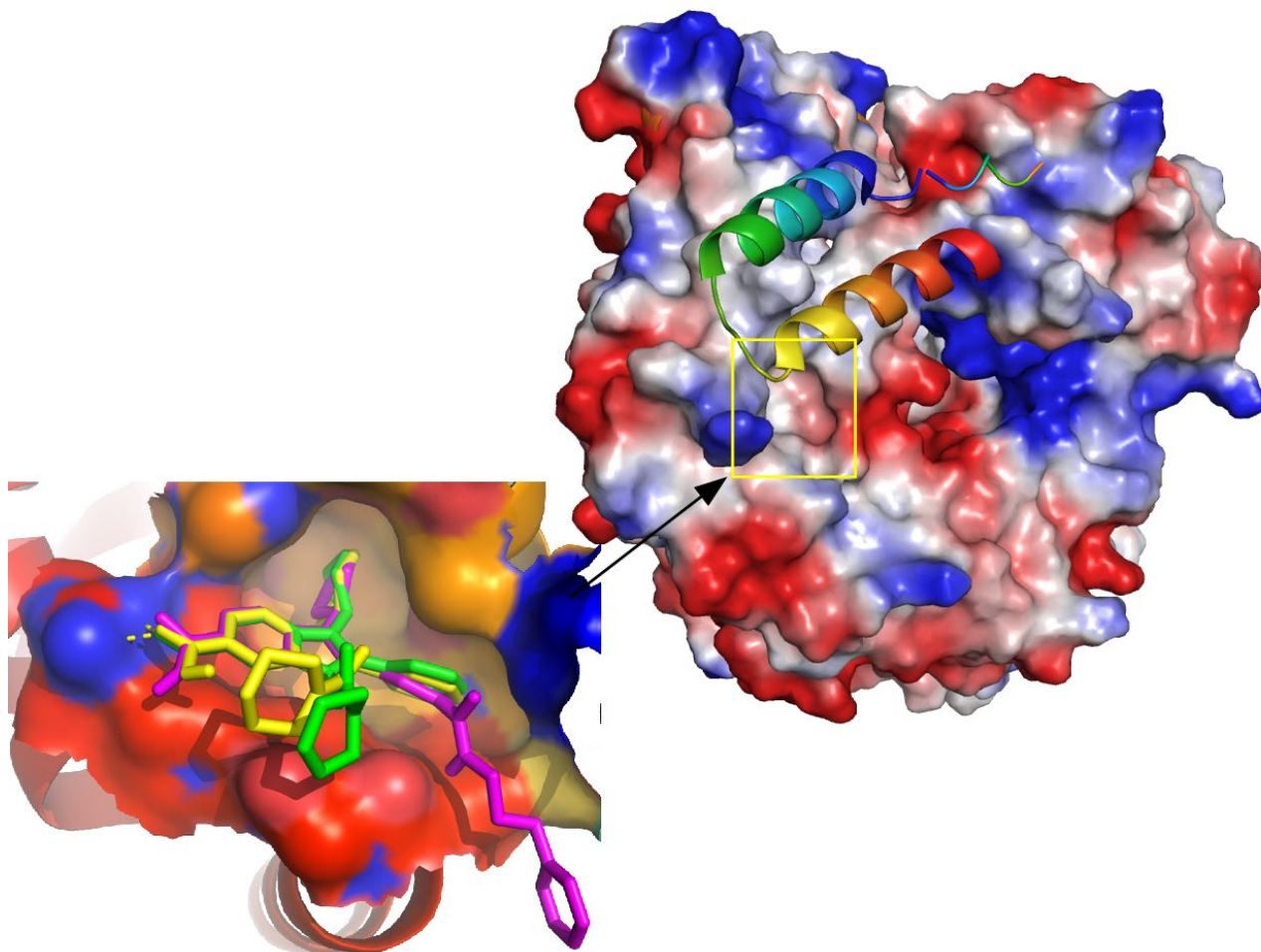


ANNUAL REPORT 2021



INSTITUTE OF RESEARCH,
DEVELOPMENT, AND
INNOVATION IN HEALTHCARE
BIOTECHNOLOGY
OF ELCHE
UNIVERSITY "MIGUEL HERNÁNDEZ"


IDiBE
UNIVERSITAS
Miguel Hernández

DIRECTOR'S FOREWORD

The Institute of Research, Development, and Innovation in Healthcare Biotechnology in Elche (IDiBE) is one of the University Research Institutes at the University *Miguel Hernandez de Elche*. The IDiBE is located in the University Campus in Elche, occupying a 4,000 sq. m. of laboratory in the Torregaitán Building. IDiBE aims to become a Research Institute that excels in frontier science and its translational to society. In the past 24 years, the IDiBE (previously IBMC) has excelled in its scientific production, in the exploitation of the generated results and technologies and its societal disseminating programs. This translational excellence has thrust the creation of spin-off companies and Joint ventures with private enterprises and local Hospitals. This seminal vision has been kept invariable and can be fully appreciated in our Annual Reports describing all our achievements in research, exploitation, training and dissemination activities. All these accomplishments are in line with the objectives set in our Plan of Actions.



As in previous years, our groups have been active in securing funding from both governmental and private sources, publishing papers (89% in Q1) that are widely cited, training young scientists with the highest scientific standards as recognized by recent audit of our Doctorate program by the AVAP, and to disseminate our activities and achievements to society through our out-reach programs (Science with tapas; And you, what do you research on?) In addition, we consolidated the Master Degree in Biotechnology and Bioengineering with the Institute of Bioengineering that is becoming a national reference in the field. In addition, we continued with the Erasmus+European Master on translational cosmetic and dermatological sciences with the Universities of Piemonte Orientale (Italy), Namur. (Belgium) and Humboldt (Germany). A major success of the Institute has been the commercialization of innovative products generated from the research projects in the fields of nutraceuticals, cosmeceuticals and biotechnology; and having 3 lead compounds in clinical development and one in pre-clinical. Our translational activities are reinforced with four technological platforms. This success has been possible thanks to our philosophy of potentiating communication and collaborations, and sharing all the infrastructures, as well as to the commitment of our administrative and technical personnel to the IDiBE project.

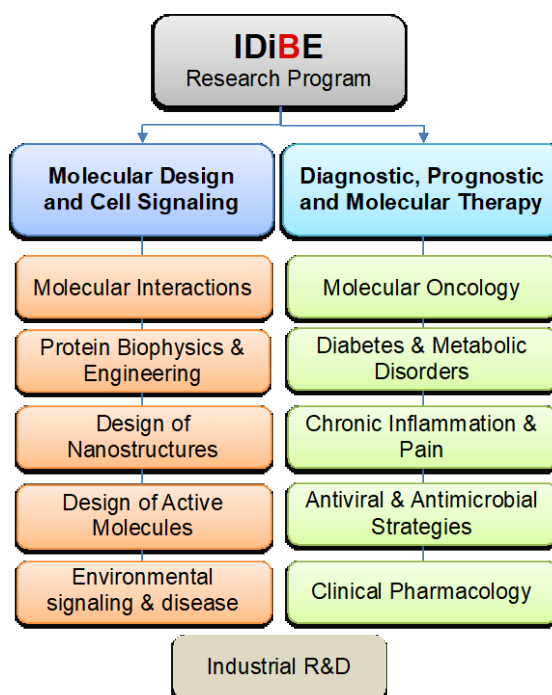
Despite the unexpected Covid-19 pandemic, the IDiBE has been able to continue working on its objectives, providing part of the deliverables. The major milestones for 2021 have been: (i) Potentiation of the technology transfer actions to the productive sectors of our society through the innovation agent; (ii) acquisition of new infrastructures funded by the GVA and the EU that have provided new technologies that will allow the Institute to embark on more competitive projects; and, (iii) award of the MCSA-ETN "PIANO" of the Horizon 2020 EU program. Furthermore, we set the basis to have a BL-2 laboratory in the Institute which will allow developing additional projects. This is in line with our current Plan of Action (2019-2022) that establishes the central mission to consolidate a multidisciplinary research program in the area of Healthcare Biotechnology eligible for a seal of excellence.

Prof. Antonio Ferrer-Montiel
IDiBE director

STRUCTURE AND GENERAL DESCRIPTION

The IDiBE Action Plan for 2019-2022

The IDiBE R&D program is organized in two major research lines that cover all the activities carried out by our teams. These lines are: (i) **Molecular Design and Cell Signaling** and, (ii) **Molecular Diagnostic, Prognostic and Therapy**. Each line is structured in specific sublines that accurately define the actions of the different groups, and also highlight the channels of communication between both research lines, which is essential for exploiting the synergies that emerge from the multidisciplinary. **An industrial R&D** line for natural extracts complements the research lines. This organization also favors internal collaborations, sharing the infrastructures, and a more rational and productive use of all resources, including the technological platforms. Consequently, in the next four-year period, the IDiBE aspires to become a center of reference in the discovery of pharmacological and biotechnological tools, with a clear translational and transfer potential. The intense and sustain work in this line is the central objective for the next four-year period, and to so agreements with PROs will be pursued which will permit reinforcing deficient areas or those that require an impetus for their consolidation, and thereby generating a unique and unprecedented project on a national and international level.



R&D organization

In scientific terms, the targets of these research areas of the IDiBE are developed as follows:

A. Molecular Design and Cell Signaling

The main objective of this research line is to advance our knowledge in the structure-function relations of small molecules and macromolecules with the aim of transforming their activity for biotechnological purposes, and to design better ligands that modulate their function, as well as nanotechnology-based systems that help their deliver to the site of action. An additional objective of this research line is to understand the cell signaling mechanisms used by environmental signals such as endocrine disruptors and other pollutants that may be the underlying cause of diseases with an increase prevalence. These studies aim to identify the molecular composition of the signaling mechanisms and to validate targets for drug intervention. Environmentally-mediated disease or aggravation of

human disease is an emerging societal challenge directly linked to progress in western countries and heavy contamination in poor countries.

This research line involves 8 research groups. The different scientific backgrounds of the researchers involved allows for a multidisciplinary approach of the societal and technological challenges investigated. The main research fields under this core line are:

1. Molecular interactions, protein biophysics and engineering. 2. Design and validation of nanostructures. 3. Design of active molecules. 4. Environmental signaling and disease.

B. Molecular Diagnostic, Prognostic and Therapy

The research line for Molecular Diagnosis, Prognostic and Therapy pursues the identification and validation of molecular markers in human and animal pathologies of high prevalence, as well as the development of diagnostic and prognostic methods and therapeutic or preventive strategies. This research line is made up of a multi-disciplinary research team, which covers from molecular aspects to semi-industrial biological actives. This multidisciplinaryity is sustained by the contribution of 8 consolidated groups, which provide a balanced composition that favors a high competitiveness in scientific contributions, raising resources, training research staff and generating exploitable and transferable technologies.

The milestones achieved in this line of research have had and have a high scientific impact as is evident from the scientific publications in internationally recognized journals, as well as the generation of unique technologies which are protected by worldwide patents and have been licensed out to interested companies. One strong point of this research line to be highlighted is the high level of national and international collaborations with public and private research organizations, which contribute to increasing the impact of the activities and their internationalization. Furthermore, the interrelation of the sub-lines which make up this line of research has reinforced the identification of synergies and common interests between groups, promoting collaborations which speed up the achievement of results and technologies.

The activities in this line clearly have a high potential for clinical translation, which has materialized in a close collaboration with the University Hospitals of Elche and Alicante, and of industrial exploitation that has led to continuous and consolidated collaborations with biotech and pharmaceutical companies. Indeed, these research lines are complemented by an additional complementary subline dealing with the industrial developments (including products and processes for healthcare biotechnology).

1. Molecular Oncology. 2. Diabetes and Metabolic disorders. 3. Chronic inflammation and pain. 4. Antiviral and antimicrobial strategies. 5. Clinical pharmacology.

MOLECULAR DESIGN AND CELL SIGNALING

MOLECULAR DESIGN AND CELL SIGNALING

Molecular Recognition and Protein Biophysics and Engineering

Group name: BIOTHERMODYNAMICS OF MOLECULAR RECOGNITION PROCESSES

Our group is involved two main research lines. On the one hand, Dr. Neira leads the research dealing with the biophysical characterization the biomolecules and interactions involved in in the phosphorylation transfer in micro-organisms, the assembly of the capsid of HIV and intrinsically disordered proteins implicated in pancreatic cancer. On the other, Dr. Gómez research activities focus on the design and characterization of nano and microparticles coated with polyelectrolytes to be used in the transport and controlled delivery of different biomolecules, the storage of labile biomolecules used as drugs and the capture and recovery of different pollutants in continental waters.

Staff

Javier Gómez Pérez

José Luis Neira Faleiro

Rocío Esquembre Tomé

Postdoctoral Researchers

Felipe Hornos Adán

Technicians

Elisa Pérez García

Publications

Hornos F, Feng H, Rizzuti B, Palomino-Schätzlein M, Wieczorek D, Neira JL, Jin J. The muscle-relaxing C-terminal peptide from troponin I populates a nascent helix, facilitating binding to tropomyosin with a potent therapeutic effect. *Journal of Biological Chemistry*. 2021, 296 doi:10.1074/jbc.RA120.016012

Rizzuti B, Lan W, Santofimia-Castaño P, Zhou Z, Velázquez-Campoy A, Abián O, Peng L, Neira JL, Xia Y, Iovanna JL. Design of Inhibitors of the Intrinsically Disordered Protein NUPR1: Balance between Drug Affinity and Target Function. *Biomolecules*, 2021, 11, 1453. doi.org/10.3390/biom11101453

Neira JL, Rizzuti B, Ortega-Alarcón D, Giudici AM, Abián O, Fárez-Vidal ME, Velázquez-Campoy A. The armadillo-repeat domain of plakophilin 1 binds the C-terminal sterile alpha motif (SAM) of p73. *BBA - General Subjects*. 2021 July 1865,(7):129914.

<https://doi.org/10.1016/j.bbagen.2021.129914>

Organization of Meetings

Moderadora de Sesión Científica (RET) - I JORNADA DE JOVENES INVESTIGADORES DEL IDIBE. Rocío Esquembre Tomé.

Number of Congress Communications

National contributions: 1

Poster presentations: 1

International contributions: 3

Poster presentations: 3

Governmental Projects and Funding

Diseño de nuevos antibióticos basados en un sistema de fosforilación exclusivo de Bacterias 01/01/2019-21/07/2022 - PROYECTOS I+D+i «RETOS INVESTIGACIÓN» DEL PROGRAMA ESTATAL DE I+D+i ORIENTADA A LOS RETOS DE LA SOCIEDAD- MICIU 2019. MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES (RTI2018-097991-B-I00). UMH. IPs: Jose Luis Neira Faleiro, F. Javier Gómez Pérez.

R&D Management

Reviewer of CONICET (JLN) (2008-...).

Reviewer of Israeli Science Foundation (JLN) (2016-...).

Reviewer for Czech Science Foundation (JLN) (2010-...).

Reviewer of ERC (JLN) (2018-...).

Editorial Boards

Board member Archives of Biochemistry and Biophysics (2010-2013). José L. Neira.

Group name: FLUORESCENT NANOMATERIALS APPLIED BIOTECHNOLOGY - FISH BIOMEDICAL NANOAPPLICATIONS

Our group is interested in the development of new fluorescent materials with applications in biological systems. On one hand, we design and develop fluorescent biosensors with high sensitivity, based on the entrapment of organic molecules and biomolecules in inorganic matrices, and characterize these hybrid materials at a molecular level in order to improve their applications. On the other hand, we work on the design, synthesis and characterization of novel fluorescent conjugated polyfluorenes, to be used as nanoparticles and nanofibers in applications such as bioimaging, drug delivery, clinical diagnosis and sensing devices for biomolecules. Other group activities include the characterization of macromolecular interactions, especially in non-conventional systems, such as ionic liquids as well as the synthesis of conjugated polymers to be applied in photonics and optoelectronics devices.

Study of animal mucosa bioactive compounds. Nanostructures for biomedical and veterinary skin applications. Evolutionary studies on short pentraxins (CRP and SAP).

Staff

Carmen Reyes Mateo Martínez

Ricardo Mallavia Marin

M^a José Martínez Tomé

Juan Alberto Falcó Graciá

Postdoctoral Researchers

Amalia Mira Carrió

Ph. D Students

Marta Rubio Camacho

Yolanda Inmaculada Alacid Martínez

Rocío Díaz Puertas

Juan Suardiáz Muro

Technicians

Elisa Pérez García

Publications

Alacid Y, Martínez-Tomé MJ, Mateo CR. Reusable Fluorescent Nanobiosensor Integrated in a Multiwell Plate for Screening and Quantification of Antidiabetic Drugs. *ACS Appl. Mater. Interfaces*, 2021, 13, 25624–25634. doi.org/10.1021/acsami.1c02505

Díaz-Arca A, Ros-Tárraga P, Martínez Tomé MJ, H. De Aza A, Meseguer-Olmo L, Mazón P, De Aza PN. Micro-/Nano-Structured Ceramic Scaffolds That Mimic Natural Cancellous Bone. *Materials* 2021, 14, 1439. doi.org/10.3390/ma14061439

Rubio-Camacho M, Martínez-Tomé MJ, Mira A, Mallavia R, Mateo CR. Formation of Multicolor Nanogels Based on Cationic Polyfluorenes and Poly(methyl vinyl ether-alt-maleic monoethyl ester): Potential Use as pH-Responsive Fluorescent Drug Carriers. *Int. J. Mol. Sci.* 2021, 22, 9607. doi.org/10.3390/ijms22179607

Falco A, Bello-Perez M, Díaz-Puertas R, Mold M, Adamek M. Update on the inactivation procedures for the vaccine development prospects of a new highly virulent RGNNV isolate. *Vaccines*, 2021, 9 (12), art. no. 1441. DOI: 10.3390/vaccines9121441

Neira JL, Palomino-Schätzlein M, Hurtado-Gómez E, Ortore MG, Falcó A. An N-terminal half fragment of the histidine phosphocarrier protein, HPr, is disordered but binds to HPr partners and shows antibacterial properties. *Biochimica et Biophysica Acta - General Subjects*, 2021, 1865 (12), art. no. 130015. DOI: 10.1016/j.bbagen.2021.130015

Mira A, Rubio-Camacho M, Alarcón D, Rodríguez-Cañas E, Fernández-Carvajal A, Falco A, Mallavia R. L-menthol-loadable electrospun fibers of pmvema anhydride for topical administration. *Pharmaceutics*, 2021, 13 (11), art. no. 1845. DOI: 10.3390/pharmaceutics13111845

Neira JL, Ortega-Alarcón D, Rizzuti B, Palomino-Schätzlein, M, Velázquez-Campoy A, Falcó A. Residual helicity at the active site of the histidine phosphocarrier, HPr, modulates binding affinity to its natural partners. *International Journal of Molecular Sciences*, 2021, 22 (19), art. no. 10805. DOI: 10.3390/ijms221910805

Bello-Perez M, Adamek M, Coll J, Figueras A, Novoa B, Falco A. Modulation of the tissue expression pattern of zebrafish crp-like molecules suggests a relevant antiviral role in fish skin. *Biology*, 2021, 10 (2), art. no. 78, pp. 1-13. DOI: 10.3390/biology10020078

Klionsky DJ, et. al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). *Autophagy*, 2021, 17 (1), pp. 1-382. DOI: 10.1080/15548627.2020.1797280

Patents

Inventores: Figueras A, Gasset M, Novoa B, Rey M, Mallavia R, Medina RM, Martínez-López A. Título: "Peptido de miticina y su uso en regeneración celular" P201831154; Concedida: 20/10/2021.

Science dissemination: outreach activities

Jornadas de divulgación científica "Ciencia con tapas". "El picor: la alerta de nuestras neuronas y cómo combatirlo", 14-12-2021.

Jornadas IDiBE DIVULGA:

- "SARS-Cov-2. Mutantes, variantes y vacunas: Las buenas y las malas noticias", 21-04-21.

- "Volando libres. El fabuloso viaje aéreo de los microbios", 30-06-21.

Jornada "Día internacional de la mujer y la niña en la ciencia en el IDiBE". Investigadoras en biotecnología sanitaria, 10-02-21.

M^a José Martínez Tomé. Comité organizador.

Number of Congress Communications

National contributions: 8

Oral presentations: 5

Poster presentations: 3

Governmental Projects and Funding

Desarrollo y evaluación traslacional de nanofibras de extractos mucilaginosos de pez con potencial terapéutico para aplicaciones en acuicultura y ganadería (MUCIPEUTICS). 01/10/2019 – PROYECTOS DE I+D+I "RETOS DE LA SOCIEDAD" 2018 (RTI2018-101969-J-I00). FEDER / Ministerio de Ciencia, Innovación y Universidades – Agencia Estatal de Investigación. UMH. IP: Juan Alberto Falcó Graciá.

Diseño de nanomateriales fluorescentes para el desarrollo de nuevas formulaciones terapéuticas y descubrimiento de nuevos fármacos. PROYECTOS DE I+D+I "RETOS DE LA SOCIEDAD" - MAT-2017-86805-R (Enero 2018- Sept2021). Ministerio de Economía, industria y Competitividad. IP: Carmen Reyes Mateo Martínez y Co-IP: Ricardo Mallavia Marín.

Plan de actuación de la UCCi UMH (2021-2022). Modalidad 4.1 Red de unidades de cultura científica y de la innovación (UCC+i). 01/07/2021 – 30/06/2022. Ministerio de Ciencia e Innovación – FECYT Innovación. IP: Marín Navarro-Soto, L.G.

Unidad preclínica para cuantificar interacciones moleculares para optimizar candidatos a fármacos. Generalitat Valenciana. IDIFEDER/2021/036. 01/01/2021 – 31/12/2022. IP: Antonio Ferrer.

Terapias metabólicas para el tratamiento de enfermedades infecciosas en peces de cultivo REf: MetDisFish. Plan Nacional de Acuicultura Convocatoria 2021. Ministerio de Agricultura, Pesca y Alimentación. 30/12/2021 – 15/10/2023. Proyecto Coordinado CSIC-UMH. IP UMH: Ricardo Mallavia Marín.

R&D Management

Reviewers of Spanish State Research Agency (AEI)

Reviewer for Nanomaterials (CRM)

Reviewer for Coating (CRM)

Reviewer for Molecules (CRM)

Reviewer for Sensors and Actuators (CRM)

Reviewer for Chemosensors (CRM)

Editorial Boards

Group name: **PROTEIN ARCHITECTURE**

The group's expertise lies in the field of protein engineering by combining theoretical (computational) and experimental approaches, for biochemical, biophysics and structural characterization of macromolecules aimed at engineering of polypeptides and peptides with new or desirable functions and properties for technological applications in biomedicine, bioengineering and in the most recent areas of nanoscience.

Proteins are dynamic nanomolecular machines ubiquitous in all living systems that adopt distinct three-dimensional (3D) structures to perform multitude of biological functions. Advance in modern molecular biology and biotechnology have improved our understanding of basic functional and architectural principles of proteins, making them attractive candidates as concept generators for technological development in biomedicine, bioengineering and in the most recent areas of nanoscience. Applying "rational design", protein engineering is the most powerful approach to obtain proteins with new or desirable functions and properties. In biomolecular engineering is of particular interest, the protein biochemical and biophysical characterization by thermodynamic, kinetic, spectroscopic and structural methods allowing us to better understanding the rules that govern the processes of interest, and the degree of involvement of proteins in these processes.

The efforts of the group are leading to get insights into the relationship between protein structure and function (or dysfunction), as well as to the creation of novel biomolecules with desirable properties to study. We approach this from a variety of angles and employ state-

Reviewer Board member of Nanomaterials (MDPI) (2020-...) (Alberto Falcó).

Reviewer Board member of Marine Drugs (MDPI) (2020-...) (Alberto Falcó).

of-the-art in silico (protein rational design, protein modeling and molecular docking for identification of novel active compounds) and in vitro molecular methods for biophysical, biochemical and structural characterization of diverse recombinant proteins by using spectroscopic techniques (Circular Dichroism, Fluorescence, Dynamic Light Scattering) and thermodynamic techniques (DSC and ITC Calorimetry).

Our studies are focused on three main lines of research:

- Protein structure regularization and effect on function.
- Protein stability, folding and oligomerization with the final aim of understanding the molecular basis of the aggregation contribution to allergenic properties of food allergens.
- Zika and dengue viruses. New direct-acting antivirals through computational and experimental tools.

Our Molecular Recognition and Protein Biophysics and Engineering division possess a protein-protein interaction facility equipped, among others, with a recently acquired TA DSC (Differential scanning nanocalorimeter), VP ITC (Isothermal Titration Calorimeter), two Circular Dichroism Spectrophotometers (J-810 and J815) and also a recently acquired Malvern nano-ZS DLS (Dynamic Light Scattering).

Staff

Ana María Fernández Escamilla

External collaborators integrated in the group

Ph.D. Luis Serrano Pubull. Director CRG Centro de Regulación Genómica (CRG) Barcelona.

Prof. Ana Grande and Prof. Enrique Viguera. Instituto de Hortofruticultura Subtropical y Mediterránea. Departamento de Biología Celular, Genética y Fisiología. Universidad de Málaga.

Ph.D. Nerea Irigoyen. Division of Virology, Department of Pathology. University of Cambridge. Cambridge, United Kingdom.

Ph.D. Tomás Mayoral Ortega. Director Técnico del Laboratorio de Genética Molecular. Laboratorio Central de Veterinaria de Madrid. Ministerio de Agricultura, Pesca y Alimentación.

Organization of Meetings

I JORNADA DE JOVENES INVESTIGADORES DEL IDIBE. 27/07/2021. Miembro del Comité Organizador: Ana María Fernández Escamilla.

Science Dissemination: Outreach Activities

Ana María Fernández Escamilla. Entrevista de Radio Local sobre el Proyecto AICO concedido por la Comunidad Valenciana titulado: Zika y Dengue: Identificación de nuevos inhibidores enzimáticos combinando estrategias computacionales y experimentales. Informativos de la Radio UMH. 11/01/2021.

Ana María Fernández Escamilla. Entrevista de Radio Local y podcast, en el Programa la "Ciencia que viene" sobre la investigación realizada en ZIKV y DENV. Informativos de la Radio UMH. 14/07/2021.

Ana María Fernández Escamilla. Entrevista para la difusión de la I Jornada de Jóvenes Investigadores del IDIBE. Informativos de la Radio UMH. 21/07/2021.

Governmental Projects and Funding

Zika y Dengue: Identificación de nuevos inhibidores enzimáticos combinando estrategias computacionales y experimentales. SUBVENCIONES PARA GRUPOS DE INVESTIGACIÓN CONSOLIDABLES AICO/2020. CONSELLERIA DE INNOVACION, UNIVERSIDADES, CIENCIA Y SOCIEDAD DIGITAL (GENERALITAT VALENCIANA). AICO/2020/026, 01/01/2020-31/12/2021. IP: Ana María Fernández Escamilla.

Terapia Antiviral de Combinacion con Inhibidores de las Actividades Exon Correctora y Mtasa del Coronavirus Sars-Cov-2 y Mutagenesis Letal Para Impedir la Evasion del Virus a la Defensa Inmunitaria Innata Antiviral. CV20-10932, 11/11/2020-11/11/2021. IP: Ana Grande Pérez.

Desarrollo de nuevos fármacos inhibidores de CDK4 dirigidos contra la interfase CDK4-cyclinaD1 para el tratamiento del glioblastoma multiforme. CONVOCATORIA 2021 DE CONCESIÓN DE AYUDAS PARA ACCIONES PREPARATORIAS DE APOYO A LA EXPLORACIÓN Y FORMULACIÓN DE FUTUROS PROYECTOS DE INVESTIGACIÓN Y DE INNOVACIÓN COORDINADAS ENTRE INVESTIGADORES/AS DE LA UNIVERSITAT MIGUEL HERNÁNDEZ Y PROFESIONALES DE FISABIO. GENERALITAT VALENCIANA Y FUNDACIÓ FISABIO. A01. IPs: José Antonio Encinar Hidalgo, Meuri del Camino de Juan Romero.

Unidad preclínica para cuantificar interacciones moleculares para optimizar candidatos a fármacos. CONSELLERIA DE INNOVACION, UNIVERSIDADES, CIENCIA Y SOCIEDAD DIGITAL (GENERALITAT VALENCIANA). IDIFEDER/2021/036. 01/01/2021-31/12/2022. IP: Antonio Vicente Ferrer Montiel.

R&D and Educational Committees

Agencia Nacional de Evaluación y Prospectiva (ANEP). A. M. Fernández Escamilla.

Scientific Society Councils

Name of the society: Red temática de Estructura y Función de Proteínas. <http://redproteinas.iqfr.csic.es/>

Name of the society: Sociedad Española de Biofísica (SBE). <http://www.sbe.es/>

Name of the society: Sociedad Española de Bioquímica y Biología Molecular (SEBBM). <http://www.sebbm.es/>

Editorial Boards

Review Editor in Frontiers in Physiology - Membrane Physiology and Membrane Biophysics (2018-.....). A. M. Fernández Escamilla.

Structure-Function Relationships in Membrane Proteins

Group name: STRUCTURE-FUNCTION RELATIONSHIP OF ION CHANNELS

Our group studies the structure-function relationships in membrane proteins, especially neuroreceptors and ion channels. The final aim is to understand how these proteins work at the molecular level and how they are modulated by lipids, ligands or other proteins in order to find new potential targets for drug discovery.

Staff

José Manuel González-Ros

José Antonio Poveda Larrosa

Postdoctoral Researchers

M^a Lourdes Renart Pérez

Ana Marcela Giudici Besseghini

Ph. D Students

Clara Díaz García

Technicians

Eva Martínez Martínez

Publications

Díaz-García C, Renart ML, Poveda JA, Giudici AM, González-Ros JM, Prieto M, Coutinho A. Probing the Structural Dynamics of the Activation Gate of KcsA Using Homo-FRET Measurements. *Int J Mol Sci.* 2021 Nov 4;22(21):11954. doi: 10.3390/ijms222111954

Giudici AM, Díaz-García C, Renart ML, Coutinho A, Prieto M, González-Ros JM, Poveda JA. Tetraoctylammonium, a Long Chain Quaternary Ammonium Blocker, Promotes a Noncollapsed, Resting-Like Inactivated State in KcsA. *Int J Mol Sci.* 2021 Jan 6;22(2):490. doi: 10.3390/ijms22020490

Neira JL, Rizzuti B, Ortega-Alarcón D, Giudici AM, Abián O, Fárez-Vidal ME, Velázquez-Campoy A. The armadillo-repeat domain of plakophilin 1 binds the C-terminal sterile alpha motif (SAM) of p73. *BBA - General Subjects.* 2021 July 1865.(7):129914. <https://doi.org/10.1016/j.bbagen.2021.129914>

Alberola-Die A, Encinar JA, Cobo R, Fernández-Ballester G, González-Ros JM, Ivorra I, Morales A. Peimine, an anti-inflammatory compound from Chinese herbal extracts, modulates muscle-type nicotinic receptors. *International Journal of Molecular Sciences.* 2021, 22, 11287-11313. doi.org/10.3390/ijms222011287

Number of Congress Communications

International contributions: 4

Oral presentations: 3

Poster presentation: 1

Governmental Projects and Funding

Estudio de los estados conformacionales del filtro de selectividad de los canales iónicos: hacia la comprensión de la permeación, selectividad e inactivación. Ref. PGC2018-093505-B-I00. 01/01/2019-31/12/2021. PROYECTOS DE I+D – GENERACIÓN DE CONOCIMIENTO, MINISTERIO DE CIENCIA, INNOVACIÓN. IPs: José Manuel González-Ros y José Antonio Poveda Larrosa.

Unidad preclínica para cuantificar interacciones moleculares para optimizar candidatos a fármacos. Proyecto de investigación IDIFEDER2021/036. IP: Antonio Ferrer Montiel

R&D Management

Reviewer for Applied Sciences (JAPL)

Reviewer for Membranes (JAPL)

Reviewer for "Archives of Biochemistry and Biophysics" (JAPL, AMG, MLR)

Reviewer for "International Journal of Molecular Sciences" (JMGR)

Evaluator for FWF Austrian Science Fund (JMGR)

Evaluator for "Agència de Gestió d'Ajuts Universitaris i de Recerca" (JMGR)

Evaluator for MINECO (JMGR)

Reviewer for "Oncotarget" (JMGR)

Editorial Boards

Associated Editor of International Journal
of Molecular Sciences (JMGR, 2019-...).

Associated Editor of International Journal
of Molecular Sciences (JAPL, 2019-...).

MOLECULAR DIAGNOSTIC, PROGNOSTIC AND THERAPY

MOLECULAR DIAGNOSTIC, PROGNOSTIC AND THERAPY

Bioactive Molecules

Group name: DESIGN AND DEVELOPMENT OF BIOACTIVE MOLECULES

The D&DBM group is composed of a multidisciplinary team of researchers and professors of Biotechnology, Food Science and Pharmacy. We are focused on the study of the biological activity and mechanism-of-action of natural compounds and their application to alleviate human chronic diseases such as cancer and obesity and also non-communicable diseases, using cell and animal models and human trials. The activity of the group is based on the scientific evidence, always looking for excellence, the social, environmental and economical impacts and high-quality results.

Our group is also involved in many translational activities to the industrial sector, collaborating in different projects and developments with industrial and non-academic partners that belong to areas such as food, pharma, functional beverages, nutraceuticals and dermo-cosmetics. To achieve these goals, our group has experience and facilities to develop extraction procedures, analytical characterization, in silico screening, cellular and animal models and the capability and expertise to develop human intervention assays.

Staff

Vicente Micol Molina

Jose Antonio Encinar Hidalgo

Enrique Barrajón Catalán

María Herranz López

Postdoctoral Researchers

Maria Dolores Olivares Vicente

Verónica Ruiz Torres

Francisco Javier Alvarez Martinez

Ph. D Students

Irene Pomares Bri

Jesica Martínez Godfrey

Noelia Sánchez Marzo

Technicians

M^a Teresa Garzón Cabrerizo

María Losada Echeberría

Publications

Ortega-Muelas M, Roche O, Fernández-Aroca DM, Encinar JA, Albandea-Rodríguez D, Arconada-Luque E, Pascual-Serra R, Muñoz I, Sánchez-Pérez I, Belandia B, Ruiz-Hidalgo MJ, Sánchez-Prieto R. ERK5 signalling pathway is a novel target of sorafenib: Implication in EGF biology. *Journal of cellular and molecular medicine* 2021, 25, (22), 10591-10603. doi: 10.1111/jcmm.16990

Alberola-Die A, Encinar JA, Cobo R, Fernández-Ballester G, González-Ros JM, Ivorra I, Morales A. Peimine, an Anti-Inflammatory Compound from Chinese Herbal Extracts, Modulates Muscle-Type Nicotinic Receptors. *Int J Mol Sci.* 2021, 22, (20). doi: 10.3390/ijms222011287

Tramonti A, Cuyàs E, Encinar JA, Pietzke M, Paone A, Verdura S, Arbusà A, Martín-Castillo B, Giardina G, Joven J, Vazquez A, Contestabile R, Cutruzzolà F, Menendez JA. Metformin Is a Pyridoxal-5'-phosphate (PLP)-Competitive Inhibitor of SHMT2. *Cancers* 2021, 13, (16). doi: 10.3390/cancers13164009

Marroqui L, Martínez-Pinna J, Castellano-Muñoz M, Dos Santos RS, Medina-Gali RM, Soriano S, Quesada I, Gustafsson JA, Encinar JA, Nadal A. Bisphenol-S and Bisphenol-F alter mouse pancreatic β -cell ion channel expression and activity and insulin release through an estrogen receptor ER β mediated pathway. *Chemosphere* 2021, 265, 129051. doi: 10.1016/j.chemosphere.2020.129051

Ruiz-Torres V, Forsythe N, Pérez-Sánchez A, Van Schaeybrocker S, Barrajón Catalán E, Micol V. A nudibranch marine extract selectively chemosensitizes colorectal cancer cells by inducing ROS-mediated endoplasmic reticulum stress. *Front. Pharmacol.* 08 April 2021. <https://doi.org/10.3389/fphar.2021>

Álvarez-Martínez FJ, Barrañón-Catalán E, Herranz-López M, Micol V. Antibacterial plant compounds, extracts and essential oils: an updated review on their effects and putative mechanisms of action. *Phytomedicine*. 19 (3-4), 253-261 2021. <https://doi.org/10.1016/j.phymed.2021.153626>

Zhong J, Barrañón-Catalán E, Lorenzo JM, Lu J, Tiwari BK. Development of Functional Foods From Marine Sources (editorial). *Front. Nutr.*, 01 December 2021 <https://doi.org/10.3389/fnut.2021.812497>

Álvarez-Martínez FJ, Rodríguez JC, Borrás-Rocher F, Barrañón-Catalán E, Micol V. The antimicrobial capacity of *Cistus salviifolius* and *Punica granatum* plant extracts against clinical pathogens is related to their polyphenolic composition. *Scientific Reports*. 2021 588, pp. 1 - 12. <https://doi.org/10.1038/s41598-020-80003-y>

Boix-Castejón M, Herranz-López M, Olivares-Vicente M, Campoy P, Caturla N, Jones J, Zazo JM, Roche E, Micol V. Effect of metabolaid® on pre- and stage 1 hypertensive patients: A randomized controlled trial. *Journal of Functional Foods*, 2021, 84, 104583. <https://doi.org/10.1016/j.jff.2021.104583>

Verdura S, Cuyàs E, Ruiz-Torres V, Micol V, Joven J, Bosch-Barrera J, Menéndez JA. Lung cancer management with silibinin: A historical and translational perspective. *Pharmaceuticals*, 2021 14(6):559. Doi: 10.3390/ph14060559

Herranz-López M, Martínez-Mayoral MA, Mora-Rodríguez C, Quesada-Martínez M, Barrañón-Catalán E, Lillo Navarro MC. Chapter: Formación Transversal y Trabajos Fin de Grado Interdisciplinares. Book: Nuevos retos educativos en la enseñanza superior frente al desafío COVID-19, Ed. Octaedro (2021). ISBN: 978-84-19023-19-3

Patents

TREATMENT OF NRF2-RELATED DISEASES. 2021-02-11. Inventors: Antonio Cuadrado Pastor (45%), Raquel Fernández Ginés (15%), José Antonio Encinar (15%), Rafaél León Martínez (5%), Juan Felipe Franco González (5%), Manuel García López (5%), María Isabel Rodríguez Franco (5%), Ana

Isabel Rojo Sanchís (5%). European and worldwide patent.

PhD Theses

Title: Antimicrobial compounds of natural origin: an opportunity for the treatment of infectious diseases resistant to antibiotics. Student: F.J. Álvarez-Martínez. Supervisors: V. Micol and E. Barrañón-Catalán. Sobresaliente cum laude with international mention. 25/05/2021.

Title: Cribado de extractos naturales a partir de subproductos de la industria frutícola para la obtención de nuevos principios activos con fines dermocosméticos. Student: L.M. Agulló-Chazarra. Supervisors: M. Herranz-López and E. Barrañón-Catalán. Sobresaliente cum laude. 25/06/2021.

Invited Talks and Courses

Title: Venciendo la resistencia a los antibióticos mediante extractos vegetales, una estrategia prometedora. Congress: 11º CONGRESO DE LA SOCIEDAD ESPAÑOLA DE FITOTERAPIA. San Juan (Alicante, Spain). E. Barrañón-Catalán; J. Álvarez-Martínez; J.C. Rodríguez-Díaz; F. Borrás; V. Micol.

Title: 1st IDiBE's Young Researchers Day. 2021. María Herranz López has participated as the Chair of a panel session.

Number of Congress Communications

International contributions: 4

Poster presentations: 2

Oral presentations: 2

National contributions: 5

Poster presentations: 4

Oral presentations: 1

Governmental Projects and Funding

New therapeutic approaches in metabolic diseases: modulation of food intake and energy balance through nutraceuticals and neurotechnology (OBRAINSITY). Proyectos Prometeo (PROMETEO/2021/059). UMH. Generalitat

Valenciana. Ips: Vicente Micol y María Herranz-López.

Determinación de las concentraciones plasmáticas de mefloquina y sus efectos clínicos en pacientes incluidos en el ensayo MEFLOCOVID19 contra COVID19. Proyectos ILISABIO (ILISABIO/2020/A31). UMH. IP: E. Barraón-Catalán.

Una innovadora aproximación metabonómica inductiva para la identificación de metabolitos derivados de polifenoles de la dieta y sus dianas moleculares (RTI2018-096724-B-C21). Ministerio de Ciencia, Innovación y Universidades. Cantidad concedida: 145.000 €. Duración: 01/01/2019 – 31/12/2021. IP: Vicente Micol y Co-IP: Enrique Barraón Catalán.

Project CIBEROBN CB12/03/30038. Fisiopatología de la Obesidad y la Nutrición (CIBEROBN) is the official funding agency for biomedical research of the Spanish government and Institute of Health Carlos III (ISCIII), 28029 Madrid, Spain (2012-present). <https://www.ciberobn.es/grupos/grupo-de-investigacion?id=14897>.

NEUROTECHeu, the ERASMUS+ European University of Brain and Technology, which includes eight universities across Europe (<https://theneurotech.eu/>). Vicente Micol is part of the management team (2021-23).

Private funding: Contracts

Título: Donación al proyecto de investigación " Nuevos compuestos antitumorales para tratar el cáncer de colon". Referencia: RURALCENTRAL1.21DN Tercero: CAJA RURAL CENTRAL S. COOP. DE CREDITO Fecha de Inicio: 21/12/2021 Fecha de Fin: 31/03/2023 Importe: 21.000,00 €.

Título: Donación al proyecto de investigación "Nuevos compuestos antitumorales para tratar el cáncer de colon". Referencia: RURALCENTRAL1.20DN Tercero: CAJA RURAL CENTRAL S. COOP. DE CREDITO Fecha de Inicio: 13/01/2021 Fecha de Fin: 31/03/2022 Importe: 30.000,00 €.

Título: Donación al proyecto de investigación "Nuevos compuestos

antitumorales para tratar el cáncer de colon". Referencia: ANOC1.20DN Tercero: ASOCIACION DE NOVELDA PARA AYUDA A PERSONAS CON CANCER (ANOC) Fecha de Inicio: 23/07/2020 Fecha de Fin: 28/02/2021 Importe: 5.000,00 €.

Título: Contrato para la realización del trabajo "Caracterización de la composición y determinación de bioactividad en muestras del sector biosanitario". Referencia: EFFITECH1.20T Tercero: ILICE EFFITECH SL Fecha de Inicio: 19/05/2020 Fecha de Fin: 18/05/2022 Importe Variable: 5.350,00 €.

Título: Donación al proyecto de investigación "Nuevos compuestos antitumorales para tratar el cáncer de colon". Referencia: RURALCENTRAL1.19DN Tercero: CAJA RURAL CENTRAL S. COOP. DE CREDITO Fecha de Inicio: 12/12/2019 Fecha de Fin: 28/02/2021 Importe: 32.000,00 €.

Título: Contrato para la realización del trabajo "Caracterización e identificación de la microflora endofítica predominante en especies vegetales mediterráneas". Referencia: INNOVATIONLABO2.20T Entidad Financiadora: INNOVATION LABO TECHNOLOGIES, S.L. Fecha de Inicio: 07/12/2020 Fecha de Fin: 06/12/2022 Investigador Principal: VICENTE MICOL MOLINA Importe: 7.749,00 €.

Technical Services and Assistance

Título: (1326-21) Análisis del contenido en antocianos mediante el método espectrofotométrico suministrado por la empresa y empleando como patrón el cloruro de Cianidina -3 -0-sambubiosido-5-0-glucosido. Referencia: 1326/21 Entidad Financiadora: PRODUCTOS DAMEL S.L Fecha de Inicio: 01/12/2021 Fecha de Fin: 10/01/2022 Importe: 516,00 €.

Título: (905-21) Evaluación Contenido y Ejecución como Experto Técnico del ejercicio fiscal 2020 del proyecto 932.177 - "INVESTIGACIÓN Y DESARROLLO DE NUEVOS INHIBIDORES IMPLICADOS EN EL VIRUS RESPIRATORIO SINCITAL". Referencia: 0905/21 Entidad Financiadora: EQA CERTIFICADOS I+D+I SLU Fecha de Inicio: 20/10/2021 Fecha de Fin: 27/10/2021 Importe: 375,00 €.

Título: (894-21) Determinación del contenido en polifenoles totales en peso/peso (w/w) empleando dos patrones diferentes para la cuantificación: ácido gálico y cloruro de cianidina. Dos muestras que se analizarán por triplicado. Referencia: 0894/21 Entidad Financiadora: BOSTON NUTRACEUTICAL PRODUCTION S.L. Fecha de Inicio: 05/10/2021 Fecha de Fin: 08/11/2021 Importe: 725,00 €.

Título: (854-21) Análisis estadístico completo y elaboración de informe detallado sobre actividades relativas a la prestación anterior, de código ANT-210203-P2. Referencia: 0854/21 Entidad Financiadora: ANTALGENICS SL Fecha de Inicio: 22/07/2021 Fecha de Fin: 09/08/2021 Importe: 2.738,00 €.

Título: (853-21) Optimización de separación de compuestos en las 6 muestras complejas suministradas mediante HPL cromatografía HPLC. Identificación y cuantificación de hidrositirosol en las 6 muestras proporcionadas mediante cromatografía HPLC acoplada a detección de masas. Referencia: 0853/21 Entidad Financiadora: BIOFERRIC INK S.L. Fecha de Inicio: 15/07/2021 Fecha de Fin: 22/11/2021 Importe: 480,00 €.

Título: (761-21) Optimización de la separación de compuestos en las 3 muestras complejas suministradas por HPL cromatografía. Identificación y cuantificación de hidrositirosol en las 3 muestras proporcionada por cromatografía HPLC acoplada a dirección de masas. Referencia: 0761/21 Entidad Financiadora: BIOPARTNER SL Fecha de Inicio: 01/07/2021 Fecha de Fin: 20/07/2021 Importe: 255,00 €.

Título: (717-21) Análisis de muestras por HPLC siguiendo el protocolo suministrado de la empresa. Referencia: 0717/21 Entidad Financiadora: ANTALGENICS SL Fecha de Inicio: 23/06/2021 Fecha de Fin: 29/11/2021 Importe: 138,00 €.

Título: (500/21) Preparación de documentación para la realización del ensayo con animales para (OIR) y Ensayo piloto de toxicidad de nueva muestra en un modelo de ratón. Referencia: 0500/21 Entidad Financiadora: ANTALGENICS SL

Fecha de Inicio: 21/05/2021 Fecha de Fin: 02/06/2021 Importe: 1.750,00 €.

Título: (403-21) Ensayo de actividad in vivo de 4 muestras (formulación problema usada en anterior proyecto, formulación problema 2 y sus vehículos correspondientes) en un modelo de ratón inmunodeprimido. Referencia: 0403/21 Entidad Financiadora: ANTALGENICS SL Fecha de Inicio: 16/04/2021 Fecha de Fin: 16/07/2021 Importe: 10.302,00 €.

Título: (61/21) Extracción de la resina con tres mezclas de polaridades diferentes: Agua, metanol y mezcla agua/metanol 1/1. Referencia: 0061/21 Entidad Financiadora: ROXALL MEDICINA ESPAÑA, S.A. Fecha de Inicio: 20/01/2021 Fecha de Fin: 05/02/2021 Importe: 625,00 €.

R&D Management

Reviewer of Agence nationale de la recherche (Francia). E. Barraji3n-Catal3n (2021-present).

Reviewer of Agencia Estatal de Investigaci3n (Espa3a). E. Barraji3n-Catal3n (2020- present).

Reviewer of Agencia Estatal de Investigaci3n (Espa3a). M. Herranz-L3pez (2021- present).

Reviewer of Agencia Estatal de Investigaci3n (Espa3a). Vicente Micol (2007- present).

E. Barraji3n-Catal3n, M. Herranz, J.A. Encinar and V. Micol are members of the BRAIN center at UMH (<https://nsfbrain.org/faculty/>). The Building Reliable Advances and Innovation in Neurotechnology Center (BRAIN Center) is an industry/university collaborative interdisciplinary center founded by the Arizona State University and the University of Houston and financed by the National Science Foundation of USA.

Editorial Boards

Board member Molecules; E. Barraji3n-Catal3n (2019-present).

Guest and Collection Editors for different special issues on "Marine Drugs", "Int. J. Mol. Sci.", "Antioxidants", "Medicines" and "Frontiers in nutrition" in the last 5

years. E. Barraji3n-Catal3n, M. Herranz-L3pez, Vicente Micol (2019-present).

Group name: INDUSTRIAL DEVELOPMENTS FOR HEALTH INGREDIENTS

In order to cover the basic activities in the field of biotechnology, it is possible to define a biotechnology product as a good or service, the development of which requires the use of one or more biotechnology techniques. On the other hand, into the specific area of "industrial biotechnology" it is convenient to highlight that scientific and technological complexity are also inherent to biotechnology and consequently, it should be understood that interfaces and overlaps among other techniques.

The main lines in that area are:

1. Optimization of industrial processes for functional beverages production and waste management for nutraceutical ingredients with a bio economy perspective.
2. Semi-industrial scale production of nutraceuticals from plants, herbs or by-products.
3. Identification & Purification of bioactive molecules from waste management, and small-scale production herein for agricultural biological pest control.
4. Identification, isolation, culture development and pilot plant scale production of microorganism for agriculture and feedstock.
5. Development of new nutritional products from fermentation processes.

The IDiBE Pilot Extraction Biotech Platform's is created for research, development and technology transfer to companies focused in Food, Pharmacy and Biotech business. The PEB plant is able to offer knowledge of high technological value and to give support to the industries in the life, health and agro food science areas. The know-how is directly transformed into a pipeline of products, processes, services and technological strategies that provide to the industries competitive and highly specialized products.

The PEB plant has complementary services for the companies, customer and the general market, such as; formulation of new food, beverage and nutraceutical ingredient development, technological analysis of bioactive compounds, technical consultancy and specialised training for employers.

The mission of PEB is generating technological strategies and solutions with high industrial value according with Bioeconomy Strategy of EU 2018. The objective is modernisation and strengthening of the industrial biotech base through the creation of new value chains and more cost-effective industrial processes.

The main activities of PEB platform in collaboration with consolidated companies in this business model are:

- h. Quality control or development of new biotech products and process
- i. Design, optimisation and industrial scale up of biotechnology process
- j. Extraction, Purification and characterization of bioactive compounds produced through green technologies

Staff

Nuria Mart3 Bru3a

Domingo Saura L3pez

Manuel Valero Roche

Maria Concepci3n Mart3nez Madrid

External collaborators integrated in the group

Prof. Dr. Francisco Martin Bermudo. UNIVERSIDAD PABLO OLAVIDE (Sevilla).

Prof. Dra. Madalina Neascu. Gut Health Theme, Rowett Institute, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen.

Prof. Dra. Farah Hosseinian. Department of Chemistry, CARLETON UNIVERSITY.

Ph. D Students

Julio Salazar Bermeo

Bryan Moreno Chamba

Publications

Gea-Botella S, Agulló L, Martí N, Martínez-Madrid MC, Lizama V, Martín-Bermudo F, Berná G, Saura D, Valero M. Carotenoids from persimmon juice processing. *Food Research International*, 2021, 141, 109882. DOI: <https://doi.org/10.1016/j.foodres.2020.109882>

Gea-Botella S, Moreno-Chamba B, de la Casa L, Salazar-Bermeo J, Martí N, Martínez-Madrid MC, Valero M, Saura D. Carotenoids from Persimmon (*Diospyros kaki* Thunb.) Byproducts Exert Photoprotective, Antioxidative and Microbial Anti-Adhesive Effects on HaCaT. *Pharmaceutics*, 2021, 13(11), 1898. DOI: <https://doi.org/10.3390/pharmaceutics13111898>

Salazar-Bermeo J, Moreno-Chamba B, Martínez-Madrid MC, Saura D, Valero M, Martí N. Potential of Persimmon Dietary Fiber Obtained from Byproducts as Antioxidant, Prebiotic and Modulating Agent of the Intestinal Epithelial Barrier Function. *Antioxidants*, 2021, 10(11), 1668. DOI: <https://doi.org/10.3390/antiox10111668>

Patents

Inventores: Saura D, Barraón-Catalán E, Martí N, Martínez R, Micol V, Valero M, Vegara Gomez S. Título: Contrato de licencia de patente 201300578 "Combinación sinérgica de flavonoides y vitamina C". Titular: MITRA SOL TECHNOLOGIES SL. Fecha inicio: 13/05/2016. Fecha fin: 12/05/2033. Referencia patente: 201300578.

Inventores: Saura D, Barraón-Catalán E, Rodríguez Díaz JC, Tomás Menor L, Martí N, Micol V. Título: Contrato de licencia de patente 201301181 "Preparado hecho a base de una combinación sinérgica de polifenoles con actividad antibiótica".

Titular: MITRA SOL TECHNOLOGIES SL. Fecha inicio: 13/05/2016. Fecha fin: 12/05/2033. Referencia patente: 201301181.

Inventores: Saura D, Barraón-Catalán E, Martí N, Martínez R, Micol V, Valero M, Vegara Gomez S. Título: Contrato de licencia de patente 201301183 "Método de producción de pectina modificada de cítricos". Titular: MITRA SOL TECHNOLOGIES SL. Fecha inicio: 13/05/2016. Fecha fin: 12/05/2033. Referencia patente: 201301183.

Inventores: Saura D, Martí N, Micol V, Valero M. Título: Contrato de licencia patente 201500423. Titular: MITRA SOL TECHNOLOGIES SL. Fecha inicio: 27/03/2013. Fecha fin: 05/06/2035. Referencia patente: 201500423.

Inventores: Saura D, Berenguer Martínez MDR, Martí N, Micol V, Valero M, Vegara Gomez S. Título: Contrato de licencia 201200830 "Equipo de expansión instantánea a vacío y ultrasonidos". Titular: MITRA SOL TECHNOLOGIES SL. Fecha inicio: 13/05/2016. Fecha fin: 12/05/2032. Referencia patente: 201200830.

Number of Congress Communications

International contributions: 3

Poster presentations: 1

Oral presentations: 2

Private Funding

Contrato para la realización del proyecto "Caracterización y aprovechamiento de subproductos de la producción industrial de licores a partir de limón (*Citrus Limon* L.). Proyectos I+D solicitados por terceros. Duración: 28/07/2021 – 27/04/2022. IPs: Nuria Martí.

Editorial Boards

Board member Antioxidants.

Board member Food Microbiology.

Chronic inflammation & pain

Group name: **Sensory Neurobiology**

CHRONIC INFLAMMATION, PAIN AND PRURITUS. Understanding sensory neural signaling.

This subline is centered in understanding the mechanisms underlying the pro-algesic sensitization of sensory neurons as well as their desensitization upon resolution of injury or diseases. Our hypothesis considers that chronification results from a lack or defective resolution of neural sensitization. We are focused in three pathologies: (i) chronic migraine as a paradigm of chronic inflammatory pain that additionally shows a strong sex dimorphism; (ii) chemotherapy induced peripheral neuropathy as a model of neuropathic pain syndrome; and, (iii) psoriatic pruritus as a model of chronic itch. The common aspect of these three conditions is the involvement of the peripheral sensory system that is sensitized by increasing its electrogenic activity. We focus on the role of ion channels involved in the generation of action potentials and in their propagation, i.e. thermoTRP channels, Na, Kv and HCN channels. Furthermore, we investigate how the activity of these channels is affected by pro-algesic agents. The aim of these studies is to validate therapeutic targets that are subsequently used in our drug discovery program to identify and develop drug candidates that restore channel activity and the neural sensitivity.

DESIGN OF BIOACTIVE MOLECULES.

Discovery of drug candidates for nociceptive precision therapy. The identification and design of bioactive molecules for different applications (anti-inflammatory, analgesic and anti-pruritus) is first based on a computational strategy using molecular modeling, docking and dynamics on the validated therapeutic targets. In addition, *in silico* screening is also applied to virtual libraries composed of thousands to millions of molecules from natural and synthetic sources. Hit compounds are validated in HTS assays, and lead compounds pharmacologically characterized *in vitro* and *in vivo*. Selected drug candidates are licensed out to biotech companies for pre-clinical and clinical development.

Staff

Antonio Ferrer Montiel

Gregorio Fernández Ballester

Asia Fernández Carvajal

Postdoctoral Researchers

David Cabañero

External collaborators integrated in the group

Rosario Gonzalez-Muñiz. Instituto de Química Médica (IQM-CSIC).

Ph. D Students

Jorge de Andrés López

David Alarcón Alarcón

Simona Giorgi

Laura Butrón García

Eva María Villalba Riquelme

Alicia Medina Peris

Angela Lamberti

Technicians

José Manuel Serrano García

Gema Osuna Tenorio

Irene Mudarra Fraguas

Publications

Nikolaeva-Koleva M, Butron L, González-Rodríguez S, Devesa I, Valente P, Serafini M, Genazzani AA, Pirali T, Fernández-Ballester G, Fernández-Carvajal A, Ferrer-Montiel A. A capsaicinoid-based soft drug, AG1529, for attenuating TRPV1-mediated histaminergic and inflammatory sensory neuron excitability. *Scientific Reports*. 2021, 11(1):246. Doi: <https://pubmed.ncbi.nlm.nih.gov/33420359/>

Bonache MA, Llabrés PJ, Martín-Escura C, De la Torre-Martínez R, Medina-Peris A, Butrón L, Gómez-Monterrey I, Roa AM, Fernández-Ballester G, Ferrer-Montiel A, Fernández-Carvajal A, González-Muñiz R. Phenylalanine-Derived β -Lactam TRPM8 Modulators. Configuration Effect on the Antagonist Activity. *International Journal of Molecular Sciences*. 2021, 22(5), 2370. <https://doi.org/10.3390/ijms22052370>

Alberola-Die A, Encinar JA, Cobo R, Fernández-Ballester G, González-Ros JM,

Ivorra I, Morales A. Peimine, an Anti-Inflammatory Compound from Chinese Herbal Extracts, Modulates Muscle-Type Nicotinic Receptors. *International Journal of Molecular Sciences*. 2021, 22, 11287. <https://doi.org/10.3390/ijms222011287>

Blair Journigan V, Alarcon Alarcon D, Feng Z, Wang Y, Liang T, Dawley D, Ruhul Amin ARM, Montano C, Van Horn W, Xie XQ, Ferrer-Montiel A, Fernández-Carvajal A. Structural and in vitro functional characterization of a menthyl TRPM8 antagonist indicates species-dependent regulation. *ACS Medicinal Chemistry Letters*. 2021, 12(5):758-767. DOI: 10.1021/acsmchemlett.1c00001

Butrón D, Zamora H, Devesa I, Treviño MA, Abian O, Velázquez-Campoy A, Bonache MA, Lagartera L, Martín-Martínez M, González-Rodríguez S, Baamonde A, Fernández-Carvajal A, Ferrer-Montiel AV, Jiménez MA, Gonzalez-Muñiz R. DD04107-Derived neuronal exocytosis inhibitor peptides: evidences for synaptotagmin-1 as a putative target. *Bioorganic Chemistry*. 2021, 115. doi: 10.1016/j.bioorg.2021.105231

Mira A, Rubio-Camacho M, Alarcón D, Rodríguez-Cañas E, Fernández-Carvajal A, Falco A, Mallavia R. L-Menthol-loadable electrospun fibers of PMVEMA anhydride for topical administration. *Pharmaceutics*. 2021, 13, 1845. doi.org/10.3390/pharmaceutics13111845

Cabañero D, Ramírez-López A, Drews E, Schmöle A, Otte DM, Wawrzczak-Bargiela A, Huerga Encabo H, Kummer S, Ferrer-Montiel A, Przewlocki R, Zimmer A, Maldonado R. Protective role of neuronal and lymphoid cannabinoid CB2 receptors in neuropathic pain. *Elife*. 2020, Jul 20;9:e55582. doi: 10.7554/eLife.55582.

González-Gil I, Zian D, Vázquez-Villa H, Hernández-Torres G, Martínez RF, Khair-Fernández N, Rivera R, Kihara Y, Devesa I, Mathivanan S, Del Valle CR, Zambrana-Infantes E, Puigdomenech M, Cincilla G, Sanchez-Martinez M, Rodríguez de Fonseca F, Ferrer-Montiel AV, Chun J, López-Vales R, López-Rodríguez ML, Ortega-Gutiérrez S. A Novel Agonist of the Type 1 Lysophosphatidic Acid Receptor (LPA1), UCM-05194, Shows Efficacy in Neuropathic Pain Amelioration. *J Med*

Chem. 2020 Mar 12;63(5):2372-2390. <https://doi.org/10.1021/acs.jmedchem.9b01287>

Cobo R, Nikolaeva-Koleva M, Alberola-Die A, Fernández-Ballester G, González-Ros JM, Ivorra I, Morales A. Mechanisms of blockade of the muscle-type nicotinic receptor by benzocaine, a permanently uncharged local anesthetic. *Neuroscience*. 2020, Jul 15;439:62-79. doi: 10.1016/j.neuroscience.2019.05.043

Creation of Spin-Off Firms

ANTALGENICS (2015-actualidad).

PROSPERA BIOTECH (2014-actualidad).

FASTBASE SOLUTIONS (2015-actualidad).

Patents

Peptides having inhibitory activity of neuronal exocytosis. MA52869 (A) (21/04/2021). A. Ferrer, G. Fernández.

Peptides having inhibitory activity on muscarinic receptor M3. MA52870 (A) (21/04/2021). A. Ferrer, G. Fernández.

TRPV1 modulator compounds. ZA201907406 (B) (27/01/2021). A. Ferrer, A. Fernández

Cosmetic and/or pharmaceutical composition containing a bacterial extracellular product from *Pseudoalteromonas antarctica*, and use thereof. ES2814552 (T3). A. Ferrer

Ferment extract of a bacterial strain for the increase of adiponectin levels. ES2821813(T3). A. Ferrer.

Compound useful in the treatment and/or care of the skin, hair and/or mucous membrane and their cosmetic or pharmaceutical compositions. ES2869180 (T3). A. Ferrer

Therapeutic pharmaceutical composition for treatment of dry eyes. JP2021107422 (A) (29/07/2021). A. Ferrer, A. Fernández.

Peptides used in the treatment and/or care of the skin, mucous membrane and hair and its use in cosmetics or pharmaceutical compositions. BR112012009264 (A2). A. Ferrer

PhD Theses

Title: Design and functional validation of pain modulators: crosstalk between TRAAK and TRPV1. Student: Magdalena Nikolaeva Koleva. Advisor: Gregorio Fernández Ballester. 17/12/2021.

Organization of Meetings

Participation in Scientific Committees:

International Workshop on Chronic Pain & Itch: Mechanisms and Circuits. San Juan de Alicante (Spain) 20-22 October 2021. Asia Fernández.

Invited Talks and Courses

Programa Conoce Fundación UMH. Antonio Ferrer.

20th FEBS Young Scientists' Forum by inspiring scientists. Antonio Ferrer.

Science Dissemination: Outreach Activities

Ciencia con Tapas. Monthly outreach activity of IDiBE.

El picor: la alerta de nuestras neuronas y cómo combatirlo. 14 dic 2021 Ciencia con Tapas. Asia Fernández.

Avances en ciencia y tecnología: Fomento del espíritu emprendedor en el aula. Junio 2021. Asia Fernández.

XIII Jornadas de San Alberto. Facultad de Ciencias Experimentales. UMH. 10 noviembre 2021.

Number of Congress Communications

National contributions: 4

Poster presentations: 4

International contributions: 15

Oral presentations: 5

Poster presentations: 10

Awards

Premio al talento docente 2021 Gregorio Fernández.

Governmental Projects and Funding

Modelos preclínicos in vitro de organoides invados con nociceptores humanos para rastrear y validar candidatos a fármacos (OPERETTA). CONSELLERIA DE

INNOVACION, UNIVERSIDADES, CIENCIA Y SOCIEDAD DIGITAL (IDIFEDER/2020/022). 2020-2021. IP: Antonio Ferrer.

Un modelo pre-clínico in vitro de nociceptores humanos para investigar el dimorfismo sexual en migraña crónica y rastrear candidatos a fármacos (HEADACHE). Agencia Estatal de Investigación. RTI2018-097189-B-C21. 2019-2021. IPs: Antonio Ferrer Montiel y Asia Fernández Carvajal.

Unidad preclínica para cuantificar interacciones moleculares para optimizar candidatos a fármacos. GENERALITAT VALENCIANA. IDIFEDER/2021/036. 2021-2022. IP: Antonio Ferrer.

Neuropatía por quimioterapia: fisiopatología, dimorfismo sexual e intervención terapéutica. ChemoTheRapy-Induced neuropathy: pathophysiology, sex dimorphism and therapeutic intervention (TRILOGY). Generalitat Valenciana, Conselleria d'Innovació, Universitats, Ciència i Societat Digital. Programa Prometeo para grupos de investigación de excelencia – PROMETEO 2021. PROMETEO/2021/031. 2021-2024. IP: Antonio Ferrer-Montiel y Ana Gomis García.

Validación y desarrollo pre-clínico de nuevos tratamientos para el dolor artrítico. Proyecto Retos Colaboración del Programa Estatal de Investigación, Desarrollo e Innovación Orientada a los Retos de la Sociedad (RTC-2017-6507-1). 2018-2021. IP: Antonio Ferrer Montiel.

Nanoparticle-based imaging and therapy of chronic pain in the dorsal root ganglion (PIANO). Horizon 2020-MSCA training Network (Ref. nº 859938). 2021-2024. IP: Antonio Ferrer.

Sistema de imagen molecular por citometría de masas. AEI-MICIN. Programa adquisición de infraestructuras (EQC2021-007485-P). IP: Antonio Ferrer.

Private funding: R&D Contracts

AntalGenics. Contrato de licencia de patente "Compuestos antagonistas del receptor TRPM8 y sus aplicaciones. Antonio Ferrer y Asia Fernández.

BCN Peptides. Evaluación pre-clínica del compuesto Parentide para dolor artrítico. Antonio Ferrer.

Private funding: Technical Services and Assistance

AntalGenics SL. Supervisión científica desarrollo inhibidores PLC. Antonio Ferrer.

Fundación KERTOR. SAP Cancer Innova Program. Antonio Ferrer.

(899-21) Evaluación Contenido y Ejecución con ex ante previo como Experto Técnico del ejercicio fiscal 2020 proyecto 933.168- "nueva síntesis química de fármaco oncológico de alta efectividad para enfermedades hematológicas" EQA CERTIFICADOS I+D+I SLU. Asia Fernández.

R&D and Educational Committees

Máster: The European Master in Translational Cosmetic and Dermatological Sciences (EMOTION). An Erasmus Mundus Master. Coordinadora: Asia Fernández.

Programa de Doctorado en Biología Molecular y celular del IDiBE Coordinadora: Asia Fernández.

Master EMOTION, coordinador Comité Científico Asesor. Antonio Ferrer.

Center of Therapeutic Innovation. Universidad de Bath. Comité Científico Asesor. A. Ferrer.

R&D Management

Coordinador de la subárea de Herramientas diagnósticas, pronósticas y terapéuticas del área de Biomedicina en la Agencia Estatal de Investigación. Antonio Ferrer Montiel.

Antiviral Strategies

Group name: ANTIVIRAL AND ANTIMICROBIAL STRATEGIES

We are carrying out research on Viral Diseases of Fish with impact on Aquaculture. Our interest is focused on the fish immune response and related topics such as viral interference, immunostimulants, vaccines and antiviral drugs. The study models are zebrafish infections with spring viremia of carp virus

Scientific Society Councils

Sociedad de Biofísica de España. Ex – presidente: Antonio Ferrer Montiel.

Representante Español IUPAB - Antonio Ferrer.

Sociedad Española de Bioquímica y Biología Molecular. Antonio Ferrer.

Red Española de Canales Iónicos. Coordinador: Antonio Ferrer Montiel.

Editorial Boards

Revista de la SEBBM (2021). Antonio Ferrer (Editor jefe).

Journal of Pharmacological Sciences (2021). A. Ferrer Montiel.

The Open Journal of Pain (2021). A. Ferrer Montiel.

Frontiers in Pharmacology (2021). A. Ferrer Montiel.

Frontiers in Neurosciences (2021). A. Ferrer Montiel.

Journal of Neurosciences (2021). A. Ferrer Montiel.

International Journal Molecular Science (2021). Antonio Ferrer.

Scientific Reports (2014-2021). A. Fernandez-Carvajal

Frontiers in Physiology (2015-2021). A. Fernandez-Carvajal.

IJMS (2020-now) Asia Fernández.

UMH editorial board A. Fernandez-Carvajal.

(SVCV) and rainbow trout infections with viral hemorrhagic septicemia virus (VHSV) and infectious pancreatic necrosis virus (IPNV). Our research efforts are intended to answer questions about what genes are the major responders after viral challenge, and which ones lead to protection against disease.

In year 2021, to promote collaboration FISABIO-UMH a joint research project with Dr. Miguel Saceda (IDiBE-FISABIO) to investigate the response of virus-infected cells to antitumoral treatments was initiated.

Staff

Luis Pérez García-Estañ

María del Mar Ortega-Villaizán

Ph. D Students

María E. Salvador Mira

Technicians

Efrén Lucas Mañogil

Publications

Chico V, Salvador-Mira ME, Nombela I, Puente-Marin S, Perez L, Mercado L, Ortega-Villaizan MM. Antiviral Function of NKEF against VHSV in Rainbow Trout. *Biology* 2021, 10(10), 1045; <https://doi.org/10.3390/biology10101045>

Salvador-Mira ME, Chico Gras V, Guzmán F, Roher N, Perez L, Ortega-Villaizan MM. Immunomodulatory lectin peptides for fish erythrocytes-targeting as potential antiviral drug delivery platforms. *Int. J. Mol. Sci.* 2021. 22(21), 11821; <https://doi.org/10.3390/ijms222111821>

Science dissemination: outreach activities

TITULO: SARS-COV-2. MUTANTES, VARIANTES Y VACUNAS. LAS BUENAS Y LAS MALAS NOTICIAS.

Science Divulcation Conferences IDiBE – UMH. Ciclo de Conferencias Divulgativas Ciencia con Tapas (IDiBE – UMH). Elche,

Group name: VIRAL MEMBRANE PROTEINS

Study of the structure and interaction of virus-derived peptide libraries comprising the viral structural and non-structural proteins with model biomembranes, aiming to identify their molecular mechanism and biological function. Screening of peptide libraries to identify membranotropic determinants, characterize the interactions in structural terms, study the structure of the membranotropic segments, and make a

April 21st, 2021. Luis Perez and Antonio Martínez-Murcia.

<https://www.youtube.com/watch?v=FIZXALgUVhI>

Governmental Projects and Funding

Enhancing antiviral responses in fish: From rational design of prophylactics to in vivo responses. PROYECTOS DE I+D+I "RETOS DE LA SOCIEDAD" – Ministerio de Ciencia Innovación y Universidades. RTI2018 – 096957 –B-C22. IP: Luis Perez; Co-IP: María del Mar Ortega-Villaizán.

Contracte per la realització de una prova de valoració d'una vacuna anti VHSV modular administrada en la dieta dels peixos així com l'establiment de les condicions generals per les que es regirà la present prestació. IP: Ortega-Villaizan Romo, María Del Mar.

Evaluación del papel dual de la proteína inducida por interferón ifitm1 en la adquisición de quimiorresistencia en cáncer y en la invasividad viral. ifitm1 y SARS-CoV-2, SARCAVIR. Acciones Preparatorias Y Proyectos De Innovación Conjuntos Entre El Personal Investigador De La Universitat Miguel Hernández De Elche Y Profesionales De La Fundació Per Al Foment De La Investigació Sanitària Y Biomèdica De La Comunitat Valenciana. IPs: Luis Perez and Miguel Saceda.

R&D Management

Expert Evaluator for Agencia Estatal de Investigación, Spain (from oct 4th 2019). Luis Pérez García-Estañ.

detailed study of the interaction, modulation and structure of these peptide segments with membranes and living cells. Developing molecular dynamics bioinformatic tools to study the interaction of viral proteins with biomembranes to find new antivirals and therapeutic targets to develop new leading compounds useful for improved combined therapies.

Staff

José Villalaín Boullón

Governmental Projects and Funding

Zika y Dengue: Identificación de nuevos inhibidores enzimáticos combinando estrategias computacionales y

experimentales. Generalitat Valenciana - AICO/2020/026.

R&D Management

Reviewer of CONICET, Argentina (2011 - ...). J. Villalaín.

Reviewer of ISF (2013 - ...). J. Villalaín.

Group name: RED BLOOD CELLS IN ANTIVIRAL IMMUNOLOGY

Fish are the phylogenetically oldest vertebrate group with an immune system with clear similarities to the immune system of mammals. However, it is an actual matter of fact that the current knowledge of the fish immune system seems to lack the key piece to complete the puzzle.

In an attempt to solve this question, our group have demonstrated that rainbow trout RBCs can respond to viral infections by themselves with an innate immune response, by means of producing antiviral molecules and exerting a paracrine antiviral communication with other cells, and with a potential adaptive immune response, by means of antigen processing and presentation and complement system regulation. Apart from this, we also focus our investigation on the search of prophylactics or therapeutics to treat the major aquaculture viral infections.

Staff

María del Mar Ortega-Villaizán Romo

Postdoctoral Researchers

Verónica Chico Gras

Ph. D Students

Maria Elizabeth Salvador Mira

Celia García Quintanilla

Technicians

Efren Lucas Mañogil

Remedios Torres Montero

Publications

Salvador-Mira M, Chico V, Arostica M, Guzmán F, Roher N, Perez L, Ortega-Villaizán MDM. Immunomodulatory Lectin-like Peptides for Fish Erythrocytes-

Targeting as Potential Antiviral Drug Delivery Platforms. *Int J Mol Sci.* 2021 Oct 30;22(21):11821. doi: 10.3390/ijms222111821

Morales-Lange B, Nombela I, Ortega-Villaizán MDM, Imarai M, Schmitt P, Mercado L. Induction of foxp3 during the Crosstalk between Antigen Presenting Like-Cells MHCII+CD83+ and Splenocytes CD4+IgM- in Rainbow Trout. *Biology (Basel).* 2021 Apr 13;10(4):324. doi: 10.3390/biology10040324

Chico V, Salvador-Mira ME, Nombela I, Puente-Marin S, Perez L, Mercado L, Ortega-Villaizán MDM. Antiviral Function of NKEF against VHSV in Rainbow Trout. *Biology (Basel).* 2021 Oct 15;10(10):1045. doi: 10.3390/biology10101045

Klionsky DJ, Abdel-Aziz AK, Abdelfatah S, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)1. *Autophagy.* 2021;17(1):1-382. doi:10.1080/15548627.2020.1797280

Patents

IFIT5 para su uso como agente antiviral (P202031141).

Invited Talks and Courses

El papel de los eritrocitos nucleados de peces en inmunología antiviral. Ciclo de Seminarios del Instituto de Biología. Instituto de Biología. Facultad de Ciencias. Pontificia Universidad Católica de Valparaíso. 31/03/2021.

Science dissemination: outreach activities

Investigadoras en Biotecnología Sanitaria. Día Internacional de la Mujer y la Niña en

la Ciencia. Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche. Universidad Miguel Hernandez. 10/02/2021. María del Mar Ortega-Villaizán Romo.

Number of Congress Communications

Total contributions: 4

Governmental Projects and Funding

Proyectos RTI- AEI/MCIU 2018. ENHANCING ANTIVIRAL RESPONSES IN FISH: From rational design of prophylactics to in vivo responses. Proyectos RTI- AEI/MCIU 2018. Ministry of Science, Innovation and Universities. RTI2018-096957-B-C22. 2019-2021. IPs: Luis Perez, María del Mar Ortega-Villaizán.

REDFLAG - Salmonid red blood cells - sensors of stress and infection. Norwegian Research Council. NRC# 302551. IP: María K. Dahle. Investigadores: María del Mar Ortega-Villaizán.

Los eritrocitos nucleados de peces: ¿células somáticas o madre? Abriendo camino hacia nuevas soluciones antivirales en acuicultura. 2020-2021. EUR2020-112098. Acciones de Dinamización Europa Excelencia 2020. Programa Estatal de Generación de Conocimiento y Fortalecimiento Científico y Tecnológico del Sistema de I+D+i. IP: María del Mar Ortega-Villaizán.

Extractos naturales para aplicación como antivirales en acuicultura (NaturAcuiVir). GVA-THINKINAZUL/ 2021/020. Generalitat Valenciana. Estrategia Conjunta de Investigación e Innovación en Ciencias Marinas - Plan Complementario de I+D+i - Plan de Recuperación, Transformación y Resiliencia. IP: María del Mar Ortega-Villaizán.

Evaluación del papel dual de la proteína inducida por interferón ifitm1 en la

adquisición de quimiorresistencia en cáncer y en la invasividad viral. ifitm1 y sars-cov-2. ILISABIO/2020/A09. 20/A09. Universidad Miguel Hernandez de Elche. IP: Luis Perez Garcia-Estañ. Investigadores: María del Mar Ortega-Villaizán

Private funding: Technical Services and Assistance

Contrato para la realización del trabajo "Determinación de la actividad viricida de materiales". INESCOPI.21T. 10/02/2021-09/04/2021.

Realització de una prova de valoració d'una vacuna anti-VHSV modular administrada en la dieta dels peixos. Fundacion Bosch i Gimpera. FUNDBOSCHGIMPERA1.22D. 31/12/2021 - 30/04/2022.

Private funding: Technical Services and Assistance

Ensayo para testar la actividad viricida de revestimientos de grafeno en la que se testaran dos concentraciones de grafeno y un material control. 1168/20. Prestación de Servicio. 17/12/2020- 09/03/2021.

Ensayo para testar la actividad viricida de 3 materiales EVA con viricida y un material control (sin viricida). Prestación de Servicio. 0353/21. 25/03/2021- 04/05/2021.

R&D Management

Expert Evaluator for Agencia Estatal de Investigación, Spain (2019-ongoing. María del Mar Ortega-Villaizán).

Editorial Boards

Editorial Board member of PLOS One (2019- ongoing).

Editorial Board member of Frontiers in Immunology (2018- ongoing).

Editorial Board member of Vaccines (2020- ongoing).

Editor in Intechopen (2020-ongoing).

Molecular and Cellular Oncology

Group name: **MOLECULAR ONCOLOGY**

The main objective of our research group is the identification of new therapeutical approaches for the treatment of different types of cancers highly resistant to conventional chemotherapy.

Glioblastomas are very resistant to either chemotherapy and radiotherapy. Since it is known that PDGFR and IGF-1R pathways are important in glioblastoma, we have evaluated the effect of PDGFR and IGF-1R inhibitors on cell cycle and cell death in glioblastoma cell lines as well in primary cultures derived from patients affected with this type of tumour. Inhibition of these signal transduction pathways could become a putative alternative therapeutical strategy for glioblastoma treatment.

We have also study the role of SOCS1 and SOCS3 genes in the radiotherapy response in glioblastoma, since both genes have been associated with tumor progression in different types of cancer.

Nanotechnology appears as a promising tool for cancer treatment, allowing a better delivery of the drug and increasing specificity. In our laboratory we have been used enzymatic therapy with the D-amino acid oxidase (DAAO from *Rhodotorula gracilis* for the treatment of cancer. One of the main advantages of this approach is that the enzyme substrate is a D-aminoacid, not present endogenously, allowing a simple regulation of the enzymatic activity. DAAO has been immobilized on magnetic nanoparticles. The effect of this experimental approach has been tested on cells from colon carcinoma, pancreatic adenocarcinoma and glioblastoma.

Staff

Miguel Saceda Sánchez

Camino de Juan Romero

Postdoctoral Researchers

M^a del Pilar García Morales

External collaborators integrated in the group

Dr. Victor Manuel Barbera Juan

Ph. D Students

Elizabeth Perez Valenciano

Salomé Araujo

Publications

Fuentes-Baile M, Pérez-Valenciano E, García-Morales P, de Juan Romero C, Bello-Gil D, Barberá VM, Rodríguez-Lescure A, Sanz JM, Alenda C, Saceda M. CLyfA-DAAO Chimeric Enzyme Bound to Magnetic Nanoparticles. A New Therapeutical Approach for Cancer Patients? *Int J Mol Sci.* 2021 Feb 2;22(3):1477. doi: 10.3390/ijms22031477

PhD Theses

Title: Combinación de una terapia enzimática con nanotecnología para el tratamiento del cáncer. Student: María Fuentes Baile. Supervisors: Miguel Saceda Sánchez. 15/09/2021.

Governmental Projects and Funding

Desarrollo de nuevas terapias y biomarcadores de utilidad para el diagnóstico y el tratamiento del glioblastoma multiforme. N^o of researchers: 4. Funding entity or bodies: FUNDACION PARA EL FOMENTO DE LA INVESTIGACION SANITARIA Y BIOMEDICA EN LA COMUNITAT VALENCIANA. Start-End date: 04/01/2021 - 31/12/2022. Total amount: 22.600 €. IP: Miguel Saceda Sánchez.

Evaluación del papel dual de la proteína inducida por interferon IFITM1 en la adquisición de quimiorresistencia en cáncer y en la invasividad viral. IFITM1 y Sars-cov-2. N^o of researchers: 5. Funding entity or bodies: FUNDACION PARA EL FOMENTO DE LA INVESTIGACION SANITARIA Y BIOMEDICA EN LA COMUNITAT VALENCIANA. Start-End date: 20/01/2021 - 20/01/2022. Total amount: 5.000 €. IP: Miguel Saceda Sánchez.

Editorial Boards

Board member Archives of Biochemistry and Biophysics (2010-2013).

Executive Editor Archives of Biochemistry and Biophysics (2013-...).

Diabetes & metabolic disorders

Group name: **DIABETES RESEARCH UNIT**

Diabetes mellitus is characterized by hyperglycaemia caused by an insulin deficiency. Its prevalence is rising, reaching 425 million people worldwide (www.idf.org). In Spain a 13.8% of adult population is diabetic and 3 of 10 people have problems with glucose metabolism (Soriguer et al, Diabetologia 2012). There are two main types of diabetes mellitus. Type 1 diabetes is caused by an autoimmune attack against β -cells, which is the cell type responsible for producing and releasing insulin, the only hormone in our organism able to decrease glucose. When the β -cell is destroyed, no more insulin is produced and, therefore, the patient depends on insulin injection. Between a 10 and 15% of diabetic persons are diagnosed as Type 1. About 80-85% of diabetics are diagnosed as Type 2, which occurs when peripheral tissues experience a decrease in insulin sensitivity or insulin resistance together with an incapacity of the β -cell to produce and secrete enough insulin to counteract such resistance. Then, hyperglycemia progresses because insulin secretion and β -cell mass are below a critical threshold.

The etiology of both diabetes types is different, but both forms are the result of genetic background and environmental factors interaction. Our research unit works to understand how different environmental factors such as high fat diet, aging and endocrine disrupting chemicals work to increase diabetes susceptibility.

We work on four different research lines:

1- The role that endocrine disrupting chemicals (EDCs) in the etiology of Diabetes. We study how exposure to EDCs at different times during life, from pregnancy to adulthood, affects insulin sensitivity as well as the function of the endocrine pancreas. We address this problem by investigating in mice how these chemicals change the expression of genes related to β -cell function, death and division, during fetal development as well as during adulthood. We combine in vivo research with ex vivo and in vitro approaches to molecularly understand

how EDCs alter β -cell function, division and death.

This should give light to the hormone receptors involved as well as the molecular pathways used and end-points affected by EDCs exposure, which will help to establish harmonizing testing protocols to identify EDCs with diabetogenic effects.

The results of this research line in the last two decades have been seminal to establish the link between EDC exposure and diabetes mellitus.

2. The physiological role of estrogen receptors ER α , ER β and GPER1 in the islet of Langerhans. Using molecular biology and electrophysiology, we study how estrogens influence the plasticity of the endocrine pancreas during the adaptation to pregnancy and obesity. This will help us to better understand sex differences in glucose regulation and the development of new chemicals that should help to establish gender-based therapeutic for diabetes.

3. Discovery of new targets for the treatment of type 1 and type 2 diabetes based on pancreatic alpha-cell strategies to survive proinflammatory and metabolic stresses. Using a combination of bioinformatics and molecular biology approaches, our aim is to identify genes and signalling pathways that allow pancreatic alpha-cells to survive under different stresses related to the onset and progression of T1D (e.g. proinflammatory cytokines) and T2D (e.g. palmitate). The results of this project will provide a better understanding of the mechanisms underlying the survival of endocrine pancreatic cells upon proinflammatory and metabolic stresses. This may open the door to the development of new therapeutic strategies aimed to preventing the loss of beta cell mass observed in the early stages of these diseases.

4. Maternal metabolic adaptations during pregnancy: implications for the development of gestational diabetes mellitus. Gestational diabetes mellitus

(GDM) is the most common metabolic disorder of pregnancy. In addition to the transient maternal hyperglycaemia during pregnancy, GDM predisposes the mother and the offspring for increased risk of developing T2D and obesity. Using animal and in vitro models we aim to understand the molecular basis of this disease and to identify altered signaling pathways leading to the development of GDM. We also aim to explore potential therapeutic tools which may present beneficial effects in the prevention and control of GDM.

Staff

Ángel Nadal Navajas

Iván Quesada Moll

Cristina Ripoll Orts

Esther Fuentes Marhuenda

Paloma Alonso Magdalena

Laura Marroquí Esclapez

Postdoctoral Researchers

Eva Tudurí López

Hilda Ferrero Hidalgo

Ruba Al Abdulla

Reinaldo Sousa dos Santos

Regla María Medina Gali

Talía Boronat Belda

External collaborators (Universidad de Alicante)

Juan Martínez-Pinna

Sergi Soriano Úbeda

Ph. D Students

Ignacio Babiloni Chust

Atenea Alexandra Pérez Serna

Roberto Sempere Navarro

Technicians

María Luisa Navarro García

María Salomé Ramón Penalva

Beatriz Bonmatí Botella

Publications

Marroquí L, Martínez-Pinna J, Castellano-Muñoz M, Dos Santos RS, Medina-Gali RM, Soriano S, Quesada I, Gustafsson JA, Encinar JA, Nadal A. Bisphenol-S and Bisphenol-F alter mouse pancreatic β -cell ion channel expression and activity and insulin release through an estrogen receptor ER β mediated pathway. *Chemosphere*. 2021 Feb;265:129051. doi: 10.1016/j.chemosphere.2020.129051

Marroquí L, Perez-Serna AA, Babiloni-Chust I, Dos Santos RS. Type I interferons as key players in pancreatic β -cell dysfunction in type 1 diabetes. *Int Rev Cell Mol Biol*. 2021;359:1-80. doi: 10.1016/bs.ircmb.2021.02.011

García-Arévalo M, Lorza-Gil E, Cardoso L, Batista TM, Araujo TR, Ramos LAF, Areas MA, Nadal A, Carneiro EM, Davel AP. Ventricular Fibrosis and Coronary Remodeling Following Short-Term Exposure of Healthy and Malnourished Mice to Bisphenol A. *Front Physiol*. 2021 Apr 12;12:638506. doi: 10.3389/fphys.2021.638506

Sala E, Vived C, Luna J, Saavedra-Ávila NA, Sengupta U, Castaño AR, Villar-Pazos S, Haba L, Verdaguer J, Ropero AB, Stratmann T, Pizarro J, Vázquez-Carrera M, Nadal A, Lahti JM, Mora C. CDK11 Promotes Cytokine-Induced Apoptosis in Pancreatic Beta Cells Independently of Glucose Concentration and Is Regulated by Inflammation in the NOD Mouse Model. *Front Immunol*. 2021 Feb 10;12:634797. doi: 10.3389/fimmu.2021.634797

Gil-Rivera M, Medina-Gali RM, Martínez-Pinna J, Soriano S. Physiology of pancreatic β -cells: Ion channels and molecular mechanisms implicated in stimulus-secretion coupling. *Int Rev Cell Mol Biol*. 2021;359:287-323. doi: 10.1016/bs.ircmb.2021.02.006

PhD Theses

Title: Papel del receptor de estrógenos β en los efectos de la exposición prenatal al bisfenol-A en la célula β pancreática. Student: Talía Boronat Belda. Advisors: Ángel Nadal y Paloma Alonso Magdalena. 13/04/2021.

Organization of meetings

I JORNADA DE JOVENES INVESTIGADORES DEL IDIBE. 27/07/2021. Miembro del Comité Organizador: Paloma Alonso-Magdalena.

23rd EUROPEAN CONGRESS ON ENDOCRINOLOGY/ECE2021. 22-25/05/2021. Moderadora de Sesiones Científicas: Paloma Alonso-Magdalena.

Jornadas SEJI: "What is going on in Diabetes research?", 2021, Laura Marroqui.

JORNADAS ADEC-UMH: INVESTIGACIÓN DIABETES. Elche 14/11/2021. Laura Marroqui.

Invited Talks and Courses

REUNION VIRTUAL GRUPO DE ISLOTES PANCREATICOS DE LA SED 2021. Endocrine disruptors and type 2 diabetes: OBERON, an integrated approach for hazard identification. 16/06/2021. Paloma Alonso-Magdalena.

Reunião Anual da Federação de Sociedades de Biologia Experimental (FeSBE). The pancreatic alpha-cell, glucagon and diabetes: old and new stories. Sao Paulo, Brasil (Congreso virtual), 2021. I. Quesada.

Current Topics in Biochemistry 2021. Pancreatic alpha-cells in diabetes and obesity: potential therapeutic approaches. Florianópolis, Brasil (Congreso virtual), 2021. I. Quesada.

II YOUNG INVESTIGATORS SYMPOSIUM CIBERDEM 2021. Identification of new therapeutic targets for the treatment of type 1 diabetes based on the survival strategies of pancreatic alpha cells. Virtual meeting, 2021, Laura Marroqui.

Credibility of scientific expertise and decision-making, ANSES Online International Symposium, organized by "Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail" (ANSES). The role of scientists in influencing public decisions and their interaction with policy makers, France, 2021. A. Nadal.

Webinar series: Current opportunities for better identification of endocrine disrupting chemicals at European level. Organized by The Member of the European Parliament Maria Arena. New hazard classes for endocrine disruptors in CLP, Belgium 2021. A. Nadal.

Science Dissemination: Outreach Activities

Laura Marroqui, Participation in the radio podcast program "La ciencia que viene", Radio UMH. (2021).

CHARLA COLOQUIO "INVESTIGADORAS EN BIOTECNOLOGIA SANITARIA". Día internacional de la mujer y la niña en la ciencia. 10/02/2021. Paloma Alonso-Magdalena.

JORNADAS ADEC-UMH: INVESTIGACIÓN DIABETES (Elche 14/11/2021):

- Promesas y realidades de las terapias para niños con diabetes tipo 1. Lo que la ciencia nos puede aportar. Laura Marroquí.

- Papel que tienen los receptores de estrógenos y los disruptores endocrinos en el desarrollo de la diabetes. Ángel Nadal.

- Diabetes durante el embarazo: buscando las causas. Paloma Alonso-Magdalena.

- Retos y logros de la juventud con diabetes tipo 1. Athenea Pérez Serna.

Asociación de diabéticos de Elche y Comarca. Papel que tienen los receptores de estrógenos y los disruptores endocrinos en el desarrollo de la diabetes. Día Mundial de la Diabetes, 14 Noviembre 2021. A. Nadal.

Number of Congress Communications

National contributions: 9

Oral presentations: 5

Poster presentations: 4

International contributions: 3

Oral presentations: 2

Poster presentations: 1

Governmental Projects and Funding

OBERON-An integrative strategy of testing systems for identification of EDs related to metabolic disorders. Proyecto del Programa Marco de la UE, European Commission. 2019-2023. IP. Paloma Alonso-Magdalena.

Papel de la señalización mediada por TGF β en las adaptaciones metabólicas maternas durante el embarazo: implicaciones para el desarrollo de la diabetes mellitus gestacional. Proyectos Plan Estatal PID 2020 (PID2020-113112RB-I00). 2021-2024. IP. Paloma Alonso-Magdalena.

Regulación de la viabilidad y de la función de las células β y α pancreáticas por los receptores de estrógenos ER β y GPER: papel en la terapia de la diabetes mellitus. Proyecto del Programa Prometeo de la GVA. IP: Ángel Nadal Navajas.

Beating Goliath: Generation Of Novel, Integrated and Internationally Harmonised Approaches for Testing Metabolism Disrupting Compounds. E Proyecto del Programa Marco de la UE, European Commission. IP: Ángel Nadal Navajas.

Efectos de la exposición simultánea a disruptores endocrinos y dieta rica en grasa sobre la célula beta pancreática e implicaciones en la diabetes mellitus de tipo 2. Plan Nacional de I+D+I. Ministerio de Ciencia e Innovación, Agencia Estatal de Investigación. IP: Angel Nadal Navajas.

Descubrimiento de nuevas dianas terapéuticas para el tratamiento de la diabetes tipo 1 y diabetes tipo 2 basadas en estrategias de supervivencia de las células alfa pancreáticas. Subvenciones a la excelencia científica de juniors investigadores-SEJI, Generalitat Valenciana IP: Laura Marroquí Esclapez.

Descifrando las respuestas inducidas por interferón-alfa de las células alfa y beta pancreáticas: una oportunidad para buscar nuevas dianas terapéuticas para la diabetes tipo 1. Agencia Estatal De Investigación (PID2020-117569RA-I00). 01/09/2021-31/08/2024. IP: Laura Marroquí Esclapez.

R&D Management

Grant Reviewer of FONDATION POUR LA RECHERCHE MEDICALE-FRM. Paloma Alonso-Magdalena

Abstract Reviewer 23rd EUROPEAN CONGRESS ON ENDOCRINOLOGY / ECE2021. Paloma Alonso-Magdalena

Reviewer for the following journals in 2021: Toxicological Sciences, International Review of Cell and Molecular Biology, JCI Insight, Journal of Nutritional Biochemistry, Environmental Pollution, Free Radical Biology and Medicine, Metabolism-Clinical and Experimental. Paloma Alonso-Magdalena.

Grant Reviewer Agence Nationale de la Recherche ANR, Francia, Ivan Quesada.

Grant Reviewer Fonds de la Recherche Scientifique FNRS, Bélgica, Ivan Quesada.

Grant Reviewer, Agencia Estatal de Investigación AEI, Ivan Quesada.

Evaluador Comunicaciones, XXXII Congreso de la Sociedad Española de Diabetes, Ivan Quesada.

Reviewer of Journals: Scientific Reports, AJP - Endocrinology and Metabolism. Ivan Quesada.

Jurados Ayudas a Proyectos de Investigación de la Sociedad Española de Diabetes SED. Ivan Quesada.

Comité Científico: Encuentros con Investigadores: "Investigación y Longevidad: buscando respuestas positivas para vidas longevas". Centro Internacional sobre el Envejecimiento (CENIE), Ivan Quesada.

Reviewer of Journals: "Archives of Biochemistry and Biophysics", "Genes", "PLOS ONE", "Frontiers in Physiology", "Chronobiology International", "Diabetes, Metabolic Syndrome and Obesity_ Targets and Therapy", "Scientific reports". Laura Marroquí.

Reviewer of Journals: Lancet Diabetes and Endocrinology, Nature Reviews of Endocrinology, eLife, Journal of Hazardous Materials, Chemosphere, Environmental Pollution, reproductive Toxicology, Scientific Reports, Journal of Physiology and Biochemistry. Angel Nadal.

Editorial Boards

Board member of Scientific Reports, Endocrine Connections and International Journal of Molecular Sciences. Paloma Alonso-Magdalen

Reviewing Editors Frontiers in Physiology: Laura Marroqui., Paloma Alonso-Magdalen

Editor Frontiers in Physiology. Ángel Nadal.

Editor Frontiers in Endocrinology. Ángel Nadal.

Editor Frontiers in Neuroscience. Ángel Nadal.

Clinical pharmacology

Group name: IMMUNOPHARMACOLOGY AND IMMUNO-ONCOLOGY

We develop translational research on immunopharmacology. Our research projects are mostly devoted to study the mechanism of action and the pharmacokinetic-pharmacodynamic relationship of drugs widely used in clinical practice in inflammatory diseases and cancer, especially in digestive diseases. In 2020, our studies were centered basically in:

1. Immunoregulatory effects of beta-blockers drugs in patients with cirrhosis in risk of development of hepatocellular carcinoma.
2. Role of inflammasome in the development of hepatocellular carcinoma.
3. Mechanism of action of antibiotics used to reduce bacterial translocation in patients with cirrhosis.
4. Pharmacokinetic-pharmacodynamic relationship of biological drugs used in inflammatory bowel diseases

Staff

Pedro Zapater Hernández

José Manuel González-Navajas

Ph. D Students

Susana Almenara de Riquer

Beatriz Lozano Ruiz

Ivan Herrera Marante

Beatriz Orts Jorquera

Cayetano Miralles Maciá

Amalia Tzoumpa

Huang Yin

Publications

Lozano-Ruiz B, Tzoumpa A, Martínez-Cardona C, Moreno D, Aransay AM, Cortazar AR, Picó J, Peiró G, Lozano J, Zapater P, Francés R, González-Navajas JM. Absent in melanoma 2 (AIM2) regulates the stability of regulatory T cells. *Int J Mol Sci.* 2022 Feb 17;23(4):2230. doi: 10.3390/ijms23042230

González-Navajas JM, Elkord E, Lee J. Editorial: CD4+ T cells in cancer immunotherapies. *Front Immunol.* 2021 Sep 6;12:737615. doi: 10.3389/fimmu.2021.737615

Lee J, Lozano-Ruiz B, Yang FM, Fan DD, Shen L, González-Navajas JM. The multifaceted role of Th1, Th9 and Th17 cells in immune checkpoint inhibition therapy. *Front Immunol.* 2021 Mar 12;12:625667. doi: 10.3389/fimmu.2021.625667

González-Navajas JM, Fan DD, Yang S, Yang FM, Lozano-Ruiz B, Lee J. The impact of Tregs on the anticancer immunity and the efficacy of immune checkpoint inhibitor therapies. *Front Immunol.* 2021 Feb 26;12:625783. doi: 10.3389/fimmu.2021.625783

Tuells J, Egoavil CM, Pena Pardo MA, Montagud AC, Montagud E, Caballero P, Zapater P, Puig-Barberá J, Hurtado-Sanchez JA. Seroprevalence Study and Cross-Sectional Survey on COVID-19 for a Plan to Reopen the University of Alicante (Spain). *Int J Environ Res Public Health.* 2021;18(4). doi:10.3390/ijerph18041908

Rodríguez-Laiz GP, Melgar P, Alcázar-López C, Franco-Campello M, Martínez-Adsuar F, Navarro-Martínez J, Gómez-Salinas L, Pascual S, Bello P, Carnicer F, Rodríguez-Soler M, Palazón JM, Mas-Serrano P, Almanza-López S, Jaime-Sánchez F, Perdiguero M, de Santiago C,

Lozano T, Irurzun J, Pérez E, Merino E, Zapater P, Lluís F. Enhanced recovery after low- and medium-risk liver transplantation. A single-center prospective observational cohort study. *Int J Surg.* 2021;85:46-54. doi:10.1016/j.ijssu.2020.12.003

Orts B, Gutierrez A, Madero L, Sempere L, Frances R, Zapater P. Clinical and Immunological Factors Associated with Recommended Trough Levels of Adalimumab and Infliximab in Patients with Crohn's Disease. *Front Pharmacol.* 2021;12:795272. doi:10.3389/fphar.2021.795272

Murcia O, Martínez-Roca A, Juárez M, Giner-Calabuig M, Alustiza M, Mira C, Mangas-Sanjuan C, Serrano E, Ruiz-Gómez FA, Baile-Maxia S, Medina L, Alenda C, Payá A, Rodríguez-Soler M, Zapater P, Jover R. Effects of Somatic Methylation in Colonic Polyps on Risk of Developing Metachronous Advanced Colorectal Lesions. *Cancers (Basel).* 2021;13(2). doi:10.3390/cancers13020246

Medina-Prado L, Mangas-Sanjuan C, Baile-Maxia S, Martínez-Roca A, Murcia O, Zarraquiños S, Rodríguez-Camacho E, Aginagalde AH, Álvarez-Urturi C, Valverde MJ, Zapater P, Bujanda L, Salas D, Portillo I, Pellisé M, Cubiella J, Jover R. Risk of Colorectal Cancer and Advanced Polyps One Year After Excision of High-Risk Adenomas. *Dis Colon Rectum.* Published online November 22, 2021. doi:10.1097/DCR.0000000000002068

Linares R, Fernández MF, Gutiérrez A, García-Villalba R, Suárez B, Zapater P, Martínez-Blázquez JA, Caparrós E, Tomás-Barberán FA, Francés R. Endocrine disruption in Crohn's disease: Bisphenol A enhances systemic inflammatory response in patients with gut barrier translocation of dysbiotic microbiota products. *FASEB J.* 2021;35(7):e21697. doi:10.1096/fj.202100481R

Bernabeu P, van-der Hofstadt C, Rodríguez-Marín J, Gutierrez A, Alonso MR, Zapater P, Jover R, Sempere L. Effectiveness of a Multicomponent Group Psychological Intervention Program in Patients with Inflammatory Bowel Disease: A Randomized Trial. *Int J Environ Res Public Health.* 2021;18(10). doi:10.3390/ijerph18105439

Governmental Projects and Funding

Effect of high salt intake in the development of hepatocellular carcinoma and the immunological profile of patients with compensated cirrhosis. 01/01/2020 – 31/12/2022 – PROYECTOS DE INVESTIGACIÓN EN SALUD – ACCIÓN ESTRATÉGICA EN SALUD 2019 (PI19/01554) – INSTITUTO DE SALUD CARLOS III. IP: José Manuel González Navajas.

The Salt-Th17 axis in tumor growth and response to immunotherapy. 01/01/2020 – 31/12/2023. PLAN GenT (CDEI-03/20-A) – CONSELLERIA DE SANITAT – GENERALITAT VALENCIANA. IP: José Manuel González Navajas.

The importance of IL-1RAP signalling in hepatocellular carcinoma. 19/05/2021 – SUBVENCIONES DEL PROGRAMA SANTIAGO GRISOLÍA – GENERALITAT VALENCIANA 2021 (GRISOLIAP/2021/083). ISABIAL. IP: José Manuel González Navajas.

R&D Management

Reviewer of Health Research Projects – Strategic Action in Health – Institute of Health Carlos III (JMGN).

Member of the Departmental Research Commission – General University Hospital of Alicante – ISABIAL (JMGN).

Reviewer 'ad hoc' for journals: *Theranostics* (IF: 11,56) and *Frontiers in Immunology* (IF: 7,56) (JMGN).

Reviewer of the National Agency for Evaluation and Prospective (ANEP) (PZH).

Reviewer of the Progress and Health Foundation, Andalusian Public Health System (PZH).

Member of the Departmental Research Commission – General University Hospital of Alicante – ISABIAL (PZH).

Member of the Research Ethics Committees of San Juan and Orihuela Hospitals (PZH).

Member of the Drug Research Ethics Committee of Elche Hospital (PZH).

Editorial Boards

Associate Editor – Frontiers in Immunology (JMGN) (2020-...).

Topic Editor – International Journal of Molecular Sciences (JMGN) (2020-...).

Group name: HEPATIC AND INTESTINAL IMMUNOBIOLOGY GROUP

Imhi lab's main line of research focuses on the immunobiology of bacterial translocation and inflammation in the gut-liver axis, with a multidisciplinary approach aimed at understanding the interaction between the microbiome and the Immune System and identifying new potentially useful targets in the recovery of homeostasis in advanced chronic liver disease and in inflammatory bowel disease.

Staff

Rubén Francés

Esther Caparrós

Isabel Gómez-Hurtado

External collaborators

Ana Gutiérrez

Pedro Zapater

Ph. D Students

Sebastián Martínez

Enrique Ángel

Raquel Linares

Publications

Linares R, Francés R, Gutiérrez A, Juanola O. Bacterial Translocation as Inflammatory Driver in Crohn's Disease. *Front Cell Dev Biol.* 2021 Sep 7;9:703310. doi: 10.3389/fcell.2021.703310. PMID: 34557484; PMCID: PMC8452966

Caparrós E, Wiest R, Scharl M, Rogler G, Gutiérrez Casbas A, Yilmaz B, Wawrzyniak M, Francés R. Dysbiotic microbiota interactions in Crohn's disease. *Gut Microbes.* 2021 Jan-Dec;13(1):1949096. doi: 10.1080/19490976.2021.1949096. PMID: 34313550; PMCID: PMC8320851

Lozano-Ruiz B, Tzoumpa A, Martínez-Cardona C, Moreno D, Aransay AM, Cortazar AR, Picó J, Peiró G, Lozano J, Zapater P, Francés R, González-Navajas JM. Absent in melanoma 2 (AIM2) regulates the stability of regulatory T cells.

Int J Mol Sci. 2022 Feb 17;23(4):2230. doi: 10.3390/ijms23042230

Orts B, Gutierrez A, Madero L, Sempere L, Frances R, Zapater P. Clinical and Immunological Factors Associated with Recommended Trough Levels of Adalimumab and Infliximab in Patients with Crohn's Disease. *Front Pharmacol.* 2021;12:795272. doi:10.3389/fphar.2021.795272

Linares R, Fernández MF, Gutiérrez A, García-Villalba R, Suárez B, Zapater P, Martínez-Blázquez JA, Caparrós E, Tomás-Barberán FA, Francés R. Endocrine disruption in Crohn's disease: Bisphenol A enhances systemic inflammatory response in patients with gut barrier translocation of dysbiotic microbiota products. *FASEB J.* 2021;35(7):e21697. doi:10.1096/fj.202100481R

Ampuero J, Aller R, Gallego-Durán R, Crespo J, Abad J, González-Rodríguez Á, Gómez-Camarero J, Caballería J, Lo Iacono O, Ibañez L, García-Samaniego J, Martín-Mateos R, Francés R, Fernández-Rodríguez C, Diago M, Soriano G, Andrade RJ, Latorre R, Jorquera F, Morillas RM, Escudero D, Estévez P, Hernández-Guerra M, Agustín S, Pareja-Megía MJ, Banales JM, Aspichueta P, Benlloch S, Rosales JM, Salmerón J, Turnes J, Romero-Gómez M; HEPAmet Registry. Definite and indeterminate nonalcoholic steatohepatitis share similar clinical features and prognosis: A longitudinal study of 1893 biopsy-proven nonalcoholic fatty liver disease subjects. *Liver Int.* 2021 Sep;41(9):2076-2086. doi: 10.1111/liv.14898. Epub 2021 May 7. PMID: 33896100.

Belinchón-Romero I, Bellot P, Romero-Pérez D, Herraiz-Romero I, Marco F, Frances R, Ramos-Rincón JM. Non-alcoholic fatty liver disease is associated with bacterial translocation and a higher inflammation response in psoriatic patients. *Sci Rep.* 2021 Apr 21;11(1):8593. doi: 10.1038/s41598-021-88043-8. PMID: 33883616; PMCID: PMC8060289.

Chaparro M, Garre A, Iborra M, Sierra-Ausín M, Barreiro-de Acosta M, Fernández-Clotet A, de Castro L, Boscá-Watts M, Casanova MJ, López-García A, Lorente R, Rodríguez C, Carbajo AY, Arroyo MT, Gutiérrez A, Hinojosa J, Martínez-Pérez T, Villoria A, Bermejo F, Busquets D, Camps B, Cañete F, Manceñido N, Monfort D, Navarro-Llavat M, Pérez-Calle JL, Ramos L, Rivero M, Angueira T, Camo Monterde P, Carpio D, García-de-la-Filia I, González-Muñoz C, Hernández L, Huguet JM, Morales VJ, Sicilia B, Vega P, Vera I, Zabana Y, Nos P, Suárez Álvarez P, Calviño-Suárez C, Ricart E, Hernández V, Mínguez M, Márquez L, Hervías Cruz D, Rubio Iturria S, Barrio J, Gargallo-Puyuelo C, Francés R, Hinojosa E, Del Moral M, Calvet X, Algaba A, Aldeguer X, Guardiola J, Mañosa M, Pajares R, Piqueras M, García-Bosch O, López Serrano P, Castro B, Lucendo AJ, Montoro M, Castro Ortiz E, Mesonero F, García-Planella E, Fuentes DA, Bort I, Delgado-Guillena P, Arias L, Iglesias A, Calvo M, Esteve M, Domènech E, Gisbert JP. Effectiveness and Safety of Ustekinumab in Ulcerative Colitis: Real-world Evidence from the ENEIDA Registry. *J Crohns Colitis*. 2021 Nov 8;15(11):1846-1851. doi: 10.1093/ecco-jcc/jjab070. PMID: 33860795; PMCID: PMC8083263.

Gil-Gómez A, Ampuero J, Rojas Á, Gallego-Durán R, Muñoz-Hernández R, Rico MC, Millán R, García-Lozano R, Francés R, Soriano G, Romero-Gómez M. Development and Validation of a Clinical-Genetic Risk Score to Predict Hepatic Encephalopathy in Patients With Liver Cirrhosis. *Am J Gastroenterol*. 2021 Jun 1;116(6):1238-1247. doi: 10.14309/ajg.0000000000001164. PMID: 33852451.

Gracia-Sancho J, Caparrós E, Fernández-Iglesias A, Francés R. Role of liver sinusoidal endothelial cells in liver diseases. *Nat Rev Gastroenterol Hepatol*. 2021 Jun;18(6):411-431. doi: 10.1038/s41575-020-00411-3. Epub 2021 Feb 15. PMID: 33589830.

López-Almela I, Romani-Pérez M, Bullich-Vilarrubias C, Benítez-Páez A, Gómez Del Pulgar EM, Francés R, Liebisch G, Sanz Y. *Bacteroides uniformis* combined with fiber amplifies metabolic and

immune benefits in obese mice. *Gut Microbes*. 2021 Jan-Dec;13(1):1-20. doi: 10.1080/19490976.2020.1865706. PMID: 33499721; PMCID: PMC8018257.

Invited Talks and Courses

Inmunidad y citocinas en EII. Congreso anual GETECCU, Madrid. 14/10/2021. Conferencia Invitada Nacional. Rubén Francés.

Factors influencing fibrosis: Microbiota. International workshop on liver and gut fibrosis, Valencia. 07/10/2021. Conferencia Invitada Internacional. Rubén Francés.

Patogenia de las manifestaciones extraintestinales inmunomediadas de la EII. Curso de Abordaje interdisciplinar de las manifestaciones extraintestinales asociadas a la Enfermedad Inflamatoria Intestinal, GETECCU, Madrid. 07/06/2021. Conferencia Invitada Nacional. Rubén Francés.

Papel del microbioma en las alteraciones inmunológicas e inflamatorias en el paciente con enfermedad hepática metabólica grasa. 3ª Reunión de Hepatología traslacional de AEEH. Alicante 22/10/2021. Conferencia Invitada Nacional. Esther Caparrós.

Number of Congress Communications

National contributions: 2

Poster presentations: 2

International contributions: 3

Poster presentations: 3

Awards

Premio Miguel Pérez-Mateo. Real Academia de Medicina y Ciencias Afines de la Comunidad Valenciana. Valencia, 2021. Esther Caparrós.

Governmental Projects and Funding

Función de LSECtin en la restricción de la transición desde la respuesta innata a la respuesta adaptativa patogénica por células T CD4+ en cirrosis. De 01/01/2020 hasta 31/12/2022. Agencia Estatal de

Investigación (PID2019-107036RB-I00). IP: Rubén Francés

Role of LSECtin in aging and the liver-brain axis in cirrhosis. De 01/01/2021 hasta 31/12/2024. Generalitat Valenciana - Conselleria de Innovación, Universidad y Ciencia (PROMETEO 2021/033). IP: Rubén Francés.

R&D and Educational Committees

Esther Caparrós. Coordinator of "Cátedra de Investigación en Cronicidad SEMERGEN UMH".

Group name: RECEPTORS AND MECHANISMS INVOLVED IN ANALGESIA

Our group is formed by professors of the University Miguel Hernández and physicians of the Department of Anaesthesia, Resuscitation and Pain Relief Therapy of the General University Hospital of Alicante. We develop translational and clinical research on pain therapy and anaesthesia. Present lines of research are:

1. Regarding translational research we are interested in the neurobiological basis of the variability in opiate actions in normal and pathological conditions, at molecular level.
2. The analgesic efficacy of radiofrequency for the relief of the Greater Trochanteric Pain Syndrome

R&D Management

Evaluador de la Agencia Estatal de investigación.

Evaluador para Agencias Internacionales de Investigación (Health Protection Office, UK; Swiss National Science Foundation; University of Brussels, Belgium; Health Research Board, Ireland; National Science Agency, Poland).

Editorial Boards

Associate Editor. Frontiers in Immunology (2020-...). Rubén Francés.

3. Ambispective comparative study of post operative cognitive dysfunction after anaesthesia using inhalatory anaesthetics in bariatric surgery

Staff

Juan José Ballesta Payá

Ph. D Students

Luis Gómez Salinas

Physicians from the General University Hospital of Alicante

Yolanda Sastre Peris

PhD THESES (2021)

Título: Compuestos antimicrobianos de origen natural: Una oportunidad para el tratamiento de enfermedades infecciosas resistentes a antibióticos

Autor: Francisco Javier Álvarez Martínez

Fecha de Lectura: 25/05/2021

Dirección: Vicente Micol Molina / Enrique Barraión Catalán

Dirección web: <https://doi.org/10.1038/s41598-020-80003-y>

Título: Cribado de extractos naturales a partir de subproductos de la industria frutícola para la obtención de nuevos principios activos con fines dermocosméticos

Autor: Luz María Agulló Chazarra

Fecha de Lectura: 25/06/2021

Dirección: María Herranz López / Enrique Barraión Catalán

Dirección web: <https://doi:10.3390/antiox9050418>

Título: Combinación de una terapia enzimática con nanotecnología para el tratamiento del cáncer

Autor: María Fuentes Baile

Fecha de Lectura: 15/09/2021

Dirección: Miguel Saceda Sánchez

Dirección web: <https://doi.org/10.3390/ijms22031477>

Título: Design and functional validation of pain modulators: crosstalk between TRAAK and TRPV1

Autor: Magdalena Nikolaeva Koleva

Fecha de Lectura: 17/12/2021

Dirección: Gregorio Fernández Ballester

Dirección web: <https://doi.org/10.1038/s41598-020-80725-z>

SEMINARS (2021)

Título: **TECNOLOGÍAS ELÉCTRICAS Y ULTRASÓNICAS PARA LA INTENSIFICACIÓN DE PROCESOS DE EXTRACCIÓN.**

Ponente / Institución: Jose V. García-Perez. Universitat Politècnica de València-Departamento de Tecnología de Alimentos.

Viernes, 15 de enero de 2021.

Título: **EL CAMINO DE EMPRENDER: DE LA CIENCIA A LA EMPRESA.**

Ponente / Institución: Marta de Vicente, Antares Consulting.

Viernes, 22 de enero de 2021.

Título: **APLICACIONES CORRELATIVAS DE LA CRITOTOMOGRAFÍA DE RAYOS X.**

Ponente / Institución: Ana Joaquina Pérez Berna, Sincrotrón ALBA.

Viernes, 12 de febrero de 2021.

Título: **NUCLEASAS CAS Y NEMATODOS EN LA CAJA DE HERRAMIENTAS PARA INVESTIGAR MUTACIONES HUMANAS.**

Ponente / Institución: Julián Cerón, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL).

Viernes, 26 de febrero de 2021.

Título: **FISIOLOGÍA MOLECULAR DE LA TRANSDUCCIÓN TÉRMICA Y EL DOLOR NEUROPÁTICO.**

Ponente / Institución: Alejandro González, Department of Medical Biochemistry and Biophysics, Instituto Karolinska.

Viernes, 5 de marzo de 2021.

Título: **PHARMACOLOGICAL MANIPULATION TO SENSITIZE GASTRIC ADENOCARCINOMA TO THERAPY.**

Ponente / Institución: Ruba Al Abdulla, Experimental Hepatology and Drug Targeting (HEVEFARM), IBSAL, University of Salamanca, Salamanca, Spain / Research Unit on Diabetes (UNIBAD) IDiBE, UMH.

Viernes, 12 de marzo de 2021.

Título: **«PISCINE ORTHOREOVIRUS (PRV) AND SALMON GILL POXVIRUS (SGPV) INFECTION IN ATLANTIC SALMON. HOST RESPONSES AND PROTECTION». INFECCIÓN POR ORTOREOVIRUS PISCINE (PRV) Y POXVIRUS BRANQUIAL DEL SALMÓN (SGPV) EN SALMÓN DEL ATLÁNTICO. RESPUESTAS Y PROTECCIÓN DEL ANFITRIÓN**

Ponente / Institución: Prof. Maria K. Dahle. UiT The Arctic University of Norway, Tromsø, Noruega.

Martes, 16 de marzo de 2021.

Título: **GLP-1 ANALOGS: A PROMISING THERAPEUTIC OPTION FOR WOLFRAM SYNDROME. (ANÁLOGOS DE GLP-1: UNA OPCIÓN TERAPÉUTICA PROMETEDORA PARA EL SÍNDROME DE WOLFRAM).**

Ponente / Institución: Mariana Igoillo-Esteve, ULB Center for Diabetes Research, Université Libre de Bruxelles, Brussels, Belgium.

Martes, 23 de marzo de 2021.

Título: **MARCADORES MOLECULARES DE INMUNIDAD INNATA EN SALMO SALAR NATURALMENTE INFECTADOS POR P. SALMONIS EN CENTROS DE CULTIVO: DE LA POBLACIÓN AL INDIVIDUO.**

Ponente / Institución: Prof. Luis Mercado Vianco. Instituto de Biología de la Pontificia Universidad Católica de Valparaíso, Chile.

Miércoles, 24 de marzo de 2021.

Título: **INFLAMMASOME-DEPENDENT AND -INDEPENDENT ROLES OF AIM2 IN LIVER INFLAMMATION, CANCER AND T CELL BIOLOGY.**

Ponente / Institución: José Manuel González Navajas. Instituto ISABIAL, Hospital General de Alicante; Departamento de Farmacología, Pediatría y Química Orgánica, UMH; Instituto IDiBE, UMH.

Viernes, 26 de marzo de 2021.

Título: **DISPOSITIVOS MÉDICOS AVANZADOS-CASOS DE ÉXITO.**

Ponente / Institución: PAVEL BARTOVSKY. AIMPLAS (Instituto Tecnológico del plástico)-Grupo de Salud.

Título: **POTENCIAL DE LA FABRICACIÓN ADITIVA EN APLICACIONES MÉDICAS: MATERIALES Y TECNOLOGÍAS.**

Ponente / Institución: RAQUEL LLORENS CHIRALT. AIMPLAS (Instituto Tecnológico del plástico)-Grupo de Salud.

Jueves, 13 de mayo de 2021.

Título: **REGULACIÓN LIPÍDICA DE LA DIMERIZACIÓN DEL SEGMENTO TRANSMEMBRANA DEL RECEPTOR EphA2.**

Ponente / Institución: Francisco Barrera, University of Tennessee.

Lunes, 5 julio de 2021.

Título: **PHYSIOLOGY OF ION CHANNELS.**

Ponente / Institución: Juan Martínez-Pinna, Universidad de Alicante.

Viernes, 5 de noviembre de 2021.

Título: **PHARMACOMETRY AND MATHEMATICAL MODELS TO OPTIMIZE THE USE AND DEVELOPMENT OF DRUGS IN INFECTIOUS DISEASES.**

Ponente / Institución: María García-Cremades Mira, Universidad Complutense de Madrid.

Viernes, 19 de noviembre de 2021.

Título: IV WORKSHOP SEJI JÓVENES INVESTIGADORES DE EXCELENCIA: WHAT IS GOING ON IN DIABETES RESEARCH?

Ponente / Institución:

Dr. Laura Marroquí (IDiBE-UMH and CIBERDEM) and Dr. Reinaldo S. dos Santos (IDiBE-UMH and CIBERDEM).

Dr. Daniela Nasteska (University of Birmingham, UK) - Differences in beta cell maturity as a desirable trait of a functional islet (I) and novel players in a functional islet (II).

Dr. Joan-Marc Servitja (Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and CIBERDEM) - Rescuing pancreatic beta cell function in type 2 diabetes.

Dr. Elisa De Franco (University of Exeter Medical School, UK) - Using gene Discovery in rare disease to gain new insights into pancreas development and function.

Dr. Diego Balboa (Centre for Genomic Regulation, Spain) - Modeling what went wrong: stem cell-derived islets to unravel how genetic defects lead to diabetes.

Martes, 30 de noviembre de 2021.

Título: WHAT HAPPENS TO GLUCOSE METABOLISM IF WE COMBINE FRUCTOSE AND PREDNISOLONE INTAKE FOR LONG-TERM PERIOD? IT IS NEVER TOO LATE TO REPAIR UNHEALTHY HABITS.

Ponente / Institución: Alex Rafacho, Universidade Federal de Santa Catarina.

Viernes, 3 de diciembre de 2021.

Título: MEDICINA PARA PECES: HACIA UNA ACUICULTURA ECONÓMICA Y AMBIENTALMENTE SOSTENIBLE.

Ponente / Institución: Patricia Pereiro, Instituto de Investigaciones Marinas (IIM-CSIC).

Viernes, 10 de diciembre de 2021.

Título: ROLE OF IONIC CHANNELS AND TRANSPORTERS IN CHEMICALLY-INDUCED NEUROTOXICITY: PH-DEPENDENT MECHANISM IN OXALIPLATIN-TREATED DRG NEURONS.

Ponente / Institución: Marianna Dionisi, Università del Piemonte Orientale.

Viernes, 17 de diciembre de 2021.

Financial and administrative management

General Manager

María Amparo García Gutiérrez

Innovation Officer

Gabriel Estañ Cerezo

Logistic Coordinator

Eva del Rio Pons

Administration team

Vicente Lucerga (Officer)

Rosa María Balonga Rodríguez

María Teresa Prieto Ávila

María Elva González Martínez

Agreements

- Center for Therapeutic Innovation (CTI) University of Bath for the secondments of researchers and PhD students.
- KAERTOR foundation for evaluating proposals to their translational programs.

Bibliometric of publications

Number of publications (WoS)	% of Q1	Mean impact factor	Total impact factor
62	89	6.022	277

Dissemination

Out-reach seminars "Science with tapas":

- "El picor: la alerta de nuestras neuronas y cómo combatirlo", 14-12-2021.

Jornadas IDiBE DIVULGA:

- "SARS-Cov-2. Mutantes, variantes y vacunas: Las buenas y las malas noticias", 21-04-21.
- "Volando libres. El fabuloso viaje aéreo de los microbios", 30-06-21.

Jornada "Día internacional de la mujer y la niña en la ciencia en el IDiBE". Investigadoras en biotecnología sanitaria, 10-02-21.

Visita guiada al IDiBE y al FESEM, 07-10-2021 y 05-11-2021.

I Jornada de jóvenes investigadores del IDiBE, 27-07-2021.

Entrepreneurship

- Prospera Biotech SL
- AntalGenics SL
- Fastbase Solutions SL
- Mitra solutions technologies SL
- IlliceEffitech SL

Clinical development

- Parentide® continues in phase II clinical trials for chronic surgical pain. Sponsor: BCN Peptides.
- Bicalutamide is advancing to phase II clinical trials for treating Sanfilippo syndrome. Sponsor BCN Peptides
- AVX-012 concludes phase II clinical trial in USA for dry eye syndrome with excellent results, and it is preparing phase III. Sponsors: Aerie Pharmaceuticals Inc.

- Nocisens, Nocisens Intense and Nocisens Baby, neurocosmetic for skin care, formulating a soft TRPV1 antagonist are marketed for alleviating sensitive skin. Sponsor: Prospera Biotech.
- The proof of concept with Oncapsisens, a novel formulation for alleviating symptoms of chemotherapy induced neuropathy, gives good results, increasing patient satisfaction with their skin. Sponsor: Prospera Biotech.
- AG1529 continues in regulated pre-clinical safety studies for chronic psoriatic pruritus. Sponsor: AntalGenics.

ANNUAL REPORT 2021

**INSTITUTE OF RESEARCH, DEVELOPMENT, AND
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IN ELCHE**

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