area: Ganadería y Pesca

Correo electrónico: JMLORENZ@ULL.ES

Titulo:

STUDIES ON FREE-LIVING AMOEBAE WITH PATHOGENIC POTENTIAL TO FISH, IMPACT IN AQUACULTURE AND SEARCH OF NEW THERAPIES (ESTUDIOS DE AMEBAS DE VIDA LIBRE CON CAPACIDAD PATÓGENA EN PECES, IMPACTO EN ACUICULTURA Y BÚSQUEDA DE NUEVAS TERAPIAS)

Resumen de la Memoria:

Aquaculture has experience an important boom in the recent years which has allowed the application of new Technologies focused on an increase in the production. However, in these exploitations systems, production could be affected by the infections that the cultured fish in these systems are likely to suffer. Recently, this research field has experienced an immense boom, hence studies are currently being developed in order to elucidate the causes and factors involved in the pathologies as well as identifying emerging and potential pathogens that could affect in the health status of the cultured animals and/or the final consumer. If we compare the existing studies on pathogens in fish reared in cages or farms, it is evident that the available data on opportunistic protozoan parasites that affect fish are minimal. These few studies have identified some genera of free-living amoebae as causative agents of pathologies in fish farms including Acanthamoeba, Naegleria, Neoparamoeba and Vanella. Therefore, in this research field the establishment of techniques for rapid and reliable identification and correct diagnosis is proposed as well as a search for treatments against protozoa affecting farmed and wild animals. We are focusing on the development of reliable isolation methods as well as molecular techniques for the identification of these amoebae using PCR and immunological tools. Also and because there is a lack of effective treatment against these pathogens, we are developing colorimetric methods for the assessment of the activity of novel active compounds against these amoebae. RNAi will be used as a tool for the identification of possible drugs targets for future therapeutics as previous experience was gained in Acanthamoeba genus which is one of the groups of pathogens that will be studied. A new method has been recently published by our group in Journal of Medical Microbiology in 2008 for the evaluation of the activity of different drugs against Acanthamoeba and we are currently developing similar tools for other genera of amoebae. The proposed study is of great interest for the exploitation point of view (Fisheries) as well as the sanitary ones, because these pathogens are highly unknown, they cause important problems in fisheries in Australia, the Caribbean and the Czech Republic and are starting to be reported (by our team in collaboration with the University of South Bohemia) as a cause of mortality in wild marine populations in the Canary Islands, Spain. This project would be helpful in order to establish the sanitary status of wild and farm animals in the area of study from the sanitary and fisheries point of view, and it could present as an innovative impact in the evaluation of the health status of wild and farm populations that are currently unknown in Spain. Finally it is important to mention that there are only two other research groups working on the same field worldwide. Thus collaborations with them (University of Tasmania, Australia and University of South Bohemia, Czech Republic) are expected in this project, mostly with visits of the applicant to these research teams.

Resumen del Curriculum Vitae:

In 2001 I started my PhD Studies in the Department of Parasitology, Ecology and Genetics of the University of La Laguna, working on free-living amoebae from Acanthamoeba genus. During the first years of my PhD thesis, I worked as a research assistant in the University of New Zealand for 3 months in 2003, working on the isolation of free-living amoebae from sea water and marine organisms for further molecular identification. During 2003, I also started to collaborate with the School of Biomedical Sciences of the University of Edinburgh, working on extracellular serine proteases of Acanthamoeba genus and also on improving isolation and storage methods for free-living amoebae for a period of 3 months. In 2004, I was accepted as an Honorary Research Fellow at the Department of Life Sciences of the University of the West Indies in Kingston, Jamaica and I was also granted a PhD grant from the Canary Islands government from this stage until the end of my PhD studies. In Jamaica, one of my supervisors was granted a project on the Epidemiology of Acanthamoeba in this region (I was included as a member of the team participating in this project) and thus, I was able to carry on working in free-living amoebae and their pathogenicity. After this stage, I returned to the University of La Laguna in order to carry on with my PhD studies and research. During this period, in 2005, I started to get interested in RNA interference (RNAi) and I developed siRNAs molecules against extracellular serine proteases of Acanthamoeba. Thus, this paper has established new techniques in the field and has become a standard reference in Acanthamoeba research having been cited many times. It also has proven the serine proteases of Acanthamoeba play a main role in the pathogenesis process of these protozoa. In order to improve my molecular biology techniques I also visited the Division of Parasitic Diseases at the Center for Disease Control and Prevention (CDC) for 2 months during this year 2005. In 2006, I visited the Malaria and Leishmania Research Centre from ministry of health and family welfare of Panjim, Goa, India to gain experience in these pathogens for 2 months. In June 2006, I defended my PhD Thesis and I was granted the highest mark (Sobresaliente cum laude) and the European PhD qualification. After that, I started a series of different postdoctoral stages at the Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh (24.29 months), working on different aspects of the cytoskeleton of Acanthamoeba., I also started to collaborate with the University Institute of Tropical Diseases and Public Health of The Canary Islands (IUETSPC) at the University of La Laguna. I have also been involved in a series of projects that have been granted to IUETSPC including a national network of Tropical Diseases (Redes Temáticas de Investigación Cooperativa, RECTIS, Enfermedades Tropicales: de la genómica al control). Finally, in December 2009, I was granted a postdoctoral grant to start a new Postdoctoral Research Fellowship at the University of Edinburgh for a period of 14 months starting from January 2010. During the 10 years of my research career, I have published 32 peer-reviewed papers included in JCR. Currently, I am co-supervising a PhD thesis in collaboration with the IUETSPC. I have also collaborated with Ophtecs Corporation, Japan. I have submitted a patent for a novel drug against Acanthamoeba which is currently in the last stage.