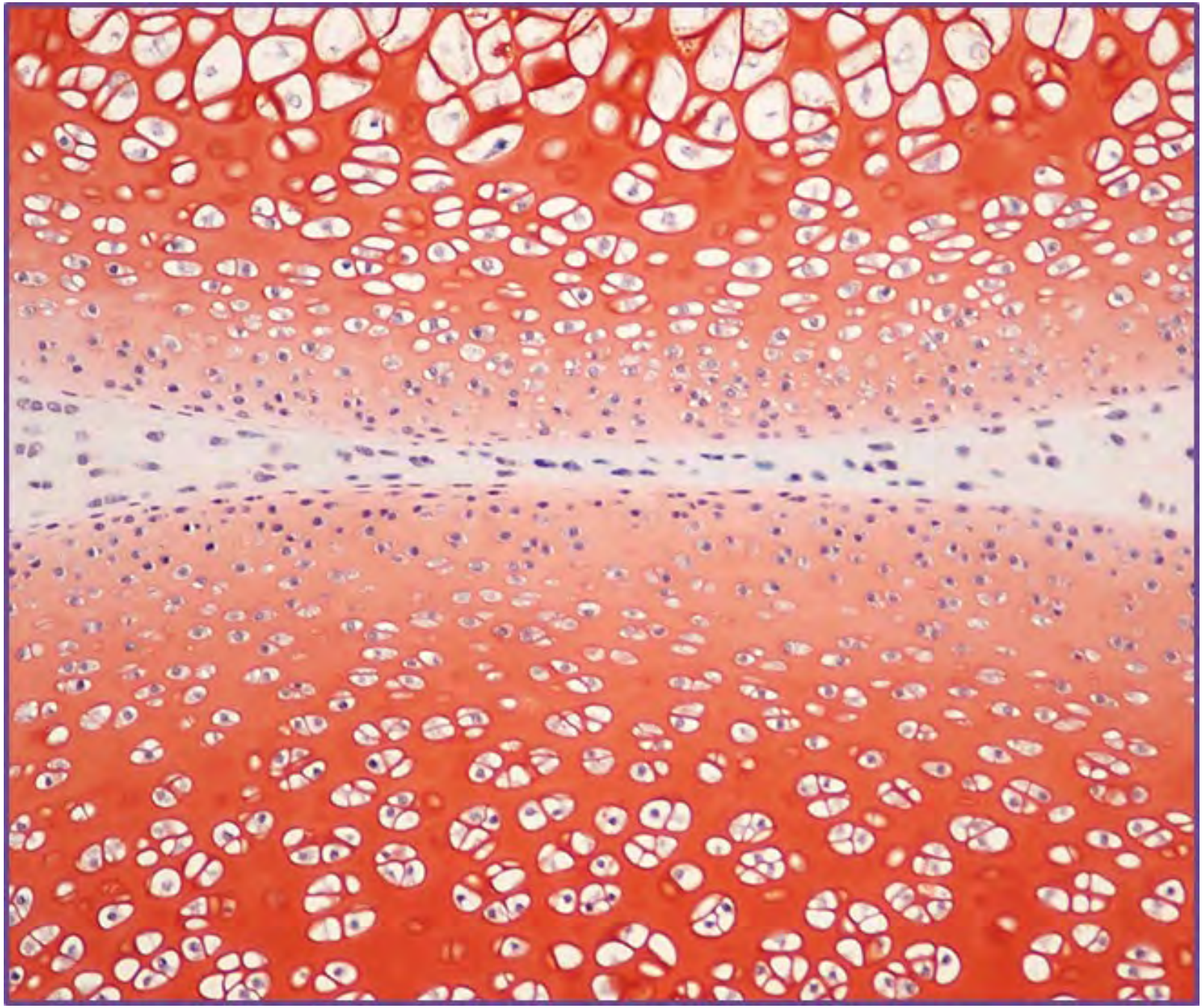
Scientific Report Years 2016-2020

Biochemistry and Molecular Biology Department

UAB
Universitat Autònoma de Barcelona



Design: Mònica Lluch

Cover image: Joan Bertolín
Safranin O staining in articular cartilage

Yeast Molecular Biology Laboratory

GROUP LEADER
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Professor

LAB MEMBERS
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Researcher
Marcel Albarcar
Postdoctoral student

Carlos Santolaria
Postdoctoral student
Mercè Robledo
Technician

RESEARCH INTERESTS

Our group is interested in several topics about the biochemistry, the molecular biology and the genomics of the yeast *Saccharomyces cerevisiae*, specifically those that are related to cell signalling trough processes of phospho-dephosphorylation. For this purpose, we investigate issues like the ion homeostasis, the response to various stresses or the cell cycle regulation.

STRATEGIC OBJECTIVES

The main objective is to obtain an overview on the yeast response to perturbations of its environment, so that we can both understand in deep the biology of this organism and to guide us towards new biotechnological applications. This includes from the understanding of the biological roles of protein phosphatases to the development of novel yeast expression vectors driven by changes in the pH of the medium.

PUBLICATIONS DURING 2016-2020

Tatjer, L., Sacristán-Reviriego, A., Casado, C., González, A., Rodríguez-Porrata, B., Palacios, L., Canadell, D., Serra-Cardona, A., Martín, H., Molina, M. & Ariño, J. (2016) The yeast Ptc1 protein phosphatase regulates a variety of cellular functions by targeting the Mkk1 kinase. Genetics. 202,141-56.

X. Castells, L. Ferrer-Font, M. Dávila, A. P. Candiota, R. Simoes, A. Fernández-Coello, A. Gabarrós, S. Boluda, A. Barceló, J. Ariño & C. Arús (2016) Improving ribosomal RNA integrity in surgically resected human brain tumor biopsies. Biopreservation and Biobanking 14, 156-164.

S. Bru, J.M. Martínez, S. Hernández-Ortega, E. Quandt, M. Rafel, J. Torres-Torronteras, R. Martí, D. Canadell, J. Ariño, S. Sharma. J. Jiménez, and J. Clotet (2016) Polyphosphate is Involved in Cell Cycle Progression and Genomic Stability in *Saccharomyces cerevisiae.* Mol. Microbiol. 101, 367-80.

Tatjer, L. González, A. Serra-Cardona, A., Barceló, A., Casamayor, A. & Ariño, J. (2016) The *Saccharomyces cerevisiae* Ptc1 protein phosphatase attenuates G2-M cell cycle blockage caused by activation of the cell wall integrity pathway Mol. Microbiol. 101, 671-687.

C. Popa, S. Gil, L. Tatjer, M. Tabuchi, N. S. Coll, J. Ariño & M. Valls (2016) The effector AWR5 from the plant pathogen *Ralstonia solanacearum* is an inhibitor of the TOR signalling pathway. Scientific Reports. 6:27058, 1-14.

Petrezselyova, S., López-Malo, M., Canadell, D., Roque, A., Serra-Cardona, A., Marqués, Mª C., Vilaprinyó, E., Alves, R., Yenush, L., & Ariño, J. (2016) Regulation of the Na^+/K^+-ATPase Ena1 expression by calcineurin/Crz1 under high pH stress: a quantitative study. Plos One. 11:e0158424.

K. Petrényi, C. Molero, Z. Kónya, F. Erdődi, J. Ariño* & V. Dombrádi* (2016)Analysis of two putative C*andida albicans* phosphopantothenoylcysteine decarboxylase / protein phosphatase Z regulatory subunits reveals an unexpected distribution of functional roles. Plos One. 11(8):e0160965A.

Roque, S. Petrezselyova, A. Serra-Cardona, & J. Ariño. 2016. Genome-wide recruitment profiling of transcription factor Crz1 in response to high pH stress. BMC Genomics 17:662.

Pérez-Sampietro, M., Serra-Cardona, A., Canadell, D., Casas, C., Ariño, J. & Herrero, E.(2016) The yeast Aft2 transcription factor determines selenite toxicity by controlling the low affinity phosphate transport system. Scientific Reports, 6:32836.

S. Bru, J. Jiménez, D. Canadell, J. Ariño & J. Clotet (2016) Improvement of biochemical methods of polyP quantification. Microbial Cell. 4, 6-15.

Peris-Peris, C., Serra-Cardona, A., Sánchez-Sanuy, F., Campo, S., Ariño, J. & San Segundo, B. (2017) Two distinct NRAMP6 isoforms function as iron and manganese transporters and contribute to disease resistance in rice. Molecular Plant-Microbe Interactions 30:385-39

Molero, C.; Casado, C. & Ariño. J. (2017) The inhibitory mechanism of Hal3 on the yeast Ppz1 phosphatase: A mutagenesis analysis. Scientific Reports. 7: 8819. 1-14.

Trevijano-Contador, N.; Cesar de Oliveira, H.; García-Rodas, R.; Rossi, S.A.; Llorente, I.; Zaballos, A.; Janbon, G.; Ariño, J. and Zaragoza, O. (2018) *Cryptococcus neoformans* can form titan-like cells in vitro in response to multiple signals. PLOS Pathogens. 14(5): e1007007 (1-37).

Santolaria, C.; Velázquez, D.; Strauss, E.; Ariño, J. (2018) Mutations at the hydrophobic core affect Hal3 trimer stability, reducing its Ppz1 inhibitory capacity but not its PPCDC moonlighting function. Scientific Reports.8(1):14701.

Zhang, C.; García-Rodas, R.; Molero, C.; de Oliveira, H.C. Tabernero, L.; Reverter, D.; Zaragoza, O. and Ariño, J. (2019) Characterization of the atypical Ppz/Hal3 phosphatase system from the pathogenic fungus *Cryptococcus neoformans.* Molecular Microbiology 111, 898-917.

Ariño, J.; Ramos, J.; Sychrova, H. (2019) Monovalent cation transporters at the plasma membrane in yeasts. Yeast 36,177–193.

Zhang, C; de la Torre, A.; Pérez-Martín, J. & Ariño, J. (2019) Protein phosphatase Ppz1 is not regulated by a Hal3-like protein in the plant pathogen *Ustilago maydis*. International Journal of Molecular Sciences 20(15).

Ariño, J.; Velázquez, D. and Casamayor, A. (2019) Ser/Thr protein phosphatases in fungi: structure, regulation and function. Microbial Cell. 2, 217-256 (*Review)*

Calafí C; López-Malo M; Velázquez D; Zhang C; Fernández-Fernández J; Rodríguez-Galán O; de la Cruz J; Ariño J & Casamayor A (2020) Overexpression of budding yeast protein phosphatase Ppz1 impairs translation. Biochim. Biophys. Acta - Mol. Cell Res., 1867, 118727.

Velázquez, D.; Albacar, M.; Zhang, C.; Calafí, C.; López-Malo, M.; Torres-Torronteras, J.; Martí, R.; Kovalchuk, S.I.; Pinson, B.; Jensen, O.N.; Daignan-Fornier, B.; Casamayor, A.; Ariño, J. (2020) Yeast Ppz1 protein phosphatase toxicity involves the alteration of multiple cellular targets. Sci. Rep., *10*, 15613 (1-21).

Calafí, C.; López-Malo, M.; Albacar, M.; Casamayor, A.; Ariño, J. (2020) The N-terminal region of yeast protein phosphatase Ppz1 is a determinant for its toxicity. International Journal of Molecular Sciences. 21, 7733 (1-16).

BOOK CHAPTERS

Canadell, D. & Ariño, J. (2016) Interactions between monovalent cations and nutrient homeostasis (*In: Membrane Transport in Yeast (Advances in Experimental Medicine and Biology series*). Vol. 892, Chapter 11. pp. 271-290. J. Ramos, H. Sychrova, M. Kschischo (Eds.), Springer.

Casamayor, A. & Ariño, J. (2020) Controlling Ser/Thr protein phosphatase PP1 activity and function through interaction with regulatory subunits, in *Enzymes – Mechanisms, Dynamics and Inhibition*. vol. 122, pp. 231-288 T. Karabencheva-Christova & C.Z. Christov, Eds. Elsevier.

OTHER PUBLICATIONS

D. Canadell, S. Bru, J. Clotet & J. Ariño.(2016) Extraction and quantification of polyphosphate in the budding yeast *Saccharomyces cerevisiae*. Bioprotocols. 6 (14).

Ariño, J. & Ramos, J. (2017) Cation fungal homeostasis. Reference Modules in Life Sciences. Elsevier.

ACTIVE PROJECTS DURING 2016-20:

Exploracion de los mecanismos de homeostasis de cationes monovalentes como nueva diana antifungica. Plan nacional de i+d+i (BFU2014-54591-c2-1-p). jan. 2015-dec. 2017

Elucidacion de la funcion y la regulacion del sistema de fosfatasas fungicas atipicas ppz1/hal3. Plan nacional de i+d+i (bfu2017-82574-p). jan. 2018-sept. 2021.

Expression of secreted leghemoglobin in yeast. Espuña R&D. 30-09-2019 to 30-03-2020. Private funding

Sistemas innovadores para la obtención de LegHemoglobina para productos análogos de la carne (INNOLEG). Espuña R&D y Coopecarn Girona SLU (Grups Operatius, DARP). 31-07-2020 to 30-09-2022. Private funding

Grup d'Aplicacions Biomèdiques de la RMN (GABRMN)

GROUP LEADER
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Predoctoral student
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Predoctoral student
Gulnur Ungan
Predoctoral student,
Zoona Javed
Predoctoral student
Marta Mulero
Predoctoral student

RESEARCH INTERESTS

The GABRMN group holds a recognized research track in the use of nuclear magnetic resonance (NMR) for biomedical applications. Main expertise fields of our group:
Acquisition, processing and interpretation of Magnetic Resonance (MR) data.
Preclinical evaluation of nanoparticulated agents in murine models.
Generation, treatment and follow-up of murine brain tumour models.
Pattern recognition analysis of MR spectroscopic/imaging data.

STRATEGIC OBJECTIVES

To improve therapy response assessment and patient management, especially regarding brain tumours. This is achieved with different research branches: human brain tumour MR data and preclinical glioblastoma MR data. Both imaging and spectroscopic MR data are used, and advanced machine learning approaches are applied.
To gain knowledge about anatomical/biochemical changes characterizing response to therapy, with special emphasis in immune system elements, searching for tissue characterization. This molecular characterization may help to gain insight into imaging biomarker of therapy response
To help clinicians integrating MR spectroscopy in their pipelines, through development of software packages devoted to quality assessment, processing and postprocessing of spectroscopic data, as well as to maintain databases of validated human MR brain tumour data.

PUBLICATIONS DURING 2016-20

Wu S, Calero-Pérez P, Arús C, Candiota AP. Anti-PD-1 Immunotherapy in preclinical GL261 Glioblastoma: Influence of Therapeutic Parameters and Non-Invasive Response Biomarker Assessment with MRSI-Based Approaches. Int J MolSci. 2020 Nov 20;21(22):8775. doi: 10.3390/ijms21228775. PMID: 33233585; PMCID: PMC7699815.

Núñez LM, Romero E, Julià-Sapé M, Ledesma-Carbayo MJ, Santos A, Arús C,Candiota AP, Vellido A. Unraveling response to temozolomide in preclinical GL261 glioblastoma with MRI/MRSI using radiomics and signal source extraction. SciRep. 2020Nov 12;10(1):19699.

Casaña-Eslava RV, Ortega-Martorell S, Lisboa PJ, Candiota AP, Julià-Sapé M,Martín-Guerrero JD, Jarman IH. Robust Conditional Independence maps of single-voxel Magnetic Resonance Spectra to elucidate associations between brain tumours and metabolites. PLoS One. 2020 Jul 1;15(7):e0235057

Wu S, Calero-Pérez P, Villamañan L, Arias-Ramos N, Pumarola M, Ortega-Martorell S, Julià-Sapé M, Arús C, Candiota AP. Anti-tumour immune response in GL261 glioblastoma generated by Temozolomide Immune-Enhancing Metronomic Schedule monitored with MRSI-based nosological images. NMR Biomed. 2020 Apr;33(4):e4229

Pi Castro D, José-López R, Fernández Flores F, Rabanal Prados RM, Mandara MT, Arús C, Pumarola Batlle M. Expression of FOXP3 in Canine Gliomas: Immunohistochemical Study of Tumor-Infiltrating Regulatory Lymphocytes. J Neuropathol Exp Neurol. 2020 Feb 1;79(2):184-193

Hernández-Villegas Y, Ortega-Martorell S, Arús C, Vellido A, Julià-Sapé M. Extraction of artefactual MRS patterns from a large database using non-negative matrix factorization. NMR Biomed. 2019 Dec 2:e4193.

Julià-Sapé M, Candiota AP, Arús C. Cancer metabolism in a snapshot: MRS(I). NMR Biomed. 2019 Oct;32(10):e4054. Villamañan L, Alcaraz E, Pinna LA, Ruzzene M, Itarte E, Arús C, Plana M, Candiota AP. Up-Regulation of the Alpha Prime Subunit of Protein Kinase CK2 as a Marker of Fast Proliferation in GL261 Cultured Cells. Pathol Oncol Res. 2019 Oct;25(4):1659-1663.

Ortega-Martorell S, Candiota AP, Thomson R, Riley P, Julia-Sape M, Olier I. Embedding MRI information into MRSI data source extraction improves brain tumour delineation in animal models. PLoS One. 2019 Aug 15;14(8):e0220809.

Mora P, Pons A, Cos M, Camins A, Muntané A, Aguilera C, Arús C, Majós C. Magnetic resonance spectroscopy in posterior fossa tumours: the tumour spectroscopic signature may improve discrimination in adults among haemangioblastoma, ependymal tumours, medulloblastoma, and metastasis. Eur Radiol. 2019 Jun;29(6):2792-2801.

Suárez-García S, Arias-Ramos N, Frias C, Candiota AP, Arús C, Lorenzo J, Ruiz-Molina D, Novio F. Dual T1/ T2 Nanoscale Coordination Polymers as Novel Contrast Agents for MRI: A Preclinical Study for Brain Tumor. ACS Appl Mater Interfaces. 2018 Nov 14;10(45):38819-38832.

Fernández-Flores F, García-Verdugo JM, Martín-Ibáñez R, Herranz C, Fondevila D, Canals JM, Arús C, Pumarola M. Characterization of the canine rostral ventricular-subventricular zone: Morphological, immunohistochemical, ultrastructural, and neurosphere assay studies. J Comp Neurol. 2018 Mar 1;526(4):721-741.

Kyathanahally SP, Mocioiu V, Pedrosa de Barros N, Slotboom J, Wright AJ, Julià-Sapé M, Arús C, Kreis R. Quality of clinical brain tumor MR spectra judged by humans and machine learning tools. Magn Reson Med. 2018 May;79(5):2500-2510.

Ferrer-Font L, Arias-Ramos N, Lope-Piedrafita S, Julià-Sapé M, Pumarola M, Arús C, Candiota AP. Metronomic treatment in immunocompetent preclinical GL261 glioblastoma: effects of cyclophosphamide and temozolomide. NMR Biomed. 2017 Sep;30(9).

Arias-Ramos N, Ferrer-Font L, Lope-Piedrafita S, Mocioiu V, Julià-Sapé M, Pumarola M, Arús C, Candiota AP. Metabolomics of Therapy Response in Preclinical Glioblastoma: A Multi-Slice MRSI-Based Volumetric Analysis for Noninvasive Assessment of Temozolomide Treatment. Metabolites. 2017 May 18;7(2):20.

Ferrer-Font L, Villamañan L, Arias-Ramos N, Vilardell J, Plana M, Ruzzene M, Pinna LA, Itarte E, Arús C, Candiota AP. Targeting Protein Kinase CK2: Evaluating CX-4945 Potential for GL261 Glioblastoma Therapy in Immunocompetent Mice. Pharmaceuticals (Basel). 2017 Feb 12;10(1):24.

Jiménez-Xarrié E, Davila M, Candiota AP, Delgado-Mederos R, Ortega-Martorell S, Julià-Sapé M, Arús C, Martí-Fàbregas J. Brain metabolic pattern analysis using a magnetic resonance spectra classification software in experimental stroke. BMC Neurosci. 2017 Jan 13;18(1):13.

Ciezka M, Acosta M, Herranz C, Canals JM, Pumarola M, Candiota AP, Arús C. Development of a transplantable glioma tumour model from genetically engineered mice: MRI/MRS/MRSI characterisation. J Neurooncol. 2016 Aug;129(1):67-76.

Delgado-Goñi T, Ortega-Martorell S, Ciezka M, Olier I, Candiota AP, Julià- Sapé M, Fernández F, Pumarola M, Lisboa PJ, Arús C. MRSI-based molecular imaging of therapy response to temozolomide in preclinical glioblastoma using source analysis. NMR Biomed. 2016 Jun;29(6):732-43.

Castells Domingo X, Ferrer-Font L, Davila M, Candiota AP, Simões RV, Fernández-Coello A, Gabarrós A, Boluda S, Barceló A, Ariño J, Arús C. Improving Ribosomal RNA Integrity in Surgically Resected Human Brain Tumor Biopsies. Biopreserv Biobank. 2016 Apr;14(2):156-64.

Mocioiu V, Ortega-Martorell S, Olier I, Jablonski M, Starcukova J, Lisboa P, Arús C, Julià-Sapé M. From raw data to data-analysis for magnetic resonance spectroscopy--the missing link: jMRUI2XML. BMC Bioinformatics. 2015 Nov 9;16:378.

Ferrer-Font L, Alcaraz E, Plana M, Candiota AP, Itarte E, Arús C. Protein Kinase CK2 Content in GL261 Mouse Glioblastoma. Pathol Oncol Res. 2016 Jul;22(3):633-7.

ACTIVE PROJECTS DURING 2016-20

Análisis de datos de espectroscopía de resonancia magnética mediante herramientas de aprendizaje de máquina para la mejora de la evaluación diagnóstica y pronóstica de los gliomas (MRS-ML). PI20/00064. Proyectos de investigación en salud (PI) 2020 (ISCIII). 1/1/2021 – 31/12/2023. 31.460 € (121.000 €, coordinated Project total)

Horizon 2020 Framework Programme for Research and Innovation, ATTRACT initiative. Grant 777222 (Third Party). Multiparametric MR approaches for non-invasive Glioblastoma therapy response follow-up (MAGRes). 20/05/2019 – 31/10/2020, 100,000€.

2018 XARDI 00016 / IU68-013944. Xarxa R+D+I en Tecnologies de la Salut (XarTEC SALUT). AGAUR. Agència de Gestió d'Ajuts Universitaris i de Recerca. IP: Alexandre Perera Lluna, 15/08/2020 to 31/12/2022, 1.338.250,00 €.

H2020-MSCA-ITN-2018, proposal: 813120, granted. INtegrating Magnetic Resonance SPectroscopy and Multimodal Imaging for Research and Education in MEDicine (INSPiRE-MED). European Comission, Marie Curie Initial Training Networks (ITN). Coordinator, Dominique Sappey-Marinier, UNIVERSITE LYON 1 CLAUDE BERNARD (FR), 01/01/2019 – 31/12/2022, 205,904.88 € (partner UAB).

SAF2014-52332-R. Imagen Molecular de glioma de alto grado para la mejora de la respuesta al tratamiento (MOLIMAGLIO). Ministerio de Economía y Competitividad, 01/01/2015 – 31/12/2017, 242,000 €.

2015-1-TR01-KA202-022634. E-learning platform for medical informatics to improve vocational and ICT practice (E-medivip). European Union, Erasmus+. Key Action: Cooperation for innovation and the exchange of good practices. 01/09/2015 – 31/08/2017. EC Grant: 217.479 € (38.127 € CIBER partner)

PITN-GA-2012-316679. Transforming Magnetic Resonance Spectroscopy into a clinical Tool-TRANSACT. European Union, Marie Curie Initial Training Networks (ITN), FP7-PEOPLE-2012-ITN. 01/03/2013 – 01/03/2017. 3.445.287,12 €

Lipid-based nanosized drug delivery systems

GROUP LEADER
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Associate Professor

LAB MEMBERS
Mercedes Camacho
Postdoctoral student
Núria Benseny
Postdoctoral student

RESEARCH INTERESTS

Liposomes, metallosomes, metallosurfactants, drug delivery systems, carbon monoxide releasing molecules.

STRATEGIC OBJECTIVES

Design and characterization of CO bearing molecules/aggregates intended for biomedical applications.

MAIN RESEARCH LINES

Synthesis and characterization of CO releasing aggregates.
Pt-metallosomes as anticancer drug delivery systems.
Use of fluorescent dyes as cation sensors into vesicular systems.

PUBLICATIONS DURING 2016-20

Direct Synthesis of Rhenium and Technetium-99m Metallosurfactants by a Transmetallation Reaction of Lipophilic. Groups: Potential Applications in the Radiolabeling of Liposomes
Jordi Borrás, Verónica Mesa, Joan Suades, and Ramon Barnadas-Rodríguez Langmuir (2020) 36: 1993-2002

Peptide Assembly on the Membrane Determines the HIV-1 Inhibitory Activity of Dual- Targeting Fusion Inhibitor Peptides. Maria J. Gomara, Yolanda Perez, Javier P. Martinez, Ramon Barnadas-Rodriguez, Anke Schultz, Hagen von Briesen, Alex Peralvarez-Marin, Andreas Meyerhans, Isabel Haro Scientific Reports (2019), 9: 3257, 1-13

Metallosomes for biomedical applications by mixing molybdenum carbonyl metallosurfactants and phospholipids. Marín-García, M.; Benseny-Cases, N.; Camacho, M.; Perrie, Y.; Suades, J.; Barnadas-Rodríguez, R Dalton Transactions (2018), 47 (40), 14293-14303

Low-toxicity metallosomes for biomedical applications by self-assembly of organometallic metallosurfactants and phospholipids. Marín-García, M.; Benseny-Cases, N.; Camacho, M.; Suades, J.; Barnadas-Rodríguez, R. Chemical Communications (2017), 53(60), 8455-8458

Supramolecular Arrangement of Molybdenum Carbonyl Metallosurfactants with CO-Releasing Properties.
Parera, Elisabet; Marín-García, Maribel; Pons, Ramon; Comelles, Francesc; Suades, Joan; Barnadas-Rodríguez, Ramon
Organometallics (2016), (35) 4, 484-493

Fourier transform infrared spectroscopy (FTIR) characterization of the interaction of anti-cancer photosensitizers with dendrimers.
Monika Dabrzalska, Nuria Benseny-Cases, Ramon Barnadas-Rodríguez, Serge Mignani, Maria Zablocka, Jean-Pierre Majoral, Maria Bryszewska, Barbara Klajnert-Maculewicz, Josep Cladera
Analytical and Bioanalytical Chemistry (2016), 408, 535–544

ACTIVE PROJECTS DURING 2016-20

Comprensión de las interacciones moleculares entre metales y sistemas biológicos para el diseño de aplicaciones biomédicas y biotecnológicas. Reference: BIO2015-67358-C2-2-P / Ministerio de Economía y Competitividad
2016-2019

Optimización de un sistema de liberación nanoterapeutica basado en dendrómetros para el tratamiento de la enfermedad de Alzheimer. Reference: SAF2017-84407-R / Ministerio de Economía y Competitividad 2018-2020

Iron transport and absorption of iron by Caco-2/Raji B cocultures and Caco-2 monocultures. Pharmanutra Spa. June 2016 – June 2019. Private funding.

Biomarkers in Veterinary and Animal Science

GROUP LEADER
Anna Bassols
Professor

GROUP MEMBERS
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Associate Professor
Natàlia Yeste
Predoctoral student
Yolanda Saco
Technician
Raquel Pato
Technician
Raquel Peña
Technician

RESEARCH INTERESTS

The problems of the most important species from the productive, food and economic point of view (pig, cattle) from different approaches:

Use of proteomic techniques to study these processes and identify biomarkers.
Study of acute phase proteins: structure, function and utility as biomarkers.
Role of brain neurotransmission in swine and cattle under stress and the influence of nutrition.

We are not fully aware of this, but the health and productive problems of farm animals are an essential aspect of the basic sciences. Diseases that can happen to humans, diseases that reduce the growth rate of animals, problems associated with animal welfare and stress ...
Proteomics offers fantastic tools to address these problems: our group has mainly studied aspects related to stress and nutrition of farm animals, especially for their economic consequences.
Quantitative and functional proteomics techniques can be applied to these problems.
We also study the acute phase response, especially the production and functions of acute phase proteins in income animals. These proteins are markers of inflammation, but also of productivity, stress and food safety.
We are also interested in the role of brain neurotransmitters in controlling behavior in pigs, especially with respect to animal welfare.

The group maintains important relations with the Veterinary Clinical Biochemistry Service (s.bioquimica.clinica@uab.cat)

We have taken collaborative projects with the reagent industry for the development and validation of reagents, mostly for acute phase proteins.

MAIN RESEARCH LINES AND STRATEGIC OBJECTIVES

The main lines of our research group are:

Biomarkers for animal science and veterinary medicine.
Enzymatic and immunological assays.
Proteomics and metabolomics for biomarker search

We achieve these goals in collaboration with leading research institutes on animal science (IRTA, INIA, Instituto Superior de Agronomia de Lisboa).

PUBLICATIONS DURING 2016-20

Factors Influencing Biomarker Range Intervals in Farm Animals (Editorial). Ana María Gutiérrez, Anna Bassols, Laura Soler, Matilde Piñeiro. Frontiers in Veterinary Science, section Veterinary Experimental and Diagnostic Pathology (2020) 7:587741.

Environmental enrichment alters monoaminergic neurotransmitters and the hippocampal proteome in pigs.
Laura Arroyo; Daniel Valent; Ricard Carreras; Raquel Pato; Josefa Sabrià; Antonio Velarde; Anna Bassols. Journal of Proteomics 2020 Vol 229, Oct 30, 103943.

Characterization of Electrolyte Content in Urine Samples through a Differential Microfluidic Sensor Based on Dumbbell-Shaped Defect Ground Structures. Muñoz-Enano, Jonathan; Vélez, Paris; Gil Barba, Marta; Jose-Cunilleras, Eduard; Bassols, Anna; Martín, Ferran. International Journal of Microwave and Wireless Technologies (2020) (Published online by Cambridge University Press April 27). http. doi.org/10.1017/S17590787220000446

Evaluating the potential role of tryptophan in calf milk replacers to facilitate weaning.
N. Yeste, A. Bassols, M. Vidal, A. Bach and M. Terré. Journal of Dairy Science (2020) 103, P7009-7017

Metabolome and Proteome Changes in Skeletal Muscle and Blood of Preruminant Calves with Leucine and Threonine Supplemented Diets. Kuai Yu, Manolis Matzapetakis, Anita Horvatić, Marta Terré, Alex Bach, Josipa Kuleš, Natalia Yeste, Néstor Gómez, Laura Arroyo, Elisabet Rodríguez-Tomàs, Raquel Peña, Nicolas Guillemin, André M. De Almeida, Peter David Eckersall, Anna Bassols. Journal of Proteomics 2020 Feb 3:103677.

Effects of a high fat diet on appetite regulatory neuropeptides and neurotransmitters and the counteracting action of adding probiotics and omega-3 fatty acids in a pig model.
Daniel Valent, Laura Arroyo, Emma Fàbrega, Maria Font-i-Furnols, María Rodríguez-Palmero, Jose Antonio Moreno-Muñoz, Joan Tibau, Anna Bassols. Beneficial Microbes (2020) 11, 347-359

Total and specific activity of superoxide dismutase (SOD) in seminal plasma are related with the cryotolerance of jackass spermatozoa. Marion Papas, Jaime Catalán, Isabel Barranco, Laura Arroyo, Anna Bassols, Marc Yeste, Jordi Miró. Cryobiology 2019 Nov 26. pii: S0011-2240(19)30537-1.

Specific activity of superoxide dismutase in stallion seminal plasma is related to sperm cryotolerance. Marion Papas, Jaime Catalán, Beatriz Fernandez-Fuertes, Laura Arroyo, Anna Bassols, Jordi Miró, Marc Yeste. Antioxidants 2019 Nov 9;8(11).

Performance, intestinal permeability, and blood metabolic profile of calves fed a milk replacer supplemented with glutamic acid.
Ahangarani, M. A, A. Bach, A. Bassols, M. Vidal, D. Valent, S. Ruiz-Herrera, and M. Terré. Journal of Dairy Science (2020) 103, 433-438

Activities of antioxidant seminal plasma enzymes (SOD, CAT, GPx and Gred) are higher in jackasses than in stallions and are correlated with sperm motility in jackasses.
Marion Papas; Laura Arroyo; Anna Bassols; Jaime Catalán, Sebastián Bonilla-Correal, Sabrina Gacem, Jordi Miró. Theriogenology 2019, 140, 180e187.

SWATH-MS quantitative proteomic investigation of intrauterine growth restriction in a porcine model reveals sex differences in hippocampus development.
Daniel Valent, Natalia Yeste, Lorenzo E. Hernández-Castellano, Laura Arroyo, Consolación García-Contreras, Marta Vázquez-Gómez, Antonio González-Bulnes, Emøke Bendixen, Anna Bassols. Journal of Proteomics 2019 Jul 30;204:103391.

I-FABP, Pig-MAP and TNF-α as biomarkers for monitoring gut-wall integrity in front of *Salmonella* Typhimurium and ETEC K88 infection in a weaned piglet model.
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Consolacion Garcia-Contreras, Daniel Valent, Marta Vazquez-Gomez, Laura Arroyo, Beatriz Isabel, Susana Astiz, Anna Bassols, Antonio Gonzalez-Bulnes. International Journal of Developmental Neuroscience (2017) 57, 72–76.

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Effect of gender and halothane genotype on cognitive bias and its relationship with fear in pigs.
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A. Marco-Ramell, A. M. de Almeida, S. Cristobal, P. Rodrigues, P. Roncada and A. Bassols. Molecular Biosystems (2016) 12, 2024 – 2035.

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Identification of biomarkers of stress in meat of pigs managed under different mixing treatments. Mamen Oliván, Verónica Fernández-Suárez, Fernando Díaz-Martínez, Verónica Sierra, Ana Coto-Montes, Beatriz de Luxán-Delgado, Raquel Peña, Anna Bassols, Emma Fàbrega, Antoni Dalmau, Antonio Velarde. British Biotechnology Journal (2016) 11, 1-13.

ACTIVE PROJECTS DURING 2016-20

Estudi de la transducció de senyals en cèl.lules eucariotes. Entidad financiadora: Generalitat de Catalunya, 2014 SGR 4, 2017 SGR 594, 2020 SGR Duración, desde: 2015 hasta: 2021. Investigador responsable: Joaquín Ariño Carmona

Desarrollo de metodos analiticos automatizables para la determinacion de biomarcadores relacionados con la mejora de la salud en ganado bovino. Entidad financiadora: MINECO Referencia proyecto: RTC-2015-3885-2 Duración: 01/01/2016-31/12/2018 Investigador responsable: M. Piñeiro (Acuvet Biotech, SL) Instituciones participantes: UAB, U Zaragoza, Zeulab SL

Estudio molecular de los efectos de la suplementación de aminoácidos en terneros amamantados mediante una aproximación bioquímica y proteómica (AMINOCRET)Entidad financiadora: MINECO Referencia proyecto: AGL2015-68463-C2-2-P Duración: 01/01/2016-31/12/2018 Investigador responsable: Anna Bassols Instituciones participantes: (Subproyecto dentro del Proyecto Coordinado “Determinación de los aminoácidos limitantes para el crecimiento de los terneros amamantados y su funcionalidad”. IP: Dra Marta Terré)

Estrategias para mitigar el riesgo y biomarcadores en el nuevo paradigma de salud y bienestar en terneros lactantes (SAFECALF). Entidad financiadora: MINECO Referencia proyecto: PID2019-104021RB-I00 Duración: 01/01/2020-31/12/2022. Investigador responsable: Sonia Martí i Maria Devant (IRTA)

Signalling in the central nervous system

GROUP LEADER
Jose Ramon Bayascas
Associate Professor

LAB MEMBERS
Sonia Pascual
Postdoctoral Researcher
Laura Martínez
Predoctoral student

RESEARCH INTERESTS

My research activity aims to understand the importance that the dysfunction of the mechanisms of signal transduction might play in brain pathology. We focussed on the PI 3-kinase/Akt signalling pathway, which controls essential roles during neuronal development and is deregulated in different mental disorders. I generated brain-specific conditional knock-in mice expressing two distinct rationally designed, crystal structure-based, point mutant forms of the PDK1 kinase, a master hub on this signalling pathway. In the PDK1 K465E mice, activation of Akt is selectively impaired, whereas in the PDK1 L155E mice, activation of most of the effectors of this signalling axis including S6K, RSK, SGK and PKC, but not Akt, is abolished.

STRATEGIC OBJECTIVES

The research activity of our group aims to define the neurodevelopmental functions of the PDK1 signalling network and its consequences to neurodegenerative and mental disease.
Funding: ISCIII; MINECO

MAIN RESEARCH LINES

To investigate whether the PDK1 K465E mice is protected from Alzheimer Disease. In the PDK1 K465E knock-in mice, reduced activation of Akt caused subtle morphogenetic defects that did not lead however to adverse behavioural outputs. We learned that the hypomorphic reduction of the Akt axis protected these mice from a number of insults disrupting homeostasis, which might singularly be also protected from neurodegeration.

To define the contribution of the PDK1 substrates different from Akt to mental disease. In the PDK1 L155E mice, the normal and exclusive activation of Akt among the different PDK1 substrates caused profound defects in the patterning of the central nervous system, leading to severe mental disorders reminiscent of human schizophrenia.

PUBLICATIONS DURING 2016-20:

Giménez-Llort L, Santana-Santana M, Bayascas JR. The Impact of the PI3K/Akt Signaling Pathway in Anxiety and Working Memory in Young and Middle-Aged PDK1 K465E Knock-In Mice. Front Behav Neurosci. 2020 May 8;14:61.

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Erazo T, Lorente M, López-Plana A, Muñoz-Guardiola P, Fernández-Nogueira P, García Martínez JA, Bragado P, Fuster G, Salazar M, Espadaler J, Hernández-Losa J, Bayascas JR, Cortal M, Vidal L, Gascón P, Gómez-Ferreria M, Alfón J, Velasco G, Domènech C, Lizcano JM. The New Antitumor Drug ABTL0812 Inhibits the Akt/mTORC1 Axis by Upregulating Tribbles-3 Pseudokinase. Clin Cancer Res. 2016 May 15;22(10):2508-19.

ACTIVE PROJECTS DURING 2016-20:

Implicacion de la ruta de señalizacion PI3K/PDK1/Akt en la enfermedad de Alzheimer analizada mediante ratones knock-in para PDK1 ENTIDAD: Agencia Estatal de Investigación - Ministerio de Ciencia, Innovación y Universidades; Modalidad Retos; Referencia: RTI2018-101249-B-I00; 108900 € DE: 2019 A: 2022

INVESTIGADOR PRINCIPAL: José Ramón BAYASCAS RAMÍREZ, UAB

Participacion de PDK1 en las respuestas a PI3K durante el desarrollo neuronal definida mediante el analisis de ratones knock-in de PDK1: implicacion en patologia mental ENTIDAD: Secretaria de Estado de Investigación, Desarrollo e Innovación-Ministerio de Economia y Competitividad; Modalidad Retos; Referencia: SAF2014- 52813-R; 145200 € DE: 2014 A: 2018

INVESTIGADOR PRINCIPAL: José Ramón BAYASCAS RAMÍREZ, UAB

Molecular basis of cardiovascular disease

GROUP LEADER
Blanco Vaca, Francisco
Associate Professor

LAB MEMBERS
Marina Canyelles
Researcher
Juan Carlos Escolà
Researcher
Marta Farràs
Postdoctoral Researcher
Josep Julve
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Giovanna Revilla
Predoctoral student
Rosa Roig
Technician
Noemí Rotllan
Ramon y Cajal Researcher
David Santos
Technician
Mireia Tondo
Researcher

RESEARCH INTERESTS

The "Metabolic basis of cardiovascular risk" group is specially interested and focused in cardiovascular diseases related to metabolic alterations such as hyperlipidemia, diabetes and obesity. Our goal is, in this context, to study pathophysiological mechanisms implicated, to evaluate new test for diagnosis of prognosis which could constitute advances in Precision Medicine, and at the experimental level to test new potential therapies.

STRATEGIC OBJECTIVES

To study the potential of cholesterol-trafficking in cellular models using clinical samples from patients with major diseases such as cardiovascular disease and Alzheimer.
To define the potential of nicotinamide in experimental cardiometabolic diseases.
To develop and apply Precision Medicine from the clinical laboratory to patients with high cardiometabolic risk

MAIN RESEARCH LINES

Role of HDL in lipid-related diseases.
Metabolic risk factors (dyslipidemia, diabetes and obesity) and cardiovascular risk.
Translation of novel biochemistry and molecular biology techniques to clinical laboratory practice especially in cardiovascular risk prevention, diabetes and obesity.

PUBLICATIONS DURING 2016-20:

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Polygenic Markers in Patients Diagnosed of Autosomal Dominant Hypercholesterolemia in Catalonia: Distribution of Weighted LDL-c-Raising SNP Scores and Refinement of Variant Selection. Martín-Campos JM*, Ruiz-Nogales S, Ibarretxe D, Ortega E, Sánchez-Pujol E, Royuela-Juncadella M, Vila À, Guerrero C, Zamora A, Soler I Ferrer C, Arroyo JA, Carreras G, Martínez-Figueroa S, Roig R, Plana N, Blanco-Vaca F*, Xarxa d'Unitats de Lípids I Arteriosclerosi Xula. Biomedicines. 2020 Sep 15;8(9):E353.

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Cedó L, Blanco-Vaca F, Escolà-Gil JC. Antiatherogenic potential of ezetimibe in sitosterolemia: beyond plant sterols lowering Atherosclerosis 2017; 260: 94-96.

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Cedó L,Santos D, Silvennoinen R, Kaipiainend L, Valledor AF, Kovanen PT, Lee-Rueckert M, Gylling H, Blanco-Vaca F*, Escolà-Gil JC*. Phytosterol-mediated inhibition of intestinal cholesterol absorption is independent of liver X receptor Molecular Nutrition & Food Research 2017 Sep;61(9).

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Cedó L,García-León A,Baila-Rueda L,Santos D, Grijalva V, Martínez-Cignoni MR, Carbó JM,López-Vilaró L, Zorzano A, Valledor AJ, Cenarro A,Lerma E, Reddy ST, Escolà-Gil JC, Blanco-Vaca F. ApoA-I mimetic administration, but not increased apoA-I-containing HDL, inhibits tumor growth in a mouse model of inherited breast cáncer Scientific Reports 2016; 6: 36387

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ACTIVE PROJECTS DURING 2016-20

Advances in the molecular diagnosis of patients with inherited dyslipidemia, with special emphasis in those of polygenic origin and in familial hypercholesterolemia PI: Francisco Blanco Vaca. Instituto Carlos III, PI14/01648. 2015-2017

Prevent premature coronary artery disease by increasing the diagnosis of familial hypercholesterolemia PI: Francisco Blanco-Vaca Marató TV3, 12-C-2015-0323. 2016-2018

TMAO and gammaBB: relation with dysfunctional HDL and coronary artery disease risk in patients with familial hypercholesterolemia and diabesity PI: Francisco Blanco Vaca Instituto Carlos III, PI18/00164. 2019-2021

CIBER de Diabetes y Enfermedades Metabólicas Asociadas (2008-present) PI group: PI: Francisco Blanco Vaca, CIBER07/08/0016.

Human ribonucleases involved in host defence

GROUP LEADER
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Associate Professor
Guillem Prats-Ejarque
Postdoctoral Researcher
Li Jiarui
Postdoctoral Researcher
Raul Anguita
Predoctoral student
Claudia Cano
Master student
Clara Villalba
Technician

RESEARCH INTERESTS

Our lab is working on the development of novel antibiotics based on the structure-functional knowledge of human secretory RNases.
Novel drugs are urgently needed to combat the emergence of multiresistant pathogen species. Understanding and targeting antimicrobial resistance is one of the global health surveillance priorities. Our research group has a longstanding consolidated experience in the structure-functional characterization of human secreted RNases, a family of small cytotoxic proteins expressed by epithelial and blood cells upon infection. Host defence RNases belonging to a unique vertebrate specific gene family, show an unusual rapid evolution rate, a trait characteristic of innate immunity proteins, providing adaptation to an ever-changing pathogen exposed environment. Antimicrobial proteins have thus been selected through evolution to work as anti-infective agents against a wide variety of pathogen intruders.
Human secretory RNases are key players of the host immunity and contribute to maintain the body fluids' sterility. They are activated upon a diversity of cellular stress injuries and mediate signaling processes, classified therafter as alarmins. Interestingly, secreted RNases can shape the non-coding RNA population and participate thereby in the host innate immune response.

STRATEGIC OBJECTIVES

We are currently exploring both the immuno-modulation and inti-infective activities of human canonical RNases. Structural-functional analysis is applied in the design and engineering of new scaffolds to develop novel antibacterial and antiviral agents. In particular, we are aiming to target microbial resistance forms, such as biofilm communities and macrophage dwelling pathogens.

MAIN RESEARCH LINES

Design of novel antimicrobial agents against biofilms and macrophage intracellular bacteria.
Search for structural recognition patterns for pathogen RNA targeting.
Characterization of RNase activities on single- stranded RNA viruses.
Search for novel antibiotics to fight antimicrobial resistance.

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ACTIVE PROJECTS DURING 2016-20

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Nova teràpia anti-infectiva (BactRNAClean) per combatre la resistència als antibiòtics. LLAVOR 2019 LLAV 00002. Indústria del Coneixement. AGAUR, Generalitat de Catalunya (20/07/2020-20/4/2021) PI: Boix Borràs, Ester.

Pattern recognition of non-coding RNA's to search for novel therapeutic targets in the fight against bacterial antimicrobial resistance. TV3-201803-10 Fundació La Marató TV 3 (01/02/2019-31/01/2022) PI: Boix Borràs, Ester.

A human derived peptide (hECP-5P36) as an novel antimicrobial agent to fight bacterial resistance. PRODUCTE. 2016 PROD 00060 FINANCING ENTITY: Indústria del Coneixement. AGAUR, Generalitat de Catalunya (01/09/2017-31/02/2019). PI: Boix Borràs, Ester.

Ribonucleases humanes del sistema Immunitari. Grup de Recerca Consolidat (GRC). 2017SGR1010 Agència de Gestió d 'Ajuts Universitaris i de Recerca, AGAUR (2017-2019). PI: Boix Borràs, Ester.

Human RNases to fight antimicrobial resistance. Learning from our own innate immunity to engineer peptide-based antibiotics. SAF2015-66007-P. Ministerio de Economia y Competitividad (MINECO). Proyectos de I+D, del Programa estatal de fomento de la investigación científica y técnica de excelencia (01/01/2016-31/12/2018) PI: Boix Borràs, Ester.

PATENTS DURING 2016-20

Antimicrobial peptide for nosocomial infections. Inventors (by order of signature): Boix, E, Torrent, M and Andreu, D. Request No: 33228412- 2020; T-2014-026EP/ PCT/EP2016/067989 Priority country: ES Date: 30/07/2015; 28/06/2016. Extended to countries: Europe, USA 28/06/2016; 01/02/2018; 29/10/2020 Entity: Universitat Autònoma de Barcelona, Universitat Pompeu Fabra

Gene therapy for Neurometabolic Diseases

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STRATEGIC OBJECTIVES

The research activity of our group is focused on the development of gene therapy strategies for diseases affecting the nervous system, both central (lysosomal storage diseases, ALS and MLC) and peripheral (genetic and acquired neuropathies) and on the elucidation of the molecular mechanisms implicated in the development of these pathologies combining the use of animal models, tissue cell culture and viral vectors.

MAIN RESEARCH LINES

Understanding and treating rare diseases affecting the central nervous system
Gene therapy is one of the most attractive treatments for diseases affecting the central nervous system (CNS) since blood-brain-barrier impairs delivery of systemically administered drugs to the cerebral parenchyma. We are working on different strategies for the treatment of Mucupolysaccharidosis type VII, Amyotrophic Lateral Sclerosis (ALS) and Meganlencephalic Leukoencephalopathy with subcortical cysts (MLC), which at the same time help us in the understanding of the mode of action of theses pathologies.

Study of the tropism of different gene therapy viral vectors in the peripheral nervous system
Gene transfer to the peripheral nervous system (PNS) is particularly challenging as it involves several cell types, most of them post-mitotic. Efficient gene transfer to certain cell types of the PNS can be of great interest for gene therapy for neurological diseases or for pain treatment. Also important, delivery or inhibition of target molecules with viral vectors can be used as a tool to analyze physiological processes in the PNS, such as interactions between glia and neurons, retrograde or anterograde transport, nerve regeneration, etc. Within the aim to determine the most efficient gene transfer vectors for each cell type in the PNS, we are characterizing the tropism of different pseudotypes of AAV vectors and different human and non-human adenoviral vectors through different routes of administration.

Gene therapy for diabetic neurological complications
Diabetic complications involve both sensorimotor and autonomic components of the peripheral nervous system (PNS). The pathology of diabetic sensorimotor neuropathy is characterized by axonal atrophy and demyelination, leading to nerve fiber loss followed by abnormal regeneration of these fibers. Despite insulin treatment or pancreas transplantation, progression of diabetic neuropathy is not stopped, indicating the need for a specific treatment at early stages of the diabetes. Our team is studying the molecular mechanisms leading to the development of diabetic neuropathy, using primary cell cultures and mouse models of the disease, with the aim to elucidate new therapeutic targets for this complication of the diabetes. In more detail, we are studying the effect of hyperglicemia in the demyelination of the PNS and the role of trophic factors or other molecules implicated in the cellular signaling between sensory neurons and Schwann cells to stimulate the expression of myelin proteins and the regeneration of the PNS.

Understanding and treating rare diseases affecting the central nervous system
Gene therapy is one of the most attractive treatments for diseases affecting the central nervous system (CNS) since blood-brain-barrier impairs delivery of systemically administered drugs to the cerebral parenchyma. We are working on different strategies for treatment of Mucupolysaccharidosis type VII, Amyotrophic Lateral Sclerosis and Meganlencephalic Leukoencephalopathy with subcortical cysts which at the same time help us in the understanding of the mode of action of theses pathologies.

PUBLICATIONS DURING 2016-20

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ACTIVE PROJECTS DURING 2016-20

Gene therapy for Megalencephalic leukoencephalopathy with subcortical cysts in two animal models of the disease. ELA International (2018-0512; 2019-2020). PI. Assumpció Bosch.

Combinatorial gene therapy strategy to target oxidative and endoplasmic reticulum stresses in type 2 diabetic neuropathy. Marató de TV3 (201607.10; 2017-2019). PI: Miguel Chillon.

Viral Production Unit. TECNIO, ACCIÓ (TECDTP16-1-0010; 2017) PI: Miguel Chillon.

Molecular study and treatment of the Muchopolysaccharidosis type VII. Spanish Health Institute Carlos-III (PI15/01271) (2016-2019). PI. Assumpció Bosch.

Viral Production Unit. TECNIO, ACCIÓ (TECDTP15-1-0007; 2016) PI: Miguel Chillon.

Gene therapy targeting neuregulins for the treatment of amyotrophic lateral sclerosis. Association française contre les myopathies (AFM-Telethon #20289, 2016-2018). Coordinated project. PI: Xavier Navarro.

Optimization and development of a therapeutic agent based on nucleic acids for the treatment of Huntington's disease. Spanish Ministery of Economy and Competitivity (RTC-2015-3731-1) (2015-2018). PI: Assumpció Bosch.

Gene therapy targeting neuregulins for the treatment of amyotrophic lateral sclerosis. Marató de TV3 (2015–2017). PI: Xavier Navarro.

Ayuda y reconocimiento de Grupo de Investigación Consolidado (GRC): Grupo de Investigación en Terapia Génica para enfermedades autoinmunes desmielinizantes. AGAUR (2014 SGR 1354) (2014 – 2016). PI: Miguel Chillón.

From Brain Gene Transfer Towards Gene Therapy: Pharmacological Assessment of AAV, CAV and LVV (BRAINVECTORS). FP7-PEOPLE-2011-IAPP (#286071) (2013-2016). PI-UAB: Miguel Chillon. Coordinator: Mauro Mezzina (EASCO, France).

PATENTS DURING 2016-20

Vectors expressing klotho for treating càncer. Inventores (p.o. de firma): C. Abraham, M. Abraham, A Bosch, M.Chillón, T. Rubinek, I. Wolf. N. de solicitud: PCT/IL2019/050913 País de prioridad: Israel. Fecha de prioridad: 28/8/19 Entidad titular: Tel-Aviv Medical Center, UAB, Klogene, ICREA. Licencing companies: Klogene.

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STRATEGIC OBJECTIVE

Our main strategic objective is to develop new gene therapy approaches for highly prevalent and rare metabolic and neurodegenerative diseases, with the ultimate goal to improve the quality of life for subjects affected by these diseases. Our studies focus on the pathophysiological causes of diabetes mellitus and its comorbidities and also of severe genetic storage diseases, generating transgenic animal models and developing gene transfer-based therapeutics.

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Laboratori d'Enginyeria Genetica Animal

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M Morro, L Vila, S Franckhauser, C Mallol, G Elias, T Ferre, M Molas, E Casana, J. Rodo, A Pujol, N. Tellez, F Bosch and A Casellas. Vitamin D Receptor Overexpression in β-Cells Ameliorates Diabetes in Mice. Diabetes (2020) May;69(5):927-939.

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ACTIVE PROJECTS DURING 2016-20

Development of mouse mutant resources for functional analyses of human diseases -Enhancing the translation of research into innovation (Infrafrontier-I3). EU, Programme “Capacities”-Call “FP7-INFRASTRUCTURES-2012-1 (Proposal No. 312325). Project Coordinator: Martin Hrabe de Angelis (HMGU, GSF National Research Centre for Environment and Health/ HGF, Germany). Principal investigator: Fatima Bosch. 01/01/2013-31/12/2016.

AAV-mediated gene therapy for the treatment of MPSIIID (Sanfilippo D). Association Française contre les Myopathies (AFM)-Téléthon. Principal investigator: Fatima Bosch. 15/05/2014-14/05/2017.

Therapeutic approaches against type 2 diabetes and obesity targeting adipose tissue with factors that increase energy expenditure. European Foundation for the Study of Diabetes (EFSD/Lilly Fellowship Programme). Principal investigator: Veronica Jimenez. 27/06/2014-26/06/2016.

Development of a European network for preclinical testing of interventions in mouse models of age and age-related diseases (MouseAGE) COST European cooperation in science and technology (COST Action BM1402). Project Coordinator: Ilaria Bellantuono (University of Sheffield, United Kingdom). 01/12/2014-30/11/2018. Project Coordinator: Ilaria Bellantuono, University of Sheffield, United Kingdom. Principal investigator (group UAB): Fatima Bosch. 01/12/2014-30/11/2018.

Laboratori d'Enginyeria Genetica Animal. Agència de Gestió d´Ajuts Universitaris i de Recerca (AGAUR), Generalitat de Catalunya (2014 SGR 1669). Principal investigator: Fatima Bosch. 01/01/2015-30/04/2017.

Nuevas aproximaciones de terapia genica para la diabetes tipo 2 y la obesidad basadas en la activacion del tejido adiposo marron y browning del tejido adiposo blanco. Ministerio de Educación y Competitividad, Plan Estatal de I+D+I (SAF2014-54866-R). Principal investigator: Fatima Bosch. 01/01/2015-31/12/2017.

BetaSel2 – Therapeutic efficacy of novel cytokines and growth factors selected in vivo to improve beta cell mass. Juvenile Diabetes Research Foundation (JDRF). Optimizing Therapeutic Strategies for Human Pancreatic Beta Cell Regeneration RFA (2-SRA-2015-59- Q-R). Project Coordinator: Mauro Giacca (ICGEB, Trieste Italy). Principal investigator: Fatima Bosch. 06/05/2015- 05/04/2017.

IPAD-MD – Research Infrastructure for Phenotyping, Archiving and Distribution of Mouse Disease Models. Promoting International Cooperation and User Engagement to Enhance Biomedical Innovation. Horizon 2020 – the Framework Programme for Research and Innovation (2014-2020)" Proposal number: 653961". Project Coordinator: Martin Hrabe de Angelis (Helmholtz Zentrum Munchen, Germany). Principal investigator (group UAB): Fatima Bosch. 01/06/2015 -30/11/2019.

Global consortium: International Mouse Phenotyping Consortium (IMPC) Several important funding bodies (NIH, EU, CSF, etc. and industry sponsors). Project Coordinator:Steve Brown, Medical Research Council Harwell, UK. Principal investigator (group UAB): Fatima Bosch. 2015-2021.

Development of an innovative gene therapy platform for rare hereditary muscle disorders (MYOCURE) Research and Innovation actions (PHC-14-2015: New therapies for rare diseases), European Commission (Project Nº 667751). Project Coordinator: (M. Chuah, Vrije Universiteit Brussel, Belgium). Principal investigator (group UAB): Fatima Bosch. 01/01/2016 -31/12/2019.

Estudios Translacionales para el Desarrollo de Terapias Genicas con Telomerasa para el Tratamiento del Infarto de Miocardio y de la Fibrosis Pulmonar. Instituto de Salud Carlos III. Accion Estrategica en Salud 2013-2016, del Programa Estatal de Investigación Orientada a los Retos de la Sociedad (DTS17/00157). Project Coordinator: Maria AntoniaBlasco Marhuenda (Centro Nacional de Investigaciones Oncologicas-Instituto de SaludCarlos III, Madrid). Principal investigator (group UAB): Fatima Bosch. 2017-2019.

Laboratori d'Enginyeria Genetica Animal i Terapia Genica. Agència de Gestió d´Ajuts Universitaris i de Recerca (AGAUR), Generalitat de Catalunya (2017 SGR 01508). (Universitat Autonoma de Barcelona). Principal investigator: Fatima Bosch. 01/01/2017- 30/09/2021.

INFRAFRONTIER2020 - Towards enduring mouse resources and services advancing research into human health and disease. INFRAFRONTIER 2020. H2020-INFRADEV-2016-1. Call INFRADEV-03-2016-2017. (Proposal No. 730879). Project Coordinator: INFRAFRONTIER GmbH, DE. Principal investigator (group UAB): Fatima Bosch. 01/01/2017-31/12/2020.

Targeting the genetic causes of diabetes through gene therapy: Therapeutic approaches for MODY. Fundació La Marató de TV3 per a l'adjudicacio d'ajudes economiques a projectes de recerca sobre Diabetis i Obesitat (201603-30-31-32). Project Coordinator: Fatima Bosch (Universitat Autonoma de Barcelona). Other participants: Steve Brown (Medical Research Council, Harvell, UK), Martin Hrabe De Angelis (Helmholtz Center Munich GmbH, German Research Center for Environmental Health, Germany). Principal investigator (group UAB): Fatima Bosch. 11/07/2017-31/12/2020.

Transferencia genica al SNC mediada por vectores AAV para el estudio y tratamiento de la neuroinflamacion asociada a diabetes y obesidad. Ministerio de Educación y Competitividad, Plan Estatal de I+D+I (SAF2017-86266-R). Principal investigator: Fatima Bosch. 01/01/2018-31/12/2020.

PATENTS DURING 2016-20

Adenoassociated virus vectors for the Treatment of Mucopolysaccharidoses. EP16382450.1. F. Bosch, V. Haurigot and C. Roca. 2016. Universitat Autònoma de Barcelona/Esteve Pharmaceuticals S.A.

Viral expression construct comprising a Fibroblast Growth Factor 21 (FGF21) coding sequence. EP17172818.1. (PCT/EP2018/063707). F. Bosch, V. Jimenez and C. Jambrina. 24/05/2017. Universitat Autònoma de Barcelona

Adenoassociated virus vectors for the Treatment of Mucopolysaccharidoses Type IV A. EP18382373.1. (PCT/EP2019/063582 (27/05/2019).F. Bosch, V. Sanchez, A. Ribera and V. Haurigot. 2018. Universitat Autònoma de Barcelona/Esteve Pharmaceuticals S.A.

Animal model of Mucopolysaccharidoses type IV A. EP18382806.0. PTC mundial PCT/EP2019/081303 (14/11/2019). F. Bosch, J. Bertolin, M. Garcia, V. Sanchez, A. M. Pujol. 15/11/2018. Universitat Autònoma de Barcelona /Esteve Pharmaceuticals S.A.

Fibroblast growth factor 21 (FGF21) gene therapy. EP18382857.3. PTC mundial PCT/EP2019/082601. F. Bosch, I. Elias, V. Jimenez, A. Ribera, I. Grass. 26/11/2018. Universitat Autònoma de Barcelona.

Recombinant vectors for the long-term treatment of Mucchopolysacharidosis. EP18382957.1. PCT/EP2019/086227 (19/12/2019). F. Bosch, S. Marco, A. Morte, C. Ramon. Universitat Autònoma de Barcelona/Esteve Pharmaceuticals S.A.

Methods for the manufacture of recombinant AAVS. EP19382220.2. F. Godia, F. Bosch, M. Garcia, L. Cervera, X. Leon, M. Molas. S. Gutierrez. 21/05/2019. Universitat Autònoma de Barcelona/ Esteve Pharmaceuticals S.A.

Modified Insulin and Glucokinase Nucleic Acids for Treating Diabetes. US63/047,965. N. Gupta; W. Shen; M. Garcia, V. Jimenez, F. Bosch. 31/05/2019. Universitat Autònoma de Barcelona /Kriya Therapeutics

Insulin gene therapy. EP19382447.1. PTC mundial (PCT/EP2020/065018). F. Bosch, I. Elias, Ribera, I. Grass. 31/05/2019. Universitat Autònoma de Barcelona.

Fibroblast growth factor 21 (FGF21) gene therapy for central nervous system disorders. EP20382442.0. F. Bosch, V. Jimenez, I. Elias, C. Jambrina, V. Sacristan, I. Grass. 26/5/2020. Universitat Autònoma de Barcelona.

Clinical Enzymology Reference Laboratory (LREC)

GROUP LEADER
Francesca Canalias
Associate Professor

LAB MEMBERS
Jessica Arribas
Technician

RESEARCH INTERESTS

To collaborate with the international organizations for standardization in the development of reference measurement procedures and enzymes reference materials in the field of clinical laboratories. Establish collaborations with companies of the diagnostic *in vitro* (IVD) to help them to meet the requirements to the European Directive 98/79/CE on *in vitro* diagnostic medical devices.

STRATEGIC OBJECTIVES

In 2008 the LREC was accredited by the Spanish accreditation body (Entidad Nacional de Acreditación, ENAC) as calibration and reference laboratory according to the International Standards ISO/IEC 17025:2005 and ISO 15195:2003 (accreditation 195/LC10.141). Since 2009, the LREC is a supplier of the reference services of the Joint Committee for Traceability in Laboratory Medicine (JCTLM). The strategic objective is to maintain the accreditation based on international standards for the enzymes of the scope and the maintenance of the quality management system through the accomplishment of quality objectives and action plans.

MAIN RESEARCH LINES

Develop, validate and verify the transferability of new primary reference measurement procedures.

Characterize new enzyme reference materials performing homogeneity, stability and commutability studies.

Assign and certifies catalytic concentration values to already developed reference materials by means of certification campaigns among laboratories.

Assign traceable values of catalytic concentration to internal calibrator materials of *in vitro* diagnostic manufacturers (facilitating to meet the requirements of the European Directive 2017/746 on in vitro diagnostic medical devices).

Assign traceable values of catalytic concentration to control materials of external evaluation quality programs (EQAS) and internal quality control (facilitating the accomplishment to the international standard ISO/IEC 17043).

Validate measurement procedures and commercial analytical systems for the measurement of catalytic concentration in patient samples in routine.

Evaluate the commutability of commercial calibrator and control materials.

PUBLICATIONS DURING 2016-20:

B González, F Canalias, S Esteve, FJ Gella, S Izquierdo, R López, R Rigo, N Serrat. Procedimineto para la transferència y revisión de intervalos de referencia biológicos. Rev Lab Clín 2017;10(2):91-94

F Canalias, M Piñeiro, R Pato, R Peña, L Bosch, L Soler, N García, F Lampreave, Y Saco, A Bassols. Preparation of canine C-reactive protein serum reference material: a feasibility study. Vet Clin Pathol 2018;47:122-129

M Piñeiro, R Pato, L Soler, R Peña, N García, C Torrente, Y Saco, F Lampreave, A Bassols, F Canalias. A new automated turbidimetric immunoassay for the measurement of canine C-reactive protein. Vet Clin Pathol 2018;47:130-137

R Rigo, A Blanco, F Canalias. Different top-down approaches to estimate measurement uncertainty of whole blood tracolimus mass concentration values. Clin Biochem 2018;57:56-61

R Rigo, A Blanco, F Canalias. Different top-down approaches to estimate measurement uncertainty of whole blood tracolimus mass concentration values. Clin Biochem 2018;57:56-61

R Rigo, P Alía, F Canalias. Measurement uncertainty and metrological traceability of whole blood cyclosporin A mass concentration results obtained by UHPLC-MS/MS. Clin Chem Lab Med 2018;56(9):1458-1468

R Rigo, F Canalias, S Esteve, FJ Gella, B González, R López. Validación de procedimientos de medida basados en la cromatografía líquida de alta resolución. Rev Lab Clín 2018;11(1):39-46

FJ Gella, MJ Andrés, R Rigo, F Canalias, R Cano, S Esteve, B González, R López, I Pérez de Algaba. Nomenclatura y unidades de las propiedades biológicas Rev Lab Clín 2018;11(2):87-92

R Rigo, F Canalias, S Esteve, FJ Gella, B González, R López. Desarrollo de procedimientos de medida basados en la cromatografía líquida de alta resolución. Rev Lab Clín 2018;11(3):137-146

R López, R Rigo, MJ Andrés, F Canalias, R Cano, S Esteve, FJ Gella, B González, I Pérez de Algaba. Procedimiento para el estudio de interferencias exógenas en la medición de magnitudes biológicas. Rev Lab Clín 2018;11(3):147-152

R Rigo, F Canalias. Traceability of immunosuppressant's mass concentration results obtained using different commercial calibrators. Clin Biochem 2019;63:113-120

K Yu K, F Canalias, D Solà-Oriol, L Arroyo, R Pato, Y Saco, M Terré, A Bassols. Age-related serum biochemical reference intervals established for unweaned calves and piglets in the post-weaning period. Front Vet Sci 2019;6:123

R Rigo, R Cano, N Alonso, MJ Andrés, F Canalias, S Esteve, FJ Gella, B González, R López, I Pérez de Algaba. Procedimiento para la interpretación de un cambio entre dos valores consecutivos de una magnitud biológica. Rev Lab Clín 2019;12(2):93-97

R Rigo, F Canalias, C El Haj, MC González, N Díaz, L Soldevila, E Benavent, O Murillo. Measurement uncertainty of β-lactam antibiotics results: Estimation and clinical impact on therapeutic drug monitoring. Clin Chem Lab Med 2020;58(2):240-250

R Rigo, D Muñoz, F Canalias. Reference change values based on uncertainty models. Clin Biochem 2020;80:31-41

L Martínez, F Marques, Y Ozarda, A Blanco, N Brouwer, F Canalias, C Cobbaert, M Thelen, W den Elzen. Big data and reference intervals: rationale, current practices harmonization and standardization prerequisites and future perspectives of indirect determination of reference intervals using routine data. Ad Lab Med 2020;20200034

R Rigo, F Canalias. Measurement uncertainty estimation for derived biological quantities. Clin Chem Lab Med 2021;59(1):e1-e7

R Rigo, N Díaz, L García, A Marcè, M Valbuena, F Canalias. Estimation of the measurement uncertainty and practical suggestion for the description of the metrological traceability in clinical laboratories. Biochem Med (Zagreb) 2021;31(1):010501

R Rigo, F Canalias. Estimation of the uncertainty of values assigned to calibration materials prepared in-house: an example for hydroxychloroquine calibrators in blood-hemolysate-based matrix. Clin Biochem 2021;89:70-76

ACTIVE PROJECTS DURING 2016-20:

"Desarrollo de métodos analíticos automatizables para la determinación de biomarcadores relacionados con la mejora de la salud en ganado bovino". RTC-2015-3885-2 del programa RETOS del MEC. IP: Matilde Piñeiro, Acuvet Biotech, S.L., 2015 - 2018

"Assignació de valors a materials de control i calibradors. Estudis de validació d'instruments i de traçabilitat metrològica". Funded by BioSystems, S.A. (Barcelona, Spain), 2016 - 2021

Gene Therapy for Central Nervous System (GT4CNS)

GROUP LEADER
Miguel Chillon
Assistant Professor
ICREA Research Professor

LAB MEMBERS
Joan Francisco Espinosa
Postdoctoral Researcher
Angel Edo
Postdoctoral Researcher
Susana Miravet
Technician
Maria Ontiveros
Technician
Javier del Rey
Technician
Rebeca Blanch
Predoctoral Student
Joan Roig
Predoctoral Student
Laura Rodríguez
Predoctoral Student
Meritxell Puig
Technician
Laia Rubio
Technician
Marc Cabrera
Technician
Marina Tarres
Technician
Marc Herrera
Technician
Jon Esandi
Predoctoral Student

PUBLICATIONS DURING 2016-20

Sánchez, B. García-Lareu, M. Puig, E. Prat, J. Ruberte, M. Chillón, V. Nunes, R. Estévez, A. Bosch. Cerebellar Astrocyte Transduction as Gene Therapy for Megalencephalic Leukoencephalopathy. Neurotherapeutics (2020). in press. doi: 10.1007/s13311-020-00865-y.

A. Bosch, M. Chillon. Gene Therapy Approaches in CNS Regenerative Medicine. Handbook of Innovations in Central Nervous System Regenerative Medicine. USA. Elsevier. (2020). 8th June 2020. pages: 375-399. ISBN: 9780128180846

G. Pagès, L. Giménez-Llort, B. García-Lareu, L. Ariza, M. Navarro, J. Ruberte, C. Casas, M. Chillón, A. Bosch. Intrathecal AAVrh10 corrects Biochemical and Histological Hallmarks of Mucopolysaccharidosis VII Mice and Improves Behavior and Survival. Human Molecular Genetics. (2019): 1;28(21):3610-3624.

Massó, A. Sánchez, A. Bosch, L. Gimenez-Llort, M. Chillon. Secreted-Klotho isoform protects against age-dependent memory deficits. Molecular Psychiatry. (2018): Sep;23(9):1-11.

M. Miralles, H. Eixarch, M. Tejero, C. Costa, K. Hirota, AR. Castaño, M. Puig, G. Stockinger, X. Montalban, A. Bosch, C. Espejo, M. Chillon. Clinical and histopathological amelioration of experimental autoimmune encephalomyelitis by AAV vectors expressing soluble IL23 receptor. Neurotherapeutics (2017): Oct;14(4):1095-1106.

ACTIVE PROJECTS DURING 2016-20

Unidad de Producción de Vectores (UPV): Personal Técnico de Apoyo. Entidad financiadora: Ministerio de Ciencia e Innovación: PTA2019-017896-I Duración: 3 años desde: 1/9/2020 hasta: 31/08/2023 Investigador principal: Miguel Chillon.

Molecular and functional characterization of new recombinant chimeric chronokines. Implications for cognitive decline associated with aging. Entidades financiadora: Ministerio Ciencia Innovación. Proyectos I+D+i Retos Sociedad. PID2019-104034RB-I00 Duración: 3 años desde: 1/6/2020 hasta: 31/05/2023 Investigador principal: Miguel Chillon.

Terapia Génica para SPG52. Entidades financiadora: Fundación La Lucha de Abril Duración: 3 años desde: 1/3/2020 hasta: 28/02/2023

Desarrollo de nuevas terapias genéticas basadas en inteinasEntidades financiadora: Ministerio Ciencia Innovación. Retos Colaboración. RTC2019006879-1 Duración: 3 años desde: 1/1/202 hasta: 30/06/2022 Investigador principal: Miguel Chillon. Coordinador (Proteodesign)

Una terapia innovadora contra el SARS-CoV-2 basada en ARN circulares (CIRCO-3) Entidades financiadora: Fundación Santander Duración: 4 años desde: 1/6/2020 hasta: 31/05/2021 Investigador principal: Miguel Chillon. Coordinador (Dra, Juana Díez, UPF)

Desarrollo de una terapia génica para el tratamiento de las formas genéticas del Síndrome Nefrótico (AAV-Crb2) Entidades financiadora: Convocatoria CERVERA 2020: IDI-20200258 Duración: 2 años desde: 1/5/20220 hasta: 30/04/2022
Investigador principal: Miguel Chillon. Coordinador: Empresa Ninevah Therapeutics)

Doctorado Industrial con Regi Jofre. Entidades financiadora: AGAUR; 2018-DI-066 Duración: 4 años desde: 1/1/2019 hasta: 31/12/2022 Investigador principal: Miguel Chillon, Assumpció Bosch y Elisabeth Rosell

Gene therapy for Megalencephalic leukoencephalopathy with subcortical cysts in two animal models of the disease. Entidades financiadora: ELA International (2018-0512) Duración: 2 años desde: 1/1/2019 hasta: 31/12/2020 Investigador principal: Assumpció Bosch

Unitat Producció de Vectors (UPV). Entidades financiadora: Ajuts per definir i potenciar els plans d'actuació en transferència tecnològica dels desenvolupadors de tecnologia candidats a ser acreditats TECNIO. ACCIÓ; TECDTP18-1-0006 (2018) PI: Miguel Chillon

Validation of the capacity of sKL in bloodstream to cross BBB and its therapeutic use in neurodegenerative and demyelinating diseases. Entidades financiadora: AGAUR (#2016LLAV00033) (2017)
PI: Miguel Chillón

ELI-KLAD:Non-invasive sensitive diagnostic for early stages of Alzheimer's Disease. Entidades financiadora: SmartMoney (2017) - UAB (T2014/34) (2018). PI: Miguel Chillón

Producción vectores para Alzheimer Disease. Entidades financiadora: Kogenix Therapeutics (2017) PI: Miguel Chillón

Unitat Producció de Vectors (UPV). Entidades financiadora: Ajuts per definir i potenciar els plans d'actuació en transferència tecnològica dels desenvolupadors de tecnologia candidats a ser acreditats. TECNIO. ACCIÓ; TECDTP16-1-0010 (2017) PI: Miguel Chillon

Gene Therapy to treat Friedreich Ataxia. CaixaImpulse (CaixaCapitalRisc) (2017). PI: Antoni Matilla .

Teràpia gènica combinada per corregir l'estrès oxidatiu i de reticle en neuropatia diabètica de tipo 2. Marato TV3. 201607.10 (2017 - 2019). PI: Miguel Chillón

Advancecat: Acceleradora pel desenvolupament de terapies avançades a Catalunya. Comunitats RIS3CAT (ACCIO y FEDER) COMRDI 15-1-0013-16 (2016 - 2019). PI: Miguel Chillon

Unitat Producció de Vectors (UPV). Entidades financiadora: Ajuts per definir i potenciar els plans d'actuació en transferència tecnològica dels desenvolupadors de tecnologia candidats a ser acreditats TECNIO. ACCIÓ; TECDTP15-1-0007 (2016). PI: Miguel Chillon

Prevención de la respuesta de anticuerpos antiidiotipos en Esclerosis Múltiple: Uso del receptor soluble de IL23 para evitar la activación de la vía Th17. Análisis de ausencia de anticuerpos anti IL23Rs en sangre. IV Convocatoria de Becas de Investigación Fundación Genzyme en Esclerosis Múltiple (2016) PI: Miguel Chillon.

Red española de adenovirus: desde la Biologia basica a la Nanobiomedicina. MICINN: Acciones de dinamización "Redes de Excelencia" (BIO2015-68990-REDT) (2016 - 2018). Investigador coordinador: Carmen San Martin (CSIC) PI UAB: Miguel Chillon

Estudio del papel de la isoforma soluble de alpha-Klotho en el inicio y progresión de déficits cognitivos: marcador de diagnóstico precoz, y molécula diana con potencial terapéutico. Entidades financiadora: ISC-III (#PI15-01270) (2016 - 2018). PI: Miguel Chillon.

Convocatoria 2015 de las ayudas Personal Técnico de Apoyo, para el tema "Vector Production Unit UAB" (#09357). Entidades financiadora: Ministerio de Economía y Competitividad. (2015 - 2018). PI: Miguel Chillon

Optimización y desarrollo de un agente terapéutico basado en ácidos nucleicos para el tratamiento de la enfermedad de Huntington. RETOS Colaboracion 2015. Ministerio de Economia y Competitividad (RTC-2015-3731-1) (2015 - 2018). PI: Assumpció Bosch

Grupo de Investigación para enfermedades autoinmunes desmielinizantes. Entidades financiadora: Agencia de Gestió d'Ajuts Universitaris i de Recerca (AGAUR). Convocatoria 2014 Generalitat de Catalunya (2014-SGR-1354) (2014-2016). PI: Miguel Chillon

From Brain Gene Transfer Towards Gene Therapy: Pharmacological Assessment of AAV, CAV and LVV (BRAINVECTORS). FP7-286071-BRAINVECTORS (2013-2016) PI-UAB: Miguel Chillon. Coordinator: Lilianne Tenembaum (Suiza)

PATENTS DURING 2016-20

C. Abraham, M. Abraham Bosch, M.Chillón, T. Rubinek, I. Wolf. Vectors expressing klotho for treating cáncer N. de solicitud: PCT/IL2019/050913. País de prioridad: Israel Fecha de prioridad: 28/8/19. Entidad titular: Tel-Aviv Medical Center, UAB, Klogene, ICREA. Licencing companies: Klogene

Structural Biology of Alzheimer's Disease

GROUP LEADER
Josep Cladera
Associate Professor

RESEARCH INTERESTS

In vitro and in vivo characterization of amyloid aggregates related to Alzheimer's disease. Biophysical Studies.
Dendrimers as polymeric antiamyloidogenic agents in Alzheimer's disease.

STRATEGIC OBJECTIVES

Characterization of early formation aggregates in brains affected by Alzheimer's disease, using synchrotron-based imaging techniques.
Brain delivery of dendrimers as antiamyloidogenic agents using liposome-based delivery systems.

MAIN RESEARCH LINES

Application of synchrotron-based infrared imaging and X-ray fluorescence microscopy to the detection of amyloid aggregated species in mouse-model and human Alzhimer's brains.
Liposome-based nanosystems for the delivery of antiamyloidogenic agents to the brain.

PUBLICATIONS DURING 2016-20

Myoglobinopathy is an adult-onset autosomal dominant myopathy with characteristic sarcoplasmic inclusions. Montse Olivé; Martin Engvall; Gianina Ravenscroft; Macarena Cabrera-Serrano; Hong Jiao; Carlo Augusto Bortolotti; Marcello Pignataro; Matteo Lambrughi; Haibo Jiang; Alistair R.R. Forrest; Núria Benseny-Cases; Stefan Hofbauer; Christian Obinger; Gianantonio Battistuzzi; Marzia Bellei; Marco Borsari; Giulia Di Rocco; Helena M. Viola; Livia C. Hool; Josep Cladera; Kristina Lagerstedt-Robinson; Fengqing Xiang; Anna Wredenberg; Francesc Miralles; Juan José Baiges; Edoardo Malfatti; Norma B. Romero; Nathalie Streichenberger; Christophe Vial; Kristl G. Claeys; Chiara S.M. Straathof; An Goris; Christoph Freyer; Martin Lammens; Guillaume Bassez; Juha Kere; Paula Clemente; Thomas Sejersen; Bjarne Udd; Noemí Vidal; Isidre Ferrer; Lars Edström; Anna Wedell; Nigel G. Laing. Nature Communications 2019, 10(1), 1396

Structural biology workflow for the expression and characterization of functional human sodium glucose transporter type 1 in Pichia pastoris. Albert Suades; Antonio Alcaraz; Esteban Cruz; Elena Álvarez-Marimon; Julian P. Whitelegge; Joan Manyosa;Josep Cladera; Alex Perálvarez-Marín. Scientific Reports 2019, 9(1), 1203

Poly(propylene imine) dendrimers with histidine-maltose Shell as novel type of nanoparticles for synapse and memory protection.
Ester Aso; Isak Martinsson; Dietmar Appelhans; Christiane Effenberg; Nuria Benseny-Cases; Josep Cladera; Gunnar Gouras; Isidre Ferrer; Oxana Klementieva. Nanomedicine: Nanotechnology, Biology, and Medicine 2019, 17, pp. 198–209

Synchrotron-Based Fourier Transform Infrared Microspectroscopy (μFTIR) Study on the Effect of Alzheimer's Aβ Amorphous and Fibrillar Aggregates on PC12 Cells. Núria Benseny-Cases; Elena Álvarez-Marimon; Hiram Castillo-Michel; Marine Cotte; Carlos Falcon; Josep Cladera. Analytical Chemistry 2018, 90(4), pp. 2772–2779.

3D membrane segmentation and quantification of intact thick cells using cryo soft X-ray transmission microscopy: A pilot study.
Rubén Cárdenes; Chong Zhang; Oxana Klementieva; Stephan Werner; Peter Guttmann; Christoph Pratsch; Josep Cladera; Bart H. Bijnens. PLoS ONE 2017, 12(4), e0174324

Pre-plaque conformational changes in Alzheimer's disease-linked Aβ and APP. O. Klementieva; K. Willén; I. Martinsson; B. Israelsson; A. Engdahl; J. Cladera; P. Uvdal; G. K. Gouras. Nature Communications 2017, 8, 14726

Helical unwinding and side-chain unlocking unravel the outward open conformation of the melibiose transporter.
Li Ying Wang; Vidhya M. Ravi; Gérard Leblanc; Esteve Padrós; Josep Cladera; Alex Perálvarez-Marín. Scientific Reports 2016, 6, 33776

Can dendrimer based nanoparticles fight neurodegenerative diseases? Current situation versus other established approaches.
Serge Mignani; Maria Bryszewska; Maria Zablocka; Barbara Klajnert-Maculewicz; Josep Cladera; Dzmitry Shcharbin; Jean Pierre Majoral. Progress in Polymer Science 2017, 64, 23–51.

Fourier transform infrared spectroscopy (FTIR) characterization of the interaction of anti-cancer photosensitizers with dendrimers.
Monika Dabrzalska; Nuria Benseny-Cases; Ramon Barnadas-Rodríguez; Serge Mignani; Maria Zablocka; Jean Pierre Majoral; Maria Bryszewska; Barbara Klajnert-Maculewicz; Josep Cladera.
Analytical and Bioanalytical Chemistry 2016, 408(2), 535–544

ACTIVE PROJECTS DURING 2016-20

Optimización de un sistema de liberación nanoterapeutica basado en dendrómetros para el tratamiento de la enfermedad de Alzheimer (RETOS 2017)
IP: Josep B Cladera Cerdà Entidad/es financiadora/s: Ministerio de Economia y Competitividad (MINECO) Fecha de inicio-fin: 01/01/2018 - 30/09/2021 Ref: 2014/67
Analysis of the structure-activity relationships of antimyotonic dystrophy hexapeptides.
RTVE Project call 'Todos somos raros'. PI: M. Beatriz Llamusí. March 2015-March 2107.

Lipid metabolism and cell death

GROUP LEADER
Enrique Claro
Professor

PUBLICATIONS DURING 2016-20

L. Cordón-Barris, S. Yang, S. Pascual-Guiral, L. Giménez-Llort, S. Lope-Piedrafita, C. Niemeyer, E. Claro, J.M. Lizcano, J.R. Bayascas (2016) Mutation of the PDK1 substrate-docking site in the developing brain causes microcephaly with abnormal brain morphogenesis independently of Akt, leading to impaired cognition and disruptive behaviors. Mol. Cell. Biol. 36, 2967–2982. ISSN 0270-7306.

Eraso-Pichot, M. Brasó-Vives, A. Golbano, C. Menacho, E. Claro, E. Galea, R. Masgrau (2018) GSEA of mouse and human mitochondriomes reveals fatty-acid oxidation in astrocytes. Glia 66, 1724-1735.

F. Riefolo, C. Matera, A. Garrido-Charles, A.M.J. Gomila, R. Sortino, L. Agnetta, E. Claro, R. Masgrau, U. Holzgrabe, M. Batlle, M. Decker, E. Guasch, P. Gorostiza (2019) Control of Cardiac Function in vivo with a Light-Regulated Drug. ChemRxiv (posted 17 dec 2018). DOI: 10.26434/chemrxiv.7472174.v2

L. Agnetta, M. Bermudez, F. Riefolo, C. Matera, E. Claro, R. Messerer, T. Littman, G. Wolber, U. Holzgrabe, M. Decker (2019) Fluorination of photoswitchable muscarinic agonists tunes receptor pharmacology and photochromic properties. J. Med. Chem. 62 (6), 3009-3020.

F. Riefolo, C. Matera, A. Garrido-Charles, A.M.J. Gomila, R. Sortino, L. Agnetta, E. Claro, R. Masgrau, U. Holzgrabe, M. Batlle, M. Decker, E. Guasch, P. Gorostiza (2019) Optical control of cardiac function with a photoswitchable muscarinic agonist. J. Am. Chem. Soc. (JACS) 141 (18), 7628-7636.

A. Barbero, F. Riefolo, C. Matera, E. Claro, M.V. Sánchez-Vives, P. Gorostiza (2019) Control of brain state transitions with light. bioRxiv (posted 5 oct 2019). DOI: 10.1101/793927

Senyalització Cel·lular i Apoptosi

GROUP LEADER
Joan Xavier Comella
Professor

LAB MEMBERS
Joaquín López
Researcher
Montserrat Solé
Postdoctoral Researcher
Anna Martínez
Postdoctoral Researcher
Raquel Badillos
Postdoctoral Researcher
Mireia Turch
Postdoctoral Researcher

RESEARCH INTERESTS

Role of death receptor antagonists (mainly FAIM) in neurodegeneration and neuron physiology

STRATEGIC OBJECTIVES

Our main research objectives at present are:
To study FAIM-L function in in vitro and in vivo models of AD, and its relation with TNF and its signaling pathways, as well in the cross-talk neuron/glia.
To characterize FAIM-L functional partners, particularly XIAP and Siva-1, and their implications in neuron physiology (neuronal plasticity) and different neurodegenerative diseases (neuronal apoptosis, synaptic degeneration).
To study the control of FAIM-L expression levels, both in physiological and pathologic states (microRNAs, transcription, splicing).

MAIN RESEARCH LINES

Our main interest is to characterize the mechanisms controlling neuronal death induced by a group of receptors collectively known as death receptors, and also the relevance of some of their intracellular antagonists. Among those, we are most interested in the antagonists expressed in nervous system, such as FAIM-L, as well as their molecular partners. Our main objective is to characterize these in neuronal differentiation and physiology, and their possible role in different pathologies, mainly neurodegenerative diseases.

We have characterized, in collaboration with different CIBERNED groups, the role of FAIM-L in the development of Alzheimer's disease, both in animal models (APP/PS1) and patients (Carriba et al., 2015). Our lab has characterized new unexpected physiological roles for FAIM-L, since we observed that it is implicated in the control of some non-apoptotic effects of caspases, such as axonal degeneration and long term depression (LTD), through modulation of XIAP levels (Martínez-Mármol et al., 2016). These events of synaptic plasticity are also modulated in neurodegenerative diseases, thus positioning FAIM-L as a good candidate for the treatment of the disease.

We have also characterized the interaction of FAIM-L and XIAP with other proapototic partners, such as Siva-1. We have verified that Siva-1, XIAP and FAIM-L interact among them, particularly through ubiquitination. Also, Siva-1 regulates GluA2 receptors internalization, and plays an opposite role to FAIM-L and XIAP on the apoptotic and non-apoptotic functions of caspase-3 (Coccia et al., 2020), which may help to better explain the role of FAIM-L in neuron physiology, and have interesting implications in the development of neurodegenerative diseases. We are now also validating the interaction of FAIM-L with other proteins of high interest in neurodegenerative diseases.

We have also described the post-transcriptional regulation of faim gene through different microRNAs, by searching in silico the miRNAs described as altered in Alzheimer's disease. Three of them have yielded positive results by directly regulating this gene (Coccia et al., 2020).

At present we are also studying the role of FAIM-L in the diabetic retinopathy, a disease correlated with the risk of suffering neurodegenerative diseases, as well as common molecular mechanisms between retinal and cerebral neurodegeneration in the context of diabetes and Alzheimer's disease.

PUBLICATIONS DURING 2016-20

Coccia E, Masanas M, López-Soriano J, Segura MF, Comella JX & Pérez-García MJ (2020). FAIM is regulated by miR-206, miR-1-3p and miR-133b Front Cell Dev Biol 2020 Dec 23;8:584606.

Coccia E, Planells-Ferrer L, Badillos-Rodríguez R, Pascual M, Segura MF, Fernández-Hernández R, López-Soriano J, Garí E, Soriano E, Barneda-Zahonero B, Moubarak RS, Pérez-García MJ, Comella JX. SIVA-1 regulates apoptosis and synaptic function by modulating XIAP interaction with the death receptor antagonist FAIM-L. Cell Death Dis. 2020 Feb 3;11(2):82.

Sáez, M.E., González-Pérez, A., Hernández-Olasagarre, B., Beà, A., Moreno-Grau, S., de Rojas I., Monté-Rubio, G., Orellana, A., Valero, S., Comella, J.X., Sanchís, D. & Ruiz A. (2019). Genome Wide Meta-Analysis identifies common genetic signatures shared by heart function and Alzheimer's disease. Sci Rep 9, 16665.

Oleshkevich E, Morancho A, Saha A, Galenkamp KMO, Grayston A, Geninatti Crich S, Alberti D, Protti N, Comella JX, Teixidor F, Rosell A & Viñas C. Combining Magnetic Nanoparticles and Icosahedral Boron Clusters in Biocompatible Inorganic Nanohybrids for Cancer Therapy. Nanomedicine, 2019 20:101986.

Fuschini G, Cotrufo T, Ros O, Muhaisen A, Andrés R, Comella JX & Soriano E. Syntaxin-1/TI-VAMP SNAREs interact with Trk receptors and are required for neurotrophin-dependent outgrowth. Oncotarget 2018,9(89):35922-35940.

Gómez-Arboledas A, Dávila JC, Sánchez-Mejías E, Navarro V, Núñez-Díaz C, Sánchez-Varo R, Sánchez-Mico MV, Trujillo-Estrada L, Fernández-Valenzuela JJ, Vizuete M, Comella JX, Galea E, Vitorica J, Gutiérrez A. Phagocytic clearance of presynaptic dystrophies by reactive astrocytes in Alzheimer's disease. GLIA 2018 637-653.

Coccia E, Calleja-Yagüe I, Planells-Ferrer L, Sanuy B, Sanz B, López-Soriano J, Moubarak RS, Munell F, Barneda-Zahonero B, Comella JX, Pérez-GarcíaMJ. Identification and characterization of new isoforms of human fas apoptotic inhibitory molecule (FAIM). PLOS ONE 2017 Oct 5;12(10):e0185327

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Bosch C, Masachs N, Expósito-Alonso D, Martinez A, Teixeira CM, Fernaud I, Pujadas L, Ulloa F, Comella JX, de Felipe J, Merchán-Pérez A, Soriano E. Reelin regulates the maturation of dendritic spines, synaptogenesis and glial ensheathment of newborn granule cells. Cer. Cor., 2016, 26(42): 82-98.

Planells-Ferrer L, Urresti J, Coccia E, Galenkamp KM, Calleja-Yagüe I, López-Soriano, J, Carriba P, Barneda-Zahonero B, Segura MF, Comella JX. FAIMs: more than death-receptor antagonists in the nervous system. J Neurochem. 2016, 6: 35775.

Jubierre L, Soriano A, Planells-Ferrer L, París-Coderch L, Tenbaum SP, Romero OA, Moubarak RS, Almazán-Moga A, Molist C, Roma J, Navarro S, Noguera R, Sánchez-Céspedes M, Comella JX, Palmer HG, Sánchez de Toledo J, Gallego S, Segura MF. BRG1/SMARCA4 is essential for neuroblastoma cell viability through modulation of cell death and survival pathways. Oncogene. 2016 Mar 21. doi: 10.1038/onc.2016.50.

Urresti J, Ruiz-Meana M, Coccia E, Arévalo JC, Castellano J, Fernández-Sanz C, Galenkamp KM, Planells-Ferrer L, Moubarak RS, Llecha-Cano N, Reix S, García-Dorado D, Barneda-Zahonero B, Comella JX. Lifeguard inhibits Fas ligand-mediated endoplasmic reticulum-calcium release mandatory for apoptosis in type II apoptotic cells. J. Biol Chem. 2016 291(3):1221-34.

ACTIVE PROJECTS DURING 2016-20

Papel del antagonista de receptores de muerte, FAIM-L, en la progresión de la enfermedad de Alzheimer FINANCING ENTITY: Ministerio de Ciencia e Innovación (PID2019-107286RB-I00). 2020-2022. PRINCIPAL RESEARCHER: Joan X. Comella & Maria José Pérez Garcia

Disfunción glial en la enfermedad de Alzheimer: implicaciones patogénicas y potencial clínico FINANCING ENTITY: CIBERNED (Proyectos Cooperativos) (2017/04) 2018-2019. PRINCIPAL RESEARCHER: Javier Vitorica (Univ. Sevilla)

Relevancia del antagonista de receptores de muerte, FAIM-L, en la enfermedad de Alzheimer. FINANCING ENTITY: Dirección General de Investigación Científica y Técnica – Ministerio de Economía y Competitividad (SAF2016-80236-R) 2017 - 2019. PRINCIPAL RESEARCHER: Joan X. Comella

Potencial patológico de los astrocitos: una nueva perspectiva en la enfermedad de Alzheimer. CIBERNED (Proyectos Cooperativos)(2015-2/02) 2016 - 2018. PRINCIPAL RESEARCHER: Joan X. Comella

Deciphering the link between astrocyte reactivity and neuronal damage in Alzheimer's disease. Fundació La Marató de TV3. 2015 - 2018. PRINCIPAL RESEARCHER: Elena Galea (UAB)

Neuroinflamación, TNF y antagonistas de los receptores de muerte (FAIM-L): relevancia en neurodegeneración. Dirección General de Investigación Científica y Técnica – Ministerio de Economía y Competitividad (SAF2013-47989-R). 2014-2016. PRINCIPAL RESEARCHER: Joan X. Comella

Preventing cardiovascular ischemic events and arresting their consequences in type 2 diabetic population: a multidisciplinary clinical and experimental approach. MINECO/ISCIII (PIE13/00027). DURATION: 2014-2016. PRINCIPAL RESEARCHER: David García-Dorado (VHIR)

Apoptosi i Neurodegeneració. Generalitat de Catalunya – AGAUR - Convocatòria de Suport al Grups de Recerca (2014SGR1609). 2014-2016. PRINCIPAL RESEARCHER: Joan X. Comella

Apoptosi i Neurodegeneració. Generalitat de Catalunya – AGAUR - Convocatòria de Suport al Grups de Recerca (2017SGR996). 2017-2020. PRINCIPAL RESEARCHER: Joan X. Comella

Chromatin Laboratory

GROUP LEADER
Joan-Ramon Daban
Emeritus Professor

RESEARCH INTERESTS

Our group was interested in the study of chromatin structure at intermediate concentrations of divalent cations. Our results led us to the proposal of the interdigitated solenoid model for the 30-nm fiber, which is now widely accepted in the chromatin literature. Since the early 2000s, we have been interested in the chromatin structure in the presence of higher cation concentrations, similar to those found in metaphase chromosomes. We have discovered that in condensed chromosomes, chromatin is densely packed forming plate-like structures instead of the typical fibers considered in the current models of metaphase chromosomes. Our electron microscopy images have shown that chromosome plates can form multilayered structures, having a thickness of approximately 6 nm each layer. These observations and further structural studies performed using atomic force microscopy have allowed us to suggest the thin-plate model for chromatin folding in metaphase chromosomes, in which we proposed that chromosomes are formed by many stacked plates oriented perpendicular to the chromatid axis. This model allows an easy physical explanation of the characteristic banding patterns of metaphase chromosomes obtained in cytogenetic studies. We have also found using electron tomography and polarizing microscopy that nucleosomes are irregularly oriented in the well-defined plates that occupy the entire volume of the chromatid. To justify the small thickness observed for the plates, we have suggested that there is an interdigitation between the successive layers. The resulting compact structure is necessary for the safe transfer of the genomic DNA to the daughter cells during mitosis. More recently, we have used synchrotron X-ray scattering techniques and cryo-electron tomography to study the internal structure and the physical properties of chromatin plates. At present, we are conducting theoretical and modeling studies on the possible biological functions of the multilaminar organization of chromosomes.

MAIN RESEARCH LINES

Chromatin structure
Mitotic chromosome structure

PUBLICATIONS DURING 2016-20

A. Chicano, E. Crosas, J. Otón, R. Melero, BD. Engel & JR. Daban (2019) Frozen-hydrated chromatin from metaphase chromosomes has an interdigitated multilayer structure. EMBO J. 38:e99769.

A. Chicano & JR. Daban (2019) Chromatin plates in the interphase nucleus. FEBS Lett. 593:810-819.

JR. Daban (2020) Supramolecular multilayer organization of chromosomes: possible functional roles of planar chromatin in gene expression and DNA replication and repair. FEBS Lett. 594:395-411.

C. elegans models of disease

GROUP LEADER
Esther Dalfó
Assistant Professor

RESEARCH INTERESTS

Mechanisms involved in the development of neurodegenerative diseases at early stages

STRATEGIC OBJECTIVES

Investigate mechanisms involved in neurodegeneration using *C elegans* as the main tool for the research

MAIN RESEARCH LINES

Investigate mechanisms involved in the dead of dopaminergic neurons in Parkinson's disease
Investigate the axis enteric system-central nervous system
Studying the symbiosis between the gastrointenstinal system and the resident microbiome

PUBLICATIONS DURING 2016-20

Andrea Coppa; Sanjib Guha; Stéphane Fourcade; Janani Parameswaran; Montserrat Ruiz; Ann B Moser; Agatha Schlüter; Michael P. Murphy; Jose Miguel Lizcano; Antonio Miranda-Vizuete; Esther Dalfó; Aurora Pujol. The peroxisomal fatty acid transporter ABCD1/PMP-4 is required in the C. elegans hypodermis for axonal maintenance: a worm model for adrenoleukodystrophy. Free Radical Biology and Medicine. Elsevier, 30/01/2020.

Peña-Díaz S, Pujols J, Pinheiro F, Santos J, Pallarés I, Navarro S, Conde-Gimenez M, García J, Salvatella X, Dalfó E, Sancho J, Ventura S. Inhibition of α-Synuclein Aggregation and Mature Fibril Disassembling With a Minimalistic Compound, ZPDm. Front Bioeng Biotechnol. 2020 Oct 16; 8:588947. doi: 10.3389/fbioe.2020.588947. eCollection 2020.

Peña-Díaz S, Pujols J, Conde-Giménez M, Čarija A, Dalfo E, García J, Navarro S, Pinheiro F, Santos J, Salvatella X, Sancho J, Ventura S.ZPD-2, a Small Compound That Inhibits α-Synuclein Amyloid Aggregation and Its Seeded Polymerization.
Front Mol Neurosci. 2019 Dec 17;12:306.

Jordi Pujols; Samuel Peña; Lázaro; Peccati; Pinheiro; Gonzalez; Carija; Navarro; Conde-Giménez; García; Guardiola; Giralt; Salvatella; Sancho; Sodupe; Outeiro; Dalfó E; Ventura. Small molecule inhibits α-synuclein aggregation, disrupts amyloid fibrils, and prevents degeneration of dopaminergic neurons. Proc Natl Acad Sci U S A.115 - 41, pp. 10481 - 10486. 02/10/2018.

Kim; Calatayud; Guha; Fernandez; Berkovitz; Carvalho; Ezquerra; Fernandez; Kapahi; Raya; Miranda; Vila; Lizcano; Caldwell; Caldwell; Consiglio; Dalfó E. The Small GTPase RAC1/CED-10 Is Essential in Maintaining Dopaminergic Neuron Function and Survival Against α-Synuclein-Induced Toxicity. Molecular Neurobiology. Springer, 10/02/2018.

Lucariello; Vidal; Vidal; Saez; Roa, L; Huertas; Pineda; Dalfo E; Dopazo; Jurado; Armstrong; Esteller. Whole exome sequencing of Rett syndrome-like patients reveals the mutational diversity of the clinical phenotype.Human Genetics. 135 - 12, pp. 1343 - 1354. Springer, 08/2016.

ACTIVE PROJECTS DURING 2016-20

Nombre del proyecto: Mecanismos convergentes entre autofagia y función axonal e influencia metabólica en la regulación de las enfermedades neurodegenerativas ISCII PI15/01255 2016 – 2018.

Wnt signalling in epithelial cancer cell invasion and chemo-resistance

GROUP LEADER
Mireia Duñach
Professor
ICREA Academia

LAB MEMBERS
Antonio Garcia de Herreros
Researcher
Beatriz del Valle
Postdoctoral Researcher
Guillem Fuertes
Postdoctoral Researcher
Javier Pastor
Master student

RESEARCH INTERESTS

This project is oriented to study how extracellular Wnt proteins control epithelial tumor cell invasion. Wnt factors regulate different cellular processes during development and disease, particularly in cancer. Wnt ligands interact with transmembrane Frizzled (Fz) receptors and different co-receptors, depending on which they stimulate canonical or non-canonical Wnt signalling pathways. The canonical Wnt3a binds to Fz and co-receptor LRP5/6 promoting β-catenin stabilization and transcriptional activation of β-catenin-dependent genes. In contrast, non-canonical Wnt5a ligand binds to Fz and co-receptor Ror2 and produces a decrease in β-catenin through the activation of the E3 ligase Siah2. Remarkably, although the effects on β-catenin levels are contrary, both Wnt5a and Wnt3a stimulate the invasion of tumor cells.

When searching common elements to canonical and non-canonical Wnts, we have recently observed that both stimulate a new branch involving Fz2, Src, Fyn and Stat3, required for transcription of canonical and non-canonical Wnt targets involved in cell invasion (see Figure 1). Both types of Wnt ligands stimulate Fz2 tyrosine phosphorylation, Fyn binding to Fz2, Fyn activation and Fyn-dependent Stat3 phosphorylation. Canonical Wnt3a and non-canonical Wnt5a require Src for Fz2 tyrosine phosphorylation; Src is activated both, by Wnt3a and Wnt5a. Remarkably, this new Fz2/Fyn/Stat3 branch is incompatible with the classical Fz2/Dishevelled /Axin pathway. However, both routes are required for the activation of tumor cell invasion by Wnt. Therefore, our results extend the knowledge of canonical Wnt signalling demonstrating additional roles for Fyn in this pathway and characterize a new route activated by all Wnts and required for cell invasion.

For both canonical and non-canonical Wnt pathways, Stat3 activation is required for transcription of epithelial-to-mesenchymal-transition-associated genes, such as Snail1 (Villarroel A *et al.*, 2020), that controls tumor cell invasion and chemo-resistance. When analysing the relative contribution of canonical and non-canonical Wnt to Snail1 expression, we have determined that it is mainly dependent on non-canonical Wnt.

Therefore, chemo-resistance in tumor cells with high Snail1 expression is alleviated by blocking the Ror2 activity. We are working in other signals controlled by non-canonical Wnts in tumor cells. This project is carried out in close collaboration with Dr. Antonio Garcia de Herreros (Cancer Program, IMIM, PRBB, Barcelona).

STRATEGIC OBJECTIVES

Study of the signaling pathways triggered by Wnt factors that activate cellular responses involved in human diseases, particularly relevant in the genesis and progression of epithelial tumors.

PUBLICATIONS DURING 2016-20

Vinyoles M, Del Valle-Pérez B, Curto J, Padilla M, Villarroel A, Yang J, García de Herreros A, Duñach M. Activation of CK1ε by PP2A/PR61ε is required for the initiation of Wnt signaling. Oncogene 2017, 36, 429-438.

Duñach M, Del Valle-Pérez B, García de Herreros A. p120-catenin in canonical Wnt signaling. Crit Rev Biochem Mol Biol. 2017, 52, 327-339.

Rima M, Daghsni M, Lopez A, Fajloun Z, Lefrancois L, Duñach M, Mori Y, Merle P, Brusés JL, De Waard M, Ronjat M. Down-regulation of the Wnt/β-catenin signaling pathway by Cacnb4. Mol Biol Cell. 2017, 28, 3699-3708.

Curto J, Del Valle-Pérez B, Villarroel A, Fuertes G, Vinyoles M, Peña R, García de Herreros A, Duñach M. CK1ε and p120-catenin control Ror2 function in non-canonical Wnt signaling. Mol Oncol. 2018, 12, 611-629.

García de Herreros A, Duñach M. Intracellular Signals Activated by Canonical Wnt Ligands Independent of GSK3 Inhibition and β-Catenin Stabilization. Cells 2019, 8, pii: E1148.

Villarroel A, Del Valle-Pérez B, Fuertes G, Curto J, Ontiveros N, Garcia de Herreros A, Duñach M. Src and Fyn define a new signaling cascade activated by canonical and non-canonical Wnt ligands and required for gene transcription and cell invasion. Cell Mol Life Sci 2020, 77, 919-935.

Mestre-Farrera A, Bruch-Oms M, Peña R, Rodríguez-Morató J, Alba-Castellón L, Comerma L, Quintela-Fandino M, Duñach M, Baulida J, Pozo ÓJ, García de Herreros A. Glutamine-Directed Migration of Cancer-Activated Fibroblasts Facilitates Epithelial Tumor Invasion. Cancer Res. 2020 Epub Nov 23. doi: 10.1158/0008-5472.CAN-20-0622

ACTIVE PROJECTS DURING 2016-20

Analysis of the Fyn/Stat3 pathway stimulated by canonical and non-canonical Wnt factors: mechanism of action and relevance in epithelial tumor cell invasion. Ministerio de Ciencia, Innovación y Universidades- Agencia Estatal de Investigación (Retos Investigación RTI2018-0099719-B-100). From 1-1-2019 to 31-12-2021.

Study of the non-canonical Wnt pathway and its role in the invasion of tumor epithelial cells. MINECO-Plan Nacional (BFU2015-65153-R). From 1-1-2016 to 31-12-2018.

Oxidoreductases in Cellular Defense and Signaling. Search of inhibitors for therapeutic purposes

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RESEARCH INTERESTS

Our current research is focused on the enzymology and molecular biology of oxidoreductases involved in mechanisms of cellular defense and signaling. We are investigating members of three oxidoreductase superfamilies participating in the metabolism of carbonyl compounds, along with other biological functions: aldo-keto reductases (AKR), medium-chain dehydrogenases/reductases (MDR) and aldehyde dehydrogenases (ALDH). We are especially interested in enzymes acting on the metabolism of signaling molecules (retinoids and prostaglandins) and associated with different human disease states, such as cancer and diabetes. Some of these enzymes are also phase I-drug metabolizing enzymes and induced under oxidative stress, being responsible for developing tumor resistance to chemotherapy. Thus, they are relevant drug targets and are well suited for the design of selective enzyme inhibitors with potential use as pharmacological agents.

MAIN RESEARCH LINES

Role of aldehyde dehydrogenases and aldo-keto reductases in retinoic acid metabolism

Development of enzyme inhibitors and drug discovery in cancer and diabetes research

Techniques: enzyme kinetics, HPLC, mammalian cell culture, molecular modeling, protein purification, recombinant DNA, fluorimetry and UV-visible spectrophotometry, X-ray crystallography.

PUBLICATIONS DURING 2016-20

Pequerul R, Vera J, Giménez-Dejoz J, Crespo I, Coines J, Porté S, Rovira C, Parés X, Farrés J (2020) Structural and kinetic features of aldehyde dehydrogenase 1A (ALDH1A) subfamily members, cancer stem cell markers active in retinoic acid biosynthesis. Arch Biochem Biophys 681:108256.

Rivas A, Pequerul R, Barracco V, Domínguez M, López S, Jiménez R, Parés X, Alvarez R, Farrés J, de Lera AR. (2020) Synthesis of C11-to-C14 methyl-shifted all-trans-retinal analogues and their activities on human aldo-keto reductases. Org Biomol Chem 18:4788-4801.

Giménez-Dejoz J, Weber S, Fernández-Pardo Á, Möller G, Adamski J, Porté S, Parés X, Farrés J (2019) Engineering aldo-keto reductase 1B10 to mimic the distinct 1B15 topology and specificity towards inhibitors and substrates, including retinoids and steroids. Chem Biol Interact 307:186-194.

Jiménez R, Pequerul R, Amor A, Lorenzo J, Metwally K, Avilés FX, Parés X, Farrés J (2019) Inhibitors of aldehyde dehydrogenases of the 1A subfamily as putative anticancer agents: Kinetic characterization and effect on human cancer cells. Chem Biol Interact 306, 123-130.

Castellví A, Crespo I, Crosas E, Cámara-Artigas A, Gavira JA, Aranda MAG, Parés X, Farrés J, Juanhuix J (2019) Efficacy of aldose reductase inhibitors is affected by oxidative stress induced under X-ray irradiation. Sci Rep 9, 3177.

Domínguez M, Pequerul R, Alvarez R, Giménez-Dejoz J, Birta E, Porté S, Rühl R, Parés X, Farrés J, de Lera AR (2018) Synthesis of apocarotenoids by acyclic cross metathesis and characterization as substrates for human retinaldehyde dehydrogenases. Tetrahedron 74: 2567-2574.

Crespo I, Giménez-Dejoz J, Porté S, Cousido-Siah A, Mitschler A, Podjarny A, Pratsinis H, Kletsas D, Parés X, Ruiz FX, Metwally K, Farrés J (2018) Design, synthesis, structure-activity relationships and X-ray structural studies of novel 1-oxopyrimido[4,5-*c*]quinoline-2-acetic acid derivatives as selective and potent inhibitors of human aldose reductase. Eur J Med Chem 152,160-174.

Giménez-Dejoz J, Weber S, Barski OA, Möller G, Adamski J, Parés X, Porté S, Farrés J (2017) Characterization of AKR1B16, a novel mouse aldo-keto reductase. Chem Biol Interact 276:182-193.

Ruiz FX, Crespo I, Álvarez S, Porté S, Giménez-Dejoz J, Cousido-Siah A, Mitschler A, de Lera ÁR, Parés X, Podjarny A, Farrés J (2017) Structural basis for the inhibition of AKR1B10 by the C3 brominated TTNPB derivative UVI2008. Chem Biol Interact 276:174-181.

Cousido-Siah A, Ruiz FX, Fanfrlík J, Giménez-Dejoz J, Mitschler A, Kamlar M, Veselý J, Ajani H, Parés X, Farrés J, Hobza P, Podjarny AD (2016) IDD388 Polyhalogenated derivatives as probes for an improved structure-based selectivity of AKR1B10 inhibitors. ACS Chem Biol 11, 2693-2705.

ACTIVE PROJECTS DURING 2016-20

"Biochemical, functional and pharmacological characterization of inhibitors (as well as their nanoencapsulation) and substrates of the aldehyde dehydrogenase family". Advanced BioDesign.

"Caracterización de proteínas en condiciones de estrés oxidativo inducido por irradiación de luz sincrotrón". CELLS-ALBA Synchrotron.

"Proteomics of proteases and oxidoreductases. A binary strategy in the discovery of ligands-drugs and its biomedical and biotechnological applicability". Ministerio de Ciencia e Innovación (BIO2016-78057-R).

Astrolab

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RESEARCH INTERESTS

Astrocytes modulate neurotransmission thanks to their bidirectional communication with neurons. Calcium signalling in astrocytes is considered the base of their excitability allowing them to respond to neurotransmitters. Moreover astrocytes provide neurons with lactate and ApoE4-containing lipoproteins to support neuronal synaptic activity. Hence a coordinated, tightly regulated but also flexible metabolism in astrocytes is crucial for brain functions.

STRATEGIC OBJECTIVES

Through the study of calcium signalling and lipid metabolism in astrocytes, the research group had two general objectives:
To fully characterize the molecular mechanisms by which astrocytes modulate synaptic transmission.
To elucidate astrocytic therapeutic targets for neurodegenerative diseases.

MAIN RESEARCH LINES

Metabolism of Astrocytes: study fatty-acid and aminoacid oxidative metabolism in astrocytes.
Astrocytic CREB: analyze the role of CREB in astrocytic calcium signalling and metabolism. •ApoE4 expression in astrocytes: characterize how expression of ApoE4, the main genetic risk of Alzheimer, regulates astrocytes, analyzing: calcium signalling and lipid metabolism.
Identify computational roles of astrocytes.
Establish astrocytes as therapeutic targets.
Use mathematics and systems biology, including artificial intelligence, to clarify astrocyte (dys)function, identify astrocyte-based molecular signatures in human fluids, and develop astrocyte-targeted therapies.

PUBLICATIONS DURING 2016-20

Larramona-Arcas R, González-Arias C, Perea G, Gutiérrez A, Vitorica J, García-Barrera T, Gómez-Ariza JL, Pascua-Maestro R, Ganfornina MD, Kara E, Hudry E, Martinez-Vicente M, Vila M, Galea E, Masgrau R. Sex-dependent calcium hyperactivity due to lysosomal-related dysfunction in astrocytes from APOE4 versus APOE3 gene targeted replacement mice. Mol Neurodegener.15:35, 2020.

Kastanenka KV, Moreno-Bote R, De Pittà M, Perea G, Eraso-Pichot A, Masgrau R, Poskanzer KE, Galea E. A roadmap to integrate astrocytes into Systems Neuroscience. Glia 2020; 68:5-26.

Riefolo F, Matera C, Garrido-Charles A, Gomila AMJ, Sortino R, Agnetta L, Claro E, Masgrau R, Holzgrabe U, Batlle M, Decker M, Guasch E, Gorostiza P. Optical Control of Cardiac Function with a Photoswitchable Muscarinic Agonist. J Am Chem Soc. 2019; 141:7628-763.

Eraso-Pichot A, Brasó-Vives M, Golbano A, Menacho C, Claro E, Galea E, Masgrau R. GSEA of mouse and human mitochondriomes reveals fatty acid oxidation in astrocytes. Glia. 2018 Aug;66(8):1724-1735.

Romeo-Guitart D, Forés J, Herrando-Grabulosa M, Valls R, Leiva-Rodríguez T, Galea E, González-Pérez F, Navarro X, Petegnief V, Bosch A, Coma M, Mas JM, Casas C. Neuroprotective Drug for Nerve Trauma Revealed Using Artificial Intelligence. Sci Rep. 8(1):1879, 2018

Gomez-Arboledas A, Davila JC, Sanchez-Mejias E, Navarro V, Nuñez-Diaz C, Sanchez-Varo R, SanchezMico MV, Trujillo-Estrada L, Fernandez-Valenzuela JJ, Vizuete M, Comella JX, Galea E, Vitorica J, Gutierrez A. Phagocytic clearance of presynaptic dystrophies by reactive astrocytes in Alzheimer’s disease. Glia, 66:637-653, 2018.

Pardo L, Valor LM, Eraso-Pichot A, Barco A, Golbano A, Hardingham GE, Masgrau R, Galea E. CREB Regulates Distinct Adaptive Transcriptional Programs in Astrocytes and Neurons. Sci Rep. 2017; 7(1):6390.

Masgrau R, Guaza C, Ransohoff RM, Galea E. Should We Stop Saying 'Glia' and 'Neuroinflammation'? Trends Mol Med. 2017; 23(6):486-500.

Hasel P, Dando O, Jiwaji Z, Baxter P, Todd AC, Heron S, Márkus NM, McQueen J, Hampton DW, Torvell M, Tiwari SS, McKay S, Eraso-Pichot A, Zorzano A, Masgrau R, Galea E, Chandran S, Wyllie DJA, Simpson TI, Hardingham GE. Neurons and neuronal activity control gene expression in astrocytes to regulate their development and metabolism. Nat Commun. 2017;8:15132.

Eraso-Pichot A, Larramona-Arcas R, Vicario-Orri E, Villalonga R, Pardo L, Galea E, Masgrau R. CREB decreases astrocytic excitability by modifying subcellular calcium fluxes via the sigma-1 receptor. Cell Mol Life Sci. 2017; 74(5):937-950.

Launay N, Ruiz M, Grau L, Ortega FJ, Illieva EV, Martinez JJ, Galea E, Ferrer I, Knecht E, Pujol A, Fourcade S. Tauroursodeoxycholic bile acid arrests axonal degeneration by inhibiting the unfolded protein response in X-linked adrenoleukodystrophy. Acta Neuropathologica 133:283-301, 2017

Pardo L, Schlüter A, Valor LM, Barco A, Giralt M, Golbano A, Hidalgo J, Jia P, Zhao Z, Jové M, Portero-Otin M, Ruiz M, Giménez-Llort L, Masgrau R, Pujol A, Galea E. Targeted activation of CREB in reactive astrocytes is neuroprotective in focal acute cortical injury. Glia. 2016; 64(5):853-74.

ACTIVE PROJECTS DURING 2016-20

2017SGR1780. Senyalització i Noves Dianes Terapeutiques (SINDIATER). Agència de Gestió d'Ajuts Universitaris i de Recerca. Convocatòria d'ajuts per donar suport als grups de recerca (SGR 2017). PI:José Miguel Lizcano. UAB. 01/01/2017 - 31/12/2020.

BFU2016-79735-P. Creb astrocitario en plasticidad y trauma cerebral. Ministerio de Economia y Competitividad (MINECO). Proyectos I+D 2016, Programa Estatal de Fomento de la Investigación Científica y Técnica de Excelencia. PI: Elena Galea (UAB). 30/12/2016 - 29/12/2019.

TV3-20141430. Deciphering the link between astrocyte reactivity and neuronal damage in Alzheimer's disease. Fundació La Marató de TV3. PI: Elena Galea (UAB). 22/05/2015 - 31/12/2017.

2014SGR0984. Recerca biomèdica en neurodegeneracio (REBINE). Agència de Gestió d'Ajuts Universitaris i de Recerca. Convocatòria d'ajuts per donar suport a les activitats dels grups de recerca (SGR 2014). PI: José Rodríguez (UAB). 01/01/2014 - 30/04/2017.

ELA-2012-033C1B. Cellular proteolysis and oxidative stress as intertwined therapeutic targets in X-ALD: Preclinical studies. European Leukodystrophy Association - ELA. PI: Elena Galea (UAB). 01/07/2013-30/06/2016

RED2018-102491-T. Clinical System Neuroscience. Redes de Investigación. Ministerio de Ciencia, Innovación y Universidades. PI: Elena Galea (UAB). 01/01/2020-31/12/2021

IU68017046.Teràpies astròcitàries per al tractament del traumatisme cranioencefàlic. Smart Money. Universitat Autònoma de Barcelona. PI: Elena Galea (UAB). 22/07/2020-21/04/2021

Cell Cycle Lab

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Predoctoral student
Ping Ren
Predoctoral student
Miguel Bustillo
Master student

RESEARCH INTERESTS

Our interest is to identify novel cell cycle control elements and pathways involved in the protection of genomic integrity and the regulation of cell proliferation.

An area of activity in our lab focuses on the DNA damage response (DDR), a surveillance mechanism that responds to insults that threaten DNA replication. In that event, the DDR blocks mitosis to avoid the segregation (mitotic anaphase) of damaged, incompletely replicated chromosomes to the two future daughter cells. Loss of such control leads to aneuploidy and genomic instability, the driving force of malignant transformation and progression. The DDR constitutes an anti-cancer barrier in early human tumorigenesis. We have recently identified (Plos Genetics, 2015) that 3 different pathways under the DDR kinase Mec1/ATM/ATR are in place to prevent anaphase in response to DNA damage. Two of them, mediated by Swe1/Wee1 and Rad53/Chk2, redundantly block mitotic Cyclin Dependent Kinase (M-Cdk1). Cdk1 is the engine that drives cell cycle progression, and M-Cdk1 is essential for cells to enter anaphase. Our results unveil an unsuspected implication of Rad53 in the control of Cdk1 activity, and reconcile the long-standing conundrum of Swe1 dispensability.

More recently, we identified that even when cells fail to trigger a full DNA damage response, the so-called Spindle Assembly Checkpoint (SAC) still prevents the segregation of incompletely replicated or damaged chromosomes (Current Genetics, 2017). Derived from such observation, the SAC emerges as an attractive target for anti-tumoral therapy. As many cancer cells are characteristically defective in ATM/ATR signaling, blocking SAC signaling might help as co-adjuvant treatment in therapies based on DNA damaging drugs, selectively pushing malignant cells into aberrant, inviable anaphases.

We also worked to demonstrate a missing prediction required to fully validate the so-called quantitative model of cell cycle regulation by Cyclin Dependent Kinases, put forward by Nobel Laureate Paul Nurse as long back as 1996. There are at least two explanations for how such regulation is achieved. According to one of the visions, cyclins confer intrinsic substrate specificity to the CDK catalytic subunit. Alternatively, the quantitative model proposes that ever-increasing levels of CDK activity are required to trigger cell cycle events from G1 to M. If a quantitative control prevails, then an early cyclin should trigger latter cycle events if accumulated at high enough levels at the right time and place. We were able to trigger DNA replication overexpressing an hyperstable allele of a G1 phase cyclin fused to a nuclear localization signal, in the absence of S, G2 and M phase Cdk1 activity (Cell Cycle, 2015).

Finally, work is going on in our lab aimed at dissecting the control of cytokinesis, the very last step of cell division, when the mother cell separates into two daughter cells. Normal cells prevent cytokinesis until anaphase is complete (two nuclei fully formed). However, such control is subverted in cancer cells, resulting in aneuploidy and genomic instability. We are currently working to obtain a time-lapse record of cytokinesis through a combination of conditional mutants and fluorescence microscopy.

PUBLICATIONS DURING 2016-20

Zeng F, Quintana DG. High-Copy Yeast Library Construction and High-Copy Rescue Genetic Screen in Saccharomyces cerevisiae (2021). Methods Mol Biol 2196:77-83.

Doñate-Macián P, Enrich-Bengoa J, Dégano IR, Quintana DG, Perálvarez-Marín A (2019). Trafficking of Stretch-Regulated TRPV2 and TRPV4 Channels Inferred Through Interactomics. Biomolecules 9:791.

Palou R, Palou G, Quintana DG (2017). A role for the spindle assembly checkpoint in the DNA damage response. Curr Genet 63:275-280.

Zhang Z, Ren P, Vashisht AA, Wohlschlegel JA, Quintana DG*, Zeng F* (2017). Cdk1-interacting protein Cip1 is regulated by the S phase checkpoint in response to genotoxic stress. Genes Cells 22:850-860.

ACTIVE PROJECTS DURING 2016-20

Regulation of chromosome segregation and cell division through Cdk1 / Regulación de la segregación cromosómica y de la división celular a través de Cdk1. BFU2015-68493-P. Ministry of Economy and Competitiveness of Spain (MINECO) and European Regional Development Fund (FEDER) (2016 – 2020). PI: David G. Quintana.

Protein Kinases in Cancer Research

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Sergio Espinosa
Predoctoral student
Iodia Bolinaga
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Marc Ferre
Master student

RESEARCH INTERESTS

Lizcano's Lab is interested in dissecting new cellular signaling pathways that control cancer cell proliferation and differentiation. We collaborate with academics and Biopharma Companies to perform preclinical development of new anticancer drugs. Specifically, we are interested in deciphering the role of the new MAP kinase ERK5 in cancer proliferation and survival. We are also interested in modulation of autophagy and endoplasmic reticulum (ER) stress as new strategies to tackle cancer
We use two different perspectives to approach fundamental problems:

Basic Research. Dissection of the mechanisms by ERK5 kinase (as well other kinases) exert a control on the proliferation and survival of tumor cells. We have contributed to propose new molecular mechanism for regulation of protein kinase Akt; discovered that tumor suppressor kinase LKB1 functions as a master kinase; or more recently, we have established a new mechanism by which ERK5 translocates to the nucleus and regulates the proliferation of tumor cells regardless of its enzymatic activity.

Research directed to pharmacological intervention in cancer. We are involved in potentiating translational aspects of our resources. We actively collaborate with Ability Pharmaceuticals SL in the preclinical/clinical development of the new antitumor drug ABTL0812, which it is Clinical Trial Phase II to treat cancer patients with advanced endometrial and squamous NSCLC cancers (NCT02201823). We have discovered a new cellular signaling pathway by which ABTL0812 exerts its antitumor action: by altering the sphingolipidoma of cancer cells, ABTL0812 induces a sustained activation of ER stress and UPR, as well as inhibition of the Akt/mTORC1, which ultimately results in activation of cytotoxic autophagy. Finally, we actively collaborate with other academic laboratories characterizing new ERK5 inhibitors with anticancer activity.

PUBLICATIONS DURING 2016-20

Discovery of a selective inhibitor of doublecortin like kinase 1. Ferguson FM, Nabet B, Raghavan S, Liu Y, Leggett AL, Kuljanin M, Kalekar RL, Yang A, He S, Wang J, Ng RWS, Sulahian R, Li L, Poulin EJ, Huang L, Koren J, Dieguez-Martinez N, Espinosa S, Zeng Z, Corona CR, Lizcano JM, Robers MB, Muthaswamy S, Haigis KM, Mancias JD, Wolpin BM, Aguirre AJ, Hahn WC, Westover KD, Gray NS. Nature Chemical Biology. 2020 Jun;16(6):635-643. doi: 10.1038/s41589-020-0506-0.

The anti-cancer drug ABTL0812 induces ER stress-mediated cytotoxic autophagy by increasing dihydroceramide levels in cancer cells. Muñoz-Guardiola P, Casas J, Megías-Roda E, Solé S, Perez-Montoyo H, Yeste-Velasco M, Erazo T, Diéguez-Martínez N, Espinosa-Gil S, Muñoz-Pinedo C, Yoldi G, Abad JL, Segura MF, Moran T, Romeo M, Bosch-Barrera J, Oaknin A, Alfón J, Domènech C, Fabriàs G, Velasco G, Lizcano JM. Autophagy. 2020 May 25:1-18.

Genetic manipulation of LKB1 elicits lethal metastatic prostate cancer. Hermanova I, Zúñiga-García P, Caro-Maldonado A, Fernandez-Ruiz S, Salvador F, Martín-Martín N, Zabala-Letona A, Nuñez-Olle M, Torrano V, Camacho L, Lizcano JM, Talamillo A, Carreira S, Gurel B, Cortazar AR, Guiu M, López JI, Martinez-Romero A, Astobiza I, Valcarcel-Jimenez L, Lorente M, Velasco G, Gomez-Muñoz A, Flores JM, Sutherland JD, Barrio R, de Bono JS, Paramio JM, Trka J, Graupera M, Gomis RR, Carracedo A. J Exp Med. 2020 Jun 1;217(6):e20191787.

SUMOylation Is Required for ERK5 Nuclear Translocation and ERK5-Mediated Cancer Cell Proliferation. Erazo T, Espinosa-Gil S, Diéguez-Martínez N, Gómez N, Lizcano JM. Int J Mol Sci. 2020 Mar 23;21(6):2203.

STK11 (LKB1) missense somatic mutant isoforms promote tumor growth, motility and inflammation.
Granado-Martínez P, Garcia-Ortega S, González-Sánchez E, McGrail K, Selgas R, Grueso J, Gil R, Naldaiz-Gastesi N, Rhodes AC, Hernandez-Losa J, Ferrer B, Canals F, Villanueva J, Méndez O, Espinosa-Gil S, Lizcano JM, Muñoz-Couselo E, García-Patos V, Recio JA. Commun Biol. 2020 Jul 9;3(1):366.

The antitumour drug ABTL0812 impairs neuroblastoma growth through endoplasmic reticulum stress-mediated autophagy and apoptosis. París-Coderch L, Soriano A, Jiménez C, Erazo T, Muñoz-Guardiola P, Masanas M, Antonelli R, Boloix A, Alfón J, Pérez-Montoyo H, Yeste-Velasco M, Domènech C, Roma J, Sánchez de Toledo J, Moreno L, Lizcano JM, Gallego S, Segura MF.
Cell Death Dis. 2020 Sep 17;11(9):773.

The peroxisomal fatty acid transporter ABCD1/PMP-4 is required in the C. elegans hypodermis for axonal maintenance: A worm model for adrenoleukodystrophy. Coppa A, Guha S, Fourcade S, Parameswaran J, Ruiz M, Moser AB, Schlüter A, Murphy MP, Lizcano JM, Miranda-Vizuete A, Dalfó E, Pujol A. Free Radic Biol Med. 2020 May 20;152:797-809.

The novel proautophagy anticancer drug ABTL0812 potentiates chemotherapy in adenocarcinoma and squamous nonsmall cell lung cancer. López-Plana A, Fernández-Nogueira P, Muñoz-Guardiola P, Solé-Sánchez S, Megías-Roda E, Pérez-Montoyo H, Jauregui P, Yeste-Velasco M, Gómez-Ferreria M, Erazo T, Ametller E, Recalde-Percaz L, Moragas-Garcia N, Noguera-Castells A, Mancino M, Morán T, Nadal E, Alfón J, Domènech C, Gascon P, Lizcano JM, Fuster G, Bragado P.Int J Cancer. 2020 Aug 15;147(4):1163-1179.

Therapeutic potential of the new TRIB3-mediated cell autophagy anticancer drug ABTL0812 in endometrial cancer.
Felip I, Moiola CP, Megino-Luque C, Lopez-Gil C, Cabrera S, Solé-Sánchez S, Muñoz-Guardiola P, Megias-Roda E, Pérez-Montoyo H, Alfon J, Yeste-Velasco M, Santacana M, Dolcet X, Reques A, Oaknin A, Rodríguez-Freixinos V, Lizcano JM, Domènech C, Gil-Moreno A, Matias-Guiu X, Colas E, Eritja N. Gynecol Oncol. 2019 May;153(2):425-435.

Neuronal Growth Factor regulates Brain Specific Kinase 1 expression by inhibiting promoter methylation and promoting Sp1 recruitment. Ramírez Martínez L, Vargas Mejía M, Espadamala J, Gomez N, Lizcano JM, López-Bayghen E. Neurochem Int. 2018 Nov;120:213-223.

Characterization of the TLR Family in Branchiostoma lanceolatum and Discovery of a Novel TLR22-Like Involved in dsRNA Recognition in Amphioxus. Ji J, Ramos-Vicente D, Navas-Pérez E, Herrera-Úbeda C, Lizcano JM, Garcia-Fernàndez J, Escrivà H, Bayés À, Roher N. Front Immunol. 2018 Nov 2;9:2525.

Structural and Atropisomeric Factors Governing the Selectivity of Pyrimido-benzodiazipinones as Inhibitors of Kinases and Bromodomains. Wang J, Erazo T, Ferguson FM, Buckley DL, Gomez N, Muñoz-Guardiola P, Diéguez-Martínez N, Deng X, Hao M, Massefski W, Fedorov O, Offei-Addo NK, Park PM, Dai L, DiBona A, Becht K, Kim ND, McKeown MR, Roberts JM, Zhang J, Sim T, Alessi DR, Bradner JE, Lizcano JM, Blacklow SC, Qi J, Xu X, Gray NS. ACS Chem Biol. 2018 Sep 21;13(9):2438-2448.

The Small GTPase RAC1/CED-10 Is Essential in Maintaining Dopaminergic Neuron Function and Survival Against α-Synuclein-Induced Toxicity. Kim H, Calatayud C, Guha S, Fernández-Carasa I, Berkowitz L, Carballo-Carbajal I, Ezquerra M, Fernández-Santiago R, Kapahi P, Raya Á, Miranda-Vizuete A, Lizcano JM, Vila M, Caldwell KA, Caldwell GA, Consiglio A, Dalfo E. Mol Neurobiol. 2018 Sep;55(9):7533-7552. doi: 10.1007/s12035-018-0881-7. Editorial: Mitogen Activated Protein Kinases. Cuenda A, Lizcano JM, Lozano J. Front Cell Dev Biol. 2017 Sep 14;5:80.

ERK5 and Cell Proliferation: Nuclear Localization Is What Matters. Gomez N, Erazo T, Lizcano JM. Front Cell Dev Biol. 2016 Sep 22;4:105.

The New Antitumor Drug ABTL0812 Inhibits the Akt/mTORC1 Axis by Upregulating Tribbles-3 Pseudokinase. Erazo T, Lorente M, López-Plana A, Muñoz-Guardiola P, Fernández-Nogueira P, García-Martínez JA, Bragado P, Fuster G, Salazar M, Espadaler J, Hernández-Losa J, Bayascas JR, Cortal M, Vidal L, Gascón P, Gómez-Ferreria M, Alfón J, Velasco G, Domènech C, Lizcano JM. Clinical Cancer Research. 2016 May 15;22(10):2508-19.

Mutation of the 3-Phosphoinositide-Dependent Protein Kinase 1 (PDK1) Substrate-Docking Site in the Developing Brain Causes Microcephaly with Abnormal Brain Morphogenesis Independently of Akt, Leading to Impaired Cognition and Disruptive Behaviors. Cordón-Barris L, Pascual-Guiral S, Yang S, Giménez-Llort L, Lope-Piedrafita S, Niemeyer C, Claro E, Lizcano JM, Bayascas JR. Mol Cell Biol. 2016 Nov 14;36(23):2967-2982.

ACTIVE PROJECTS DURING 2016-20

Nuevas terapias anticáncer basadas en la modulación de la MAP kinasa ERK5

Funding Agency: Ministerio de Ciencia e Innovación. Plan Nacional de I+D+I 2020-2022. Proyectos de I+D+i orientada a los Retos de la Sociedad (Ref PID2019-107561RB-I00) Jun 2020-May 2023 IP: Jose Miguel Lizcano

Nuevas estrategias para incrementar efectividad de los tratamientos con ABTL0812. MINECO, Programa Retos-Colaboracion 2017 (RTC-2017-6261-1). Sept 2018-June 2021. IP: Jose Miguel Lizcano (partner UAB)

Desarrollo de nuevas herramientas farmacológicas antitumorales que dirijan su acción al silenciamiento o a la inhibición de la MAP kinasa ERK5. Ministerio de Ciencia, Innovación y Universidades. Plan Nacional de I+D+I (SAF2015-64237-R). 2016- 2019 IP: Jose Miguel Lizcano

Terapia personalizada contra ERK5 en neuroblastoma
Funding Agency: Asociación Española contra el Cáncer (AECC) de Barcelona. Oncología 2015-2016. IP: Aroa Soriano Fernández.

Nuevas aproximaciones terapéuticas basadas en derivados de ácidos grasos esenciales dirigidos a enfermedades oncológicas y neurológicas no cubiertas. MINECO, Programa INNPACTO 2017 (RTC-2017-6261-1) Sept 2012-Dec 2016. IP: Jose Miguel Lizcano (partner UAB).

PATENTS DURING 2016-20

A pharmaceutical combination for the treatment of a cancer. C. Domènech, J. Alfón, Pérez-Montoyo H, Segura M, Lizcano JM. Application no.: EPO 18722621.2 – 1109. Date of filing: 16-5-2017 Priority country: Europe. Holder entity: Ability Pharmaceuticals S.L.

Stress Protein Kinases

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Associate Professor

RESEARCH INTERESTS

We are interested in how cell metabolism, signalling pathways, and gene expression are rewired in pathological conditions such as Lesch-Nyhan disease, a metabolic illness with severe neurological manifestations, or in cells submitted to hyperosmotic shock, a common stress that cells have faced during millions of years since their emergence.

STRATEGIC OBJECTIVES

We study the cellular abnormalities in Lesch-Nyhan disease and the potential treatments to revert these alterations. We also aim to understand the mechanisms that regulate osmostress-induced apoptosis and meiotic progression, and the role of stress protein kinases in these processes.

MAIN RESEARCH LINES

Purine nucleotides and cellular alterations in Lesch-Nyhan diseaseLesch-Nyhan disease is an illness with severe neurological manifestations, including dystonia, spasticity, cognitive deficit, and self-injurious behavior. The illness is caused by a deficiency in the purine savage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGprt). How a simple alteration in the purine metabolism produces dramatic effects in human behaviour is still a mystery. HGprt deficiency is associated with a relatively selective dysfunction of brain dopamine systems. Different hypotheses have been suggested, some of them claiming for purine abnormalities and/or the accumulation of a toxic metabolite in the brain. We propose that ATP depletion and ZMP accumulation can induce cellular alterations accounting for brain dysfunction. We are investigating the cellular changes induced by HGprt deficiency and how to revert these alterations.

Role of stress protein kinases in cell death and meiosis. The aim of this project is to determine the role of the stress protein kinases AMPK, JNK and p38 during oocyte death induced by hyperosmotic shock and during meiotic progression induced by progesterone. We use Xenopus oocytes as a model system, which have great advantages for biochemical manipulation.

PUBLICATIONS DURING 2016-20

López JM, Outtrim EL, Fu R, Sutcliffe DJ, Torres RJ, Jinnah HA. Physiological levels of folic acid reveal purine alterations in Lesch-Nyhan disease. Proc Natl Acad Sci U S A. 2020; 117: 12071-12079.

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PATENTS DURING 2016-20

López JM, Campas C, Gil J. Novel therapeutic use of riboside of 5-aminoimidazole-4- carboxamide (acadesine). Date: 21-3-2002. WO Application: WO 03/080076 A1. Institution: Universidad de Barcelona. Designated states: Europe (all the countries from UE), EEUU, Australia, Canada, Mexico, South Corea, New Zealand. Companies that have exploited it: Advanced In Vitro Cell Technologies, S.A. (Advancell), Nexus Oncology Ltd.

Phase I and II clinical trials have been conducted in patients with chronic B-type lymphocytic leukemia with positive results (Cancer Chemother Pharmacol 2013; 71: 581-591). The patent has remained active until 2016.

Short description: Acadesine (also known as AICA-riboside or AICAR) induces apoptosis in B cells of patients with chronic lymphocytic leukemia (CLL) while T cells are not affected. The differential effect of acadesine on B and T lymphocytes represents a therapeutic advantage over the use of cladribine, fludarabine and other nucleosides currently used in the treatment of this disease.

Protein Engineering and Proteomics

GROUP LEADERS

Julia Lorenzo
Assistant Professor

Francesc Xavier Avilés
Emeritus Professor

LAB MEMBERS

Josep Vendrelll
Professor

David Montpeyó
Postdoctoral Researcher, assistant professor

Sergi Rodriguez-Calado
Postdoctoral Researcher

Eddi Pradas
Postdoctoral Researcher

Paula Alsonso
Postdoctoral Researcher

Pau Sarlé
Master student

RESEARCH INTERESTS

The Protein Engineering group is mainly interested in several research lines, centered in the use on natural or modified peptides, proteins and bioactive molecules to create new biotechnological, nanotechnological and biomedical tools and approaches. The group deals with several research lines, centered on:

Looking for peptide/protein based natural and synthetic constructs with bioactive properties useful for plant protection, insect-microbe deterrence and sanitary-medical applications, like asthma and cancer.
Develop new drug delivery systems based in engineered enzymes for their use as therapeutics, like in lysosomal storage diseases.
Design of new strategies for an efficient drug delivery for brain and other tissues. Thus, we are particularly interested in nanomaterials for the treatment of glioblastoma and Parkinson's disease.

The experimental approaches used are HPLC, Mass spectrometry, protein & DNA sequencing & cloning, recombinant protein production, proteomics, NMR, Xray crystallography and computer-based approaches. We also work in the development of nanomaterials for specific delivery, encapsulation, or nanoconjugation of enzymes/inhibitors and small compounds for biomedical purposes as well as in their study in cell/microbial cultures and in animal models to test their efficacy and safety.
To efficiently do so and the former goals, we have established collaborations with research groups well recognized at the Catalonia, Spain and international level. A particularly close and strong collaboration is kept with the Oxido-reductases Goup of our Dept. of Biochemistry and Mol Biol of UAB. Also with groups from other institutions, like Synchroton Alba, CSIC, ICN2, VHIR, UCM, PRINCIPE Felipe Res. Inst-VAL., CEA-Saclay, MPI-Munich, IJS-Slovenia, Univ. Uppsala, Univ. Cambridge, Univ. Notre-Dame, A. Einstein College Med-NY, Univ. Habana, Univ. LaPlata, Univ. Concepción, UNAM-CostaRica, Universidad Nova de Lisboa), and with the firms ABD Biodesing and Nanonica Europe ..., with fruitful exchanges and projects. Noteworthy is the formative task, spirit, aims and large experience of our group at the Master and PhD levels, with national and foreign hosted students.

STRATEGIC OBJECTIVES

Medical and biotechnological applications of bioactive molecules, peptide-proteins and nanoparticles.

Cell cultures, for assays and as protein-factories. Evaluation in cell cultures and in vivo experimental models of new antitumor and drug-oriented agents.
Biocompatibility, biodelivery and biodistribution of nanomaterials.
Brain and lysosomal drug delivery.
Alterations in cytoskeletal proteins.
Signalling pathways involved in their efficacy.

MAIN RESEARCH LINES

The group has varied interests at the interface of biochemistry, structural biology, proteomics-interactomics, bioconjugation, functional materials and nanomedicine. Our selected or designed peptide-proteins, inhibitors and nanosystems are developed for various biomedical applications, ranging from asthma, cancer therapeutics to neurodegenerative disease interventions. Also for other biotechnological applications.

PUBLICATIONS DURING 2016-20

Ada Rebeca Contreras Rodríguez, Javier Saiz-Poseu, Javier García-Pardo, Beatriz García, Julia Lorenzo, Isaac Ojea-Jiménez, Dimitrios Komilis, Josep Sedó, Felix Busqué, Antoni Sánchez,* Daniel Ruiz-Molina and Xavier Font. Biocompatible polydopamine-like particles for the removal of heavy metals at extremely low concentrations. RSC Adv. 2106. 6. 40058-66.

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Garcia-Pardo J, Tanco S, Díaz L, Dasgupta S, Fernandez-Recio J, Lorenzo J, Avilés FX*, Fricker LD*. Substrate specificity of human metallocarboxypeptidase D: Comparison of the two active carboxypeptidase domains. PLOSOne 2017. Nov 13;12(11):e0187778.

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Indarte M, Lazza CM, Assis D, Caffini NO, Juliano MA, Avilés FX, Daura X, López LM, Trejo SA. A Bowman-Birk protease inhibitor purified cloned, sequence and characterized from the seeds of Maclura pomifera (Raf.) Schneid Planta. 2017;245(2):343-353.

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Cotabarren J., Rosso AM, Tellechea M., Javier García-Pardo J., Lorenzo J., Obregón WD, Parisi MG. Adding value to the chia (Salvia hispanica L.) expeller: Production of bioactive peptides with antioxidant properties by enzymatic hydrolysis with Papain. Food Chem. 2019. 274: 848-856.

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Covaleda G., Gallego P., Vendrell J., Georgiadis D., Lorenzo J., Dive V., Avilés F.X.*, Reverter D.*, Devel L*. Synthesis and structural/functional characterization of selective M14 metallo-carboxypeptidase inhibitors based on phosphinic pseudo peptide scaffold: Implications on the design of specific optical probes. J Med Chem. 2019. 62(4):1917-31.

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Jamila Djafari, Adrián Fernández-Lodeiro, Javier Fernández-Lodeiro, Hugo M. Santos, Julia Lorenzo*, Sergi Rodriguez-Calado, José Luis Capelo-Martínez, Carlos Lodeiro*. Study and Preparation of multifunctional Poly(L-Lysine)@Hyaluronic acid nanopolyplexes for the effective delivery of tumor suppressive MiR-34a into triple negative breast cancer cells. Materials. 2020. 20(23): 5309.

ACTIVE PROJECTS DURING 2016-20

INTERACTOMICA DISEÑO DE SONDAS E IMAGEN DE CARBOXIPEPTIDASAS. EN TRANSITO DE LA FUNCION A LA APLICABILIDAD. Ministerio de economía y competitividad (MINECO). Programa RETOS 2013. REF. BIO2013-44973-R (2014 – 2016). IPs: F. X. Avilés/J Vendrell

Member of COST Action CA TRANSAUTOPHAGY: European Network of Multidisciplinary Research and Translation of Autophagy knowledge Financing Entity: EC From: 01/10/2015 to: 31/12/2018 Coordinator: Caty Casas (UAB, Spain); Participant: Julia Lorenzo

PROTEOMICS OF PROTEASES AND OXIDOREDUCTASES. A binary strategy in the discovery of ligands-drugs and its biomedical and biotechnological applicability. (Ref. BIO2016-78057-R). Ministerio de economía y competitividad (MINECO). Programa RETOS 2016. (2017 –2019) IPs: FRANCESC XAVIER Avilés y Jaume Farrés.

Grup consolidat de la Generalitat de Cataluña 2017 SGR 1584. Protein Engineering and Proteomics Group. Generalitat de Cataluña. (2017 – 2020) IP: F. X. Avilés

ESTUDIOS IN VITRO E IN VIVO DE NUEVOS NANOVEHICULOS PARA TERAGNOSTICA DE ENFERMEDADES CEREBRALES. (RTI2018-098027-B-C22) Ministerio de economía y competitividad (MINECO). Programa RETOS 2018. (2019 - 2021). IP: Julia Lorenzo Rivera

Development of new nanotechnological based Enzyme Replacement. Therapy for Parkinsons disease: restoration of lysosomal glucocerebrosidase activity through enzyme-polymer nanoconjugation of GBA. Fundación BBVA Consortium: VHIR/UAB/ICN (2020 - 2023). IP: Marta Martínez Vicente (VHIR), Participant: Julia Lorenzo

Synaptic pharmacology lab

GROUP LEADER
Jordi Ortiz
Associate Professor
Carles Gil
Associate Professor

LAB MEMBERS
Sally Hamdoun
Postdoctoral Researcher
Clàudia Armengol
Master student
Joel Maldonado
Student

RESEARCH INTERESTS

Basic knowledge of the biochemical targets for psychotropic drugs. This includes dopaminergic and other neurotransmitter receptors, transporters and enzymes affected by antipsychotics, drugs of abuse and treatments for dyskinesias.

STRATEGIC OBJECTIVES

To validate experimentally models of the synaptic mechanisms of action of psychotropic drugs and its utility to translate add-on medications to clinical settings.

MAIN RESEARCH LINES

Molecular interactions of dopamine D2 receptors, activation mechanisms, intracellular signalling and cross-talk.

PUBLICATIONS DURING 2016-20

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Gutiérrez-Sacristán A, Bravo A, Portero-Tresserra M, Valverde O, Armario A, Blanco-Gandía MC, Farré A, Fernández-Ibarrondo L, Fonseca F, Giraldo J, Leis A, Mané A, Mayer MA, Montagud-Romero S, Nadal R, Ortiz J, Pavon FJ, Perez E, Rodríguez-Arias M, Serrano A, Torrens M, Warnault V, Sanz F, FurlongLI. Text mining and expert curation to develop a database on psychiatric diseases and their genes. Database – The Journal of Biological Databases and Curation, 2017; 1-9

Hoffmann HM, Crouzin N, Moreno E, Raivio N, Fuentes S, McCormick PJ, Ortiz J*, Vignes M (Jordi Ortiz y Michel Vignes declaran haber contribuido por igual a este artículo). Long-lasting impairment of mGluR5-activated intracellular pathways in the striatum after withdrawal of cocaine self-administration. International Journal of Neuropsychopharmacology, 2017;20(1):72-82.

ACTIVE PROJECTS DURING 2016-20

Aproximación multidisciplinar a la complejidad farmacológica de las dianas de fármacos en trastornos neurológicos y psiquiátricos. Ministerio de Economía y Competitividad. SAF2017-87199-R. (2017 - 2021). CoIPs: Jesús Giraldo Arjonilla y Jordi Ortiz de Pablo

Investigación mediante métodos matemáticos, computacionales y bioquímicos del crosstalk entre los receptores mGlu5 y D2: Relevancia para el tratamiento de la esquizofrenia.Ministerio de Economía y Competitividad. SAF2014-58396R. (2015 – 2017). CoIPs: Jesús Giraldo Arjonilla y Jordi Ortiz de Pablo

CIBER Salud Mental (CIBERSAM), CB19/09/00029
http://www.cibersam.es/grupos/grupo-de-investigacion?id=23808
Instituto de Salud Carlos III Entidades participantes: Corporación Sanitaria Parc Taulí y Universidad Autónoma de Barcelona. Investigador responsable: Diego Palao Vidal

Interactomics in Physiopathology: Proteins, Peptides, and Membranes

GROUP LEADER
Alex Perálvarez
Associate Professor

LAB MEMBERS
Jennifer Enrich
Predoctoral student

RESEARCH INTERESTS

In humans, cells and cellular compartments use membrane proteins (MP) as the first sensors and actuators towards the environment. Cells communicate with other cells, pathogens, or the media by means of membrane proteins. Thus, it is key to know how membrane proteins exert their function, especially considering that most of the pharma industry therapeutic targets are membrane proteins, such as ion channels, GPCRs, transporters, etc. Structure and function of membrane proteins are intrinsically related, and membrane protein structural biology is a challenge, thus out-of-the-box strategies are required to understand the interactions of proteins and membranes and the implications in pathophysiology. In order to gain this knowledge, we propose a multidisciplinary and multiperspective approach combining wet and dry lab experiments.

STRATEGIC OBJECTIVES

Computational aided drug design (CADD) together with experimental methods to allow the identification of new ligand binding sites and new ligands for TRPV channels.

Cross-interactions of endogenous neuropeptides in membrane environments related to amyloid and neurodegenerative disorders

MAIN RESEARCH LINES

Trp channels pharmacology and pathophysiology
Amyloid and misfolding
Membrane protein structural biophysics

PUBLICATIONS DURING 2016-20

Raul Ondono, Ángel Lirio, Carlos Elvira, Elena Álvarez-Marimon, Claudia Provenzano, BeatriceCardinali, ManuelPérez-Alonso, Alex Perálvarez-Marín, José I. Borrell, Germana Falcone, Roger Estrada-Tejedor (2020) Design of novel small molecule base-pair recognizers of toxic CUG RNA transcripts characteristics of DM1. Computational and Structural Biotechnology Journal IF: 6.018

Sanchez-Molina P, Kreuzer M, Benseny-Cases N, Valente T, Almolda B, González B, Castellano B, Perálvarez-Marín A.*(2020) From Mouse to Human: Comparative Analysis between Grey and White Matter by Synchrotron-Fourier Transformed Infrared Microspectroscopy. Biomolecules. 10(8):1099. (*corresponding author) IF: 4.694

Carlos Martínez-Torró, Sergi Torres-Puig, Marta Monge, Lucía Sánchez-Alba, Miguel González-Martín, Marina Marcos-Silva, Alex Perálvarez-Marín, Francesc Canals, Enrique Querol, Jaume Piñol & Oscar Q. Pich (2020) Transcriptional response to metal starvation in the emerging pathogen Mycoplasma genitalium is mediated by Fur-dependent and –independent regulatory pathways, Emerging Microbes & Infections, 9:1,5-19

Pau Doñate-Macián, Jennifer Enrich-Bengoa, Irene R Dégano, David G Quintana, Alex Perálvarez-Marín* (2019) Trafficking of Stretch-Regulated TRPV2 and TRPV4 Channels Inferred Through Interactomics. Biomolecules 9 (12), 791 (* corresponding author)

Pol Picón-Pagès, Jaume Bonet, Javier García-García, Joan Garcia-Buendia, Daniela Gutierrez, Javier Valle, Carmen ES Gómez-Casuso, Valeriya Sidelkivska, Alejandra Alvarez, Alex Perálvarez-Marín, Albert Suades, Xavier Fernàndez-Busquets, David Andreu, Rubén Vicente, Baldomero Oliva, Francisco J Muñoz. (2019) Human albumin impairs amyloid β-peptide fibrillation through its C-terminus: From docking Modeling to protection against neurotoxicity in Alzheimer's disease Computational and Structural Biotechnology Journal

Maria J Gomara, Yolanda Perez, Javier P Martinez, Ramon Barnadas-Rodriguez, Anke Schultz, Hagen Von Briesen, Alex Peralvarez-Marin, Andreas Meyerhans, Isabel Haro (2019) Peptide assembly on the membrane determines the HIV-1 inhibitory activity of dual-targeting fusion inhibitor peptides. Scientific reports 9 (1), 3257

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Doñate-Macián, Pau; Álvarez-Marimon, Elena; Sepulcre, Francesc; Vázquez-Ibar, José Luis; Perálvarez-Marín, Alex* (2019). The Membrane Proximal Domain of TRPV1 and TRPV2 Channels Mediates Protein–Protein Interactions and Lipid Binding In Vitro. International Journal of Molecular Sciences, 20(3): 682.

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Doñate-Macián, Pau; Gómez, Antonio; Dégano, Irene R; Perálvarez-Marín, Alex*; (2018) A TRPV2 interactome-based signature for prognosis in glioblastoma patients. Oncotarget, 9(26): 18400.

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ACTIVE PROJECTS DURING 2016-20

TRPs - Structure-based characterization of novel TRPV inhibitors PRACE Call 21. 2020-2021

IMPLICACIONES FISIOPATOLOGICAS DE LA COMUNICACION MICROGLIA-OLIGODENDROCITO: DE LA MIELINIZACION. 2017-2020

Protein Structure

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SRATEGIC OBJECTIVES

El nostre laboratori utilitza la cristal·lografia de proteïnes amb radiació sincrotró com un procediment important per desxifrar els mecanismes moleculars que estan darrere de l'estructura atòmica de proteïnes i complexos de proteïnes. En el nostre laboratori combinem aquesta tècnica estructural de gran abast amb una caracterització funcional i bioquímic utilitzant ja sigui in vitro o en mètodes in vivo. En les últimes dècades la caracterització de proteïnes-funció de les proteïnes i complexos de proteïnes han llançat llum en els descobriments més rellevants en la bioquímica i la biologia molecular.

MAIN RESERACH LINES:

SUMO i ubiquitina són petits modificadors de proteïnes que es poden unir mitjançant un enllaç peptídic iso-a residus de lisina de les proteïnes diana. Aquest tipus de modificació post-traduccional és molt comú i regular gairebé tots els processos de la vida cel·lular, incloent la divisió cel·lular, la reparació de l'ADN o l'expressió gènica. Per exemple, la modificació de la ubiquitina a través de Lys48 regula la vida mitjana de moltes proteïnes per degradació amb el sistema de proteasoma i és essencial per a la homeòstasi de proteïna en la cèl·lula.

La conjugació de ubiquitina i SUMO (UBL) a proteïnes diana es porta a terme a través d'una cascada enzimàtica de múltiples etapes conservada a través d' E1 (enzim d'activació), E2 (enzim de conjugació) i E3 (enzim lligasa). Al revés, els enzims deubiquitinating (Dubs) poden eliminar la ubiquitina per catalitzar la hidròlisi de l'enllaç isopéptido. Per tant, la ubiquitina i SUMO conjugació i deconjugation són equilibrats i estretament regulada per E3 lligases conjugació i Dubs desconjugación.

Caracterització estructural / funcional de l'enzim deubiquitinating USP25

Human USP25 (i USP28) es deubiuquitinating proteases que controlen els nivells d'objectius importants en la cèl·lula i són regulats, entre d'altres sistemes, per SUMO conjugaiton en el domini N-terminal. USP25 (i USP28) són proteïnes modulars compostes per tres dominis: un domini regulador N-terminal que interactuen amb les cadenes d'ubiquitina; un domini d'USP-com a central amb els residus catalítics i que inclou una llarga inserció en el medi del domini; i un domini C-terminal que interactua amb substrats específics, com ara els tankyrases informar recentment implicats en la ruta / β-cateninA Wnt
Hem resolt recentment l'estructura cristal·lina de USP25 , que revela la presència d'una estructura homotetramérica que està implicada en un mecanisme regulador innovador de l'activitat deubiquitinating.

Caracterització estructural / funcional del complex Smc5 / 6, un enzim ligasa SUMO E3 multimérica.

SMC (Manteniment Estructural dels Cromosomes) complexos són topològicament molècules tancat format per dos allargats SMC subunitats i per un nombre diferent d'elements no SMC associats (NSE). SMC proteïnes contenen tres dominis diferents: un capçal de ATPasa estructuralment relacionada amb la de ABC transportadors (nomenades en endavant " CAP "), una regió estesa bobina en espiral (" ARM ") i una heterodimerización o frontissa de domini (" FRONTISSA "). Cada complex SMC té funcions específiques i essencials: cohesió manté connexions entre cromàtides germanes, condensina compacta cromosomes i Smc5 / junypromou la disjunció cromosòmica. Malgrat aquestes funcions aparentment dispars, totes les SMC complexos comparteixen una propietat comuna, que és organitzar cromosomes abraçant topològicament ADN dins la seva estructura en forma d'anell.

Recentment hem demostrat que la Nse2 ligasa SUMO E3 al Smc5 / juny complex, un jugador crítica durant la reparació de l'ADN de recombinació, s'estimula directament mitjançant la unió a ADN. L'activació de Sumoylation requereix la interacció electrostàtica entre l'ADN i un pegat carregat positivament en el ARM domini de la Smc5 subunitat, que actua com un sensor d'ADN que, posteriorment, promou una estimulació de la Nse2 activitat ligasa. Aquests resultats revelen un nou mecanisme per millorar una activitat lligasa SUMO E3 per l'ADN d'unió directa i per a restringir Sumoylation en el veïnatge d'aquests Smc5 / 6-Nse2 molècules que participen en l'ADN.

Depenent de la temperatura d'activació d'una esterasa hyperthermophilic

Les esterases i lipases són biocatalitzadors molt importants per a fins industrials, ja que catalitzen reaccions de síntesi o hidròlisi dels enllaços èster lipídics. En un acord general, esterases (EC 3.1.1.1) prefereixen curt a cadenes mitjanes fins C10 de monoésteres, mentre que les lipases (EC 3.1.1.3) poden hidrolitzar triglicèrids de cadena llarga insolubles en aigua. La esterasa Pf2001 de Pyrococcus furiosus arriba a la seva activitat òptima entre 70 i 80 ° C. Hem resolt recentment l'estructura cristal·lina de la esterasa Pf2001, que mostra dues conformacions diferents:monòmer i dímer . Les estructures revelen reordenaments importants en el subdomini "cap" entre el monòmer i el dímer, per la formació d'una extensa interfície helicoïdal entrellaçats. D'altra banda, la interfície de dímer és essencial per a la formació de la cadena hidròfob per selectivitat de substrat, segons el que confirmat per mutagènesi i anàlisi cinètica. Proposem un nou mecanisme d'activació depenent de la temperatura de l' esterasa Pf2001 per dimerització.

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ACTIVE PROJECTS DURING 2016-20

Estudios estructurales y funcionales de los mecanismos de regulacion de la via de SUMO/ubiquitin. 2019 - 2021 “Plan Nacional” from the “Ministerio de Ciencia, Innovación y Universidades” (PGC2018-098423-B-I00).

Caracterización estructural de modificación por SUMO de processos de reparación del DNA. 2016 - 2018 “Plan Nacional” from the “Ministerio de Economia y Competitividad” (BFU2015-66417-P).

Molecular Biology of Synaptic Dysfunction in Neurodegenerative Diseases

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RESEARCH INTERESTS & STRATEGIC OBJECTIVES

During the last years, the basic objective of our research team has been the study of the cellular and molecular mechanisms involved in the synaptic dysfunction and neuronal death as a straight approach for the understanding of neurodegeneration in diverse pathologies. At present, the laboratory is focused in the study of the mechanisms involved in early dysfunction of synaptic activity in Alzheimer's disease.

During the last decade, the idea that the alteration of synaptic function in Alzheimer's Disease (AD) occurs well before neurodegeneration is becoming widely accepted. Moreover, it has been suggested that the progressive accumulation of self-aggregates of Aβ as oligomers (oAβ) would mediate this synaptic dysfunction, leading to the initial cognitive deficits observed in mild cognitive impairment (MCI) and earlier AD stages. In this context, we have found, transient learning and memory deficits in $APP_{Sw,Ind}$ and 3xTg-AD transgenic mice at ages when the presence of oAβ was detected well before the appearance of amyloid plaques (España et al., Biol Psychiatry, 67:513-21, 2010; España et al., J. Neurosci, 30: 9402-10, 2010). We believe that these early memory deficits are a good model to study the processes occurring during the initial stages of the disease at the MCI level or previous asymptomatic stages of AD.

In this context our main interest is the study of the mechanisms involved in the alteration of synaptic activity and learning and memory dysfunction associated to early stages in Alzheimer's disease as a way to identify novel therapeutic targets and biomarkers for earlier diagnosis and functional recovery. In particular, he is exploring the altered regulation of functional synaptic glutamate receptors in experimental AD models by a combination of different processes including transcriptional and post-transcriptional gene regulation, changes in receptors regulatory proteins or alteration in the neurovascular unit affecting the release of angineurins.

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ACTIVE PROJECTS DURING 2016-20

Role of Nr4a2/Nurr1 in early synaptic dysfunction and cognitive impairment in Alzheimer disease. Programa Nacional de Biomedicina, Ministerio de Economía y Competitividad. Referencia: SAF2017-89271-R. January 2018 – December 2020. Principal Investigator: José Rodríguez Alvarez

Study of exosomal microRNA from CSF as a biomarker for frontotemporal dementia and as a tool to understand the biological basis of the pathology. Ministerio de Economia y Competitividad. CIBERNED Collaboratives Projects. January 2018 - December 2019. Project Coordinator: Jordi Clarimon Echevarria. Principal Investigator of sub-project: José Rodríguez Alvarez

Neuroregulin-driven gene therapy for the treatment of motoneuron degeneration in ALS. Ministerio de Economia y Competitividad. CIBERNED Collaboratives Projects. October 2015 - September 2017. Project Coordinator: Xavier Navarro Acebes. Principal Investigator of sub-project: José Rodríguez Alvarez

Molecular mechanisms involved in glutamatergic synapses dysfunction in early stages of Alzheimer disease. Programa Nacional de Biomedicina. Ministerio de Economía y Competitividad. SAF2014-59697-R. January 2015 – December 2017.

Principal Investigator: José Rodríguez Alvarez
Searching new biomarkers and therapeutic targets related to cognitive deficits in early stages of Alzheimer's Disease: Role of AKAP79/150, CPT1C and SSAO/VAP-1 in Ab-mediated AMPAR dysfunction. Fundació La Marato de TV3 2013-343. April 2015 - March 2018. Principal Investigator: José Rodríguez Alvarez

PATENTS DURING 2016-20

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Epigenetic regulation of chromatin structure

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RESEARCH INTERESTS

Our research is focused on histone H1 and its role in the epigenetic regulation of chromatin higher-order structure and dynamics. In humans, there are seven H1 somatic subtypes or variants. H1 subtypes are present in different proportions, depending on the cell type and stage of development. While H1 subtypes can compensate for the H1 depletion of one or two subtypes, numerous studies suggest that they are functionally distinct. H1 subtype composition is also altered in pathological states, especially in cancer, highlighting the importance of H1 for cellular homeostasis. Therefore, we are interested in studying the regulation of the expression of H1 subtypes in health and disease. Our findings may provide further evidence of the functional differentiation of H1 subtypes, the compensatory effects upon H1 perturbation, and the role of H1 in carcinogenesis.

STRATEGIC OBJECTIVES

The main target of our work is to understand how the H1 subtype composition is regulated at transcriptional and post-transcriptional levels, combining genomic and proteomic approaches. We also aim to study of H1 alterations in cancer and their role in this disease.

MAIN RESEARCH LINES

Transcriptional regulation of the H1.0 and H1x gene promoters and their role in the compensation of H1 variants upon perturbation.
Role of the epitranscriptome in the regulation of H1 somatic subtypes.

Regulation of the mRNA and protein levels of H1 somatic subtypes in cancer cell lines.

Alterations of H1 subtypes in cancer: Levels of mRNA, proteins, and PTMs.

PUBLICATIONS DURING 2016-20

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ACTIVE PROJECTS DURING 2016-20

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Self-organization in biological systems

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RESEARCH INTERESTS

In nature we can find multiple examples of patterns and organized arrangements that have been exploited for biological purposes by living beings since their origin. In this context, with the aim to guarantee the correct development of biochemical reactions and biological processes, cells require the spatiotemporal organization of their components.

Cells achieve this organization through mechanical actions such as active transport and membrane isolated compartments but also by exploiting the physicochemical properties of molecules. Specifically, the last is employed to attract and concentrate different components from the cellular milieu.

Our lab is focused on understand the self-organization of protein mixtures through the study of their interactions at molecular level. In this sense, protein interactions can result in different organized assemblages with diverse biophysical properties and biological purposes. They can build strong and resistant amyloid fibrils with structural, adaptative and epigenetic purposes. But also, active, sensitive and modulable biological condensates with metabolic and regulatory functions.

PUBLICATIONS DURING 2016-20

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de Groot, NS*; Torrent Burgas, M; Ravarani, CN; Trusina, A; Ventura, S; Babu, MM. The fitness cost and benefit of phase-separated protein deposits. Molecular Systems Biology. 15(4):e8075. 2019. (*Corresponding author)

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Chavali, S; Chavali, P; Chalancon, G; de Groot, NS; Gemayel, R; Latysheva, N; Ing-Simmons, E; Verstrepen, KJ; Balaji, S; Babu, MM. Constraints and consequences of the emergence of amino acid repeats in eukaryotic proteins. Nature Structural and Molecular Biology. 9, 765-777. 2017.

Carijaa, A; Navarro, S; de Groot, NS; Ventura, S. Protein aggregation into insoluble deposits protects from oxidative stress. Redox Biology. 12, 699-711. 2017.

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Neurobiology of Alzheimer's disease

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RESEARCH INTERESTS

Our research efforts are currently focused on understanding how brain functions during memory processing and the cellular and molecular mechanisms involved in brain dysfunction, memory loss and neurodegeneration in age-related cognitive disorders. Our lab combines molecular approaches and cutting-edge genomic, transcriptomic and proteomic methodologies to better understand the molecular pathways causing neuronal dysfunction, memory loss and neurodegeneration in Alzheimer's disease.
Saura's lab investigates the transcriptional pathways that regulate synaptic plasticity underlying cognition and memory, which allows a better understanding of the mechanisms mediating gene expression changes causing synaptic dysfunction and memory loss in cognitive disorders and dementia, especially in Alzheimer's disease.
We use pioneering approaches to generate novel transgenic and knockout mouse models of neurodegeneration that are used for testing new therapeutic strategies (pharmacological, gene therapy, cognitive stimulation…) for future treatment of age-related dementia disorders. Our research projects provide knowledge of novel molecular targets and therapeutic strategies for early treatment of Alzheimer's disease and related neurological disorders.

STRATEGIC OBJECTIVES

Cellular and molecular mechanisms underlying Alzheimer's disease
Develop novel therapeutic approaches for neuropsychiatric and memory loss symptoms
Translational and knowledge transfer of Alzheimer's disease research to society

MAIN RESEARCH LINES

Mechanisms of synaptic dysfunction and neurodegeneration in Alzheimer's disease
Novel research tools and models of neurodegeneration
Therapies for Alzheimer's disease and cognitive disorders

PUBLICATIONS DURING 2016-20

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Protein Folding and Conformational Diseases

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RESEARCH INTERESTS

Our lab uses a multidisciplinary approach to address fundamental aspects of protein folding, misfolding and aggregation. In addition to define the basic mechanistic principles underlying these processes, we aim to understand how their deregulation leads to the onset of human conformational diseases and to develop innovative therapeutics and diagnostic tools to target these pathologies. Moreover, this knowledge should allow us to design and produce novel and better protein-based biopharmaceuticals as well as the development of new self-assembled functional materials for nanotechnology applications.

STRATEGIC OBJECTIVES

Developing new molecules for therapeutic and diagnostic use in Parkinson's disease.
Developing new drugs to treat Transthyretin Amyloidosis.
Design of new protein-based functional nanomaterials for biomedical applications.
Understanding the link between protein phase separation and disease.
Developing new computational tools to forecast and design protein aggregation.

MAIN RESEARCH LINES

Towards early diagnostic of Parkinson's disease and its prevention using pharmacological chaperones

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is still incurable. PD is associated with the death of dopaminergic neurons in the brain. There is substantial evidence supporting the aggregation of the protein α-Synuclein (α-Syn) as a key event in pathogenesis of PD, emerging thus as a privileged therapeutic target. We have recently identified and designed small compounds and peptides able to inhibit α-Syn aggregation with extremely high potency *in vitro* and in animal models. We aim to develop these molecules into lead compounds for the therapeutics of PD.
Early detection of PD is a long-pursued objective. A predictive test would revolutionize clinical care, research and treatment

Biochemical analysis evidenced an elevation of α-Syn aggregates in the biofluids of patients, suggesting that this feature might be used as a diagnostic biomarker for PD. We aim to develop an orthogonal approach towards the development of a sensitive automated diagnostic assay based on the specific detection of early α-Syn aggregates in biofluids.

Transthyretin amyloidosis: Pharmacological chaperones as a therapeutic approach

Transthyretin amyloidosis (ATTR) is the most common form of familial amyloidosis. In ATTR, destabilizing mutations in the protein transthyretin (TTR) causes amyloid fibres to build up, which, depending on the mutation, are deposited in different organs, such as the brain, the nerves or the myocardium, causing them to malfunction and bringing the various forms of the disease. To prevent disease progress, a liver transplant or heart transplant is needed. However, the use of pharmacologic chaperones that stabilize the structure of TTR is emerging as a non-invasive therapeutic means to halt the disease. In this context, we have repurposed a molecule originally intended to treat Parkinson's, as perhaps, the most effective drug for these diseases, already in clinical trials. We pursue both to test its efficacy for previously unaddressed forms of ATTR, with special emphasis of those occurring in the brain, and to use structure based design to generate second generation, more powerful, drugs.

Amyloid assemblies for nanotechnology purposes

The extraordinary stability and tunable assembly of amyloid fibrils make them very attractive targets in nanotechnology. Most efforts so far have been focused on the use of short synthetic peptides as the bioactive components of such materials, and an analogous approach for inducing globular proteins to assemble into functional nanofibres has been much less explored. The main limitations to create mono- or multi-component nanofibres that contain functional globular proteins come from the requirement to prevent their aggregation during expression, to maintain them in a soluble state during purification and storage, and to be able to induce their assembly at a desired time and place.

We aim to exploit our combined computational/experimental expertise to design and produce new molecules fulfilling these properties for a range of biomedical and biotechnological applications, including enzyme catalysis, biosensors, electronics, tissue engineering, drug delivery and immunotherapy.

Phase separation of prion-like proteins in disease

Amyloids become infectious in prion diseases. Nevertheless, not all prion proteins are disease-related; in yeast, they help for environmental adaptation. Most yeast prions contain a low complexity (LC) prion domain responsible for their self-assembly and propagation. Proteins from other organisms such as bacteria, plants, and humans do also bear prion-like domains indicating that their aggregated state might also be beneficial for the cell. Human prion-like proteins are involved in the formation of membraneless intracellular compartments through liquid-liquid phase separation using their LC domains to favor functional interactions between specific partners. However, these proteins are inherently aggregation-prone, and the liquid state can revert into an aberrant solid-state responsible for several pathologies, including inflammatory and neurodegenerative disorders and cancer. We aim to identify molecules that can target this reaction and prevent the progression of associated pathologies.

Towards the design and control of protein solubility

The fast development of protein therapeutics- monoclonal antibodies, replacement enzymes and hormones- is providing improved therapies for a wide range of human diseases, taking advantage of their high specificity towards their targets. One of the major challenges that one should face during the development of protein-based biopharmaceuticals is their inherent propensity to aggregate. Indeed, protein therapeutic agents are both stored and typically administered at very high concentrations. Under these conditions they can easily aggregate, impacting the product's developability, stability, formulation, and immunogenicity. Traditionally, attempts to improve protein solubility have exploited experimental trial and error approaches. However, they are expensive, difficult to perform and time consuming.

We have overcome these limitations developing a series of computational tools for the automated design of protein sequences and structures displaying improved solubility, without compromising their thermodynamic stability and function. These algorithms account for the prediction of the impact of the environment on polypeptides' structural order and solubility and should be useful for the development of new biotherapeutics.

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ICREA Academia 2015 ICREA-Generalitat de Catalunya (Spain). 2016-20. PI: S. Ventura

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COST ACTION BM1405: NON-GLOBULAR PROTEINS: FROM SEQUENCE TO STRUCTURE, FUNCTION AND APPLICATION IN MOLECULAR PHYSIOPATHOLOGY. European Union; European Cooperation in the field of Scientific and Technical Research. 2014-2018 Principal Investigator: S. Tossato / Spanish Coordinator: S. Ventura

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Protein Design and Immunotherapy

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PUBLICATIONS DURING 2016-20

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Cell Death, Senescence and Survival

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ACTIVE PROJECTS DURING 2016-20

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