

ANNUAL REPORT OF SCIENTIFIC ACTIVITY

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ANNUAL
REPORT OF
SCIENTIFIC
ACTIVITY

2020

FOREWORD IP

IIS-PRINCESA 2020



■ LETTER FROM THE SCIENTIFIC DIRECTOR

■ MEMBERS OF THE INSTITUTE

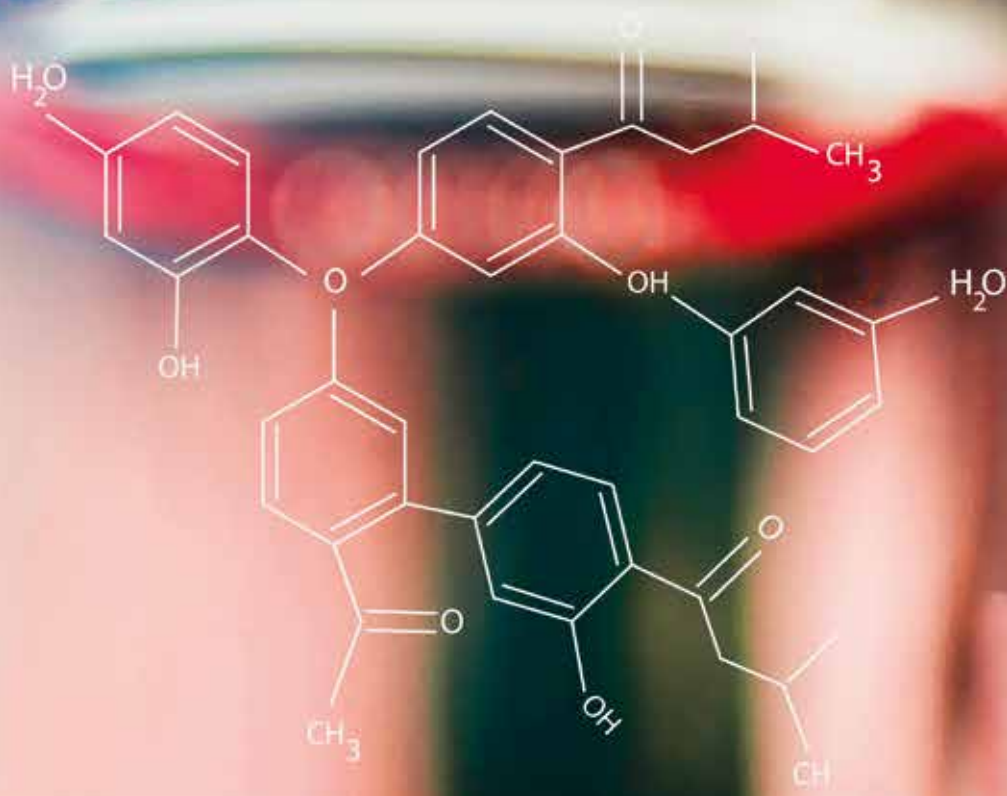
■ ORGANIZATIONAL CHART

■ SCIENTIFIC PLATFORMS

■ RESEARCH AREAS

■ SCIENTIFIC OUTPUT

■ COMMUNICATION AND DISSEMINATION



LETTER FROM THE SCIENTIFIC DIRECTOR



Francisco Sánchez Madrid
SCIENTIFIC DIRECTOR

The year 2020 has been one of those years that none of us would have liked to endure, marked by the pandemic produced by the SARS-COV-2 virus. During the first semester of the year, our health care personnel had to fight in the front line against a previously unknown disease. The news coming from colleagues, friends and family getting sick, was one of the hardest experiences that the Hospital has had to live through. Nevertheless, opportunities always arise from any bad experience and this year has been especially good in terms of scientific results. We have collaborated in the development of methods for detecting antibodies against COVID-19, and we have continued investigating with more enthusiasm than ever, if possible, to contribute to the improvement of the health of the population.

This year has also been important for our institution because the procedure to renew the Institute's accreditation has begun. This procedure has taken place along with the approval of the Strategic Plan for the years 2020-2024, as well as the renewal of most of the Committees, with a strong commitment to gender parity among their members. Additionally, our HRS4R certification has undergone the mid-term evaluation with excellent results. These results position our Institute as a centre of excellence in Human Resources in research, attractive for recruiting new talent, and align our Human Resources policies with the good practices of the European Union.

As I mentioned before, this year the scientific output has increased substantially, resulting in a phenomenon that could be called the "COVID Effect". This phenomenon was due, on the one hand to the rapid publication of new articles on the pandemic and its effects, and on the other hand, to the speeding of publication of results pending to publish, favoured by the time in which some of our researchers had to stay away from the lab working from home during lockdown. Thus, this year the number of publications has reached 707, showing an increase of 49% compared to 2019. Similarly, the accumulated impact factor has increased 41%, reaching the figure of 3997.075. Our researchers have led 44% of all the articles in



*Thus, this year the number of publications has reached 707, showing an **increase of 49% compared to 2019**. Similarly, the accumulated impact factor has increased 41%, reaching the figure of 3997.075. Our researchers have led 44% of all the articles in which they participated*

which they participated. It is also worth highlighting the commitment of our centre to make scientific discoveries available to society; accordingly, more than half of all our articles have been published in Open Access journals.

The number of clinical trial agreements signed during this year has also experienced a considerable increase of 36%, from 105 in 2019 to 143 in 2020.

The number of thesis defences was, showing an increase in the last months of the year. This year 2 national patents and some royalties have been registered, in addition to a national patent granted.

We must not forget other activities in which members of the Institute are also involved, such as teaching and healthcare. Throughout this year our staff have also had to make an effort to adapt these activities to the new circumstances, with the aim of keeping offering quality services.

The audit for the accreditation of the Institute is expected to take place in the first months of 2021. The members of the Institute will face this process knowing that in previous years they have done a great job, and expecting to renew this accreditation for the next five years. Several challenges will have to be addressed in these years, such as the generational change, the implementation of new Open Science systems and data management plans, and raising of funds from the new calls included in the Recovery and Resilience Facility.

Like every year, I would not like to finish without acknowledging the work done by all the members of our Institute, who are truly responsible for the good outcome of our research. Thanks to the effort and help of each one of them the research results shown in this report are better year after year. Thank you for your effort and dedication. ■

MEMBERS OF THE INSTITUTE

The Health Research Institute of the University Hospital La Princesa was constituted on December 15, 2009 under an agreement signed by the Madrid Health Service - representing the University Hospitals La Princesa, Santa Cristina, and the children's Hospital Niño Jesús - the Autonomous University of Madrid, the Biomedical Research Foundation of the University Hospital La Princesa and the Agency "Pedro Laín Entralgo" of the Community of Madrid for Training, Research and Health Studies. Almost a year later, after an audit from

the Institute of Health Carlos III, it got the Accreditation as a Health Research Institute.

In 2013 the activity of the Agency of Training, Research and Health Studies of the Community of Madrid "Pedro Laín Entralgo" was finished, and its functions were assumed by the Ministry of Health of the Community of Madrid, in particular by its the General Directorate of Research, Training and Documentation. ■



**Hospital Universitario
de La Princesa**



**Hospital Universitario
Santa Cristina**



**Hospital Universitario
Niño Jesús**



**Comunidad
de Madrid**

Dirección General de Investigación,
Docencia y Documentación
CONSEJERÍA DE SANIDAD

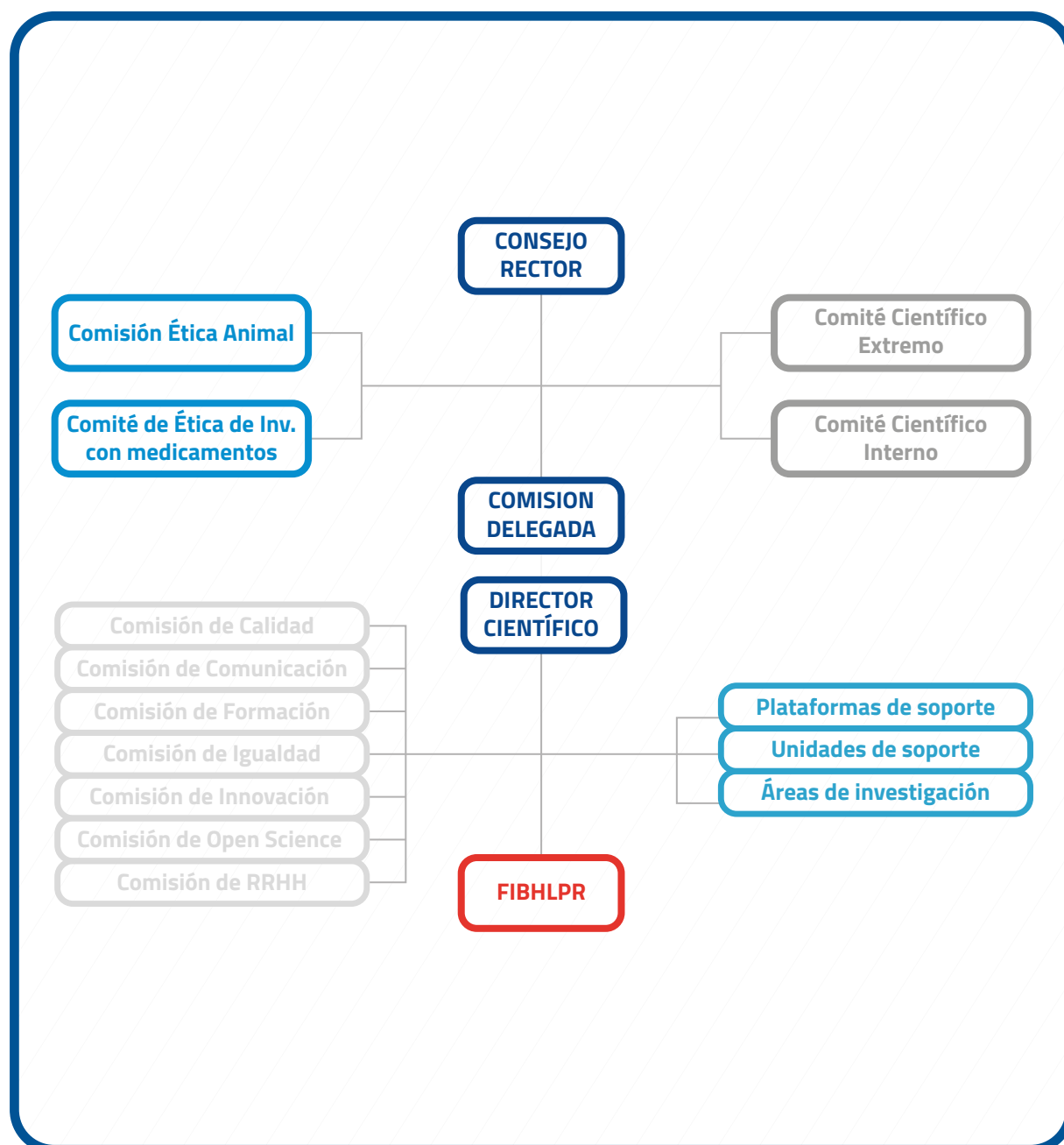


**Universidad Autónoma
de Madrid**





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Immunology Department, Hospital Universitario La Princesa

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Clinical Pharmacology Department, Hospital Universitario La Princesa

VICE-CHAIRMAN**Dolores Ochoa Mazarro**

Clinical Pharmacology Department, Hospital Universitario La Princesa

MEMBERS**Ángel Carlos Abanades Cuenca**

Patient representative

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Anesthesiology Department, Hospital Universitario La Princesa

Carmen del Arco Galán

Emergency Department, Hospital Universitario La Princesa

Santos Castañeda Sanz

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Andrés López Romero

Family and Community Medicine, Primary Care

Concepción Martínez Nieto

Pharmacy Department, Hospital Universitario La Princesa

Pablo Montalvo Rebuelta

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Nurse, Hospital Universitario La Princesa

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Medical Oncology Department, Hospital Universitario La Princesa

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Internal Medicine Department, Hospital Universitario La Princesa

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Biobank, Hospital Universitario La Princesa

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German Fernández Carracedo

Cecilia López García

FOUNDATION FOR BIOMEDICAL RESEARCH (FIBHLPR)

DIRECTOR

Rosario Ortiz de Urbina Barba

HUMAN RESOURCES DEPARTMENT

María Mar Martín Cuenca

PROJECTS MANAGEMENT DEPARTMENT

Jesús Santamaría Pérez

María del Carmen Barrio Fuentes

The following table shows information about the expenses and income of the Foundation, followed by the Situation Balance:

	2020	2019
Income	8.005.466	7.736.059 €
Expenses	7.990.091	7.725.647 €

ACTIVE ASSETS

<i>Non-current active asset</i>	
Intangible fixed assets	44.401
Material fixed assets	528.460
<i>Current active assets</i>	
Debtors and Client to collect	983.038
Financial short term investments	0
Cash	14.277.330
Total Active Assets	15.833.229

PASSIVE ASSETS

<i>Net Worth</i>	
Own funds	2.420.431
Non-refundable grants	755.391
<i>Non-current Passive Assets</i>	
Long term debts	0
<i>Current Passive Assets</i>	
Short term provisions	5.810.556
Refundable grants	3.860.292
Creditors to pay	642.523
Short term accruals	2.344.036
Total Passive Assets	15.833.229

ACCOUNTING DEPARTMENT

Jorge Gómez Juan

CLINICAL TRIALS MANAGEMENT DEPARTMENT

Esther Polanco Paz

Sara Cardenal Rodríguez

Fabián Zamora Alarcón

RESEARCH MANAGEMENT DEPARTMENT

Jesús Capa Algara

SECRETARY

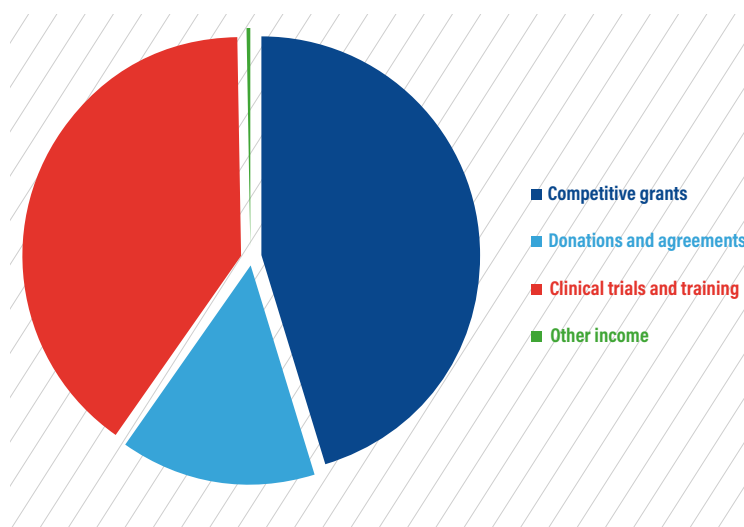
Ana Aroca Martínez

WARD STAFF

José Corrochano de la Cruz

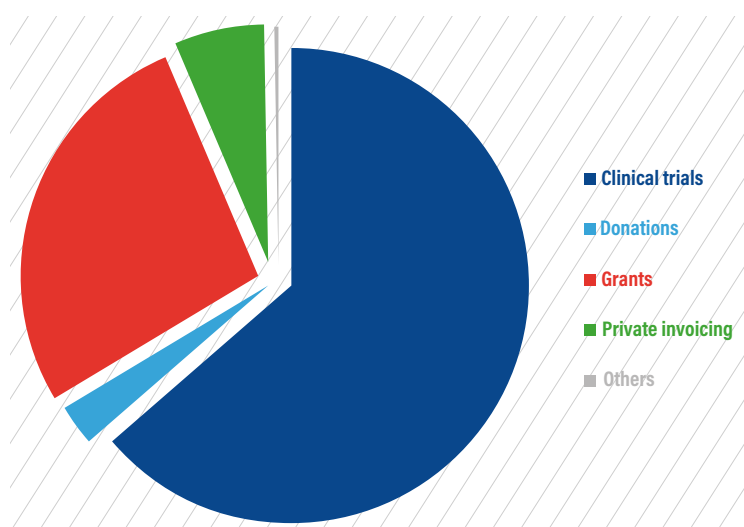
Below is shown the information on the income obtained by the Foundation for Biomedical Research, with the income sources grouped as obtained through competitive grants, clinical trials, private invoicing, donations, or other income.

Competitive grants	Donations and agreements	Clinical trials and training	Other income
3.641.725	1.151.629	3.210.467	1.645



Finally, a graph is shown with the overhead income according to its origin and use.

Overhead income according to its origin:



Use of overhead income:

Personnel - Research (Platforms + Research programs)	46%
Products and services – Equipment – Repairs	39%
Reserves	15%



Scientific Platforms

PLATFORM SUPPORT

BIOBANK

The main mission of Biobank is focused on the development of collections of quality biological samples for the use by the scientific community. Its main tasks are: foster the setting of new collections, provide the scientific community access to biological samples and associated data, guarantee the rights of patients donating samples, and advice to investigators about the use and handling of biological samples.

SCIENTIFIC COORDINATOR

Mara Ortega Gómez

SCIENTIFIC COMMITTEE

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Scientific Management Support Unit

Ramón Colomer Bosch

Medical Oncology Department

Isidoro González Álvaro

Rheumatology Department

José A. Jiménez Heffernan

Pathology Department

Carlos Manuel Olivier Gómez

Urology Department

TECHNICAL STAFF

Laura Gómez Cabañas

Ángel Lancho Sánchez

Plataforma ISCIII.



METHODOLOGICAL UNIT

It aims to provide to IP research teams support for the development and implementation of research projects in order to increase the excellence of the scientific activity of IIS-Princesa.

COORDINATOR

Francisco Javier Aspa Marco

MEDICAL WRITER

Manuel Gómez Gutiérrez

SCIENTIFIC MANAGEMENT SUPPORT UNIT

The Scientific Management Support Unit of IIS-Princesa has as main objective the organization, planning and coordination of all structures of support for the scientific environment and the researchers of the Institute, under the supervision of the Scientific Director of the Institute.

COORDINATOR

Francisco Javier Aspa Marco

"WHITE" ROOM

The "white" room located in the Niño Jesús Hospital, is a facility specialized to work with minimal or absent levels of contamination that meets the requirements of Good Manufacturing Practices (GMP). The "white" Room has Certification of Compliance with GMP since April 2010, both for Cell Therapy and Gene Therapy.

COORDINADOR DE LA UNIDAD DE TERAPIAS AVANZADAS

Manuel Ramírez Orellana

FLOW CYTOMETRY UNIT

The Flow Cytometry Unit is located in the Department of Immunology and Molecular Biology, University Hospital of La Princesa and has recently joined

the Network of Laboratories of Public Research Organizations (REDLAB) of the Community of Madrid.

The unit provides instrumentation and technical assistance to the researchers to perform both immunophenotype analysis and cell sorting based on fluorescence parameters.

COORDINATOR

Cecilia Muñoz Calleja

GENOMIC UNIT

The Genomics Unit is responsible for the development and implementation of technologies for molecular biology and genomics, equipment maintenance, and provision of technical advice on various technologies to research groups. It uses different technologies as spectrophotometry, automated extraction of nucleic acids, RNA integrity determination, conventional PCR and RT-PCR, real time PCR and RT-PCR, software for search and integration of experimental data and, recently, massive sequencing.

TECHNICAL DIRECTOR

Fernando Carrasco Ramiro

ELECTRONIC MICROSCOPE SERVICE

The Electron Microscopy Service of UAM provides technical assistance and scientific support to research groups interested in using electron microscopy techniques for ultrastructural analysis of biological samples and immunodetection of antigens. It has a transmission electron microscope and the material needed for sample preparation.

TECHNICAL DIRECTOR

María Teresa Rejas Marco

PROTEOMIC UNIT

Proteomics service's objectives are to provide the research groups with support and scientific and technical advice in the identification and characterization of proteins by mass spectrometry (MS) techniques.

COORDINATOR

Ana Isabel Marina Ramirez

HIGH DEFINITION VIDEOMICROSCOPY

The Institute Videomicroscopy Service provides the infrastructure and scientific expertise needed for studies of fluorescence, confocal and evanescent wave microscopy, with special emphasis on the observation of dynamic processes in living cell.

COORDINATOR

Noa B. Martín Cofreces

TECHNICIAN

Francisca Molina Jiménez

ANIMAL FACILITY

The Veterinary Office of the Universidad Autónoma de Madrid offers its services to our Institute. It is a service whose purpose is to maintain, produce and control animals for experimental research.

DIRECTOR

David Muñoz Valverde

DATA ANALYSIS UNIT

The Data Analysis Unit (DAU) has the objective of supporting the research groups of the Institute. The main objective of the DAU is to implement and develop numerical algorithms for the analysis and visualization of biomedical data. The UAD collaborates actively with the groups that need this expertise, and provides advice on specific issues in everything related to the analysis of data. It also carries out training activities related to data analysis tools.

COORDINATOR

Guillermo J. Ortega Rabbione

MEMBERS

Ancor Sanz-García

BIOINFORMATICIAN

Jorge García Martínez

UNITS

BIOLOGICAL AND TARGETED
THERAPIES UNIT

Biological therapies are the result of the large parallel progress in understanding the pathogenesis of chronic inflammatory and autoimmune diseases and in biotechnology. Their development is one of the most significant changes in recent decades. This Unit coordinates effective treatments (with high cost) ensuring their sustainability. The main idea is to contribute to the better use of biological therapies based on criteria of scientific thoroughness, safety, efficiency and cost-effectiveness.

COORDINATOR

Rosario García de Vicuña Pinedo
Rheumatology Department

MULTIDISCIPLINAR TEAM

María Chaparro Sánchez
Gastroenterology Department

Esteban Daudén Tello
Dermatology Department

Isidoro González Álvaro
Rheumatology Department

María del Mar Llamas Velasco
Dermatology Department

Virginia Meca Lallana
Neurology Department

Alberto Morell Baladrón
Hospital Pharmacy Department

Rosario Ortiz de Urbina Barba
Fundación para la Investigación Biomédica Hospital Universitario La Princesa

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Gastroenterology Department

Esther Ramírez Herraiz

Hospital Pharmacy Department

CLINICAL TRIALS UNIT

The Clinical Trials Unit was created with the primary objective of promoting clinical research as well as providing support to researchers. Clinical trials or observational studies promoted and/or led by researchers are considered independent clinical research.

DIRECTOR

Francisco Abad Santos

DEPUTY DIRECTOR

Dolores Ochoa Mazarro

COORDINATOR

Manuel Román Martínez

STAFF

Paola Camargo Mamani

Diana María Campodónico

Ana Casajus Rey

María Eugenia Flores Ruiz

Laura García Castro

Antía Gómez Fernández

Sergio Luquero Bueno

Beatriz Mariscal Campo

Samuel Martín Vílchez

Alejandro de Miguel Cáceres

Gina Paola Mejía Abril

Jaime Pérez Calvo

Soledad Rubio Domínguez

Elena Santos Molina

Tamara de la Torre Muñoz

SECRETARY

Rebeca Manzanares López

Ana del Río Moreno

Irene Román Martínez

PLATAFORMA ISCIII.



INNOVATION UNIT

The Innovation Unit of the Hospital de La Princesa was born with the foundation of the Research Institute, and is responsible, with the existing resources, to analyze new technological trends and their implementation at the Institute.

The Innovation Unit of the Health Research Institute Hospital Universitario de La Princesa was consolidated when it joined the Platform for Innovation in Medical and Health Technologies (ITEMAS), getting access to the funding of the 2013 call for grants from the Strategic Action in Health, from Institute of Health Carlos III.

COORDINATOR

Francisco Sánchez Madrid

Scientific Director of Instituto de Investigación Sanitaria Hospital Universitario La Princesa

INNOVATION COMMITTEE

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Emergency Department

Gustavo Casero Balboa

Management and general services Director

Elena Español Pueyo

Communication Department

Francisco Redondo Montserrat

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Quality Coordinator

**SECRETARY INNOVATION COMMITTEE
AND INNOVACION STAFF****Antonio Rodríguez Hita****PLATAFORMA ISCIII.****COMMITTEES****QUALITY COMMITTEE**

To achieve objective results of excellence and get a continuous improvement, the Quality Commission not only elaborates, but also continuously monitors the implementation of quality procedures established in our Institute.

COORDINATOR**M^a Angels Figuerola Tejerina**

Preventive Medicine Department

QUALITY COMMITTEE**Arantazu Alfranca González**

Immunology Department

Francisco Javier Aspa Marco

Scientific Management Support Unit

Ramón Colomer Bosch

Medical Oncology Department

Mara Ortega Gómez

Biobank

SECRETARY**Jesús Capa Algara**

Research Management

EDUCATION COMMITTEE

One of the priorities set by the IIS-Princesa is the promotion and development of training programs for professionals who are part of the Centre, with a focus on training for translational research to improve the competitiveness of institutions and the qualifications of the personnel that integrates them.

In this sense, all entities that are part of the Health Research Institute Hospital Universitario de La Princesa have an established training and teaching track, and have a wide training offer at all levels (training of undergraduate, graduate, and Continuing Specialized Health).

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Scientific Management Support Unit, Hospital Universitario La Princesa

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Head of studies Resident Doctor

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Fernando Ramasco Rueda

Continuous Training Coordinator

Francisco Rodríguez Salvanés

Diagnosis Training Unit

Jesús Sanz Sanz

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SECRETARY

Jesús Capa Algara

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HUMAN RESOURCES COMMITTEE

COORDINATOR

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Human Resources Department

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Nursing Department

Nuria Romero Laorden

Medical Oncology Department

SECRETARY

Jesús Capa Algara

Research Management

COMMITTEE FOR EQUAL OPPORTUNITIES AND DIVERSITY MANAGEMENT

The Committee for Equal Opportunities acts as the main body responsible for promoting and coordinating the Institute's gender equality policies.

Sara Cardenal Rodríguez

Clinical Trial Department

María Chaparro Sánchez

Gastroenterology Department,

Sergio Luquero Bueno

Clinical Trial Unit

Noa Beatriz Martín Cofreces

Immunology Department

María del Mar Martín Cuenca

Human Resources Department

María del Rosario Ortiz de Urbina Barba

Director Fundación para la Investigación
Biomédica Hospital Universitario de La Princesa

Nuria Romero Laorden

Medical Oncology Department

SECRETARY

Jesús Capa Algara

Research Management

OPEN SCIENCE COMMITTEE

The Open Science Committee will act as the main body responsible for promoting and coordinating Open Science policies within the framework of the IIS Princesa.

Sara Cardenal Rodríguez

Clinical Trial Department

María Chaparro Sánchez

Gastroenterology Department

Sergio Luquero Bueno

Clinical Trial Unit

Noa Beatriz Martín Cofreces

Immunology Department

María del Mar Martín Cuenca

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Research Management



Research Areas

AREA 1: CELLULAR AND MOLECULAR ETIOPATHOGENIC MECHANISMS IN INFLAMMATORY AND AUTOIMMUNE DISEASES

COORDINATOR:

Francisco Sánchez Madrid

DEPUTY DIRECTOR:

Julie Ann Chowen King

General objectives:

1. Unravel the molecular and cellular mechanisms that control crucial biological processes in inflammatory / autoimmune based diseases.
2. Identify molecular entities and cellular processes that can be used as targets for the action of new drugs for inflammatory / autoimmune based diseases.
3. Implement advanced experimental techniques and new animal models of disease that will allow improving basic studies to analyse pathophysiological mechanisms, and perform pre-clinical studies.
4. Promote translational research by fostering interactions between basic and clinical groups.

Five most relevant publications of the area:

Hernansanz-Agustín, Pablo, Choya Foces, Carmen, Carregal-Romero, Susana, Ramos, Elena, Oliva, Tamara, Villa-Piña, Tamara, Moreno, Laura, Izquierdo-Álvarez, Alicia, Cabrera-García JD, Cortés, Ana, Lechuga-Vieco, Ana Victoria, Jadiya, Pooja, Navarro, Elisa, Parada, Esther, Palomino Antolín, Alejandra, Tello, Daniel, Acín-Pérez, Rebeca, Rodríguez-Aguilera, Juan Carlos, Navas, Plácido, Cogolludo, Ángel, López-Montero, Iván, Martínez-Del-Pozo, Álvaro, Egea Máiquez, Francisco Javier, García López, Manuela, Elrod, John W, Ruíz-Cabello, Jesús, Bogdanova, Anna,

Enríquez, José Antonio, Martínez Ruiz, Antonio. **Na⁺ controls hypoxic signalling by the mitochondrial respiratory chain.** NATURE 586 (7828): 287-291. 2020. PMID: 32728214. IF: 42,778. DOI: 10.1038/s41586-020-2551-y.

Sevilla-Montero J, Labrousse-Arias D, Fernández-Pérez C, Fernández-Blanco L, Barreira B, Mondéjar-Parreño G, Alfaro-Arnedo E, López IP, Pérez-Rial S, Peces-Barba G, Pichel JG, Peinado VI, Cogolludo Á, Calzada MJ. **Cigarette Smoke Directly Promotes Pulmonary Arterial Remodeling and Kv7.4 Channel Dysfunction.** Am J Respir Crit Care Med 203 (10): 1290-1305. 2020. PMID: 33306938. IF: 17,452. DOI: 10.1164/rccm.201911-2238OC.

Martin-Cofreces, N. B., Chichon, F. J., Calvo, E., Torralba, D., Bustos-Moran, E., Dosil, S. G., Rojas-Gomez, A., Bonzon-Kulichenko, E., Lopez, J. A., Oton, J., Sorrentino, A., Zabala, J. C., Vernos, I, Vazquez, J., Valpuesta, J. M., Sanchez-Madrid, F. **The chaperonin CCT controls T cell receptor-driven 3D configuration of centrioles.** Sci Adv 6 (49). 2020. PMID: 33268369. IF: 13,116. DOI: 10.1126/sciadv.abb7242.

Sanchez-Cerrillo, Ildelfonso, Landete Rodríguez, Pedro, Aldave, Beatriz, Sánchez Alonso, Santiago, Sanchez-Azofra, Ana, Marcos-Jimenez, Ana, Avalos, Elena, Alcaraz-Serna, Ana, de los Santos Gil, Ignacio, Mateu-Albero, Tamara, Esparcia, Laura, Lopez-Sanz, Celia, Martinez-Fleta, Pedro, Gabrie, Ligia, del Campo Guerola, Luciana, de la Fuente Flores, Hortensia, Calzada García, María Josefa, González Álvaro, Isidoro, Alfranca González, Arantzazu, Sánchez Madrid, Francisco, Muñoz Calleja, Cecilia, Soriano Ortiz, Joan Bautista, Ancochea Bermúdez, Julio, Martín Gayo, Enrique, REINMUN COVID EDE-PIMIC Grp. **COVID-19 severity associates with pulmonary redistribution of CD1c(+) DCs and inflammatory transitional and nonclassical monocytes.** J Clin Invest 130 (12): 6290-6300.



Areas:

3



Research:

23



Research group:

50



Personnel dedicated
to research: 518



Men:

204



Women:

314

2020. PMID: 32784290. IF: 11,864. DOI: 10.1172/JCI140335.

González-Tajuelo, Rafael, de la Fuente-Fernández, María, Morales-Cano, Daniel, Muñoz Callejas, Antonio, González Sánchez, María Elena, Silván Montoya, Javier, Serrador, Juan Manuel, Cadenas Álvarez, Susana, Barreira, Bianca, Espartero-Santos, Marina, Gamallo, Carlos, Vicente Rabaneda, Esther Francisca, Castañeda Sanz, Santos, Pérez-Vizcaíno, Francisco, Cogolludo, Ángel, Jiménez Borreguero, Luis Jesús, Urzainqui Mayayo, Ana Carmen. **PSGL1-deficient mice develop spontaneous pulmonary hypertension associated to systemic sclerosis.** *Arthritis Rheumatol* 72 (3): 477-487. 2020. PMID: 31509349. IF: 9,586. DOI: 10.1002/art.41100.

Line 1 Intercellular communication in the inflammatory response.

Group 1 **Francisco Sánchez Madrid**
Group 2 **Esteban Veiga Chacón**
Group 3 **María Yáñez Mó**
Group 56 **Ana Carmen Urzainqui Mayayo**

Line 2 Cellular and molecular responses to hypoxia.

Group 9 **Julián Aragonés López**
Group 7 **Antonio Martínez Ruiz**
Group 8 **María Josefa Calzada García**
Group 10 **Susana Cadenas Álvarez**

Line 3 Animal models of inflammatory diseases and intercellular signalling.

Group 11 **Federico Mayor Menéndez**
Group 12 **Manuel Fresno Escudero**
Group 13 **Petronila Penela Márquez**
Group 17 **Cristina Murga Montesinos**
Group 18 **Miguel Ángel Íñiguez Peña**

Line 5 Cellular mechanisms and molecular determinants of allergy-based diseases.

Group 20 **Carlos Blanco Guerra**
Group 15 **María Dolores Ibáñez Sandín**

Line 6 Inflammatory processes in nephrological diseases.

Group 21 **José Antonio Sánchez Tomero**

Line 7 Inflammatory mechanisms in pulmonary diseases.

Group 22 **Julio Ancochea Bermúdez**

Line 8 Inflammatory response in hepatic diseases.

Group 24 **Pedro Lorenzo Majano Rodríguez**
Group 23 **Luisa Consuelo García Buey**

Line 9 Mechanisms and mediators of endocrine diseases.

Group 25 **Mónica Marazuela Azpiroz**

Line 10 Children's development (obesity and growth).

Group 26 **Jesús Argente Oliver**

Line 11 Metabolic syndrome and vascular risk.

Group 5 **Carmelo García Monzón**
Group 42 **Águeda Gonzalez Rodríguez**

**AREA 2:
TRANSLATIONAL NEUROSCIENCE**

COORDINATOR:

José Luis Ayuso Mateos

DEPUTY DIRECTOR:

María Dolores Ochoa Mazarro

General objectives:

1. Design, synthesis and characterization of new compounds with potential neuroprotective effect on neurodegenerative diseases and stroke.
2. Search for biomarkers for early diagnosis, study of progression and response to treatment in these diseases.
3. Drug characterization in preclinical studies in animal models and in clinical trials in humans.
4. Expand the knowledge about affective disorders in the population, studying risk factors, clinical evolution and response to treatment, in order to improve the mental health of the population.

Five most relevant publications of each area:

Calzaferri F, Ruiz-Ruiz C, de Diego AMG, de Pascual R, Méndez-López I, Cano-Abad MF, Maneu V, de los Ríos C, Gandía L, García AG.

The purinergic P2X7 receptor as a potential drug target to combat neuroinflammation in neurodegenerative diseases.

Med Res Rev 40 (6): 2427-2465. 2020. PMID: 32677086. IF: 9,300. DOI: 10.1002/med.21710.

Cebrian, Jose, Gonzalez-Martinez, Alicia, Garcia-Blanco, Maria J., Celdran-Vivancos, Diego, Lopez Palacios, Eduardo, Reig-Rosello, Gemma, Casado-Fernandez, Laura, Vivancos, Jose, Beatriz Gago-Veiga, Ana. **Headache and impaired consciousness level associated with SARS-CoV-2 in CSF.** NEUROLOGY 95 (6): 266-268. 2020. PMID: 32641532. IF: 8,770. DOI: 10.1212/WNL.0000000000010213.

Farre-Alins, Victor, Narros-Fernandez, Paloma, Palomino-Antolin, Alejandra, Decouty-Perez, Celine, Lopez-Rodriguez, Ana Belen, Parada, Esther, Munoz-Montero, Alicia, Gomez-Rangel, Vanessa, Lopez-Manoz, Francisco, Ramos, Eva, Gonzalez-Rodriguez, Agueda, Gandia, Luis, Romero, Alejandro, Egea, Javier. **Melatonin Reduces NLRP3 Inflammasome Activation by Increasing alpha 7 nAChR-Mediated Autophagic Flux.** Antioxidants (Basel) 9 (12): 2020. PMID: 33353046. IF: 5,014. DOI: 10.3390/antiox9121299.

de la Torre-luque, Alejandro, Ayuso-Mateos, Jose Luis. **The course of depression in late life: a longitudinal perspective.** Epidemiol Psychiatr Sci 29: 2020. PMID: 32723402. IF: 5,876. DOI: 10.1017/S204579602000058X.

Fernandez-Mendivil, Cristina, Arreola, Miguel A., Hohsfield, Lindsay A., Green, Kim N., Lopez, Manuela G. **Aging and Progression of Beta-Amyloid Pathology in Alzheimer's Disease Correlates with Microgli-**

al Heme-Oxygenase-1 Overexpression.

Antioxidants (Basel) 9 (7): 2020. PMID: 32708329. IF: 5,014. DOI: 10.3390/antiox9070644.

Line 1 Neuropharmacology and neuroprotection.

Group 16 **Manuela García López**

Group 28 **Cristóbal de los Ríos Salgado**

Group 60 **Rafael León Martínez**

Group 41 **Javier Egea Maiquez**

Line 3 Clinical pharmacology and pharmacogenetics.

Group 32 **Francisco Abad Santos**

Line 4 Diagnostic and therapeutic advances in affective disorders.

Group 33 **José Luis Ayuso Mateos**

Line 5 Neurosurgery of epilepsy.

Group 34 **Jesús Pastor Gómez**

Line 6 Cerebrovascular diseases.

Group 35 **José Aurelio Vivancos Mora**

AREA 3: ADVANCED THERAPIES AND INDIVIDUALIZED MEDICINE

COORDINATOR:

Isidoro González Álvaro

DEPUTY DIRECTOR:

María Chaparro Sánchez

General objectives:

1. Identification of biomarkers that allow predicting the prognosis and / or response to treatment in inflammatory, infectious or tumor diseases.
2. Optimization of biological therapies by identifying biomarkers predictive of therapy response.
3. Identification of new drugs and / or therapeutic targets.
4. Search for new treatments and improvement in the efficacy and safety of treatments and in the management of their effects on the quality of life of patients.

Five most relevant publications of each area:

Chaparro Sánchez, María, Gordillo, Jordi, Domenech, Eugeni, Esteve, Maria, Barreiro-de Acosta, Manuel, Villoria, Albert, Iglesias-Flores, Eva, Blasí, Mercedes, Naves, Juan E., Benitez, Olga, Nieto, Laura, Calvet, Xavier, Garcia-Sanchez, Valle, Ramon Villagrasa, Jose, Marín Gómez, Alicia Carmen, García Donday, María, Abad Santos, Francisco, Pérez Gisbert, Francisco Javier. **Fendrix vs Engerix-B for Primo-Vaccination Against Hepatitis B Infection in Patients With Inflammatory Bowel Disease: A Randomized Clinical Trial.** Am J Gastroenterol 115 (11): 1802-1811. 2020. PMID: 33156099. IF: 10,171. DOI: 10.14309/ajg.0000000000000926.

Ruano, David, Lopez-Martin, Jose A., Moreno, Lucas, Lassaletta, Alvaro, Bautista, Francisco, Andion, Maitane, Hernandez, Carmen, Gonzalez-Murillo, Africa, Melen, Gustavo, Alemany, Ramon, Madero, Luis, Garcia-Castro, Javier, Ramirez, Manuel. **First-in-Human, First-in-Child Trial of Autologous MSCs Carrying the Oncolytic Virus Icovir-5 in Patients with Advanced Tumors.** MOL THER 28 (4): 1033-1042. 2020. PMID: 32053771. IF: 8,986. DOI: 10.1016/j.jymthe.2020.01.019.

Cortese, Bernardo, Di Palma, Gaetano, Guimaraes, Marcos Garcia, Piraino, Davide, Orrego, Pedro Silva, Buccheri, Dario, Rivero, Fernando, Perotto, Anna, Zambelli, Giulia, Alfonso, Fernando. **Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease PICCOLETO II Randomized Clinical Trial.** JACC Cardiovasc Interv 13 (24): 2840-2849. 2020. PMID: 33248978. IF: 8,432. DOI: 10.1016/j.jcin.2020.08.035.

Llamas-Velasco M, Muñoz-Hernández P, Lázaro-González J, Reolid-Pérez A, Abad-Santamaría B, Fraga J, Daudén-Tello E. **Thrombotic occlusive vasculopathy in skin biopsy from a livedoid lesion of a COVID-19 patient.** Br J Dermatol 183 (3): 591-593. 2020. PMID: 32407552. IF: 7,000. DOI: 10.1111/bjd.19222.

Rogado J, Romero-Laorden N, Sanchez-Torres JM, Ramos-Levi AM, Pacheco-Barcia V, Ballesteros AI, Arranz R, Lorenzo A, Gullon P, Garrido A, Serra López-Matencio JM, Donnay O, Adrados M, Costas P, Aspa J, Alfranca A, Mondejar

R, Colomer R. **Effect of excess weight and immune-related adverse events on the efficacy of cancer immunotherapy with anti-PD-1 antibodies.** ONCOIMMUNOLOGY 9 (1): 1751548-1751548. 2020. PMID: 32363123. IF: 5,869. DOI: 10.1080/2162402X.2020.1751548.

Line 1 Prognostic and predictor markers in autoimmune diseases.

Group 36 **Isidoro González Álvaro**

Group 37 **Esteban Daudén Tello**

Line 2 Esophagogastrointestinal inflammatory diseases.

Group 38 **Javier Pérez Gisbert**

Line 3 Progenitors and cell therapy.

Group 39 **Luis Madero López**

Line 4 Advanced therapies in oncohematology.

Group 44 **Juan Luis Steegmann Olmedillas**

Line 5 Biological, cellular and molecular monitoring in oncohematology.

Group 45 **Elena Fernández Ruiz**

Group 46 **Cecilia Muñoz Calleja**

Line 6 New diagnostic and therapeutic advances in cardiovascular diseases.

Group 58 **Fernando Alfonso Manterola**

Group 48 **Luis Jesús Jiménez Borreguero**

Group 57 **Carmen Suárez Fernández**

Group 49 **Blanca Novella Arribas**

Line 7 New therapies in infectious pathologies.

Group 50 **Ignacio de los Santos Gil**

Group 51 **Javier Aspa Marco**

Group 52 **Teresa Alarcón Caverro**

Line 8 Individualized medicine in solid tumors.

Group 40 **Ramón Colomer Bosch**

Group 53 **Almudena Zapatero Laborda**

Group 54 **Laura Cerezo Padellano**

Group 59 **Carlos Manuel Olivier Gómez**

Group Asociado 3 **José Cordero Ampuero**



SCIENTIFIC OUTPUT

GLOBAL ANALYSIS

Publications:

	Total	Impact Factor	Main Impact Factor	% D1	%Q1	% IF>10	% International collaborations	% Open Access	% Leadership ²
Publications	707	3997.075	5.65	21	53	7	38	54	44
Articles	633	3637.323	5.75	21	54	11	37	52	41
Editorial	35	195.668	5.59	31	37	7	37	61	77
Review	39	164.084	4.20	21	54	0	41	72	56

New Projects:

New Research projects in 2020: 15.

New Human Resources grants in 2020: 10.

Clinical Trials:

Ongoing Clinical Trials during the year 2020: 430

Clinical Trial agreements signed in 2020: 146

Clinical Practice Guidelines:

Clinical practice guidelines: 20

*Patents:**Total number of patents or useful models:*

59 applications, **9** granted and **4** licensed / transferred.

Number of spin-offs and start-ups created and active:

1 start-up created in 2018 and active as of December 31, 2020.

Theses:

Number of theses defended: **10**

Number of theses with European mention: **3**

NATIONAL APPLICATIONS	NATIONAL PATENTS GRANTED	ROYALTY APPLICATIONS
2	1	1

Number of innovations generated by IIS (2020):

16 projects enrolled in the year and **43** in development phase in 2020.

*Total number innovation projects generated by IIS: 89.**Number of patents or useful models during 2020:*

8 applications, **5** granted and **1** licensed / transferred.

Communication:

Number of sessions / communication conferences held: **36**

Number of press releases: **16**

Number of news published in printed press: **16**

News in other audiovisual media (Radio TV): **93** (**41** in TV, **52** in Radio)

Number of news in specialised and non-specialised digital media: **75**

Number of Research Bulletin "Factor de Impacto" with the last scientific news with wide dissemination among patients, researchers and media: **3** (one of them was monographic on COVID-19 research in the Institute).

Number of visitors to the website: From June **55,156**

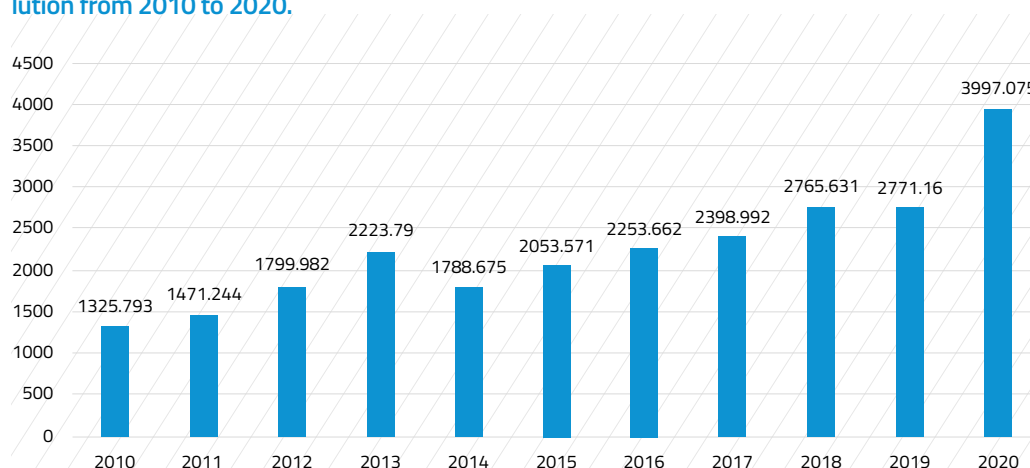
Evolution of staff according to their profile in the European Research Career:

	01/01/2020	31/12/2020
First Stage Researcher (R1):	40	39
Recognised Researcher (R2)	145	152
Established Researcher (R3)	28	30
Leading Researcher (R4)	70	69

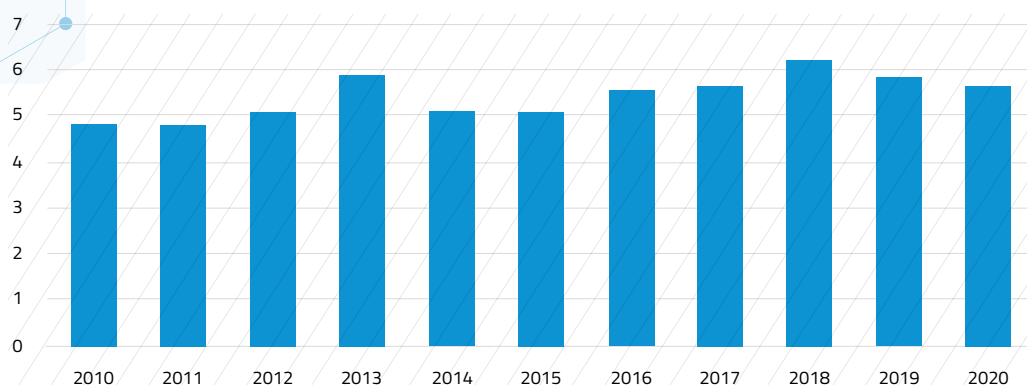
PUBLICATIONS

During 2020, the number of publications has increased significantly compared to 2019, reaching 707, which represents an increase of 48.8%. This increase is mainly due to the number of publications on COVID-19. The increase in publications was also associated with an increase in the accumulated impact factor, which almost reached 4,000 points. Although this increase was higher than usual, it reflects the upward trend that the Institute had been achieving in recent years.

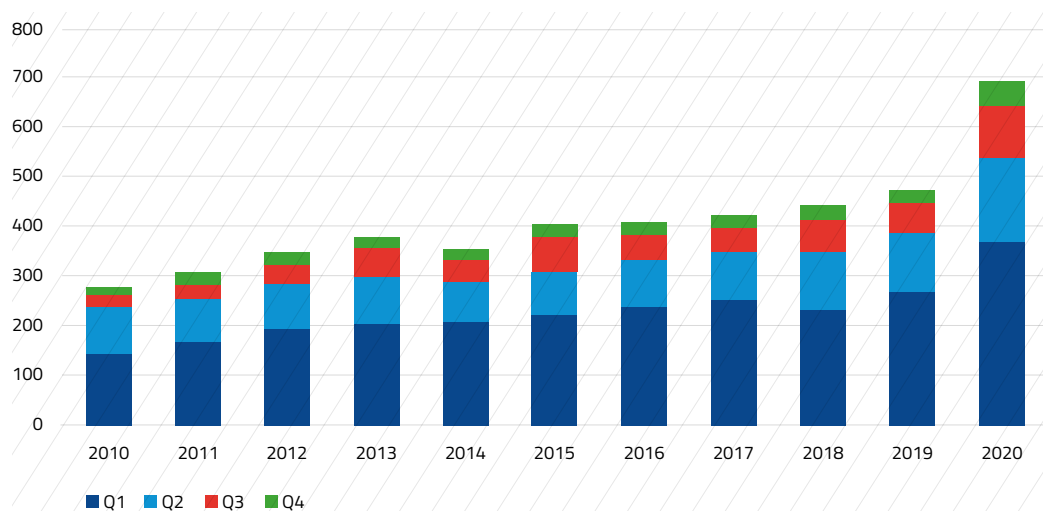
The following graph shows the historical evolution from 2010 to 2020.



Although the number of publications has increased significantly, as discussed above, the mean impact factor has slightly decreased since last year from a factor of 5.8 to 5.6. This reduction is not relevant, because values between 5.5 and 6 are considered very positive. The following table shows the evolution of the mean impact factor from 2010 to 2020.

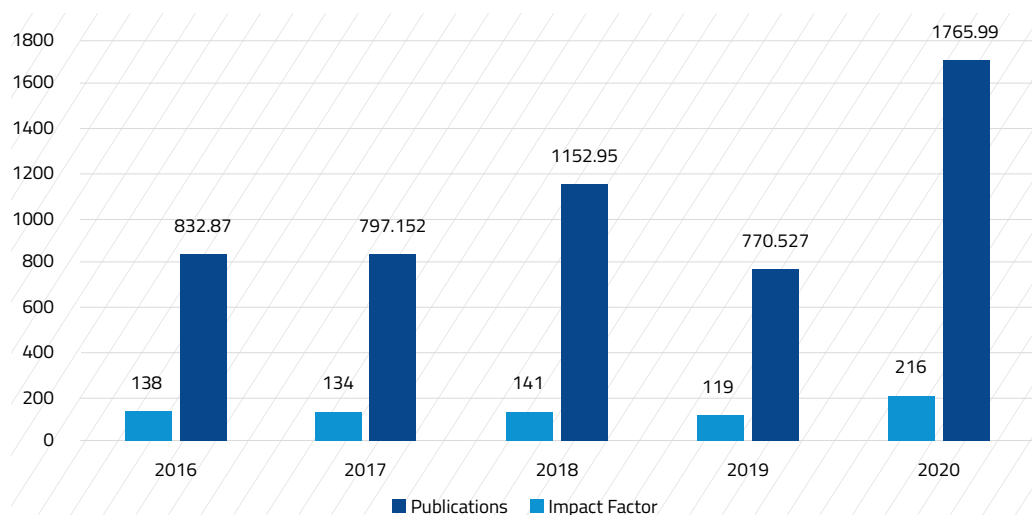
Mean Impact Factor

Regarding the distribution by quartiles, more than 50% of the publications in 2020 were published in first quartile journals and more than 70% in first and second quartile journals. The following table shows a graph with the distribution of publications by quartile from 2010 to 2020.

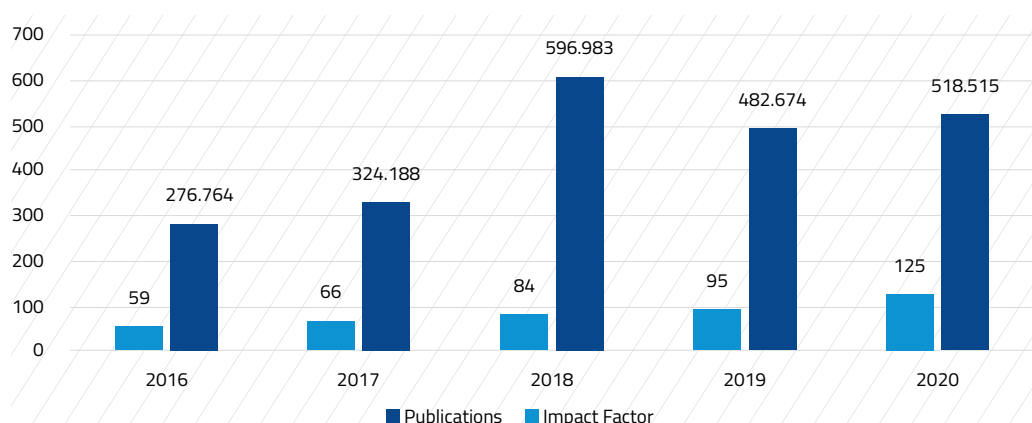


A more detailed analysis of the evolution of publications and the impact factor since 2016, for each of the three areas of the IIS, shows an increase with respect to previous years, both in the number of publications and in the mean impact factor. The increase in the mean impact factor is especially relevant in area 1, where its value has doubled compared to 2019. In contrast, this parameter has remained similar to previous years in Area 2, whereas in Area 3 has maintained its continuous growing trend.

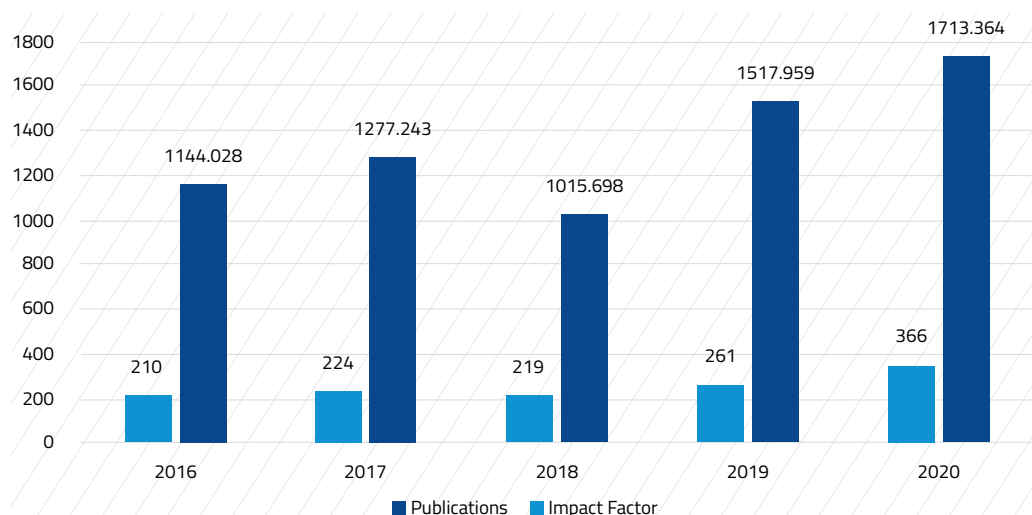
Area 1:
*Cellular and molecular etiopathogenic
mechanisms in inflammatory and
autoimmune diseases*



Area 2:
Translational neuroscience



Area 3:
Advanced therapies and individualized medicine



SCIENTIFIC PRODUCTION

A detailed list of the journals in which IIS articles have been published is shown below. The journals are sorted from highest to lowest by the number of publications and includes the journal quartile and its impact factor.

	ISSN	Total of publication	Quartil	Impact Factor
New England Journal of Medicine	0028-4793	1	Q1	74,699
Lancet	0140-6736	7	Q1	60,392
Nature	0028-0836	3	Q1	42,778
Science	0036-8075	1	Q1	41,845
Cell	0092-8674	1	Q1	38,637
Nature Medicine	1078-8956	1	Q1	36,13
Cancer Cell	1535-6108	1	Q1	26,602
Lancet Diabetes Endo	2213-8587	1	Q1	25,34
Lancet Respiratory Medicine	2213-2600	3	Q1	25,094
Lancet Infectious Diseases	1473-3099	1	Q1	24,446
Circulation	0009-7322	1	Q1	23,603
European Heart Journal	0195-668X	3	Q1	22,673
Lancet Global Health	2214-109X	1	Q1	21,597
Journal of the American College of Cardiology	0735-1097	3	Q1	20,589
Journal of Hepatology	0168-8278	3	Q1	20,582
Annals of Oncology	0923-7534	1	Q1	18,274
Eur Urol	0302-2838	1	Q1	17,947
Blood	0006-4971	1	Q1	17,543
American Journal of Respiratory and Critical Care Medicine	1073-449X	1	Q1	17,452
Gastroenterology	0016-5085	1	Q1	17,373
The Lancet Public Health	2468-2667	1	Q1	16,292
Journal of Extracellular Vesicles	2001-3078	1	Q1	14,976
Hepatology	0270-9139	2	Q1	14,679
Science Advances	2375-2548	1	Q1	13,116
European Respiratory Journal	0903-1936	3	Q1	12,339
Nature Communications	2041-1723	3	Q1	12,121
Journal of Clinical Investigation	0021-9738	1	Q1	11,864
Trends in Molecular Medicine	1471-4914	1	Q1	11,099
Journal of Hematology & Oncology	1756-8722	2	Q1	11,059
Journal of Allergy and Clinical Immunology	0091-6749	1	Q1	10,228
The American Journal of Gastroenterology	0002-9270	1	Q1	10,171
Redox Biology	2213-2317	3	Q1	9,986
Journal for Immunotherapy of Cancer	2051-1426	1	Q1	9,913
Arthritis & Rheumatology	2326-5191	1	Q1	9,586

Progress in Neurobiology	0301-0082	1	Q1	9,371
Medicinal Research Reviews	0198-6325	1	Q1	9,3
Isme J	1751-7362	1	Q1	9,18
Mol Ther	1525-0016	1	Q1	8,986
Embo Molecular Medicine	1757-4676	1	Q1	8,821
Neurology	0028-3878	2	Q1	8,77
Allergy	0105-4538	2	Q1	8,706
Leukemia	0887-6924	1	Q1	8,665
Journal of Crohns & Colitis	1873-9946	7	Q1	8,658
Clinical Gastroenterology and Hepatology	1542-3565	3	Q1	8,549
Ophthalmology	0161-6420	1	Q1	8,47
Jacc-Cardiovascular Interventions	1936-8798	7	Q1	8,432
Clinical Infectious Diseases	1058-4838	1	Q1	8,313
Chest	0012-3692	1	Q1	8,308
Journal of the American Academy of Dermatology	0190-9622	2	Q1	8,277
Cell Reports	2211-1247	1	Q1	8,109
Cochrane Database of Systematic Reviews	1469-493X	1	Q1	7,89
Autoimmunity Reviews	1568-9972	1	Q1	7,767
Environment International	0160-4120	1	Q1	7,577
Diabetologia	0012-186X	1	Q1	7,518
Alimentary Pharmacology & Therapeutics	0269-2813	4	Q1	7,515
EMBO Reports	1469-221X	1	Q1	7,497
Adv Healthc Mater	2192-2640	1	Q1	7,367
Am J Transplant	1600-6135	2	Q1	7,338
European Journal of Cancer	0959-8049	1	Q1	7,275
Aging Cell	1474-9718	1	Q1	7,238
Carbohydrate Polymers	0144-8617	1	Q1	7,182
European Journal of Epidemiology	0393-2990	1	Q1	7,135
Clinical Microbiology and Infection	1198-743X	1	Q1	7,117
Haematologica	0390-6078	1	Q1	7,116
PLOS Biology	1544-9173	1	Q1	7,076
British Journal of Dermatology	0007-0963	3	Q1	7
American Journal of Hematology	0361-8609	2	Q1	6,973
British Journal of Anaesthesia	0007-0912	1	Q1	6,88
Journal of Clinical Immunology	0271-9142	1	Q1	6,78
Journal of Autoimmunity	0896-8411	1	Q1	6,658

Arteriosclerosis Thrombosis and Vascular Biology	1079-5642	1	Q1	6,604
SCI Total Environ	0048-9697	1	Q1	6,551
Cellular and Molecular Life Sciences	1420-682X	2	Q1	6,496
Science Signaling	1945-0877	1	Q1	6,467
Critical Care	1466-609X	1	Q1	6,407
Cancer and Metastasis Reviews	0167-7659	2	Q1	6,4
Clin Nutr	0261-5614	2	Q1	6,36
Fertil Steril	0015-0282	1	Q1	6,312
Cell Death & Disease	2041-4889	2	Q1	6,304
Emerging Infectious Diseases	1080-6040	1	Q1	6,259
Reviews in Endocrine & Metabolic Disorders	1389-9155	1	Q1	6,192
Drugs	0012-6667	1	Q1	6,189
Cancers	2072-6694	6	Q1	6,126
Journal of Pathology	0022-3417	1	Q1	5,979
Pharmacological Research	1043-6618	1	Q1	5,893
Epidemiology and Psychiatric Sciences	2045-7960	1	Q1	5,876
Oncoimmunology	2162-402X	1	Q1	5,869
Journal of Bone and Mineral Research	0884-0431	1	Q1	5,854
Annals of Emergency Medicine	0196-0644	1	Q1	5,799
Transl Stroke Res	1868-4483	1	Q1	5,78
Environ Res	0013-9351	1	Q1	5,715
Rheumatology	1462-0324	4	Q1	5,606
European Journal of Medicinal Chemistry	0223-5234	2	Q1	5,572
J Mol Diagn	1525-1578	1	Q1	5,553
Journal of Cellular Physiology	0021-9541	1	Q1	5,546
Acta Physiologica	1748-1708	1	Q1	5,542
British Journal of Haematology	0007-1048	2	Q1	5,518
Cellular Physiology and Biochemistry	1015-8987	1	Q1	5,5
Circulation-Cardiovascular Interventions	1941-7640	1	Q1	5,493
Journal of Antimicrobial Chemotherapy	0305-7453	4	Q1	5,439
Multiple Sclerosis Journal	1352-4585	1	Q1	5,412
Journal of Clinical Endocrinology & Metabolism	0021-972X	4	Q1	5,399
Talanta	0039-9140	1	Q1	5,339
Molecular Nutrition & Food Research	1613-4125	1	Q1	5,309
Exercise Immunology Review	1077-5552	1	Q1	5,3
Journal of the European Academy of Dermatology and Venereology	0926-9959	5	Q1	5,248

Heart	1355-6037	1	Q1	5,213
J Parkinson Dis	1877-7171	1	Q1	5,178
Liver International	1478-3223	2	Q1	5,175
Oncotarget	1949-2553	1	Q1	5,168
International Journal of Cancer	0020-7136	2	Q1	5,145
Frontiers in Immunology	1664-3224	2	Q1	5,085
J Med Internet Res	1438-8871	1	Q1	5,034
Antioxidants	2076-3921	7	Q1	5,014
Breast Cancer Res	1465-5411	1	Q2	4,988
Annals Of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology	1081-1206	1	Q1	4,969
Faseb Journal	0892-6638	1	Q1	4,966
Biochemical Pharmacology	0006-2952	1	Q1	4,96
Archivos de Bronconeumologia	0300-2896	7	Q1	4,957
Journal of Clinical Epidemiology	0895-4356	1	Q1	4,952
Journal of Medical Genetics	0022-2593	1	Q1	4,943
Antimicrobial Agents and Chemotherapy	0066-4804	1	Q1	4,904
Journal of Immunology	0022-1767	1	Q2	4,886
Biomarker Research	2050-7771	1	Q1	4,866
Journal of Infection	0163-4453	2	Q1	4,842
Bioorg Chem	0045-2068	1	Q1	4,831
Endocrine-Related Cancer	1351-0088	1	Q1	4,8
J Headache Pain	1129-2369	2	Q1	4,797
CNS Drugs	1172-7047	1	Q1	4,786
Journal of Cystic Fibrosis	1569-1993	1	Q1	4,759
Seminars in Arthritis and Rheumatism	0049-0172	5	Q1	4,751
Bone Marrow Transplantation	0268-3369	9	Q1	4,725
Biomedicines	2227-9059	1	Q1	4,717
Depress Anxiety	1091-4269	1	Q1	4,702
European Journal of Nutrition	1436-6207	1	Q1	4,664
Disease Models & Mechanisms	1754-8403	1	Q1	4,651
Revista Espanola de Cardiologia	1885-5857	4	Q1	4,642
Appl Clay Sci	0169-1317	2	Q1	4,605
Journal of the American Heart Association	2047-9980	2	Q1	4,605
Clin Pharmacokinet	0312-5963	2	Q1	4,604
Carcinogenesis	0143-3334	1	Q2	4,603
International Journal of Molecular Sciences	1422-0067	9	Q1	4,556
Nutrients	2072-6643	5	Q1	4,546
Apoptosis	1360-8185	1	Q2	4,543
European Journal of Neurology	1351-5101	5	Q1	4,516

AIDS	0269-9370	1	Q1	4,511
Journal of Virology	0022-538X	1	Q1	4,501
ACS Chemical Neuroscience	1948-7193	1	Q1	4,486
European Psychiatry	0924-9338	1	Q1	4,464
Journal of Neurointerventional Surgery	1759-8478	1	Q1	4,46
Journal of Personalized Medicine	2075-4426	1	Q1	4,433
International Journal of Obesity	0307-0565	1	Q1	4,419
Thrombosis and Haemostasis	0340-6245	1	Q1	4,379
Journal of the American Medical Directors Association	1525-8610	1	Q1	4,367
Cells	2073-4409	6	Q2	4,366
Neurobiol Aging	0197-4580	1	Q1	4,347
Nanomaterials-Basel	2079-4991	1	Q2	4,324
Amyloid	1350-6129	1	Q1	4,323
Infectious Diseases and Therapy	2193-8229	1	Q1	4,307
Inflammatory Bowel Diseases	1078-0998	1	Q2	4,261
Frontiers in Pharmacology	1663-9812	2	Q1	4,225
Clinical and Experimental Allergy	0954-7894	1	Q2	4,217
Frontiers in Medicine	2296-858X	3	Q1	4,188
American Heart Journal	0002-8703	1	Q2	4,153
Bone	8756-3282	1	Q2	4,147
Frontiers in Cellular and Infection Microbiology	2235-2988	1	Q2	4,123
Biochimica et Biophysica Acta	0167-4889	1	Q2	4,105
Arthritis Research & Therapy	1478-6354	1	Q1	4,103
European Radiology	0938-7994	2	Q1	4,101
Antiviral Research	0166-3542	1	Q1	4,101
Metabolites	2218-1989	1	Q2	4,097
Foods (Basel, Switzerland)	2304-8158	2	Q1	4,092
Biomolecules	2218-273X	1	Q2	4,082
Frontiers in Molecular Neuroscience	1662-5099	1	Q2	4,057
Arthritis Care & Research	2151-464X	2	Q2	4,056
Europace	1099-5129	1	Q2	4,045
Headache	0017-8748	1	Q1	4,041
Nutritional Neuroscience	1028-415X	1	Q2	4,028
Acta Dermato-Venereologica	0001-5555	1	Q1	4,016
Helicobacter	1083-4389	4	Q2	4
Scientific Reports	2045-2322	14	Q1	3,998
Eurointervention	1774-024X	5	Q2	3,993
Cellular Signalling	0898-6568	1	Q2	3,968
Clinical and Translational Gastroenterology	2155-384X	1	Q2	3,968
EJSO-Eur J Surg Onc	0748-7983	1	Q1	3,959
J Neurol	0340-5354	1	Q1	3,956

Pituitary	1386-341X	1	Q2	3,954
Contact Dermatitis	0105-1873	9	Q1	3,952
Endocrinology	0013-7227	1	Q2	3,934
Respiratory Research	1465-993X	2	Q2	3,924
Atherosclerosis	0021-9150	1	Q1	3,919
Journal of Affective Disorders	0165-0327	2	Q1	3,892
PLOS Neglected Tropical Diseases	1935-2735	1	Q1	3,885
Advances in Therapy	0741-238X	2	Q1	3,871
Osteoporosis International	0937-941X	1	Q2	3,864
Occup Environ Med	1351-0711	1	Q1	3,824
Expert Review of Clinical Immunology	1744-666X	1	Q2	3,792
Genes-Basel	2073-4425	2	Q2	3,759
Breast	0960-9776	1	Q1	3,754
British Journal of Clinical Pharmacology	0306-5251	1	Q2	3,74
Open Forum Infectious Diseases	2328-8957	2	Q2	3,656
Frontiers in Endocrinology	1664-2392	1	Q2	3,644
Pancreatology	1424-3903	1	Q2	3,629
Journal of Sleep Research	0962-1105	1	Q2	3,623
SOC Sci Med	0277-9536	1	Q1	3,616
BMC Genomics	1471-2164	1	Q2	3,594
Digestive and Liver Disease	1590-8658	2	Q2	3,57
Clin Lung Cancer	1525-7304	1	Q2	3,55
United European Gastroenterology Journal	2050-6406	2	Q2	3,549
Clinical and Experimental Immunology	0009-9104	1	Q2	3,532
Therapeutic Advances in Gastroenterology	1756-283X	1	Q2	3,52
Experimental Hematology and Oncology	2162-3619	1	Q2	3,492
Cancer Medicine	2045-7634	1	Q2	3,491
Journal of Investigational Allergology & Clinical Immunology	1018-9068	3	Q2	3,488
European Journal of Clinical Investigation	0014-2972	1	Q1	3,481
Expert Review of Clinical Pharmacology	1751-2433	1	Q2	3,481
JAIDS-Journal of Acquired Immune Deficiency Syndromes	1525-4135	1	Q2	3,475
Journal of Gastroenterology and Hepatology	0815-9319	1	Q2	3,437
Cellular Microbiology	1462-5814	1	Q2	3,43
Pediatric Obesity	2047-6310	1	Q1	3,429
CTS-Clin Transl Sci	1752-8054	1	Q2	3,373
Experimental Dermatology	0906-6705	1	Q1	3,368

Journal of Rheumatology	0315-162X	2	Q2	3,35
Toxicology and Applied Pharmacology	0041-008X	1	Q2	3,347
Journal of Epidemiology and Community Health	0143-005X	1	Q1	3,342
Brain Sciences	2076-3425	4	Q2	3,332
Clinical and Experimental Rheumatology	0392-856X	14	Q2	3,319
Can J Psychiat	0706-7437	1	Q1	3,313
J Cardiovasc Transl	1937-5387	1	Q2	3,312
Journal of clinical medicine	2077-0383	12	Q1	3,303
Annals of Translational Medicine	2305-5839	2	Q2	3,297
Front Neuroanat	1662-5129	1	Q1	3,292
Health Place	1353-8292	1	Q1	3,29
New J Chem	1144-0546	1	Q2	3,288
Molecules	1420-3049	2	Q2	3,267
Endocrine	1355-008X	2	Q3	3,235
International Journal of Cardiology	0167-5273	4	Q2	3,229
Expert Opinion on Biological Therapy	1471-2598	1	Q2	3,224
Emergencias	1137-6821	2	Q1	3,173
Pflugers Archiv-European Journal of Physiology	0031-6768	1	Q2	3,158
Bmc Cancer	1471-2407	2	Q3	3,15
Surg Endosc	0930-2794	1	Q1	3,149
Journal of Intensive Care Medicine	0885-0666	1	Q2	3,142
Cerebellum	1473-4222	1	Q2	3,129
Journal of Psychopharmacology	0269-8811	1	Q2	3,121
Journal of the Neurological Sciences	0022-510X	1	Q2	3,115
Respiratory Medicine	0954-6111	2	Q2	3,095
J Anxiety Disord	0887-6185	1	Q1	3,079
Neuroscience	0306-4522	2	Q2	3,056
Minerva Med	0026-4806	1	Q1	3,031
Leukemia & Lymphoma	1042-8194	1	Q2	2,969
Prostaglandins Leukotrienes and Essential Fatty Acids	0952-3278	1	Q3	2,932
Pharmacogenomics Journal	1470-269X	2	Q2	2,91
Virchows Arch	0945-6317	1	Q2	2,906
Annals of Hematology	0939-5555	1	Q2	2,904
Frontiers in neurology	1664-2295	2	Q2	2,889
Multiple Sclerosis and Related Disorders	2211-0348	1	Q2	2,889
Journal of Neuroendocrinology	0953-8194	1	Q3	2,886
ACS Omega	2470-1343	1	Q2	2,87
Thrombosis Research	0049-3848	1	Q2	2,869
International Journal of Environmental Research and Public Health	1661-7827	1	Q1	2,849

European Journal of Clinical Microbiology & Infectious Diseases	0934-9723	2	Q2	2,837
Radiat Oncol	1748-717X	1	Q2	2,817
J Nutr Health Aging	1279-7707	2	Q3	2,791
International Journal Of Chronic Obstructive Pulmonary Disease	1178-2005	1	Q2	2,772
Digestive Diseases And Sciences	0163-2116	1	Q3	2,751
Pediatric Research	0031-3998	2	Q1	2,747
PloS one	1932-6203	6	Q2	2,74
Clinical & Translational Oncology	1699-048X	3	Q3	2,737
Journal of Orthopaedic Research	0736-0266	1	Q2	2,728
Journal of Clinical Hypertension	1524-6175	1	Q2	2,719
Anaerobe	1075-9964	1	Q3	2,709
BMC Psychiatry	1471-244X	1	Q2	2,704
BMC Infectious Diseases	1471-2334	1	Q3	2,688
International Journal Of Geriatric Psychiatry	0885-6230	3	Q1	2,675
Basic & Clinical Pharmacology & Toxicology	1742-7835	1	Q3	2,651
Frontiers in Pediatrics	2296-2360	1	Q1	2,634
Malaria Journal	1475-2875	1	Q1	2,631
Human Vaccines & Immunotherapeutics	2164-5515	1	Q2	2,619
Oral Dis	1354-523X	1	Q1	2,613
Journal of Gastrointestinal Surgery	1091-255X	1	Q2	2,573
American Journal of Cardiology	0002-9149	2	Q2	2,57
Child Abuse Neglect	0145-2134	1	Q1	2,569
Hormone and Metabolic Research	0018-5043	1	Q3	2,562
J Adv Nurs	0309-2402	1	Q1	2,561
Acta Tropica	0001-706X	1	Q1	2,555
Psychology & Health	0887-0446	1	Q1	2,534
Seizure-European Journal of Epilepsy	1059-1311	1	Q3	2,522
BMJ Open	2044-6055	2	Q2	2,496
Infectious Diseases (title changes)	2374-4235	1	Q3	2,494
Journal of Geriatric Cardiology	1671-5411	1	Q2	2,491
Physica Medica-European Journal of Medical Physics	1120-1797	1	Q2	2,485
Aging & Mental Health	1360-7863	3	Q1	2,478
J Clin Pathol	0021-9746	1	Q2	2,46
Neurological Sciences	1590-1874	2	Q3	2,415
Journal of Pain Research	1178-7090	1	Q3	2,386
Medicina Intensiva	0210-5691	2	Q3	2,363
Crisis-The Journal of Crisis Intervention and Suicide Prevention	0227-5910	1	Q2	2,356
Pediatric Blood & Cancer	1545-5009	1	Q2	2,355
Journal of Happiness Studies	1389-4978	3	Q1	2,344

Pharmacogenomics	1462-2416	2	Q3	2,339
Dermatologic Therapy	1396-0296	6	Q2	2,327
Journal of Clinical Densitometry	1094-6950	1	Q3	2,31
Prehosp Emerg Care	1090-3127	1	Q2	2,29
Neurologia (Barcelona, Spain)	0213-4853	7	Q3	2,283
Clinical Drug Investigation	1173-2563	1	Q3	2,267
Journal of Human Hypertension	0950-9240	1	Q3	2,26
J Cardiothor Vasc An	1053-0770	1	Q3	2,258
European Journal of Gastroenterology & Hepatology	0954-691X	2	Q4	2,251
Lupus	0961-2033	2	Q3	2,251
Neuroradiology	0028-3940	1	Q3	2,238
Disability and Rehabilitation	0963-8288	1	Q1	2,222
Current Pharmaceutical Design	1381-6128	1	Q3	2,208
Expert Review of Medical Devices	1743-4440	1	Q3	2,2
Injury Prev	1353-8047	4	Q2	2,191
Hormone Research in Paediatrics	1663-2818	3	Q2	2,174
Journal of Dermatological Treatment	0954-6634	1	Q2	2,156
American Journal of Medical Genetics Part A	1552-4825	1	Q3	2,125
Journal of Geriatric Psychiatry and Neurology	0891-9887	1	Q3	2,125
Human Psychopharmacology-Clinical And Experimental	0885-6222	1	Q3	2,112
Ocular immunology and inflammation	0030-6053	1	Q2	2,112
Injury-International Journal of the Care of the Injured	0020-1383	4	Q2	2,106
Surgical Infections	1096-2964	1	Q2	2,102
International Journal of Oral and Maxillofacial Surgery	0901-5027	2	Q2	2,068
International Journal of Dermatology	0011-9059	2	Q3	2,067
J Thromb Thrombolys	0929-5305	1	Q3	2,054
Health Soc Care Comm	0966-0410	1	Q1	2,05
Journal of Thoracic Disease	2072-1439	1	Q3	2,046
Catheterization and Cardiovascular Interventions	1522-1946	4	Q3	2,044
Neurourology and Urodynamics	0733-2467	1	Q3	2,037
Cardiovasc Inter Rad	0174-1551	1	Q3	2,034
J Med Ethics	0306-6800	1	Q1	2,021
Rheumatology International	0172-8172	2	Q3	1,984
International Journal of Cardiovascular Imaging	1569-5794	5	Q3	1,969
Med Microbiol Immun	0300-8584	1	Q3	1,961
Scand J Surg	1457-4969	1	Q2	1,95

J Womens Health	1540-9996	1	Q1	1,933
Telemed e-Health	1530-5627	1	Q3	1,931
Journal of Asthma	0277-0903	1	Q3	1,899
Trials	1745-6215	1	Q3	1,883
J Bras Pneumol	1806-3713	1	Q4	1,87
World Neurosurgery	1878-8750	2	Q3	1,829
J Mol Evol	0022-2844	1	Q3	1,821
Acta Neurochirurgica	0001-6268	1	Q3	1,817
Cardiology	0008-6312	1	Q3	1,791
Australasian Journal of Dermatology	0004-8380	1	Q3	1,789
Journal of Stroke & Cerebrovascular Diseases	1052-3057	2	Q4	1,787
Bmc Pharmacology & Toxicology	2050-6511	1	Q4	1,771
Journal of Cranio-Maxillofacial Surgery	1010-5182	1	Q3	1,766
J Ultras Med	0278-4297	1	Q2	1,759
Clinical Simulation in Nursing	1876-1399	1	Q2	1,713
Journal of Microbiological Methods	0167-7012	1	Q4	1,707
Enfermedades Infecciosas y Microbiología Clínica	0213-005X	3	Q4	1,654
Eur J Ophthalmol	1120-6721	1	Q3	1,642
Medicina Clínica	0025-7753	4	Q3	1,635
J Clin Apheresis	0733-2459	1	Q4	1,629
Growth Hormone & Igf Research	1096-6374	1	Q4	1,618
Medicina Oral Patología Oral y Cirugía Bucal	1698-6946	1	Q3	1,596
Revista Española de Enfermedades Digestivas	1130-0108	5	Q4	1,591
Gastroenterología y Hepatología	0210-5705	11	Q4	1,581
Gaceta Sanitaria	0213-9111	1	Q3	1,564
Nefrología	0211-6995	3	Q4	1,544
Int J Occup Med Env	1232-1087	1	Q3	1,541
Int J Technol Assess	0266-4623	1	Q3	1,494
Interv Neuroradiol	1591-0199	1	Q4	1,479
Journal of Comparative Effectiveness Research	2042-6305	1	Q4	1,468
Neuroreport	0959-4965	1	Q4	1,394
Presse Med	0755-4982	1	Q3	1,388
Surg Laparo Endo Per	1530-4515	1	Q3	1,382
Journal of Cutaneous Pathology	0303-6987	2	Q3	1,373
Int J Qual Stud Heal	1748-2623	1	Q3	1,368
Coronary Artery Disease	0954-6928	3	Q4	1,335
Cirugía Española	0009-739X	7	Q3	1,323

Revista Clinica Espanola	0014-2565	5	Q3	1,304
Journal of Pediatric Endocrinology & Metabolism	0334-018X	2	Q3	1,278
Diagnostic Cytopathology	8755-1039	2	Q3	1,229
Acta Cytologica	0001-5547	1	Q4	1,226
Annals of the Royal College of Surgeons of England	0035-8843	1	Q4	1,22
Medicina-Lithuania	1010-660X	1	Q3	1,205
Eur Neurol	0014-3022	2	Q4	1,182
Endocrinologia Diabetes y Nutricion	2530-0180	1	Q4	1,18
Revista Espanola de Quimioterapia	0214-3429	6	Q4	1,132
American Journal of Dermatopathology	0193-1091	3	Q4	1,102
Atención Primaria	0212-6567	1	Q3	1,087
Giornale Italiano di Dermatologia e Venereologia	0392-0488	1	Q4	1,056
Therapeutic Apheresis and Dialysis	1744-9979	1	Q4	1,041
Cutis	0011-4162	1	Q4	1,022

PATENTS

Innovation improves the quality of life of the citizens, through the improvement of the healthcare and it is used for the launching of new products and services. In this sense, IIS Princesa is actively committed to Innovation and the transfer of innovative advances to industry. As a sign of this commitment, researchers at our center, in collaboration with other institutions, have developed the patents shown below.

NATIONAL APPLICATIONS OF PATENTS

Title: Método de detección temprano de daño hepático mediante proteínas morfogenéticas óseas (BMPs) en biopsia líquida.

Number: P202030678

Date of applicant: 02/07/2020.

Owners/s: Fundación de Investigación Hospital Universitario de La Princesa (100%).

Inventors: Patricia Marañón Barnusell, Paloma Narros Fernández, Esther Rey Fernández, Carmelo García Monzón, Javier Egea Máiquez, Águeda González Rodríguez.

Title: Método de para determinar la evolución del daño cerebral agudo y composición farmacéutica para su tratamiento.

Number: P202031194.

Date of applicant: 30/11/2020.

Owners/s: Fundación de Investigación Hospital Universitario de La Princesa (52%); Fundación para la Investigación Biomédica del Hospital Universitario La Paz (24%); Universidad Autónoma de Madrid (4%) Fundación para la Investigación Biomédica del Hospital 12 de Octubre (20%).

Inventors: Francisco Javier Egea Máiquez, Víctor Farré Alins, Alejandra Palomino Antolín, Paloma Narros Fernández, Juliana Martins Rosa, Esther Parada Pérez, Borja Jesús Hernández García, José María Roda Frade, Santiago Yus Teruel, Alfonso Lagares Gómez-Abascal, Cristina Sánchez Carabias, Luis Gandía Juan.

NATIONAL PATENTS GRANTED

Title: Método no invasivo para determinar la presión intra-craneal mediante la actividad bioeléctrica del cerebro.

Number: P201730943

Grant date: 03/02/2020.

Owners/s: Fundación de Investigación Hospital Universitario de La Princesa (100%).

Inventors: Ancor Sanz García, Jesús Pastor Gómez, Lorena Carolina Vega Zelaya, María Del Carmen Torrecilla López, María Gema Vega González, Fernando Monasterio Chicharro, Rafael García De Sola, Paloma Pulido Rivas, Cristina Virginia Torres Díaz.

ROYALTY APPLICATIONS IN SPAIN

Title: Seroreactivity assay to the cysteine-like protease of SARS Cov2 efficiently discriminates between Covid 19-infected and uninfected individuals.

Authors: Hugh Thomson Reyburn, Mar Valés Gómez, Jose Miguel Rodríguez Frade, Jose María Casanovas Suelves, Eduardo López Granados, Carmen Cámara Hijón, Pilar Nozal Aranda, Arantzazu Alfranca González, Pedro Martínez Fleta, Francisco Sánchez Madrid

Necessary collaborators: Gloria Esteso Tornero, Daniel Fernández Soto.



COMPETITIVE PROJECTS

GRANTS:

Funding Institution	Call	Calls granted
Instituto de Salud Carlos III	Proyectos de Investigación en Salud	12
	Investigación Clínica Independiente	1
Gilead	Becas Gilead a la Investigación Biomédica	1
Comisión Europea	H2020	1

Research staff fully or partially funded through competitive calls in 2020:

Funding Institution	Call	Calls granted
Instituto de Salud Carlos III	PFIS	3
	Sara Borrell	1
	Gestor GIS	1
	Juan Rodes	3
	Rio Hortega	3
	Miguel Servet I	1
Comunidad de Madrid	Ayudante de Investigación	2

DEFENDED DOCTORAL THESES

The thesis represents a systematic and exhaustive research work on a subject, which is considered a crucial step in the training of new generations of researchers. During 2020, 13 theses have been defended by member of the IIS. Three of them was a European thesis.

THESES

Doctoral candidate	Title	Director/s	Defense date
Diab Cáceres, Layla	Fibrosis Quística y calidad de vida en adultos. Valoración del estudio radiológico	Ancochea Bermúdez, Julio Girón Moreno, Rosa María	09/09/2020
Zubiaur Precioso, Pablo	Research for clinical pharmacogenetics implementation: from candidate gene studies to physiologically based pharmacokinetic modelling	Abad Santos, Francisco Saiz Rodríguez, Miriam	18/12/2020
López Arribas, Raquel	Diseño, síntesis y evaluación farmacológica de nuevos análogos de ácido okadaico con diana en la proteína fosfatasa 2A: interés en cáncer de pulmón y enfermedad de Alzheimer	Cristóbal de los Ríos Salgado Carmen Montiel López	23/10/2020
Koller, Dora	Evaluation of genetic polymorphisms associated with the metabolic effects of aripiprazole and olanzapine	Abad Santos, Francisco	23/07/2020
Moreno Agostino, Darío	New evidence on determinants & course of a focus on older adults: Subjective wellbeing in the general population	José Luis Ayuso Mateos Marta Miret García	13/07/2020
Escudero Díez, Carmelo	Desarrollo de un procedimiento de inmunoterapia oral con huevo: La clara de huevo deshidratada como fuente alergénica, eficacia, seguridad y estudio inmunológico	María Dolores Ibáñez Sandín	03/07/2020
Ruiz Ruiz, Cristina	The ATP-gated P2X7 receptor as a novel therapeutic target for amyotrophic lateral sclerosis	Antonio García García	03/03/2020
Leónidas Espinoza Vega, Manuel	Movilización de linfocitos infiltrantes de tumor a sangre periférica en un modelo murino de neuroblastoma. Análisis inmunofenotípico, clonar y funcional	Manuel Ramírez Orellana Ana Lourdes Luis Huertas	15/09/2020
Rodríguez Jiménez, Pedro	Estudio del papel inmunopatogénico de las moléculas TROMBOSPONDINA-1 y GADD45-ALFA en la psoriasis	Hortensia de la Fuente Flores María del Mar Llamas Velasco	28/09/2020
Martín Ramírez, Alexandra	Evaluación de métodos de diagnóstico de malaria para su utilización en programas de control y eliminación en las zonas endémicas	Laura María Cardeñoso Domingo José Miguel Rubio Muñoz	27/11/2020

EUROPEAN THESES

Doctoral candidate	Title	Director/s	Defense date
Luengo Martín, Enrique	The coming of age of selective types of autophagy for the treatment of Alzheimer's disease and related tauopathies	García López, Manuela	18/12/2020
Concepción Arcones, Alba	Influence of GRK2 levels in the modulation of glucose homeostasis in health and disease	Murga Montesinos, Cristina Mayor Menéndez, Federico	29/10/2020
Franco Luzón, Lidia	Estudio de efectos inmunes sobre el tumor, de mecanismos de resistencia y de las características biológicas de la terapia Celyvir	Manuel Ramírez Orellana África González Murillo	26/06/2020

CLINICAL GUIDELINES

Clinical Guidelines are the compendium of recommendations based on the systematic review of evidence and the evaluation of benefits and risks of different alternatives, with the aim of improving patients' healthcare. During 2020, IIS Princesa researchers have participated in the development of 20 clinical guidelines.

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nary Units (SEMICYUC), the Spanish Society of Otorhinolaryngology and Head and Neck Surgery (SEORL-CCC) and the Spanish Society of Anesthesiology and Resuscitation (SEDAR) on tracheotomy in patients with COVID-19 infection. Acta Otorrinolaringol Esp 71: 386-392. 2020. PMID: 32513456. DOI: 10.1016/j.otorri.2020.04.002.

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Cisneros Serrano, Carolina Victoria. **Guía Española para el Manejo del Asma GEMA 5.0.** Guía Española para el Manejo del Asma GEMA 5.0.

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CLINICAL TRIALS

Clinical Trials represent an indication of being at the forefront of R+D in the health sector. They

provide a benefit to society based on the most innovative treatments and the most advanced techniques, with special aim of improving the health and well-being of citizens. During 2020, 146 new agreements have been signed for clinical trials led by IIS members.

Daudén Tello, Esteban. **Búsqueda de marcadores genéticos predictores de respuesta a secukinumab en el tratamiento de la psoriasis.** Sponsored by: Novartis Farmacéutica, S.A.

Romero Laorden, Nuria / Olivier Gómez, Carlos. **Estudio observacional para describir retrospectivamente la evolución de los pacientes con cáncer de próstata a lo largo de la enfermedad a través de la reutilización de los registros electrónicos de salud con inteligencia artificial (ESTUDIO OVERVIEW).** Sponsored by: JANSSEN-CILAG, S.A.

Pérez Gisbert, Javier. **Impacto de la telemonitorización en el manejo de la enfermedad inflamatoria intestinal compleja en España: estudio multicéntrico TECCU.** Sponsored by: GETECCU.

Vivancos Mora, José Aurelio. **Prevención de ictus en sobrevivientes de hemorragia intracerebral con fibrilación auricular- Subestudio de modelización predictiva.** Sponsored by: Imperial College of Science, Technology and Medicine. EudraCT: 2018-002176-41.

Zapatero Laborda, Almudena. **PEACE V: un ensayo aleatorizado de fase II para el tratamiento de rescate de metástasis del cáncer de próstata nodal recurrente.** Sponsored by: Universidad de Gante.

Romero Laorden, Nuria. **Eficacia del atezolizumab con radioterapia concomitante en pacientes con cáncer de vejiga músculo-invasivo.** Sponsored by: Grupo Español de Oncología Genitourinaria, SOGUG. EudraCT: 2018-004348-47.

Reyes Copa, Guillermo. **Comparación de prótesis sin sutura frente a prótesis convencionales**

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Mejía Abril, Gina Paola. **Identificación de factores clínicos y farmacogenéticos predictores de respuesta a nuevos anticoagulantes orales en el tratamiento de la fibrilación auricular no valvular.** Sponsored by: Fundación para la Investigación Biomédica del Hospital Universitario de la Princesa.

Loscertales Pueyo, Javier. **Estudio de fase 3b, multicéntrico, abierto y con un solo grupo, de acalabrutinib (ACP-196) en sujetos con leucemia linfocítica crónica.** Sponsored by: AstraZeneca UK LIMITED. EudraCT: 2019-001573-89.

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Rabaneda Vicente, Esther. **Estudio internacional, multicéntrico, activo, paralelo controlado, abierto, randomizado, con tres ramas de tratamiento para comparar la respuesta de la inflamación sinovial evaluada por ecografía a baricitinib, en monoterapia o combinado con metotrexat.** Sponsored by: Instituto de Investigación Sanitaria Fundación Jiménez Díaz. EudraCT: 2018-004558-30.

López Manzanares, Lydia. **Estudio en fase II, aleatorizado, doble ciego y controlado con placebo de K0706 en pacientes con enfermedad de Parkinson incipiente.** Sponsored by: Sun Pharma Advanced Research Company Limited. EudraCT: 2018-000337-15.

García Buey, Luisa Consuelo. **Estudio fase I (primera vez en humanos), multicéntrico, aleatorizado, simple ciego y de escalado controlado de dosis para evaluar la reactogenicidad, la seguridad, la inmunogenicidad y la eficacia de las vacunas**

frente al VHB basadas en vectores virales. Sponsored by: GlaxoSmithKline, S.A. EudraCT: 2017-001452-55.

García Buey, Luisa Consuelo. **Estudio complementario para evaluar la diseminación de ChAd155-hli-VHB en un subgrupo de pacientes con hepatitis B crónica incluidos en el estudio fase I (primera vez en humanos), aleatorizado, multicéntrico y simple ciego TH HBV VV-001.** Sponsored by: GlaxoSmithKline, S.A. EudraCT: 2017-002574-39.

López Manzanares, Lydia. **Monitorización de la Movilidad de enfermos de Parkinson con fines terapéuticos - Ensayo Clínico.** Sponsored by: Consorci Sanitari de l'Alt Penedès i Garraf.

Marazuela Azpiroz, Mónica. **Ensayo Clínico en fase 3, aleatorizado, doble ciego, controlado con placebo, multicéntrico, para evaluar la eficacia y seguridad de octreotida subcutánea de liberación prolongada (CAM2029) en pacientes con acromegalia.** Sponsored by: Camurus AB. EudraCT: 2019-001191-11.

Marazuela Azpiroz, Mónica. **Ensayo en fase 3, abierto, de grupo único y multicéntrico, para evaluar la seguridad a largo plazo de octreotida (CAM2029) subcutánea de liberación prolongada en pacientes con acromegalia.** Sponsored by: Camurus AB. EudraCT: 2019-002190-66.

Llamas Velasco, Mar. **Estudio de resultados sanitarios en la psoriasis (PSoHO): estudio observacional internacional de resultados sanitarios durante 3 años sobre el tratamiento biológico de la psoriasis en placas de moderada a grave.** Sponsored by: Eli Lilly and Company.

Alfonso Manterola, Fernando. **REFORM: Estudio prospectivo, aleatorizado y de no inferioridad para determinar la seguridad y la eficacia del balón recubierto de fármaco Biolimus A9™, para el tratamiento de la reestenosis intra-stent: Primer ensayo clínico en el ser humano (First-in-Man study).** Sponsored by: BIOSENSORS EUROPE SA.

Sáez Béjar, Carmen María. **Terapia antibiótica corta comparada con el tratamiento antibiótico convencional en pacientes con endocarditis infecciosa por cocos gram positivos: ensayo clínico aleatorizado.** Sponsored by: D^a Carmen Olmos Blanco. EudraCT: 2019-003358-10.

González Moreno, Leticia. **Ensayo doble ciego, aleatorizado, controlado con placebo, fase IIb sobre la eficacia y seguridad de comprimidos de ácido norursodesoxicólico en pacientes con esteatohepatitis no alcohólica (EHNA).** Sponsored by: Dr. Falk Pharma GmbH. EudraCT: 2018-003443-31.

Moreno Carriles, Rosa María. **Eficacia y seguridad en la administración intraarterial de REX-001 en el tratamiento de úlceras isquémicas en pacientes con isquemia crítica de extremidades inferiores de categoría 5 según la clasificación de Rutherford y diabetes mellitus: un ensayo piv.** Sponsored by: Rexgenero Biosciences S. L.

Delgado Jimenez, Yolanda. **Estudio de extensión de retirada, aleatorizado, doble ciego y multicéntrico para demostrar la eficacia, seguridad y tolerabilidad a largo plazo de secukinumab subcutáneo en pacientes con hidradenitis supurativa de moderada a grave.** Sponsored by: Novartis Farmacéutica, S.A. EudraCT: 2019-003230-17.

López Manzanares, Lydia. **Estudio observacional, prospectivo, multinacional, multicéntrico que compara la efectividad de safinamida, rasagilina y otros "tratamientos estándar" como tratamiento complementario a la levodopa (l-dopa) en pacientes con enfermedad de parkinson (ep) fluctuante-SUCCESS.** Sponsored by: Zambon S.p.A.

Ortiz García, Ana. **Calidad asistencial en el manejo clínico de la Artritis Reumatoide atendiendo a la estrategia Treat to Target (T2T).** Sponsored by: Fundación Española de Reumatología.

Suárez Fernández, Carmen. **Fibrilación auricular en la práctica real en el manejo de la anticoagulación oral- AFIRMA 4.0.** Sponsored by: PFIZER S.L.U.

Alfonso Manterola, Fernando. **Estrategias de revascularización completa percutánea con stents recubiertos de polímeros biodegradables liberadores de sirolimus en pacientes con síndromes coronarios agudos y enfermedad de múltiples vasos, estudio BioVasc.** Sponsored by: Thoraxcentrum Research B.V.

del Arco Galán, Carmen. **Estudio Observacional Prospectivo acerca del manejo perioperatorio / periprocedimiento de los fármacos antitrombóticos en el "mundo real": REGISTRO REQXAA.** Sponsored by: Fundación Española de Farmacia Hospitalaria (FEFH).

García Vadillo, Jesús Alberto. **Estudio observacional, transversal sobre la facilidad de uso del dispositivo de inyección Terrosa Pen®.** Sponsored by: GEDEON RICHTER IBÉRICA S.A.U.

Morell Baladrón, Alberto. **Estudio de satisfacción y calidad vida en pacientes con enfermedad inmunomediada atendidos por los servicios de farmacia hospitalaria. Estudio SACVINFA.**

Meca Lallana, Virginia. **Estudio observacional sobre la efectividad y perfil de seguridad de alemtuzumab (Lemtrada®) en pacientes con esclerosis múltiple remitente recurrente tratados en la Comunidad de Madrid según las condiciones de práctica clínica habitual.** Sponsored by: Sanofi-Aventis, S.A.

Santander Vaquero, Cecilio. **Ensayo multicéntrico, aleatorizado, doble ciego, de grupos paralelos, controlado con placebo para investigar el uso de benralizumab para la esofagitis eosinofílica (MESSINA).** Sponsored by: Astra-Zeneca AB. EudraCT: 2019-002871-32.

López Manzanares, Lydia. **Estudio en fase III, de 182 semanas de duración y abierto sobre**

la seguridad y la tolerabilidad de TD-9855 en el tratamiento de la hipotensión ortostática neurogénica sintomática (HONs) en sujetos con fallo autonómico primario. Sponsored by: Theravance Biopharma Ireland Limited. EudraCT: 2019-002425-30.

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Ochoa Mazarro, Dolores. **Estudio fase I/IIa, de primera administración en humanos, aleatorizado, con observador ciego para evaluar la seguridad, reactogenicidad e inmunogenicidad de tres dosis diferentes de VAC52416 (EXPEC10V) en adultos de entre 60 y 85 años con un estado de sa.** Sponsored by: JANSSEN-CILAG, S.A. EudraCT: 2020-000657-27.

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Pérez Lucendo, Arís. **Delirio en pacientes críticos con infección por SARS-COV-2.”** Sponsored by: Respira. Fundación Española del Pulmón. SEPAR.

Ochoa Mazarro, Dolores. **Estudio fase 2a, aleatorizado, doble ciego, controlado con placebo,**

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López Manzanares, Lydia. **Ensayo de fase III, doble ciego, aleatorizado, controlado con placebo, de grupos paralelos, de dosis flexible y de 27 semanas para evaluar la eficacia, la seguridad y la tolerabilidad de tavapadón como tratamiento adyuvante para la enfermedad de Parkinson.** Sponsored by: Cerevel Therapeutics LLC. EudraCT: 2019-002951-40.

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García Buey, Luisa Consuelo. **Incidencia y gravedad de la infección por sars-cov2 (covid-19) en pacientes con hepatitis crónica por virus b en tratamiento con tenofovir o entecavir en España.** Sponsored by: Hospital Universitario del Henares.

Romero Laorden, Nuria. **Estudio aleatorizado, doble ciego, controlado con placebo de fase III de niraparib en combinación con acetato de abiraterona y prednisona frente a acetato de abiraterona y prednisona para el tratamiento de participantes con cáncer de próstata metastásico.** Sponsored by: JANSSEN-CILAG, S.A. EudraCT: 2020-002209-25.

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Ochoa Mazarro, Dolores. **Ensayo clínico cruzado, aleatorizado de bioequivalencia de vildagliptina/metformina 50/1000 mg comprimidos recubiertos con película, tras su administración oral en dosis única a voluntarios sanos con comida.** Sponsored by: Laboratorios Normon S.A. EudraCT: 2020-003619-81.

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De los Santos Gil, Ignacio. **Estudio Fase IIb, aleatorizado, con grupo control activo, parcialmente cegado, de búsqueda de dosis de GSK3640254 en comparación con un brazo control de dolutegravir, cada uno en combinación con inhibidores de la transcriptasa inversa análogos de nucleó.** Sponsored by: LABORATORIOS ViiV HEALTHCARE, S.L. EudraCT: 2019-004435-23.

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Rocío Martín, Esmeralda. **Valor diagnóstico de los potenciales evocados miogénicos vestibulares en el vértigo posicional paroxístico benigno.**

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del Arco Galán, Carmen. **Seguridad tras la Cardioversión Urgente de la Fibrilación Auricular.** Sponsored by: .

García de Vicuña, Rosario. **Evaluación del riesgo cardiovascular y de sus determinantes, en pacientes con artritis reumatoide, espondilitis anquilosante y artritis psoriásica.** Sponsored by: Fundación Española de Reumatología.

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Communication and

The concept of communicating science in journals or scientific congresses is deeply rooted in the field of scientific research, but scientists are becoming increasingly more aware of the need to disseminate science among citizens, which partly finance research with their taxes.

Communication of biomedical research allows the population to know and understand biomedical advances with application or possible application in human health, making the citizen more knowledgeable about the diseases that affect society.

The IIS Princesa uses two main tools to carry out this task: the web (www.iis-princesa.org) and the newsletter "Impact Factor". The Institute website www.iis-princesa.org, renewed in 2016 to adapt to the new trends of users, presents the most important news about its members, as well as information about courses, congresses, job offers or detailed information of

research groups. In addition, the website offers other services, such as the research calls alert service, which provides up to date information to subscribers about public and private, national or international calls.

The Impact Factor newsletter, published by the IIS Princesa since 2011, both in paper and electronic formats, shows the most outstanding scientific advances, the most relevant news and the successes of our researchers.

These activities are reinforced with the active participation of the IIS Princesa in the Science Week of the Community of Madrid which offers entertaining, interesting and important talks about the latest scientific research, in a format accessible to the public.

Number of sessions / communication conferences:

Fecha/s	Título	Ponente/Director
9-ene	Role of L-type amino acid transporter in skin inflammation.	Danay Cebrián
15-ene	Estudio genético diferencial (ImmunoChip) entre artritis reumatoide seropositiva y seronegativa	Nuria Montes Casado
16-ene	Estudio de las características farmacocinéticas y farmacodinámicas del anticuerpo monoclonal Natalizumab	José María Serra
22-ene	Dificultades para el desarrollo final de EASI (early arthritis severity index) y nuevas aproximaciones para resolverlas	Sebastián Rodríguez García
23-ene	El papel regulador de CD69 en la migración mediada por CCR7 en células dendríticas	Amalia Lamana
29-ene	Mecanismos moleculares de control de la presión arterial en situaciones especiales	Emilia Roy Vallejo
30-ene	Linfocitos entrenados con bacterias como próxima generación de inmunoterapias contra cáncer	Esteban Veiga
6-feb	Tailoring dendritic cells through nucleic acid sensors to boost HIV-specific CD8+ T cell responses	Marta Calvet
12-feb	Utilidad de la determinación de masa ósea de metacarpienos por DEXA como biomarcador en artritis de reciente comienzo	Irene Llorente Cubas
13-feb	Oxidized low-density lipoprotein binding to CD69 regulates the expression of PD-1	María Jiménez Fernández
20-feb	PD-L1: más allá del sistema inmune	Giulia Setti
26-feb	Niveles de expresión de Galectina 1 en pacientes con artritis reumatoide. ¿Un posible biomarcador en esta enfermedad?	Ana Triguero Martínez
27-feb	PSGL-1 and ADAM8 in the neutrophil extracellular traps	Antonio Muñoz Callejas
22-oct	Visión práctica sobre la inmunidad frente a SARS-Cov-2	Francisco Sánchez Madrid
29-oct	Caracterización de poblaciones mieloides diferencialmente afectadas en pacientes COVID-19	Ildefonso Sánchez Cerrillo
5-nov	Deregulated cellular circuits driving immunoglobulins and complement consumption associate with the severity of COVID-19	Ana Marcos Jiménez
12-nov	SARS-CoV-2 Cysteine-like Protease antibodies can be detected in serum and saliva of COVID-19 seropositive individuals	Pedro Martín-Fleta

Dissemination

19-nov	La Chaperonina CCT interviene en la reorganización de la red mitocondrial de la célula T, regulando su metabolismo durante la sinapsis inmune	Noa Martín Cófreces
26-nov	A new role for circulating T follicular helper cells in humoral response to anti-PD-1 therapy	Santiago Sánchez Alonso
3-dic	Effects of Cigarette Smoke on Pulmonary Arterial Remodeling	Javier Sevilla
10-dic	La entrada de sodio en la mitocondria regula la fosforilación oxidativa y las señales redox en la respuesta a hipoxia	Antonio Martínez Ruiz

Courses

Fecha/s	Título	Ponente/Director
21-23-ene	Curso de Soporte Cardiovascular avanzado	Mariano Aguilar Mulet.
28-29-ene	Curso de Soporte Vital Básico	Mariano Aguilar Mulet.
18-20-feb	Curso de Soporte Cardiovascular avanzado	Mariano Aguilar Mulet.
25-26-feb	Curso de Soporte Vital Básico	Mariano Aguilar Mulet.
3-nov	La Fábrica de Ideas Princesa, taller práctico de creatividad y pensamiento divergente	Jorge Gómez Zamora / Antonio Rodríguez Hita / Elena Español Pueyo
4-nov	¿Qué significa Respirar?	Javier Aspa Marco
5-nov	Simulación clínica Hospital de La Princesa Abróchense los cinturones	Rosa Méndez Hernández / Jesús M. Nieves Alonso
6-nov	¿Cómo es la vida de un medicamento? Etapas del desarrollo clínico	Dolores Ochoa Mazarro / Manuel Román / Samuel Martín
6-nov	Inmunología del tubo digestivo: del laboratorio a los pacientes	Samuel Fernández Tomé / Lorena Ortega Moreno / Alicia C. Marín / Irene Mora
10-nov	Cirugía mínimamente invasiva. Cirugía del siglo XXI	Guillermo Reyes Copa / Elena Martín Pérez / Ramón Moreno Balsalobre
10-nov	Biobancos: con-cienciados investigando junto a ti	Mara Ortega Gómez / Laura Gómez Cabañas / Ángel Lancha Sánchez
11-nov	Dale un giro a tu dolor, aprende a manejarlo	Almudena Mateos González
11-nov	Tatuajes, piercings y enfermedades de transmisión sexual. Mitos y realidades	Pedro Rodríguez / Alejandra Reolid
12-nov	Investigación biomédica translacional. De la investigación básica a la aplicación clínica.	Francisca Molina Jiménez / Jennifer Fernández Pacheco / Cecilio Santander Vaquero / Sergio Casabona Francés / Pedro Lorenzo Majano Rodríguez
13-nov	Investigación traslacional: línea directa entre el laboratorio y el paciente	Águeda González Rodríguez / Javier Egea Maíquez / Yaiza García / Patricia Marañón / Paloma Narros

ANNUAL
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ACTIVITY

2020



AREA 1



CELLULAR AND MOLECULAR ETIOPATHOGENIC MECHANISMS IN INFLAMMATORY AND AUTOIMMUNE DISEASES



- **LINE 1.1** INTERCELLULAR COMMUNICATION IN THE INFLAMMATORY RESPONSE
- **LINE 1.2** CELLULAR AND MOLECULAR RESPONSES TO HYPOXIA
- **LINE 1.3** ANIMAL MODELS OF INFLAMMATORY DISEASES AND INTERCELLULAR SIGNALLING
- **LINE 1.5** CELLULAR MECHANISMS AND MOLECULAR DETERMINANTS OF ALLERGY BASED DISEASES
- **LINE 1.6** INFLAMMATORY PROCESSES IN NEPHROLOGICAL DISEASES
- **LINE 1.7** INFLAMMATORY MECHANISMS IN PULMONARY DISEASES
- **LINE 1.8** INFLAMMATORY RESPONSE IN HEPATIC DISEASES
- **LINE 1.9** MECHANISMS AND MEDIATORS OF ENDOCRINE DISEASES
- **LINE 1.10** CHILDREN'S DEVELOPMENT (OBESITY AND GROWTH)
- **LINE 1.11** METABOLIC SYNDROME AND VASCULAR RISK

GROUP 1



Head of laboratory



Research interest

LINE 1.1 INTERCELLULAR COMMUNICATION IN THE INFLAMMATORY RESPONSE



Sánchez Madrid, Francisco



Group members

- Alfranca González, Arantzazu
- Bustos Morán, Eugenio
- Cibrián Vera, Danay
- Fernández Delgado, Irene
- Fernández Messina, Lola
- de la Fuente Flores, Hortensia
- Martín Cofreces, Noa Beatriz
- Martín Gayo, Enrique
- Moreno Gonzalo, Olga
- Ramírez Huesca, Marta Esther
- Saiz Álvarez, María Laura
- Sánchez Alonso, Santiago
- Ursa Pecharromán, María Ángeles
- Vallejo Rodríguez, María Ángeles
- Vara Vega, Alicia
- Villarroya Beltri, Carolina

Activation of the adaptive immune response requires the formation of intimate contacts between antigen-bearing cells (e.g. dendritic cells, DC) and T lymphocytes. These contacts ('immune synapses') act as hubs that transmit activating signals from the DC to the T cell, driving its differentiation and proliferation. However, information also travels in reverse, from the T cell to the DC. Reverse transmission depends of receptor-dependent adhesive contacts, soluble factors, and vesicles, e.g. exosomes. Exosomes are small extracellular vesicles biosynthesized from multi-vesicular bodies (MVB) and released towards the DC through MVB fusion with the plasma membrane. This group aims to determine the extent, nature and function of the information transferred from T cells towards DCs in exosomes through synaptic contacts. We will characterize the role of specific bits of information originated within the T cell and carried by exosomes, e.g. membrane transporters for specific metabolites, captured by the DC during the establishment and maintenance of synaptic contacts. The regulation of anti-viral and anti-bacterial genes determining the ability of DCs to respond to these challenges will define their Alert State. We are assessing the role of epigenetic changes at a DNA level in function of post-synaptic DCs, alone and in combination with metabolic changes and post-translational modifications to specific proteins, for example, Ubiquitin-like modifiers such as ISGylation. Cell viability, survival, and migration of post-synaptic DCs will be determined in vivo. We will also characterize the role of ISGylation on the Alert state during T-DC synapsis and inflammation. Finally, the role of the L-type amino-acid transporter 1 molecule (LAT1) and L-tryptophan metabolism will be analyzed in the context of the immune response associated to atherosclerosis and skin-inflammatory diseases in animal models to identify the mo-

lecular basis of these autoimmune diseases. These studies will open new avenues for vaccination strat-

egies and novel therapies to treat autoimmune-related diseases.



Major grants

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- Sánchez Madrid, Francisco. Inmunometabolismo de la psoriasis (IPD). Ayudas a equipos de investigación científica Fundación BBVA. 2018-2021.
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- Martín Gayo, Enrique / Soriano Ortiz, Joan B. Estudio de casos y controles de determinantes epidemiológicos e inmunológicos de infección incidente grave por SARS-CoV-2 y COVID-19 SDRA en UCI versus dos tipos de controles (EDEPIMIC). Subvención COVID Comunidad de Madrid. 2020.
- Sánchez Madrid, Francisco. Dinámica de la respuesta inmunitaria como predictor del curso evolutivo de la enfermedad COVID-19. Implicaciones para la toma de decisiones terapéuticas. PREDINMUNCOVID. Fondo Supera Covid-19 CRUE-Banco Santander. 2020-2021.



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GROUP 2



Head of laboratory



Veiga Chacón, Esteban



Group members

- Cruz Adalia, Aranzazu
- Torres Torresano, Mónica



Research interest

We are interested in the study of the interactions occurring between pathogenic bacteria and cells of the immune system. Recently, we discover a novel way for bacterial capture by T cells i.e. Bacterial transinfection. Some pathogenic bacteria (*Listeria monocytogenes*, *Salmonella enterica* and *Shigella flexneri*) are able to invade T lymphocytes in vivo and modify their behaviour. We were able to dissect the way of bacterial uptake by T cells; transinfection from previously in-

fected dendritic cells (DCs). The transinfection process requires direct contact between the two cells and it is highly enhanced by antigen presentation. This novel mechanism of T cells for bacteria capture is thousandsfold more effective than direct infections and it is driven by T cells. Note that some viruses e.g. HIV, use a similar transinfection mechanism to gain DC4+ T cells from infected DCs. Strikingly, trans infected T cells killed the captured bacteria within the first hours after infection and did it more efficiently than professional phagocytes like DCs.

These results show that T cells, paradigm of cells of adaptive immunity can perform functions that were supposed to be exclusive of components of the innate immunity; T lymphocytes can capture and kill bacteria in a manner reminiscent of innate immunity. Moreover, transinfected (ti) T cells secrete large amounts of proinflammatory cytokines (IL-6, interferon- γ and, TNF- γ), which are known to play important roles in bacterial clearance and protect efficiently in vivo from *Listeria monocytogenes* challenge.

With this background we are developing 4 major lines of research. o1 We are investigating whether tiT cells are bona fine antigen presenting cells (we have data showing that tiT cells are excellent cross-presenting cells), and the molecular mechanisms driving the novel roles of tiT cells. o2 We are studying the possible use of tiT cells in cancer immunotherapy due to their excellent cross-priming abilities and their hyper-inflammatory nature. We have data confirming that tiT cells are new very promising troops joining the fight against cancer. o3 We are expanding our knowledge in transinfection as a mechanism to capture/destroy/present bacterial antigens to B cells. o4 We will test whether tiLymphocytes could protect from bacterial infections as an, alternative to antibiotics, which is an issue of major relevance, as antimicrobial resistance has become an increasingly serious threat to global public health according to the world health organization.



Major grants

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GROUP 3



Head of laboratory



Yáñez Mó, María



Research interest

Our group is focused on the characterization of tetraspanin-enriched microdomains (TEMs), specialized membrane platforms involved in cell-cell adhesion and migration processes. These membrane platforms are connected to different cytoskeletal components and signalling pathways. We have demonstrated a functional connection of tetraspanin CD81 with the dNTP hydrolase SAMHD1 that results in regulation of nucleotide metabolism downstream TEMs. This axis was proven to be relevant during HIV infectious cycle, and was protected through a patent that describes CD81 as a new target to fight against HIV infection.

In addition, tetraspanin proteins are among the most abundant proteins on extracellular vesicles (EVs). EVs represent a novel mechanism of intercellular communication as vehicles for bioactive proteins, lipids, and RNAs. In our group, we are exploiting the tools against tetraspanin molecules to develop new isolation, detection and quantification devices. We are also interested in deciphering the role of tetraspanins in EV biogenesis and uptake by the target cell. Finally, we are developing synthetic exosome mimetics by the use of tetraspanin-based tools.



Group members

- Benayas López, Beatriz
- López Martín, Soraya
- Toribio Serrano, Víctor



Major grants

- Yáñez Mó, María. Estudio del potencial biotecnológico de herramientas frente a tetraspaninas en cáncer, secreción de exosomas y agentes vacunales. BIO2017-86500-R. Agencia Estatal de Investigación. 2018-2020.
- Yáñez Mó, María. Translational NeTwork for the CLinical application of Extracellular VesicleS (Tentacles). RED2018-102411-T. Agencia Estatal de Investigación. 2020-2021.



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GROUP 56



Head of laboratory



Urzainqui Mayayo, Ana Carmen



Group members

- **González Sánchez, María Elena**
- **Muñoz Callejas, Antonio**
- **Silván Montoya, Javier**



Research interest

P-Selectin Glycoprotein Ligand-1 (PSGL-1) is a leukocyte receptor that interacts with P-, E- and L-Selectins and is responsible for the initial steps of leukocyte extravasation to inflammation sites. Our laboratory has described that PSGL-1 acts as an immunoregulatory receptor that participates in the generation of regulatory T cells (Treg) and contributes to the maintenance of peripheral tolerance in mice. We described that PSGL-1

knock-out (KO) mice develop a progressive autoimmune disease similar to systemic sclerosis (SSc) (Pérez-Frías et al, Arthritis and Rheumatol 2014). In addition, we observed that the absence of P-Selectin, main PSGL-1 ligand, causes an autoimmune syndrome similar to human systemic lupus erythematosus (SLE), with generation of anti-dsDNA autoantibodies, immune complex deposits in skin and kidney and hypersensitivity to UV light, characteristics that could match those of SLE (González-Tajuelo et al., Sci Reports 2017). Interestingly, we have recently described that P-Selectin and PSGL-1 aged female KO mice develop pulmonary arterial hypertension (PAH), the most severe form of connective tissue-related autoimmune diseases, due to increased levels of Angiotensin II and endothelial dysfunction, with low production of NO (González-Tajuelo et al., Arthritis and Rheumatol. 2019). Remarkably, clinical studies with patients indicate that PSGL-1 and P-selectin expression is altered in both diseases. SSc patients have reduced PSGL-1 expression in B cells and increased expression in monocytes, dendritic cells and T cells. In addition, our data show the association of high PSGL-1 expression with the presence of interstitial lung disease (ILD) in SSc patients and that 75% or more circulating pDCs expressing ADAM8 associate with the presence of SSc. (Silván J et al, J Invest Dermatol, 2018). Lupus patients present reduced expression of P-selectin in skin vessels and reduced expression of PSGL-1 in neutrophils correlating with disease activity. Given all these findings, our main goal is to study the molecular and cellular alterations that underlie the pathology of these diseases.

Main research lines:

- Study of the interstitial pneumonia associated to scleroderma (SSc-ILD) and lupus (SLE-ILD), which is one of the main causes of death in these diseases.
- Analysis of the cells and molecular components implicated in the development of this pathology to find molecular alterations that could be potential treatment targets.

- Targeted therapy for ILD treatment using PSGL-1 KO mice and P-selectin KO mice as models of SSc-ILD and SLE-ILD, respectively.
- Analysis of PSGL-1 as possible regulator of cellular proteostasis and its contribution to scleroderma and SLE pathology.



Major grants

- Urzainqui Mayayo, Ana Carmen. Estudio de la interacción PSGL-1/P-selectina y las señales inducidas en HAP, esclerodermia y lupus. Estudio de los mecanismos moleculares alterados en ausencia de PSGL-1 o P-selectina. PI17/01819. ISCIII. 2018-2020.

Granted 2020:

- Urzainqui Mayayo, Ana Carmen. Estudio de la relevancia de la interacción PSGL-1/P-selectina en la proteostasis celular y generación de NETS y su posible implicación en la patogénesis de esclerodermia y lupus. PI20/01690. ISCIII. 2021-2023.
- González Sánchez, Elena. Tratamiento intratraqueal de la neumonía intersticial asociada a esclerodermia (SSc-ILD), con el fármaco everolimus en ratones PSGL-1 KO. Beca Cátedra EPID Futuro. 2020-2021.



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GROUP 9

LINE 1.2 CELLULAR AND MOLECULAR RESPONSES TO HYPOXIA



Head of laboratory



Aragonés López, Julián



Group members

- Bouthelier de Pedro, Antonio
- Elorza Peregrina, Ainara Estíbaliz
- Fuertes Yebra, Esther
- Meléndez Rodríguez, Florinda del Coral
- Mesa Ciller, Claudia
- Ordóñez Navadijo, Ángel
- Soro Arnaiz, Inés
- Torres Capelli, María del Mar
- Urrutia Elorduy, Andrés Amalio
- Yang Li, Qilong Oscar



Research interest

An insufficient oxygen supply (hypoxia) is a hallmark of numerous life-threatening pathologies with unmet medical needs such as solid tumor growth,

chronic obstructive pulmonary disease (COPD), ischemic diseases and obesity. Cells are equipped with oxygen-sensing systems to mount a programmed response when oxygen becomes limited. Hypoxia-inducible factors (HIF1, HIF2 and HIF3) are central regulators of this cellular response to oxygen fluctuations. Our current research interest is focused on the role of the HIF oxygen sensing pathways in cancer, pulmonary disease and obesity. In particular, we are mainly interested in cellular metabolic reprogramming, which is one of the central biological functions executed by the HIF factors. 1) HIF factors and renal cell carcinoma: the HIF factors are induced in hypoxic areas in the inner core of the solid tumors but in clear cell renal cell carcinoma (ccRCC) - which loss Vhl (the main repressor of HIFs in normoxia) - show constitutive HIF expression irrespectively of the oxygen levels of the tumor. In these tumors HIF1 shows its cell autonomous anti-proliferative capability, whereas HIF2 acts as an oncoprotein. Therefore, ccRCC are being studied extensively to understand the role of HIF in cancer biology. Our studies have shown that the HIF2a isoform acts as an mTORC1 activator through the amino acid carrier SLC7A5, which is essential to sustain ccRCC tumor growth. We have recently found a novel link between glucose and lipid metabolism and HIF factors, which impact remarkably in ccRCC progression. Independently of these projects in ccRCC tumor metabolism, we have recently initiated a project identifying unanticipated molecular links between HIF pathways and cancer immunology. 2) HIF factors and airway dysfunction in pulmonary disease: Pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and sleep-apnea hypoapnea syndrome (SAHS) are the most common respiratory diseases causing illness and death, and are being projected to be the third leading cause of death worldwide by 2020. They are characterized by an insufficient level of oxygen in the blood (hypoxemia), continuous in the COPD and intermittent in the SAHS, and they are associated to pulmonary oxidative damage, an exaggerated inflammatory response

in the lung and systemically. Surprisingly, despite the fact that lung tissue – bronchial epithelium – is a first barrier encountered by oxygen, the role of the HIF oxygen-sensing responses in lung pathophysiology remains largely unknown. Based on (i) our recent studies about the HIF pathways as activators of proliferative markers in bronchial epithelium including mTORC1, we are currently studying together in collaboration with other researchers including pneumologists in Hospital de la Princesa IIS-IP (Dr. Julio Ancochea) the role of HIF oxygen sensing pathways in (i) lung protection and repair (ii) ventilation and (iii) their potential to identify novel biomarkers for diagnosis and prognosis of fatal respiratory diseases. 3) Role of HIF oxygen sensing pathways in cellular adaptation to hypoxia through the mitochondrial reprogramming. Along this line, NDUFA4L2 is a target gene of hypoxia-inducible factors (HIF) that has the ability to decrease overall mitochondrial oxygen consumption through the inhibition of mitochondrial complex I. These properties of NDUFA4L2 also diminish the production of reactive oxygen species (ROS) in mitochondria, which is essential for cell protection against oxidative damage associated to hypoxic scenarios. Thus, although the protective role of NDUFA4L2 in in vitro scenarios where ROS are important for cell viability is well known, it is also crucial to know the pathophysiological role of NDUFA4L2 in vivo. We have recently generated NDUFA4L2-deficient mice to understand its in vivo role in disease models associated to hypoxia



Major grants

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- Aragonés López, Julián. Papel de los factores de respuesta a hipoxia HIF1/2 en la regulación del metabolismo de aminoácidos y su impacto en fisiopatología. PID2019-106371RB-I00. Agencia Estatal de Investigación. 2020-2023.



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GROUP 7



Head of laboratory



Martínez Ruiz, Antonio



Research interest

The research of the group is centred on two main
lines:

1. Redox signalling in the response to hypoxia

We previously showed that different cell types produce a superoxide burst in acute hypoxia, which can be a signal for cell adaptation through acute responses as well as through activation of the HIF pathway. We have investigated the mechanisms that lead to this acute production of superoxide. We have discovered that hypoxia triggers a conformational shift in mitochondrial complex I that increases its D form, which acidifies the mitochondrial matrix, and that this functional shift of complex I is a key step in the superoxide burst. We have also discovered that mitochondrial Na⁺/Ca²⁺ exchanger (NCLX) is involved in this superoxide burst, showing that mitochondrial Na⁺ import by NCLX alters oxidative phosphorylation and induces superoxide production. We are now investigating the involvement of NCLX in reperfusion after stroke. Our work proposes NCLX as a pharmacological target in the treatment of diseases in which hypoxia and reactive oxygen species production are present.



Group members

- Choya Foces, Carmen
- Delgado Martín, Susana
- Hugo Pereira, Martín

2. Oxidative post-translational modifications and redox proteomics

We have studied the functional role of Ras S-nitrosylation as a regulator of neurogenesis, and of actin S-nitrosylation as a regulator of the immune synapse. We previously developed methods for detecting cysteine oxidative post-translational modifications (thiol redox proteomics), which we have applied to the study of neurogenesis, ebbsen-induced oxidative stress and drug-induced erythrocyte death. We are currently applying those methods to the study of clinical samples, starting with the study of the thiol redox proteome of heart valves, comparing samples from the two main diseases that lead to valve replacement and normo-functional valves from heart donors.



Major grants

- Martínez Ruiz, Antonio. Daño oxidativo en reperusión tras ictus: detección proteómica de dianas redox y papel del intercambiador mitocondrial de sodio/calcio NCLX. RTI2018-094203-B-I00. Agencia Estatal de Investigación. 2019-2022.



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GROUP 8



Head of laboratory



Calzada García, María Josefa

tracellular protein thrombospondin-1 (TSP-1) in the context of chronic pulmonary diseases characterized by a decrease in oxygen tension and pulmonary hypertension, these including Pulmonary Arterial Hypertension (PAH) and Chronic obstructive pulmonary disease (COPD).

These pathologies are rapidly progressive pulmonary vascular diseases with a multifactorial etiopathogenesis that result in loss of pulmonary function and emphysema, right-sided heart failure and ultimately death. However, the underlying cellular and molecular mechanisms are largely unknown. Our recently published results shed light on some of the processes in which TSP-1 actively participates in the development of PAH and point to this protein as a causal molecule in experimental and clinical PAH and therefore represents a candidate therapeutic target (Rogers NM. et al. Cardiovascular Res. 2017; Labrousse-Arias D. et al Cardiovascular Res. 2016). In addition TSP1 has been observed in epithelial, bronchial and alveolar macrophage cells of patients with COPD, increase that is magnified as the disease progresses. We are currently investigating the role of hypoxia/TSP-1 and smoke exposure/TSP-1 in vascular remodeling in chronic lung diseases such as PAH and COPD. In particular, the role of TSP-1 in arterial muscularization, and whether it promotes the differentiation of pulmonary artery adventitial fibroblasts (PAAF) into more contractile myofibroblasts.



Group members

– **Sevilla Montero, Javier**



Research interest

Hypoxia plays critical roles in the pathobiology of many diseases, these including cancer and chronic lung disease, with a high prevalence and morbidity. Understanding how cells sense and respond to changes in oxygen availability and the physiologic or pathologic consequences in the context of chronic diseases will have a positive impact in the diagnosis and treatment of these pathologies. Our group is currently investigating the role of hypoxia in the regulation of the ma-

To these aims we have optimized techniques such as Traction Force Microscopy (TFM) to evaluate the functional relevance of contractility molecular markers on these cells and CLARITY, a technique that allows high-resolution information from a complex system, while maintaining the global perspective needed to understand system function.



Major grants

Granted 2020:

- Calzada García, María José. Efectos del humo de tabaco en la vasculatura pulmonar. Mecanismos moleculares subyacentes al desarrollo de hipertensión pulmonar secundaria a EPOC. Agencia Estatal de Investigación. PID2019-104406RB-100. 2020-2023.



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GROUP 10



Head of laboratory



Cadenas Álvarez, Susana



Group members



Research interest

Our group studies the function of mitochondria within cells and their implication in the development of pathological conditions. Uncoupling proteins (UCPs) have been involved in the control of mitochondrial reactive oxygen species (ROS) production and the protection against oxidative stress. Since oxidative stress underlies a wide variety of pathophysiological processes, UCPs are potentially important drug targets. The elucidation of the molecular pathways that control their expression and activity is essential to develop strategies for modulating

their function. An efficient response to oxidative damage is crucial for cell survival, and Nrf2 (nuclear factor erythroid 2-related factor 2) is an essential transcription factor that regulates the expression of several antioxidant genes via binding to the antioxidant response element (ARE), and plays a pivotal role in cellular defense against oxidative stress. Among several pathologies related to oxidative stress, we are particularly interested in cardiac ischemia-reperfusion (IR) injury. Reperfusion of ischemic myocardium results in an excessive production of ROS that may cause tissue damage.

Our group pursues three main lines of research. 1) The regulation of the expression and function of UCP3 in response to oxidative stress. We have previously found that the treatment with hydrogen peroxide (H₂O₂) or 4-hydroxy-2-nonenal induces UCP3 expression in cells from mouse heart and skeletal muscle. This effect is mediated by the transcription factor Nrf2. Moreover, we have shown that UCP3 upregulation is accompanied by an increase in the proton conductance of the inner mitochondrial membrane, which results in a decreased production of mitochondrial ROS and, consequently, in an increased cell survival. We are currently investigating the effects of low oxygen concentrations on UCP3 expression and their functional consequences. 2) The protective role of UCP3 against IR injury and its involvement in ischemic preconditioning (IPC). We have detected Nrf2 nuclear accumulation and increased UCP3 protein in intact mouse hearts subjected to IR, a condition known to increase ROS generation. We are currently studying the potential protective role of UCP3 against IR injury and its involvement in IPC in the isolated perfused mouse heart and in vivo. 3) The implication of Nrf2 in IPC. There is experimental evidence showing that Nrf2 activation protects against IR injury. By using Nrf2 activators and Nrf2 knockout mice, we will study the role of this factor in IPC and the molecular mechanisms involved. In addition, we have established a collaboration with cardiac surgeons to study the molecular and cellular alterations taking place in the ischemic human heart.



Major grants

- Cadenas Álvarez, Susana. Mecanismos de cardioprotección sensibles al estado redo en el daño por isquemia-reperfusión. ISCIII. PI19/01030. 2020-2022.



Publications (1)

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GROUP 11



Head of laboratory



Mayor Menéndez, Federico



Group members

- Asensio López, Alejandro
- Caballero Lombraña, Álvaro
- Martins Neves, María Margarida
- Ortega Giménez, Alba
- Ramos Barbeito, Paula
- Ribas Núñez, Catalina
- Sanz Flores, María



Research interest

Our laboratory is investigating key nodes in signalling networks involved in prevalent age-related pathologies such as metabolic/cardiovascular diseases and cancer.

The GRK2 kinase is one of those key signalling hubs. The canonical role of GRK2 is to regulate, together with arrestins, signalling mediated by multiple G protein-coupled receptors (GPCR), a family of hundreds of membrane proteins of key

physiological and pharmacological importance. In addition, we and other groups have unveiled that GRK2 can also impact cell signalling networks by directly interacting and/or phosphorylating non-GPCR components of transduction cascades (such as HDAC6, IRS1, PI3K, EPAC, Mdm2, Smads or p38 Mapk). Our group has reported that some of such integrated interactions underlie the participation of GRK2 in the control of cell migration, proliferation angiogenesis or insulin resistance (IR).

Importantly, GRK2 levels/activity are altered in human pathologies such as cancer, inflammation and cardiovascular/ metabolic diseases related to IR. We seek to understand the mechanisms leading to altered GRK2 expression in these clinical situations, how concurrent changes in GRK2 levels (involving different cell types and tissues) integrate at the cellular and organism level, and how they can foster disease progression, by using cellular and animal models (including hemizygous, conditional and tissue-specific GRK2-deficient animals), as well as samples from patients or animal models of disease. This is critical to assess the feasibility of GRK2 as a useful diagnostic biomarker and/or therapeutic target.

The group pursues three main lines of investigation:

1) GRK2 as an oncomodulator in specific tumor types. Investigate how changes in GRK2 expression in different tumors (breast, colon, squamous cell carcinomas) and cell types within a given tumor (tumor, macrophages and endothelial cells) might promote different aspects of tumor progression (proliferation, survival, angiogenesis, metastatic invasion) by modulating either GPCRs or HDAC6-governed networks, among others.

2) Analyze the GRK2 hub as a central integrator of signalling cascades relevant to IR-related pathologies and co-morbidities in different tissues and cell types (adipose, liver, pancreas, heart, macrophages/ immune cells), by simultaneously modulating both the insulin cascade and key GPCRs controlling metabolic homeostasis, nutrient sensing or insulin secretion/sensitivity

3) Explore the functional implications of the Gq interactome. We have unveiled novel interactions of Gq with PB1-domain containing proteins such as PKC ϵ , and we are investigating the functional impact of this new Gq interactome in cell death, autophagy and oxidative stress processes and in the development of cardiovascular diseases.



Major grants

- Mayor Menéndez, Federico. CIBER-CB. CB16/11/00278. ISCIII. 2017-2021.
- Mayor Menéndez, Federico / Murga Montesinos, Cristina. GRK2 como nodo de señalización integrador en situaciones fisiopatológicas. SAF2017-84125-R. Agencia Estatal de Investigación. 2017-2020.
- Mayor Menéndez, Federico. INFLAMUNE-CM: Nuevos mecanismos moleculares y celulares implicados en la fisiopatología inmune y enfermedades inflamatorias. B2017/BMD-3671. Comunidad de Madrid. 2018-2021.
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- Mayor Menéndez, Federico. Interactome rewiring by phosphorylation and acetylation barcodes: implications in metabolic reprogramming in breast cancer. Fundación Ramón Areces. 2019-2021.

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- Mayor Menéndez, Federico. The 1 adrenergic receptor (1AR)- calpain – GRK2 axis as a new pharmacological target to reduce reperfusion injury and post-infarction remodelling. CIBER-CV. Intramural. 2020-2023.



Publications (6)

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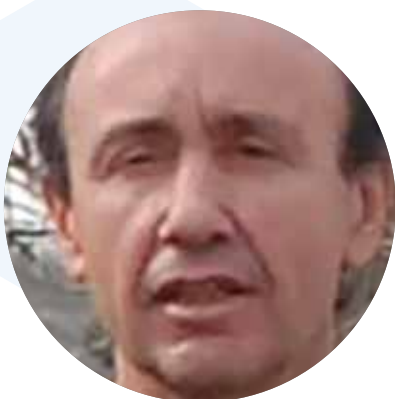
GROUP 12



Head of laboratory



Research interest



Fresno Escudero, Manuel



Group members

- Arranz de Miguel, Alicia
- Barrocal López, Beatriz
- Callejas Hernández, Francisco
- Cuesta Rubio, Natalia
- de Chorro y de Villa-Ceballos, María de los Ángeles
- Galán Martínez, Javier
- García Prieto, Teresa
- Gironès Pujol, Nuria
- Jiménez Martínez, Marta
- Maza Moreno, María del Carmen
- Stamatakis Andriani, Konstantinos
- Torres Gérica, Patricia

We are analyzing the involvement of Pathogen recognition receptors (as TLRs or galectin) and Cyclooxygenase (Cox)-2/prostaglandins (PGs) in the immune system and inflammatory pathologies as obesity, cancer and sepsis. We have found that PG-F2a negatively regulates adipocyte differentiation through the transcription factor NFAT. Moreover, NFATc4 deficiency induces obesity in mice indicating a key role in obesity. We also found that galectin-1 (Gal-1) deficiency abolished diet induced obesity and insulin resistance in mice. Gal-1 is needed for the differentiation of preadipocytes by regulation of the key proadipogenic transcription factor PPAR- γ and in the differentiation of brown adipocytes.

Cox2 inhibitors reduce cancer but their therapeutic use has been hampered by their side effects. As an alternative, we have analyzed genes regulated by Cox2 or PGs that may provide a protooncogenic advantage. Among those, mPGES-1, DUSP10, Trop2 and many from the TGF β pathway, as PMEPA1, which, interestingly, were induced by PGF2a. DUSP10 controls stress response to serum deprivation and confluence arrest and binds and dephosphorylates Yes-associated protein 1 (YAP) in colorectal cancer. PGF2a TGF β -PMEPA1 pathway is a critical mediator of epithelial plasticity and ovarian carcinoma progression. Those molecules are amenable to drug discovery, lacking the unwanted side effects of COX-2 pharmacological inhibitors.

Interestingly, PGF2a induces Cox-2 and DUSP10, having a very important pathogenic role in animal models of inflammatory bowel disease (IBD), a leading cause of colorectal cancer, since the use of pharmacological PGF2a antagonists prevents IBD. On the other hand, TCFL5 is a member of the bHLH transcription factor family with multiple isoforms in

both humans and mice. Complete deletion of the isoforms drastically reduces tumor properties of colon cancer cells. Interestingly, the two major isoforms (TCFL5 and CHA) showed a reciprocal regulation and different functions in the cell, with CHA exercising a protumoral effect. TCFL5 / CHA expression is essential for NFkB2 activity regulating the expression of anti-apoptotic genes such as BCL2 and also controlling the expression of the pluripotency markers SOX2, NANOG and KLF4.

We have also defined a set of genes regulated by TCFL5/CHA in leukemia cell lines and established their role in the prognosis and development of B- and T-acute lymphoblastic leukemia and in normal hematopoiesis. The expression of TCFL5 and CHA was associated with greater severity in lymphoma and myeloma samples from patients. Last but not least, using Tcfl5 deficient mice, we found that TCFL5 is involved in the formation of germinal centers and in the stage of differentiation of pro-B to pre-B cells, two processes that are not only characterized by a high proliferation rate but are also MYC dependent. The lack of TCFL5 caused a radical decrease in the levels of the most important molecules in BCR signalling, such as SYK and BLNK, resulting in an inability to respond to stimuli, an increase in cell death and an abnormal cell cycle.

Using Tcfl5 deficient mice, we found that TCFL5 is expressed in early mouse embryonic development during the preimplantation period and plays a role in the differentiation of embryonic cells to germline precursors by controlling the expression of genes important in this differentiation.

Finally, in the infection by the protozoan parasite *T. cruzi* we are working on the impact of *T. cruzi* genetic variability on the clinical outcome and immunopathology of Chagas' disease as well as drug susceptibility. All intended for improved understanding and prevention of Chagas' disease. Different genetic lineages have been defined in *Trypanosoma cruzi*, the causative agent of Chagas' disease. However, understanding of their comparative biology and pathogenesis is fragmentary. We have identified different T dependent immune responses both in patients and mouse models, which differ depending on the infecting strain. Besides, we are studying how the parasite enters, infects and escapes destruction by myeloid cells, defining Slamf1 (CD150) as a new *T. cruzi* receptor. In contrast, we found that Slamf8 (CD353) is a cell surface receptor that is expressed upon activation of macrophages by IFN- γ and plays a negative role in the infection through repression of NADPH oxidase. We have studied the role that CD4+ T cell subsets and myeloid subclasses including myeloid-derived suppressor cells (MDSC) may play in the immunopathogenesis of Chagas' disease, with special focus on myocarditis in animal models and in patients. Different heart immunopathogenic responses depend on host genetics. Nonetheless, Systems Biology approaches have allowed us defining immunopathogenic markers independent of host and parasite genetics. We have found many metabolic alterations in *T. cruzi* infection suggesting a stressful condition in the heart, some of which can be used as biomarkers. Serum miRNAs are also excellent biomarkers of Chagas' disease progression.



Major grants

- Fresno Escudero, Manuel. Red de Investigación Colaborativa en Enfermedades Tropicales (RICET). RD16/0027/0006. ISCIII. 2017-2021.
- Fresno Escudero, Manuel. INFLAMUNE-CM. Nuevos mecanismos moleculares y celulares implicados en la fisiopatología inmune y enfermedades inflamatorias. B2017/BMD-3671. Comunidad de Madrid. 2018-2021.
- Fresno Escudero, Manuel. Validación de dianas farmacológicas neuroinflamatorias para el trat-



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■ Fresno Escudero, Manuel. Estudios del ambiente microbiano e inflamatorio de las bolsas periodontales. Association Médicale contre les Infections Buccales. 2019-2020.

■ Gironés Pujol, Nuria. Abordaje multiómico al estudio de la inmunopatogénesis de la enfermedad de Chagas. PGC2018-096132-B-100. AEI. 2019-2021.

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GROUP 13



Head of laboratory



Penela Márquez, Petronila

The histopathological variety and molecular heterogeneity of breast tumours make difficult to achieve efficient treatments. In breast cancer, the main altered proteins responsible for genomic instability and heterogeneity are ATM kinase, Brca1 ligase and the tumour suppressor transcription factor p53. Notably, in ~ 80% of ductal breast carcinomas p53 is restrained by activation/amplification of the ligase Mdm2, but therapies based on these targets are not yet satisfactory. Another important problem is the emergence of resistance amongst all breast cancer subtypes, paralleled by enhanced genomic instability and tumour metabolic reprogramming. These limitations in current therapies highlight the need for deeper understanding of complex pathways leading to breast cancer development and progression.



Group members

- **Albitre Sanz, Ángela**
- **Ortiz del Castillo, Belén**
- **Rivas Guerrero, Verónica**

The objective of our group is to identify regulatory nodes that integrate multiple cellular inputs and environmental cues for modifying tumour hallmarks such as genomic instability. Understanding how adaptable and dynamic signalling networks interact with breast cancer susceptibility genes will pave the way for better therapeutic approaches.



Research interest

Breast cancer is a disease of high prevalence with around 25,000 new diagnoses in Spain each year. Its incidence is much higher in the developed world, suggesting that the western lifestyle with unhealthy dietary habits (excessive caloric intake, overweight, obesity) and chronic stress states (adrenergic overstimulation) may influence the onset and progression of this disease.

Results of our laboratory suggest that intertwined alterations of the serine-threonine kinase GRK2 and the Mdm2 ligase are key for cell-autonomous malignant transformation, as well as in the interplay of the transformed cell with the tumour micro-environment and the systemic condition of the patient. Our results indicate that these proteins modulate each other differently in normal epithelial cells and in tumour cells, responding in different ways to signals that stimulate adrenergic receptors and other G-protein coupled receptors (GPCR) or growth factor tyrosine kinase receptors (RTK).

In this context, our research aims to characterize the role of these nodes (GRK2, Mdm2 and other ligases), and the relevant phosphorylated and ubiquitinated



proteins, in diverse cellular processes such as cell cycle control and cell division, differentiation, energy metabolism or senescence, which are key in maintaining a normal cell behaviour. We also aim to gain insight into the interplay of these molecules with hormonal (adrenergic, estrogenic) and metabolic stress on genomic stability and pro-tumoral stroma remodelling, by analysing diverse processes that facilitate tumour growth and dissemination such as tumour angiogenesis.



Major grants

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GROUP 17



Head of laboratory



Murga Montesinos, Cristina

An important point of control in the metabolic, stress and inflammatory network of routes is the signaling hub of the G protein-coupled receptor kinase 2 (GRK2), that emerges as a pivotal control point in the onset and/or progression of these diseases.

In this line, our group focuses its research efforts on the following lines:

1. Analysis of the phenotypic differences in the response of mice with decreased or increased levels of GRK2 towards several types of metabolic challenges under physiological and pathological conditions. We are unveiling whether the response of different metabolically-relevant tissues to these challenges varies with GRK2 dosage. Also whether the levels of GRK2 itself may allow for a better adaptation of each tissue to different metabolic situations or even serve as biomarkers of disease. We have recently published research that describes the influence of GRK2 on the control of pancreatic insulin secretion and on glucagon-induced hepatic glucose production.



Group members

- **Concepción Arcones, Alba**
- **Cruces Sande, Marta**

2. Changes in the levels of GRK2 protein in macrophages and other inflammatory cells contribute to the control of insulin sensitivity, adiposity and obesity in animal models of disease. We have published how myeloid GRK2 affects whole body responses such as glycaemic control and hepatic inflammation. Furthermore, we described the influence of the perivascular adipose tissue of animals with low GRK2 levels in myeloid cells on the response of vessels to different vasoconstrictor and vasodilator stimuli in the face of vascular dysfunction and vascular insulin resistance developed by a high fat diet.



Research interest

Pathological insults and metabolic cues are increasingly being regarded as key modulators of immunological responses and inflammatory processes. Thus, metabolic signals that affect inflammatory routes are a strategic focus of research to unveil the mechanistic basis of human physiology, but also of different pathologies, in particular those with an inflammatory or metabolic component such as insulin resistance, obesity, metabolic dysregulation and cardiovascular conditions.

3. Finally, we have recently reported that the expression of GRK2 in different tissues shows sexual dimorphism, and we have also published that changes in the amount of this kinase in cardiac and

skeletal muscle with age do not follow the same pattern in male and female mice. This is particularly important since the dynamics of GRK2 appears to parallel the increase in cardiovascular risk that is observed in females after menopause. We are

therefore investigating whether these gender-specific changes in the amount of GRK2 may reflect or, additionally, can impact the sexual dimorphism observed for cardiovascular risk with age using models of pre and post-menopausal female mice.



Major grants

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GROUP 18



Head of laboratory



Iñiguez Peña, Miguel Ángel

which includes prostaglandins and leukotrienes. Current knowledge shows their key role as signalling molecules in an array of pathophysiological processes, being regarded as critical mediators in a variety of inflammatory diseases such as arthritis, atherosclerosis and cancer. Our current research is focused on a particular class of electrophilic compounds named cyclopentenones (CyPGs), which play an important role in the inflammatory process, acting as anti-inflammatory pro-resolving agents.

Electrophilic fatty acid species also include nitro-containing fatty acids as nitroalkene derivatives of linoleic and oleic acid (LNO₂ and OA-NO₂). These compounds are a novel class of endogenous, electrophilic mediators that can also exert adaptive anti-inflammatory signalling reactions.

Our research is aimed to the study of the molecular mechanisms involved in the actions displayed by these electrophilic fatty acids as modulators of inflammation and the immune response. To this end, we analyze their influence on diverse parameters of macrophage and T lymphocyte function, focusing on their effects on transcriptional activation and gene expression and their consequences on cell activation and differentiation.

Research on the molecular and cellular basis of the actions of electrophilic fatty acids in inflammation and the immune response is required to clearly understand the potential benefits and risks of pharmaceutical intervention with these lipids in the onset and progress of inflammatory diseases.



Group members

- **Bago Plaza, Ángel**
- **Renshaw Calderón, Ana**



Research interest

Fatty acid modification results in the production of bioactive lipids as oxo or nitro fatty acids, agents that can modulate the activation, differentiation and function of different cell types, as those involved in the inflammatory process and the immune response. Their actions take place through their ability to covalently modify transcriptional regulatory proteins and enzymes and to activate various nuclear and membrane receptors, finally modifying protein function and altering patterns of gene expression.

Enzymatic oxygenation of fatty acids generates signalling mediators, as those of the eicosanoids lipid family,



Major grants

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Head of laboratory



Blanco Guerra, Carlos Alberto



Group members

- Belver González, María Teresa
- Daschner, Álvaro
- de Frutos Moreno, María Consolación
- las Heras Almazán, María Paloma
- Múgica García, María Victoria
- Ramos García, Tania María
- Valls Sánchez, Ana María
- Vega de la Osada, Francisco Félix



Research interest

Allergic diseases are increasing worldwide, related to a complex interaction between genetic and environmental factors, and reaching prevalence rates higher than 30%. Among them, respiratory allergy, including bronchial asthma and rhinoconjunctivitis, is a research priority target for most health organizations.

GROUP 20

Nowadays, allergen specific immunotherapy is the only way to modify the natural course of allergic respiratory diseases. Meanwhile, food & drug allergies are rising problems, due to both the potential severity of reactions and to its great impact on patient quality of life. It is noteworthy that cross-reactions between certain food- and inhalant-allergens lead to a complex group of clinical syndromes, complicating the management of allergic patients. Among cross-reacting pan-allergens, profilins are one of the most relevant in the Mediterranean area.

In this context, our group has these main research lines, in collaboration with the new allergy research network ARADYAL (ISCIII RD16/0006):

- Immunotherapy for respiratory allergy: a 2 year placebo controlled clinical trial has been recently finished, checking immunological changes induced by grass-pollen immunotherapy on respiratory allergy.
- A study on adverse reactions to iodinated contrasts and gadolinium has been started by Dr. Vega, in which tolerance to alternative contrasts is assessed by means of a protocol of fast challenge tests at full dose. First results will be published soon and a doctoral PhD project based on these results is planned
- Food allergy: we have started collaborating in a research project (Retos Investigación: Proyectos I+D+i 2017, MINECO) with Dra. Cuadrado from INIA (National Food Research Institute), focused on nut allergy, which is one of the most prevalent and severe food allergies. Both DNA- and immunological- biosensors for detecting peanut, hazelnut, pistachio and cashew allergens will be developed.
- We have also focused on sensitization to the pollen-food pan-allergen profilin, which is as-

sociated with bronchial asthma, fruit allergy and poor immunotherapy response. On one side, mechanisms responsible for food allergy in profilin-sensitized patients have been studied in the context of a research project led by Dr. Barber (from San Pablo C.E.U. University). On the other side, a study focused on T-cell response repertoire to profilin, in collaboration with ALK-Denmark, has been performed.

- A study on severe bronchial asthma treated with biological drugs, in collaboration with San Pablo CEU university, is also planned.

- Finally, Dr. Daschner continues with its productive research lines on Anisakis allergy which made it possible, in a collaborative study with the ISCIII, to perform an epidemiological analysis on Hospitalizations due to Anisakiasis and establish a new estimate of nationwide allergy cases. He continues to work in the field of Evolutionary Medicine with a pluridisciplinary approach and in collaboration with the National Museum of Natural Sciences.



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GROUP 15



Head of laboratory



Ibáñez Sandín, María Dolores



Group members

- Escudero Díez, Carmelo
- Rodríguez del Río, Pablo
- Sánchez García, Silvia



Research interest

The main research programs ongoing are: oral immunotherapy with several foods, the study of epidemiologic and component resolved diagnosis of nut allergy, the study on the description of egg allergy immunophenotypes, the study of allergy to penicillins in children below 14 years old and the study on the different diagnostic procedures of exercise-induced asthma in children.

Food allergy:

Food immunotherapy:

Our objectives in this field include:

- Design of protocols of oral immunotherapy for egg and wheat allergy that improve time consumption, efficacy and safety.
- Determine the efficacy of the aforementioned food immunotherapy protocols in the long term from clinical and immunological points of view.
- Develop a food immunotherapy National Guideline along with other centres and specialists in the field, under the framework of the SEICAP and the SEICAP.
- Finish the project "OmaBase": Registry of cases of Omalizumab use in the treatment of food allergy. Multicentre Registry of cases of patients allergic to food (milk, eggs and/or vegetables), treated with omalizumab alone or associated to immunotherapy". This Project is developing and is now in its final phase, registering the cases of patients allergic to food treated with Omalizumab under any indication, and following the evolution of their food allergy, regardless of the concomitant use of food immunotherapy.

▪ Fish oral immunotherapy: This multicentre project, approved by the ethical committee of the HNJ and the AEMPS, and supported by the SEICAP, is currently starting.

▪ Peanut oral immunotherapy: This multicentre project, approved by the ethical committee of the HNJ and the AEMPS, and supported by the SEICAP, is currently starting.



Food allergy epidemiology and food allergens:

- AFRUSEN registry: "Registry of new cases of nut allergy in a paediatric population clinical characteristics and sensitization. Multicentre Study". The main objectives are to describe the clinical features and sensitization patterns (molecular diagnosis) of new onset diagnosis of allergy to the most frequently consumed nuts in Spain and stratify it according to the different regions.
- OVALE clinical trial: "Description through a microarray assay of immunophenotypes in the antigen recognition in egg proteins allergy in a paediatric population. This multicentre project, aims to follow a cohort of newly diagnosed egg allergic patients and describe the different clinical and immunological profiles according to their evolution."

Asthma:

It is our goal to develop a position statement based on expert consensus in the diagnosis of Exercise-Induced asthma in children.

Drug allergy:

APENIN survey: "Study of penicillin allergy in childhood". This study aims to evaluate the efficiency of the penicillin allergy diagnostic tools among a paediatric population in a real life setting in different Spanish allergy departments. In a second stage, a diagnostic procedure algorithm is planned to be delivered for children below 14 years old.



Major grants

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GROUP 21



Head of laboratory



Barril Cuadrado, Guillermina



Group members

- Álvarez Chiva, Vicente
- Fernández Perpén, Antonio Carlos
- Giorgi González, Martin Giovanni
- Herráez Jiménez, Isabel
- Núñez Sánchez, Almudena
- Quiroga Gili, Borja
- Ruano Suárez, Pablo
- Salanova Villanueva, Laura
- Sánchez González, María Carmen



Research interest

Peritoneal Dialysis (PD): Our main line of work is focused on the study of the mechanisms involved in the damage induced by PD on the peritoneal membrane. Also, we studied the influence of several drugs (Paricalcitol, Ta-

moxifen, Roxiglitazona) in preventing and repairing damage to the peritoneal membrane. In the next years we will try to clarify which are the mechanisms responsible for the hyalinizing vascular disease, the role of alternatively activated macrophages in the progression of peritoneal damage and we will analyze the morphological and immunohistochemical findings in peritoneal biopsies from patients treated with conventional or biocompatible liquids. An ongoing project aims to design a microchip for early noninvasive diagnosis of mesothelial to mesenchymal transition in peritoneal membrane using the peritoneal effluent. Preliminary data have shown that peritoneal dialysis, in animals subjected to a cerebral ischemic damage, is able to decrease the cerebral damage induced by high glutamate levels. In collaboration with the Neurology Service we are conducting a clinical trial in patients to determine whether peritoneal dialysis can protect from ischemic brain damage in the acute phase of ischemic stroke.

Nutrition in Renal disease: We have studied the importance of exercise in proper nutrition and survival of patients with advanced chronic kidney disease and the effect of physical training. We have studied the introduction of new scores for nutritional assessment of renal patients and we intend to study the balance of myocytokines and its relation to muscle strength and functionality.

Alterations of Bone and Mineral Metabolism in Chronic Kidney Disease (CKD): FGF23 is a molecule involved in the metabolism of phosphorus but can be important as a marker of cardiovascular pathology and survival in renal disease. We have designed a clinical trial, which is already funded, to analyze the behavior of FGF23 and PTH fragments in patients with chronic kidney

disease on peritoneal dialysis program treated with cinacalcet.

Down's Syndrome. We are developing a study to evaluate renal function in a large group of these patients followed regularly in a monographic consultation. The incidence of cardiovascular complications and bone mineral metabolism will also be studied.

Hepatorenal polycystosis of the adult. New drugs have been introduced in the last few years that have demonstrated, in preliminary trials, that they improve the prognosis of patients with polycystosis. We are trying to determine the mechanisms that significantly affect the progression of these patients towards renal failure, and implement measures to prevent this progression



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GROUP 22



Head of laboratory



Research interest



Ancochea Bermúdez, Julio



Group members

- Alonso Pérez, Tamara
- Capote Moreno, Ana Laura
- Cisneros Serrano, Carolina Victoria
- García Castillo, Elena
- Girón Moreno, Rosa María
- Gómez Punter, Rosa Mar
- Landete Rodríguez, Pedro
- Pastor Sanz, María Teresa
- Pérez González, María Patricia
- Rubio Bueno, Pilar
- Soriano Ortiz, Joan Bautista
- Valenzuela, Claudia
- Vázquez Espinosa, Emma
- Zamora García, Enrique Domingo

Consultant Advisor:

- Melero Moreno, Carlos

Inflammation and reparative process in lung diseases. Chronic obstructive pulmonary disease (COPD). Apnea-Hypopnea Syndrome. Idiopathic pulmonary fibrosis (IPF). Immunopathogeny. Molecular diagnosis. Cellular diagnosis. New therapeutic approaches. New care models.

Pulmonary diseases are an important social and healthcare topic, related to its high prevalence and associated morbimortality. In recent years, our group has worked on different topics related to lung diseases, as it is reflected in our publications carried out in collaboration with other working groups.

General objectives: 1. Promote research into lung diseases. 2. Promote care quality in the therapeutic approach of patients with chronic lung diseases. 3. Promote research transfer into lung diseases. 4. Create new lines of investigation in coordination with other working groups.

Research interests: The Pulmonology Department of La Princesa Hospital is part of the R+D Biomedicine Programme. HUP ConSEPOC-CM: Inflammation and hypoxia: mechanisms of development and progression of COPD and SAHS. Several active clinical trials will be developed during next years on different respiratory diseases (COPD, asthma, idiopathic pulmonary fibrosis, bronchiectasis and cystic fibrosis). Several projects received grants from the Spanish Society of Respiratory Pathology (SEPAR) and other entities.

Plan of actions for 2016-2019

- Further develop, maintain and strengthen the respiratory group on chronic respiratory conditions at the La Princesa Investigation Institute (IP).

- Complete the European proposal study M-BREATH (COPD Monitoring and Biomarkers) requested to the European Union Horizon 2020.
- TackSHS Project: Tackling secondhand tobacco smoke and e-cigarette emissions: exposure assessment, novel interventions, impact on lung diseases and economic burden in diverse European populations. Topic: Global Alliance for Chronic Diseases. Prevention and treatment of lung diseases. Reference: HCO-06-2015.

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- Girón Moreno, Rosa María. Efecto de las infecciones por *Pseudomonas aeruginosa* asociadas a fibrosis quística sobre la estructura de exosomas secretados por el epitelio pulmonar. Becas SEPAR. 2020.



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- García Monzón, Carmelo / Landete Rodríguez, Pedro. Caracterización de los mediadores moleculares clave de la enfermedad hepática grasa metabólica asociada al síndrome de apnea obstructiva del sueño: Implicaciones diagnósticas y terapéuticas. PI20/00837. ISCIII. 2021-2023.
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GROUP 24



Head of laboratory



Research interest



Majano Rodríguez, Pedro Lorenzo



Group members

- Casabona Francés, Sergio
- de la Morena López, Felipe
- Fernández-Pacheco Esteban, Jennifer
- Herranz Pérez, Raquel
- Laserna Mendieta, Emilio José
- Martín Domínguez, Verónica
- Miranda García, Pablo
- Molina Jiménez, Francisca
- Moreno Monteagudo, José Andrés
- Pérez Fernández, María Teresa
- Santander Vaquero, Cecilio

**Associated Clinical Group Hospital
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- Lucendo Villarín, Alfredo José
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- Arias González, Laura
- González Cervera, Jesús

MAIN:

Eosinophilic Esophagitis (EoE) is a chronic inflammatory disease of the esophagus with an immune-allergic basis. EoE is clinically characterized by symptoms of esophageal dysfunction, and histologically by an eosinophil-predominant inflammatory infiltrate. In the absence of treatment, the natural history of EoE consists in a progressive fibrous remodeling of the organ into the formation of strictures that reduce the esophageal caliber and aggravate the symptoms. Currently, endoscopic biopsies are the only reliable method to diagnose the disease and monitor the response to therapy.

In this project, we aim to analyze changes in the expression of genes and proteins in esophageal biopsies of adult patients with EoE, induced after being treated as recommended in European clinical practice guidelines, and compared with healthy subjects. Changes in the expression of mRNA (mRNAseq), proteins (proteomic) and in the secreted proteins (multiplexed Elisa) will be measured, and lymphocyte populations in both esophageal tissue and peripheral blood of EoE patients will be characterized (flow cytometry). Data obtained by these massive analysis techniques, together with markers of the progression of esophageal fibrosis and alteration in esophageal distensibility (as determined by EndoFLIP) will allow us selecting a series of candidate markers related to the presence of the disease, its inflammatory activity and fibrotic changes, as well as predicting response to treatment. As a final aim, we will try to define a set of biomarkers to be further studied in a larger cohort (validation).

SECONDARY:

Gastroesophageal reflux disease (GERD) is the most prevalent gastrointestinal disorder in industrialized countries. Key mechanisms

of disease include abnormal oesophagogastric junction structure and function, and impaired oesophageal clearance. Recent studies have challenged the traditional notion that reflux esophagitis develops only when esophageal surface epithelial cells are exposed to chemical injury from refluxed acid.

In this line, we wanted to characterize lymphocyte populations in both esophageal tissue and peripheral blood of GERD patients by multiplexed flow cytometry. Data obtained by these techniques will be related to the presence of the disease and its inflammatory activity.



Major grants

- Majano Rodríguez, Pedro Lorenzo / Santander Vaquero, Cecilio. Esofagitis eosinofílica: estudios en biopsia esofágica y sangre periférica para la identificación de biomarcadores de la enfermedad y de la respuesta al tratamiento. PI17/00008. ISCIII. 2018-2020.
- Santander Vaquero, Cecilio. Esofagitis Eosinofílica: proteómica de biopsia esofágica y sangre periférica para la identificación de biomarcadores de la enfermedad y de la respuesta al tratamiento. Asociación Española de Gastroenterología. 2019-2020.
- Majano Rodríguez, Pedro. Esofagitis eosinofílica: proteómica de biopsia esofágica para la identificación de biomarcadores de la enfermedad y de la respuesta al tratamiento en Esfagitis Eosinofílica. ProteoRED-ISCIII. 2019-2020.

Major Grants Associated Clinical Group Hospital General de Tomelloso

- Lucendo Villarín, Alfredo José. Caracterización de la actividad de receptores Toll-like (TLRs) en la fisiopatología de la esofagitis eosinofílica. Asociación Española de Esfagitis Eosinofílica (AEDESEO) – Nestlé. 2018-2020.



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GROUP 23



Head of laboratory



García Buey, Luisa Consuelo



Group members

- **González Moreno, Leticia**
- **Mendoza Jiménez-Ridruejo, Jorge**
- **Moreno Otero, Ricardo**
- **Real Martínez, Yolanda**



Research interest

During the last years our research group has been particularly focused on identifying non-invasive prognostic biomarkers of chronic liver disease (CLD) progression to cirrhosis and hepatocellular carcinoma (HCC).

HCC is the second leading cause of cancer death worldwide and has a high mortality rate because it is only diagnosed in advanced stages, at which available treatments are no longer effective. There-

fore, new tools that improve the diagnosis and treatment of HCC patients are needed.

The altered expression of angiogenic and fibrogenic-related factors during the course of CLD to HCC may provide a valuable tool for the non-invasive assessment of liver fibrosis, key for clinical decision-making. Among other clinical and demographic variables, we found that peripheral levels of angiopoietins significantly correlated with hepatic fibrosis in patients with chronic hepatitis C (CHC). Such finding allowed us to develop a novel index for non-invasive evaluation of liver fibrosis, AngioScore, which was further validated in an independent series of patients. In addition, our group reported a significant increment of TIE2-expressing monocytes (TEMs) in the peripheral blood of patients with CHC. Monocytes, essential precursors of antigen-presenting cells, notably contribute to the pathogenesis of chronic inflammatory diseases and cancer. We proposed that chronic expansion of TEMs, which are characterized by their marked proangiogenic properties and notable immunosuppressive nature, might prevent proper immune response and promote mechanisms that cause liver damage. The expression of the angiopoietin receptor Tie2 in the surface of this subtype of monocytes might serve as useful "tag" for the non-invasive monitoring of CLD progression in a simple blood test. Moreover, we believe that a more in depth understanding of TEM regulation can lead to important therapeutic advances. Interestingly, in the meantime, other authors described that TEMs might work as a useful cellular diagnostic and prognostic biomarker for HCC.

Furthermore, we have also characterized the significance of certain genetic variants of HDACs and other angiogenic factors, receptors and mediators, in relation to fibrosis progression.

Therapeutic options and diagnostic procedures in hepatology have quickly advanced during the last decade, in particular, the management of

viral hepatitis. Hepatitis C has become a curable disease with a sustained 99% response using direct-acting antiviral therapeutic regimens.

With the increasing number of individuals with diabetes and obesity, non-alcoholic fatty liver disease (NAFLD) is becoming increasingly prevalent, affecting more than one-quarter of adults in the world. In addition to liver cancer, we have other research lines:

- Actions for micro-elimination of HCV infection.
- Interaction between DAA for Chronic Hepatitis C infection and hepatocellular carcinoma
- Non invasive evaluation of non alcoholic fatty liver disease.
- Chronic cholestatic liver disease: Primary Sclerosing Cholangitis and Primary Biliary Cholangitis.



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GROUP 25



Head of laboratory



Research interest



Marazuela Azpíroz, Mónica



Group members

- Aguirre Moreno, Nerea
- Araujo Castro, Marta
- Caldas Álvarez, María
- Carrillo Lozano, Elena
- Knott Torcal, Carolina
- Martínez Hernández, Rebeca
- Pérez Casas, Andrés
- Pérez Gómez, Alberto Luis
- Ramos Levi, Ana María
- Ruiz Roso Guerra, María de Belén
- Sampedro Núñez, Miguel Antonio
- Serrano Somavilla, Ana

Our current and future work involve different research fields in endocrine diseases. We are studying the role of immunoregulatory molecules in patients with autoimmune thyroid diseases (AITD) including Hashimoto's thyroiditis (HT), Graves' disease (GD) and Graves' ophthalmopathy (GO). During the last years, we have discovered that patients with AITD have altered populations of regulatory T cells (Treg), augmented Th17 cells, a defective production of Tr1 regulatory cells and abnormalities in Natural Killer cell levels (Endocrine 2016 51(3):478-89; J Clin Endocrinol Metab 2017 feb 1; 102(2):672-680; J Clin Endocrinol Metab 2018 103: 3359-3367; J Clin Endocrinol Metab, 2020, Vol. 105, No. 11, 1-11). We are also studying additional regulatory molecules in these patients, such as VIP (Scientific Reports 2020; 10:13018). These abnormalities in immunoregulatory molecules may contribute to the pathogenesis and/or auto perpetuation of AITD.

We have also studied the expression of miRNAs (miRNome) in thyroid samples from patients with AITD and healthy controls and the potential use of selected miRNAs as biomarkers in serum samples from AITD patients. Our results in this field included characterizing the role of microvesicles (MVs) and microRNAs in the pathogenesis of AITD. We have demonstrated that MVs may have a relevant role in AITD as modulators of the immune response, mainly through the inhibition of Treg cell differentiation and the induction of Th17 cells (J Clin Endocrinol Metab 2015, 100:12). Furthermore, we have developed a 5-miRNA signature that could be an independent risk factor for developing AITD and for predisposition to a worse clinical picture in GD patients (J Clin Endocrinol Metab. 2018 Mar 1;103(3):1139-1150).

We also participated in a collaborative project in the study of immunoregulatory molecules and miRNAs in different immune-mediated inflammatory diseases (IMID) including rheumatoid arthritis, psoriasis, inflammatory bowel disease and AITD, to try to find new predictive biomarkers (immunoregulatory molecules) of IMID severity and responsiveness to biological therapies. We have identified a signature model that can contribute to an improvement in the detection of severe IMID forms, and also reveal common events present in several IMIDs, thereby studying possible links between the different types of diseases (Journal of Autoimmunity 111 (2020) 102472).

In the last years, we are integrating the power of omics in characterizing new clinical approaches and susceptibility pathways in AITD. We have carried out an integration study of miRNAs and mRNAs in order to search for new candidate genes and miRNAs to be used as potential biomarkers and / or therapeutic targets. The results of this project led to the study new susceptibility pathways in AITD such as ciliogenesis. We observed, for the first time, the important role in the etiopathogenesis of AITD of genes involved in cilia regulation (EBioMedicine. 2019 Dec;50:329-342).

Our next approach is to characterize the cell type specific transcriptomic heterogeneity and regulatory networks in thyrocytes and infiltrating T lymphocytes in AITD thyroid tissue, taking advantage of digital pathology approaches such as Visium Spatial Gene Expression.

Another area of investigation of the group is the study of mechanisms resulting in evasion of immune attack in gastroentero-pancreatic neuroendocrine tumors (GEP-NETs). We have found that PD-1 expression is detected in a small but significant proportion of GEP-NETs and that the presence of this receptor is significantly associated to increased malignancy (Scientific Reports | (2018) 8:17812). Furthermore we have confirmed that specific mechanisms that increase nutrient uptake, such as LAT-1 and GLUT-1, are increased in GEP-NETs, which might be related to their proliferation and metastatic capacity (Cancers 2020, 12, 2968).

Our group also leads the Spanish Molecular Registry of Pituitary Adenomas (REMAH) with 1,400 patients registered (Oncologist. 2018 Apr;23(4):422-432). This strategy allows for comparative and relational analysis between the molecular profile of the different types of adenoma and the clinical phenotype of patients, which may provide a better understanding of the condition and potentially help in treatment selection (Endocr Relat Cancer. 2020 Jun;27(6):375-389). Deepening into the knowledge of these molecular patterns will enable to better understand this condition and adopt more appropriate decisions on the treatment and follow-up of pituitary tumors. Furthermore, the identification of new molecules using Tissue Microarrays in these tumors will allow us testing the effect of new treatments, thus increasing the range of adenomas that can be treated pharmacologically.

In summary, our group has an extensive and relevant research trajectory and a high number of scientific publications in impact journals in the aforementioned areas of knowledge. Likewise, it has an important basic-clinical translational research component, based on a global approach to the study of the aforementioned endocrinological disorders, covering not only the most basic aspects, but also those related to their pathophysiology, diagnosis and treatment.



Major grants

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GROUP 26



Head of laboratory



Research interest



Argente Oliver, Jesús



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- Canelles Ortiz, Sandra
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How the genetic make-up of an individual interacts with the early maternal/neonatal and postnatal environments to culminate in obesity and its secondary complications, is being studied with both clinical and basic approaches. Genetic studies are performed to identify mutations in genes involved in monogenic obesity, to identify new candidate genes and to analyze polygenic and epigenetic causes of obesity. Diverse new candidate genes have been identified and are being further investigated, as well as the interaction genotype/phenotype and ethnic influences. Metabolomic studies are underway to better understand the processes involved in the development of insulin resistance and type 2 diabetes in obese children. Metabolites that may be involved in this process have been identified and will be further studied. In addition, it appears that this process may differ between males and females even prepubertally and this will be further explored. We have recently identified a new monogenic cause of pathological human growth that courses with skeletal abnormalities. The underlying cause is due to affection of the insulin-like growth factor (IGF) system and this new syndrome will be thoroughly analyzed and new concepts of the physiological functioning of the IGF system pursued.

Animal models are employed to analyze how poor maternal and/or neonatal nutrition, stress or changes in specific hormones during neonatal life affect adult metabolism, with special attention focused on the differential responses of males and females. Studies analyzing the effect of increased central leptin levels on insulin signaling in the CNS and adipose tissue demonstrate a relationship between insulin resistance, hypothalamic inflammation and energy homeostasis. Hypothalamic glial cells are a main focus of investigation for their newly recognized role in metabolic control. We have shown them to respond to

weight gain and metabolic hormones such as leptin. Current interest includes analysis of glial responses to specific nutrients and how this could influence the metabolic outcome to weight gain. The implications of weight gain and abnormal circulating levels of leptin and insulin have also been implicated in increased susceptibility to neurodegenerative diseases, with this susceptibility being different between males and females. Future studies are planned to determine the role of astrocytes in mediating the protective and/or detrimental responses to high fat diet intake on neurodegeneration.



Major grants

- Chowen, Julie Ann / Frago Fernández, Laura María. Cross-talk entre los astrocitos hipotalámicos y el tejido adiposo perivascular en el metabolismo energético y la función cardiovascular: Impacto de las modificaciones en la dieta. FFU2017-82565-C2-1-R. Ministerio de Ciencia, Innovación y Universidades. 2018-2022.
- Argente Oliver, Jesús. Estudio de nuevos factores reguladores identificados en el sistema GH/IGF: Implicaciones en patología humana, análisis de los mecanismos involucrados y desarrollo de nuevas terapias potenciales. PI19/00166. ISCIII. 2020-2022.



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GROUP 5

LINE 1.11 METABOLIC SYNDROME AND VASCULAR RISK



Head of laboratory



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Research interest

Nonalcoholic fatty liver disease (NAFLD) is an increasingly common chronic liver disease around the world with a diverse histopathological spectrum ranging from simple steatosis without significant inflammation to steatohepatitis (NASH) with varying stages of fibrosis and, ultimately, cirrhosis and he-

patocellular carcinoma. It is well known that NAFLD occurs more frequently in obese and diabetics, being currently considered as the hepatic manifestation of the metabolic syndrome. Although the molecular mechanisms involved in the pathogenesis of NAFLD and progression to NASH remain incompletely defined, most investigations indicate that insulin resistance plays a pivotal role in NAFLD setup. Since NASH is becoming one of the most frequent causes of cirrhosis and liver transplantation in the developed countries, it is crucial to identify populations at risk for NASH in order to prioritize the diagnostic and therapeutic interventions on those patients with an increased risk for liver disease progression.

Our group seek three main research lines for the next five years. 1) To unravel the molecular mechanisms involved in the pathogenesis of NASH searching for potential therapeutic targets. We are exploring the role of autophagy in the development of NASH. We recently reported that autophagic flux is impaired in hepatocytes from NASH patients and murine models of NASH and we are, therefore, proposing to investigate in the next future whether therapies aimed to restore the autophagic flux might prevent or attenuate the progression of NAFLD. We are also addressing the role of intermittent hypoxia in the pathogenesis of NAFLD by analyzing the expression levels of hypoxia-inducible factors 1 and 2 in liver biopsies and serum of NASH patients and murine models of NASH as well as the impact of hypoxia on the mitochondrial function in human hepatocytes under experimental conditions of lipid overload. 2) Identification of biomarkers able to be used for non-invasive diagnosis of NASH. We have shown that genetic variants of SLC2A1 are associated with NAFLD and that circulating levels of soluble CD36 is an independent factor associated with advanced steatosis in NAFLD but not in patients with chronic hepatitis C virus (HCV) infection. More recently, we have reported that the combination of ultrasound and HOMA score is useful for noninvasive diagnosis of patients with

NASH. We are now pursuing diagnostic tools based on ELISA multiplex using proteins of pathogenic relevance in chronic liver diseases. 3) Impact of the new direct-acting antivirals on carbohydrate and lipid metabolism in patients with chronic hepatitis C treated with these highly effective antiviral drugs: Implications for the cardiovascular morbidity and mortality. It is well known that chronic HCV infection is associated with insulin resistance and type 2 diabetes mellitus together with alterations in hepatic lipid metabolism. The discovery of new direct-acting antiviral agents has become a huge advance in the treatment of HCV infection. Among them, sofosbuvir and other new antivirals in combination with ribavirin has improved considerably the sustained virological response of HCV infection. However, little is known about their effects on carbohydrate and lipid metabolic profiles in patients treated with these new direct-acting agents and their potential mechanistic actions. On that basis, we propose to determine the effects of sofosbuvir and other direct-acting antivirals on HCV-induced metabolic complications such as insulin resistance, hyperglycemia and dyslipidemia. Moreover, the impact of therapy with sofosbuvir and other related agents on metabolic disturbances induced by the impairment of autophagic flux in HCV infection will be analyzed. In summary, we believe that our lines of investigation could shed light, in the next future, on key aspects for the pathogenesis and therapy of NAFLD and other chronic liver diseases as well as for the noninvasive diagnosis of NASH.



Major grants

- García Monzón, Carmelo. Identificación y evaluación de biomarcadores relacionados con la hipoxia para el diagnóstico no invasivo de la enfermedad hepática grasa no alcohólica y del daño vascular asociado. PI17/00535. ISCIII. 2018-2020.

Granted 2020:

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metabólica asociada al síndrome de apnea obstructiva del sueño: Implicaciones diagnósticas y terapéuticas. PI20/00837. ISCIII. 2021-2023.

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GROUP 42



Head of laboratory



González Rodríguez, Águeda



Group members

- Domínguez Alcón, Lucía Soledad
- El Bouayadi Mohamed, Liliam
- Marañón Barnusell, Patricia
- Muñoz Olmedo, José Manuel
- Peñaloza González, Ángela Lucía
- Rey Fernández, Esther



Research interest

Today's lifestyle is characterised by an abundance of calories, reduced physical activity and increased life expectancy, which has triggered the incidence of obesity in epidemic proportions in recent decades, and is particularly alarming in the child population. This increase in obesity incidence is associated with a series of metabolic pathologies, including type 2 diabetes mellitus,

non-alcoholic fatty liver disease and atherosclerosis, which have led to research projects dedicated to clarifying the molecular mechanisms that trigger them. This grouping of metabolic and cardiovascular risk factors is known as Metabolic Syndrome.

Our research group is made up of basic and clinical researchers, who actively collaborate to develop high level translational research focused on the study of the molecular bases of Metabolic Syndrome and hepatic pathologies. The group therefore pursues three fundamental lines of research.

1. Study of metabolic complications associated with chronic diseases. On the one hand, we are evaluating the effects of sofosbuvir, one of the new direct-acting antiviral agents that has become a breakthrough in the treatment of chronic hepatitis C, metabolic complications and cell death associated with that disease. On the other hand, we are exploring possible factors (degree of systemic inflammation and hypoxia, among others) responsible for the association between the most prevalent chronic respiratory diseases and the appearance of cardiovascular and metabolic disorders.

2. Identification and characterisation of new molecular targets involved in peripheral insulin resistance associated with metabolic damage. We are looking for new therapeutic targets associated with inflammatory processes, studying their implication in inflammation induced by a high-fat diet and consequences on insulin response in peripheral tissues, including the liver.

3. Impact of Bone Morphogenetic Proteins on hepatic pathophysiology. Bone morphogenetic proteins are growth factors that are booming due to their pleiotropic role in different cellular processes, but their involvement in the pathogenesis of the liver is a topic that has hard-

ly been investigated. Liver pathophysiology includes non-alcoholic fatty liver disease (NAFLD), acute liver failure, liver fibrosis or cirrhosis, viral hepatitis, hepatocellular carcinoma and alcoholic fatty liver. This line of research therefore seeks to identify the role of these proteins in liver damage progression, leading to the generation of new direct biomarkers for non-invasive diagnosis/prognosis of the different evolutionary phases of these pathologies, thus contributing to the design of new, more effective and less invasive diagnostic tools.



Major grants

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AREA 2



TRANSLATIONAL NEUROSCIENCE



- **LINE 2.1** NEUROPHARMACOLOGY AND NEUROPROTECTION
- **LINE 2.3** CLINICAL PHARMACOLOGY AND PHARMACOGENETICS
- **LINE 2.4** DIAGNOSTIC AND THERAPEUTIC ADVANCES IN AFFECTIVE DISORDERS
- **LINE 2.5** NEUROSURGERY OF EPILEPSY
- **LINE 2.6** CEREBROVASCULAR DISEASES

GROUP 16



Head of laboratory



García López, Manuela



Group members

- Baena Roper, Irene
- Fernández Mendivil, Cristina
- García López, Manuela
- Lantigua Romero, Sara
- Luengo Martín, Enrique
- Peñasco Iglesias, Sara
- Rodríguez Ortega, Elisa
- del Sastre López, Eric
- Trigo Alonso, Paula



Research interest

Neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and stroke represent an appalling cost, both in financial and human terms. Treatments for neurodegenerative diseases are destined to

become the most significant health challenge for this generation. To date, no therapeutic strategy has proven effective and millions have been invested in therapeutic trials that have failed. There is therefore an urgent and pressing need to identify novel therapeutic strategies that might protect or rescue vulnerable neurons in these dreadful diseases. In this context, our main research lines are:

- 1.** Identification of therapeutic targets to develop new drugs for neurodegeneration. We are particularly interested in understanding how oxidative stress, neuroinflammation and changes in the autophagic flux participate in neurodegeneration, in order to develop pharmacological interventions to regulate these pathological conditions.
- 2.** Development of in vitro and in vivo preclinical models that better mimic the human neurodegenerative disease. Availability of preclinical models that better represent the human disease will greatly improve translation of preclinical results to human disease.
- 3.** Search of novel therapeutic strategies for neurodegeneration based on medicinal chemistry, combination therapy and drug repurposing. Since oxidative stress, neuroinflammation and impairment of autophagy have been implicated in neurodegeneration, impacting on several of these processes with multitarget compounds or combination of drugs with complementary mechanisms of action is sought, to have better therapeutic profile than just impacting on a single target. For example, Nrf2 inducers combined with scavenger effect, the inhibition of several enzymes related to neurological disorders and agonist of the nicotinic acetylcholine receptors are currently being developed in our group.



Major grants

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GROUP 28



Head of laboratory



de los Ríos Salgado, Cristóbal



Research interest

My current work focuses on the validation of new therapeutic targets for the treatment of the central nervous system. During the latest years, it has been stated that the most accepted hypotheses to explain the development of Alzheimer's disease have not given the expected crops. For this reason, new approaches have to be aimed. Since I started my scientific career as an independent investigator, I have focused on drug discovery on alternative biological targets to treat neurodegenerative diseases, like the mitochondrial Na/Ca exchanger (NCLX) and the phosphoprotein phosphatase PP2A. In my lab, we are designing and synthesizing new compounds able to selectively act on these targets. Also, we have described a family of benzothiazepine derivatives that overcome the blocking effect of the best-known NCLX blocker CGP37178, the unique tool since the 1980s. Finally, we are developing the first family of ligands with demonstrated direct activity as PP2A activators. Many of these compounds present promising results in experiments assessing the neuroprotective effect, as they mitigate the neuronal death induced by toxic stimuli mimicking physiopathological events where the selected targets are implicated.



Group members

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- Calzaferri, Francesco
- Cano Abad, María Francisca
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- Martín Alcala, Gabriel
- Méndez López, Iago
- Ortega Cruz, Diana
- de Pascual y del Castillo, Ricardo
- Ruiz Ruiz, Cristina
- Viejo de Navas, Lucía



Major grants

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GROUP 60



Head of laboratory



León Martínez, Rafael



Group members

- Abril Comesaña, Sheila
- Buendía Abaitua, Izaskun
- Crisman Vigil, Enrique
- Duarte Flórez, Pablo
- Franco González, Juan Felipe
- Matesanz Sánchez, Rocío
- Mayo Mariscal de Gante, Paloma Pilar
- Michalska Dziama, Patrycja



Research interest

Neurodegenerative diseases (NDDs) are a group of diseases that encompass around 600 pathologies, among which the most prevalent are: Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease HD and amyotrophic lateral sclerosis (ALS). Given that the main risk factor in these diseases is age, NDDs will be the biggest health challenge in the coming decades due to the increase in life expectancy and the gradual aging of the population. AD stands out as the most prevalent. During the last two decades, an immense effort has been made to try to develop effective treatments for these diseases, although their success has been very limited or null in most cases. The precise causes of failure of developing treatments in the clinic are unknown. A possible cause, increasingly accepted, is that the selection of therapeutic targets has been based on the genetic aspects of these diseases. Currently, NDDs are considered multifactorial diseases and, therefore, the "one drug one target" approach would not be effective in stopping their progress. At present it is considered that the combination of targets in a single molecule will be decisive for obtaining really effective drugs, a strategy called "multi-target drugs".

The research line is subdivided into 4 research sub-lines, where non-conventional targets have been combined with each other, or with other targets already established to integrate them into a new compound.

- Design, synthesis and pharmacological evaluation of new multifunctional hybrids as inducers of Nrf2 and free radical sequestering effect. The design and synthesis of new hybrids of melatonin (a potent natural antioxidant) and Nrf2 inducers for the treatment of NDDs is addressed.
- Design, synthesis and pharmacological evaluation of non-electrophilic Nrf2 inducers and inhibitors of the GSK3 enzyme. The synthesis of new multipotent derivatives capable of inducing the Nrf2-ARE response and inhibiting the activity of the GSK3 β enzyme is addressed.

- Design, synthesis and pharmacological evaluation of dual GSK3 and AChE inhibitors and Nrf2 inducers for the treatment of Alzheimer's disease, combining the three targets directly involved in AD.

- Design, synthesis and biological evaluation of three-dimensional enantioselective structures as inducers of Nrf2 and modulation of acetylcholine receptors for the treatment of neuro-degenerative diseases.



Major grants

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GROUP 41



Head of laboratory



Egea Máiquez, Francisco Javier



Group members

- Farré Alins, Víctor
- Narros Fernández, Paloma
- Palomino Antolín, Alejandra



Research interest

Acute brain injuries, such as stroke and traumatic brain injury, account for 10% of deaths and are the leading cause of disability worldwide (GBD 2013 Mortality and Causes of Death Collaborators, 2015). The pathophysiology of acute brain injuries is complex and multifactorial and, currently, it is difficult to treat pharmacologically and represent an unmet need at clinical level. In recent years, inflammatory processes (pronounced in this type of pathologies)

have become the main agents that contribute to aggravate acute brain injuries and, therefore, have become very promising therapeutic targets.

Our group focuses on studying the role of inflammation and immunity in the pathogenesis of these diseases. Specifically, we study the mechanisms that control the activation of the innate immune system and its application to the search for new therapeutic targets and new prognostic / diagnostic biomarkers in stroke, traumatic brain injury and neurodegenerative diseases.

1. Study of the mechanisms that control the activation of the innate immune system.

Inflammasomes are multi-protein molecular platforms involved in the activation of caspase-1. After activation of caspase-1, interleukins pro-IL-1 β and pro-IL-18 are processed and released to initiate the inflammatory process. NLRP3 is the only NOD receptor (NLR, NOD-like receptors) that responds to both danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). NLRP3 is activated in response to a wide variety of infectious stimuli or cellular stress caused by different signs of sterile danger, such as high concentrations of extracellular ATP, oxidative stress, and β -amyloid aggregates. Our main work focuses on studying the transduction of the signals that activate inflammation and, specifically, the participation of mitochondria in this process.

2. Search for new therapeutic targets to treat acute brain injuries.

The mechanisms studied in line 1 are validated in "in vitro" and "in vivo" models of cerebral ischemia (transient middle cerebral artery occlusion, tMCAO model) and traumatic brain injury (closed head injury model).

3. Search for new diagnostic/prognostic biomarkers of inflammatory origin.

We study the potential role of new biomarkers in samples of traumatic brain injury patients and we try to validate them using the models described in line 2.



Major grants

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GROUP 32



Head of laboratory



Abad Santos, Francisco



Group members

- Almenara de Riquer, Susana
- Belmonte Campillo, Carmen
- Campodónico, Diana María
- Flores Ruiz, María Eugenia
- Gil Divasson, Pedro
- González Rojano, Esperanza
- Hernández Martínez, María José
- Koller, Dora
- Martín Vílchez, Samuel
- Mejía Abril, Gina Paola
- Ochoa Mazarro, María Dolores
- Ovejero Benito, María del Carmen
- Pérez Hernández, Concepción
- Pintos Sánchez, Elena
- Román Martínez, Irene
- Román Martínez, Manuel
- Romero Palacián, Daniel Rafael
- Saiz Rodríguez, Miriam
- Santos Molina, Elena
- Zubiaur Precioso, Pablo



Research interest

The aim of the research conducted by this group is to increase pharmacogenetic, pharmacokinetic and pharmacodynamic knowledge of drugs in order to predict patients' response in terms of effectiveness and safety.

Our group has extensive experience in conducting phase I, II and III clinical trials. We have a clinical trials unit (UECHUP), with capacity for 18 subjects on the 7th floor of the Hospital Universitario de la Princesa. The clinical trials conducted include phase 1 clinical trials (e.g. bioequivalence or first in human trials), and clinical trials in patients to evaluate the effectiveness of new drugs, in collaboration with various specialists at the hospital and with primary care. Our group conducts more than 20 clinical trials each year, and this number is expected to increase due to demand from the pharmaceutical industry. Last year, several clinical trials on the COVID-19 vaccine were conducted in our unit.

The group's research focuses mainly on the pharmacogenetics of several drugs prescribed for the treatment of various diseases, so that eventually this knowledge could help physicians to prescribe the best treatment for each patient in a personalised way. In 2020, 311 patients benefited from pharmacogenetic testing. We have also implemented pharmacogenetic testing through OpenArray, using a customised chip that can simultaneously analyse 120 SNPs located in 43 different genes. This technology has enabled us to significantly increase our portfolio of pharmacogenetic tests available to support physicians in prescribing medicines. Seven funded projects were active in 2020. In addition to projects funded in previous years, Francisco Abad Santos received new funding in 2020 (ICI20/00131) to evaluate a pharmacogenetics-guided tramadol prescribing strategy. Another important line of research focuses on therapeutic drug monitoring, mainly for antipsychotics and tyrosine kinase inhibitors.



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GROUP 33



Head of laboratory



Ayuso Mateos, José Luis



Research interest

Our team has been devoted to researching the nosology of mental disorders, the epidemiology of mental disorders in general population, the study of the efficacy and efficiency of clinical interventions in affective disorders and the assessment of the health status, quality of life and well-being by means of analysing large populations data.

On the one hand, in 2017 we have maintained some projects and research lines: we have sustained our collaboration with the WHO and have contributed to the revision of the International Classification of Diseases 11th edition (ICD-11). Furthermore, we have intended to contribute to the promotion of mental health not only at a European level but also in Low and middle income countries (LAMICs) and focused in improvement of health systems. We have participated in an international project (EMERALD project) funded by the EU aimed to enhance mental health in LAMICs by means of improvement of all the systems related to health care.

Following H2020 strategic plan, we have consolidated our research line on active aging and wellbeing. We have been working in the project ATHLOS - Ageing Trajectories of Health: Longitudinal Opportunities and Synergies, and PATHWAYS - Participation To Healthy Workplaces And inclusive Strategies in the Work Sector. In addition, we have been conducting a multi-approach study for the identification of the available interventions for targeting psychosocial difficulties in major depression (meta-analyses and expert consultation) (MARATONE project).

Additionally, we have maintained our interest in the study of the environmental and genetic risk



Group members

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- **Cabello Salmerón, María**
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- **Ezquiaga Terrazas, María Elena**
- **Fernandez Natal, Cora**
- **de la Fuente Carrillo, Javier**
- **Izquierdo Zarzo, Ana**
- **Lara Pérez, Elvira**
- **Leal Leturia, Itziar**
- **López García, María Pilar**
- **Martín María, Natalia**
- **Martínez Cano, Herminio**
- **Miret García, Marta**
- **Moreno Agostino, Darío**
- **Rico Uribe, Laura Alejandra**
- **Sánchez Carro, Yolanda**
- **de la Torre Luque, Alejandro F.**
- **Viera Campos, Alba**

factors for the development of psychotic episodes (AGES-CM project).

On the other hand, we have been working on several new research projects:

1) "Trajectories on mental health, physical health and functioning: Third wave survey of a Spanish cohort of the adult population", which is aimed to carry out a third time point assessment to know trajectories of health in ageing people as well as recruiting new people to make generational comparisons.

2) "CIBERSAM cohorts about FEP cases and controls", which is aimed to create a common cohort from different existing cohorts with first episode patients and controls, and follow-up the common cohort at 5, 10 and 15 years.

3) "Emotional fluctuation in daily life. Ecological analysis of depressive symptomatology in the general population" which is aimed to analyse the mood fluctuations throughout the day in a general population sample using mobile Apps.

4) "European Welfare Models and Mental Well-being in Final Years of Life", which is addressed to gather information on the components of wellbeing and welfare in people older than 80 years.

5) "Peripheral oxidative stress and inflammatory markers in Major Depressive Disorder", focuses on finding biological markers in Major Depressive Disorder.

6) "Metabolic Dysfunctions associated with Pharmacological Treatment of Schizophrenia (TREATMENT)" in which we evaluate how short-term antipsychotic drug responses impact long-term metabolic control to identify and validate biomarkers with clinically predictive value for targeting drug induced metabolic dysfunctions.

7) "Psychiatric Ratings using Intermediate Stratified Markers (PRISM)", whose overall objective is to develop a quantitative biological approach to

the understanding and classification of the endophenotypes that contribute to neuropsychiatric diseases, to accelerate the discovery and development of better treatments for patients with Alzheimer and Schizophrenia.



Major grants

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■ López García, Pilar. TREATMENT: Training European Network: Metabolic Dysfunctions associated with Pharmacological Treatment of Schizophrenia. 674921. Comisión Europea. 2016-2020.

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GROUP 34



Head of laboratory



Pastor Gómez, Jesús



Research interest

Epilepsy, movement disorders and some psychiatric pathologies are among the main targets for functional neurosurgery. They share several properties that make them interesting for our research line.

Drug-resistant epilepsy affects 20-30% of patients suffering epilepsy worldwide. One of the most efficacious treatments is surgery, including resective techniques and neuromodulation in different forms. Presurgical evaluation usually requires the use of very deep studies (e.g. morphological and functional MRI) or invasive techniques (intracranial electrodes), which are also used during treatment (electrocorticographic recordings or extracellular recordings for Deep Brain Stimulation -DBS). In the same way, several pathologies affecting basal ganglia need different ancillary tests to characterize the illness (genetic, nuclear medicine, morphological MRI) and to carry out the treatment (DBS).

Altogether, this set of human illness offers a unique opportunity to study the underlying pathophysiological processes. Understanding these processes is the first step to its rational treatment

Our research line is integrated by clinical researchers which are part of national reference units for the treatment of refractory epilepsy and surgical treatment of movement disorders. Therefore, our scientific interests include all aspects around functional neurosurgery and, especially, epilepsy and basal ganglia pathologies.

The topics we are working on include the following:

- a. Identification of basal ganglia subnuclei by extracellular recording.



Group members

- Carvajal Molina, Fernando
- de Dios Tomás, Eva
- Domínguez Gadea, Luis
- García Navarrete, Eduardo
- Luque Cárdenas, Cecilia
- Martín Plasencia, Pilar
- Meilan Paz, María Luisa
- Navas García, Marta
- Pintor Zamora, Miguel
- Pulido Rivas, Paloma
- Rocío Martín, Esmeralda
- Torres Díaz, Cristina Virginia
- Vega Zelaya, Lorena Carolina
- Wix Ramos, Rybel

b. Physiopathology of somatosensory thalamus, by means of somatosensory evoked potentials, electrically elicited.

c. Connectivity in epilepsy. To do that, we are studying diffusion tensor imaging and fractional anisotropy, as well as electrophysiological recordings acquired by means of scalp or intracranial recordings.

d. Genetics and epi-genetics in epilepsy.

e. Quantified EEG (qEEG) to use as biomarker for different pathologies. Among those fields specially targeted by this technique are patients in Intensive Care Units and neurological and psychiatric illness.

f. Cortico-cortical connectivity, especially for language function.



Major grants

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- Torres Díaz, Cristina Virginia. Caracterización molecular, epigenética y estudio de tetraploidias en pacientes epilépticos fármaco resistentes del lóbulo temporal. PI17/02244. ISCIII. 2018-2020.



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GROUP 35



Head of laboratory



Vivancos Mora, José Aurelio



Group members

- Aguirre Hernández, Clara
- Carreras Rodríguez, Teresa
- Fernández Alén, José Antonio
- Gago Veiga, Ana Beatriz
- García Vaz, Fabiola
- González García, Beatriz
- López Manzanares, Lydia
- Meca Lallana, Virginia
- Mora Pérez, Noemí
- Nombela Merchán, Florentino
- Ramos Martín, Carmen
- Reig Roselló, Gemma
- Sobrado Sanz, Mónica
- de Toledo Heras, María
- Trillo Senin, Santiago
- Vázquez Doce, Aránzazu
- Ximenez-Carrillo Rico, Álvaro
- Zapata Wainberg, Gustavo Enrique

Associated Group

- Ayala Rodrigo, José Luis
- Pagán Ortiz, Josué
- Risco Martín, José Luis



Research interest

THE MAIN RESEARCH LINES OF THIS GROUP ARE:

Stroke and Cerebrovascular Diseases

- Biomolecular markers of ischemia and new therapeutic targets
- Interventional neuroradiology and emerging therapies
- Population-based health services delivery / stroke code system
- Telemedicine
- New devices for capture of parameters by telemetry in the stroke Unit
- Detection of atrial fibrillation using a new ECG monitoring device based on biomedical textiles (wearables)

Movement Disorders

- Parkinson disease in young patients
- Parkinson disease. Follow-up and control helped by new technologies

Cephaleas

- Study of the response variables to botulinum toxin and anti- CGRP monoclonal antibodies
- Glutamate and headaches

- Non-invasive outpatient monitoring of biometric and biophysical variables as a method for prediction of migraine crises

Cognitive impairment and dementia

- Detection of early Alzheimer's disease and search for new therapeutic targets.
- Language disorders of neurodegenerative origin
- Management of behavior alteration in the context of patients with dementia

Multiple Sclerosis

- Outcome markers and new therapies
- Immunopathogenesis of multiple sclerosis and monoclonal antibody therapies
- Therapeutic compliance of first line disease-modifying therapies in patients with multiple sclerosis

Epilepsy

- Drug-refractory epilepsy
- Genetic alterations in refractory epilepsy
- Non-convulsive epileptic status
- Neuroimaging in the emergency epileptic patient

Neuromuscular diseases

- Immunopathogenesis of myasthenia gravis



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Associated Group Publications (1)

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ANNUAL
REPORT OF
SCIENTIFIC
ACTIVITY

2020



AREA 3



ADVANCED THERAPIES AND INDIVIDUALIZED MEDICINE



- **LINE 3.1** PROGNOSTIC AND PREDICTOR MARKERS IN AUTOIMMUNE DISEASES
- **LINE 3.2** ESOPHAGOGASTROINTESTINAL INFLAMMATORY DISEASES
- **LINE 3.3** PROGENITORS AND CELL THERAPY
- **LINE 3.4** ADVANCED THERAPIES IN ONCOHEMATOLOGY
- **LINE 3.5** BIOLOGICAL, CELLULAR AND MOLECULAR MONITORING IN ONCOHEMATOLOGY
- **LINE 3.6** NEW DIAGNOSTIC AND THERAPEUTIC ADVANCES IN CARDIOVASCULAR DISEASES
- **LINE 3.7** NEW THERAPIES IN INFECTIOUS PATHOLOGIES
- **LINE 3.8** INDIVIDUALIZED MEDICINE IN SOLID TUMORS

GROUP 36



Head of laboratory



Research interest



González Álvaro, Isidoro



Group members

- **Álvaro-Gracia Álvaro, José María**
- **Castañeda Sanz, Santos**
- **García de Vicuña Pinedo, Rosario**
- **García Vadillo, Jesús Alberto**
- **Gómez León, María de las Nieves**
- **Llorente Cubas, Irene María**
- **Montes Casado, Nuria**
- **Ortiz García, Ana María**
- **Rodríguez García, Sebastián de la Cruz**
- **Tomero Muriel, Eva Gloria**
- **Triguero Martínez, Ana**
- **Uriarte Ecenarro, Miren**
- **Velasco Ripoll, Teresa**
- **Vicente Rabaneda, Esther Francisca**

The main goal for our group is personalized medicine in the field of autoimmune/inflammatory rheumatic disorders (mainly rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, giant cell arteritis and scleroderma). Our efforts are focused on providing new knowledge about two unmet needs for rheumatologists: severity biomarkers and predictors of response to disease modifying anti-rheumatic drugs, either synthetic or biological. For the last five years, to achieve these objectives, we have consolidated our collaborations both at a local level in our Institute and at national level.

Regarding the first, in 2013 we were involved in the development of BioMID project that was granted by the PIE program (Integrated Projects for Excellence at Health Research Institutes) from the Instituto de Salud Carlos III (ISCIII). This is a project that intends to deepen in personalized medicine in the field of biological therapies for immune mediated inflammatory diseases. Although the project will end in 2018, our group will continue including patients in the IIS-IP Bio-bank, and we will expand the sample collection to JAK-inhibitors.

On the other hand, we maintain an intense collaborative effort with groups of the Network of Inflammation and Rheumatic Diseases (RIER), which belongs to the RETICS program of the ISCIII. Our research has mainly focused on the detection of prognostic and cardiovascular risk factors in rheumatoid arthritis, as well as the study of security aspects in biological therapies. During the last two years, and especially during 2020, we have collaborated with Dr Amaya Puig Kröger to deepen in the understanding of their mechanism

of action, resulting in the possible development of efficient biomarkers to predict response to these drugs. In addition, many other rheumatologic diseases such as scleroderma, systemic lupus erythematosus, systemic vasculitis, osteoporosis, and osteoarthritis, are objectives of our research work. As a result of the intense activity of the group, some of its members have been called to participate in the elaboration of several documents establishing consensus guidelines for the rational use of biological therapies or imaging techniques in which the establishment of proper cost/benefit ratio is of great importance in the current economic situation.

Obviously, the COVID-19 outbreak has conditioned the research of our group and several members have been involved in collaborative efforts with many other groups of IIS-IP and other Institutions, such as Universidad Complutense de Madrid and Centro Nacional de Biotecnología, to develop different research lines that have led not only to several publications, but also to interesting observations. Results from these studies have helped to select patients that can benefit most from being treated with IL-6 receptor blockade, or have established the relevance of detecting SARS-Cov-2 viremia in serum samples as a predictor of severity. This information has been already transmitted to physicians involved in treating COVID-19 patients, allowing to improve the management of these patients.

For the next years, our efforts will continue to focus on discovering new biomarkers that may allow to more efficiently treat patients with immune mediated inflammatory disorders. In addition, we will also focus on how to improve response to COVID-19 vaccination in a population (patients treated with immune-modulatory drugs) that usually presents a decreased response to vaccines.



Major grants

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GROUP 37



Head of laboratory



Research interest

The investigation activity of the Group at present and for the following years is focused on:

1) Immune-mediated inflammatory diseases (IMiD), particularly including psoriasis, atopic dermatitis and hidradenitis. The main lines of investigation are: a) Immunoregulatory molecules as biomarkers predicting response to biological therapies and disease severity in IMiDs. These are a group of diseases that display inflammation as a major pathogenic mechanism. Their long-term impact has been alleviated by the implementation of biological therapy. Despite the growing knowledge on the etiopathogenesis of these diseases and the marked improvement in their management represented by biologic therapy, markers of the severity of the disease or to predict whether patients will be refractory to treatment are lacking. We are searching for new predictive biomarkers of IMiD severity and responsiveness to biologics; b) Gene Expression Profile in patients with IMiDs c) Epigenetic biomarkers as predictors of therapeutic response to biologic drugs in psoriasis; d) Immunoregulatory molecules and their therapeutic potential. We investigate the possible role of GADD45, ICOSL, TSP-1, and galectins in the immunopathogenesis of psoriasis, and the possibility of finding new therapeutic targets for the treatment of this disease; e) Survival analysis of conventional systemic therapies and biologics in psoriasis; f) Identification of Copy-Number Variants associated with the risk of developing psoriasis and psoriatic arthritis, using a genome-wide analysis approach; g) Study of optimization strategies (dose reduction, increase of the administration interval) in the treatment of moderate-to-severe psoriasis with systemic agents; h) Regulation of CXCL12 and RAPTOR by novel miRNAs and their role during the inflammatory process in Psoriasis; i) Integrative study of systemic inflammation in chronic inflammatory



Daudén Tello, Esteban



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- **Gómez Gago, María Jesús**
- **Llamas Velasco, María del Mar**
- **Muñoz Hernández, Patricia**
- **Sánchez Pérez, Abilio Javier**

skin diseases and its association with cardiovascular disease.

2) Eczematous dermatitis. Study on the prevalence of allergens as responsible for allergic contact dermatitis in the Spanish population

3) Connective Tissue Diseases. Determination of the association of myositis-specific autoantibodies and myositis-associated autoantibodies with clinically amyopathic dermatomyositis.

4) Photobiology. Studies on epidemiology, clinical phenotypes, and photobiology of solar urticaria.

Major grants

- Daudén Tello, Esteban. Regulación de la expresión de CXCL12 y RAPTOR por miRNAs novedades y su papel en el proceso inflamatorio de la Psoriasis. PI17/01972. ISCIII. 2018-2020.

Granted 2020:

- Llamas Velasco, Mar. Caracterización clínico-patológica de las manifestaciones cutáneas de la infección por SARS-CoV-2. Subvención COVID Comunidad de Madrid. 2020.

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GROUP 38



Head of laboratory



Research interest



Pérez Gisbert, Francisco Javier



Group members

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- Ortega Moreno, Lorena
- Pérez Nyssen, Olga Raquel

The Gastrointestinal Inflammatory Diseases Group focuses mainly on the understanding and management of Inflammatory Bowel Disease and *Helicobacter pylori* infection. The Group's Clinical and epidemiological research area is specialized in coordinating large-scale collaborative networks of gastroenterologists from more than 100 Spanish and 250 European hospitals.

The Translational research area leads multiple projects in collaboration with several Services at La Princesa University Hospital (Immunology, Pathology, Microbiology, Clinical Pharmacology, Pharmacy, Rheumatology, Dermatology, Neurology, etc.), Organic Chemistry Department at the Complutense University, Cooperative Biosciences Research Centre from Euskadi (CIC BioGUNE), the Galician Genomics Foundation, the National Center for Cardiovascular Research (CNIC), the National Center for Oncology Research (CNIO), the Asturian Institute of Dairy Products (IPLA-CSIC), the Institute of Food Science Research (CIAL-CSIC) and the Institute of Molecular Biology and Genetics (IBGM, University of Valladolid-CSIC). Internationally, the group leads projects with the National Institutes of Health of U.S.A. (U.S. N.I.H.) and the Karolinska Institute (Sweden) and has collaborative projects and interactions with the Imperial College London & St Mark's Institute (UK), the University of Manchester (UK) and the University of Lund (Sweden).

Finally, the Group is strongly oriented to the transference to society and the scientific community, founding several programs for the advancement of biomedical research and evidence-based clinical practice. The Group has promoted multiple collaboration agreements between: 1) National scientific societies: Asociación Española

de Gastroenterología (AEG), Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU), Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica (SEGHNP), Sociedad Española de Medicina de Familia y Comunitaria (SEMFyC), Sociedad Española de Médicos de Atención Primaria (SEMERGEN), Sociedad Española de Médicos Generales y de Familia (SEMG); 2) International scientific societies: European Helicobacter and Microbiota Study Group (EHMSG), European Crohn's and Colitis Organisation (ECCO), European Society for Primary Care Gastroenterology (ESPCG); 3) Institutions: Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Universidad Autónoma de Madrid (UAM), Vanderbilt University; 4) Patient advocacy groups; and 5) The private sector.

Prominent lines

1. Inflammatory Bowel Disease (IBD)

1.1. Clinical Investigation in IBD

Coordination and participation in numerous (more than 20) clinical trials and studies in different phases, with the participation of many (>100) centers; the most outstanding ones are mentioned below:

- Direction and coordination of the "Comprehensive study of mechanisms underlying inflammatory bowel disease: a multi-omic approach of a newly diagnosed cohort" (PI19/01034), with 15 participating centers.
- Direction and coordination of the "Epidemiological study of the incidence of inflammatory bowel disease in Spain" (P-FIS, FI17/00143), with more than 100 participating centers.
- Direction and coordination of the clinical trial "Identification of predictive biomarkers for response to biologic therapies in inflammatory bowel disease by proteomic and mass cytometry approaches" (P-FISPI18/00622), with 19 participating centers.
- Direction and coordination of the clinical trial "Withdrawal of anti-TNF treatment in patients with inflammatory bowel disease: Multicenter, prospective and randomized clinical trial" (P-FIS15/00560), with 50 participating centers.
- Direction and coordination of the "Prospective and multicenter study on the epidemiology and "omic" characteristics of newly diagnosed inflammatory bowel disease in Spain" (FIS16 /01296), with 17 participating centers.
- Direction and coordination of the national Spanish registry DUMBO: "Safety of inflammatory bowel disease drugs during pregnancy and breastfeeding: mothers and babies' outcomes" (Independent Clinical Research Program, ICI9/00083), with 60 participating centers. Co-sponsored by Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).
- Coordination of the "Spanish Registry of Crohn's Disease and Ulcerative Colitis" (ENEIDA).
- Direction and coordination of the SUSTAIN study: "Effectiveness and tolerability of ustekinumab in clinical practice in patients with active Crohn's disease".
- Spanish coordination of the multicenter study "Ib-dCancer and seRious infections in Europe: I-CARE". Endorsed by GETECCU and GETAID. 2015-2022.
- Coordination of the study "A Post-Authorization Safety Study of Golimumab in Ulcerative Colitis Using the Spanish ENEIDA Registry". At the request of the European Medicine's Agency (EMA). Endorsed by GETECCU. 2015-2022.
- Coordination of the multicenter international study "An Active Surveillance, Post-Authorisation Study to Characterize the Safety of Tofacitinib in Patients with Moderately to Severely Active Ulcerative Colitis in the Post-Approval Setting Using Data from UR-CARE database". At the request of the European Medicine's Agency (EMA). Endorsed by GETECCU and GETAID. 2019-2023.

- Member of the International Steering Committee of the UR-CARE platform (United Registries of Clinical Assessment and Research). Endorsed by ECCO.

1.2. Biologic agents in IBD

- Identification of predictive markers of response to different biological agents.
- Correlation between anti-TNF levels and response to treatment.
- Effectiveness of new biological drugs for IBD treatment in clinical practice.
- Safety of biologic agents in IBD.
- Outcomes after switching to biosimilar agents in IBD patients.
- Comprehensive understanding of the mechanisms of action and modulatory effects of biological agents to treat IBD

1.3. Multi-omic approach for the study of IBD mechanisms

- Proteomic characterization of extracellular vesicles in IBD patients.
- Identification and validation of new biomarkers based on proteome of extracellular vesicles.
- Metabolomic characterization of newly-diagnosed IBD patients.
- Proteomic characterization of involved intestinal tissue in newly-diagnosed IBD patients.

1.4 Immunity in IBD

- Vaccination optimization in IBD patients.
- Immunological alterations after Hepatitis B virus (HBV) vaccination.
- Predictive variables of HBV vaccination response.

- Mechanisms of antibody production against anti-TNF treatments, and their relation with treatment response.

- Characterization of intestinal dendritic cells and macrophages, and their circulating precursors, in IBD patients with different affected tissues

- Identification of the mechanisms mediating the recruitment of circulating dendritic cells and monocyte subsets towards the inflamed mucosa in IBD patients.

- Study on the phenotype and distribution of B lymphocytes and plasma cells throughout the intestine, and characterization of their circulating precursors, in IBD patients.

- Identification and characterization of novel bio-active peptides secreted by the commensal microbiota and derived from dietary proteins with immunomodulatory properties over the intestinal mucosa in IBD patients.

1.5. New diagnostic methods

- Genetic/Pharmacogenetics and individualized medicine in IBD.

- Improved diagnosis of concomitant diseases in IBD.

- Characterization of the homing profile of circulating dendritic cells and monocyte subsets as novel biomarkers in IBD.

- Circulating antibodies against microbiota peptides as novel biomarkers in IBD.

1.6. New therapies

- Identification of new therapeutic targets in IBD (PSGL-1, MT1-MMP, IFG-1, ERB, CB1 and CB2).

- LncRNA from colon biopsies and plasma-derived EVs as markers of IBD.

2. *H. pylori* infection

- Implementation Science and evaluation of clinical practice: evidence based recommendations on real routine practice.
- Gastroenterology: International coordination of the European Registry on *H. pylori* management, a prospective study of clinical practice including 250 hospitals of 29 European countries.
- Primary Care: Surveys on practitioners, evaluation of clinical registries and development of dissemination programs.
- Prevalence, transmission, resistance, and socio-sanitary factors of infection.
- Effect of eradication treatment on intestinal microbiota.
- Validation of new diagnostic methods.
- In situ and in vivo detection and treatment with multifunctional nanomaterials.

3. *Eosinophilic Esophagitis*

- Analysis of the changes in both gene and protein expression in esophageal biopsies of adult patients with eosinophilic esophagitis (EoE) compared with healthy subjects.
- Selection of candidate markers related to the presence of the disease or inflammatory and fibrotic activity, as well as predicting response to treatments.
- Analysis of esophageal compliance measured by Endoflip® system, and differences compared to healthy subjects.

4. AEG-REDCap Platform

- Direction and coordination of the Online Platform for collaborative Research AEG-REDCap with over 70 projects and >1,500 researchers from 45 countries.

- Management of the AEG-REDCap Strategic Line at CIBERehd.



Major grants

- Pérez Gisbert, Javier. Identificación de biomarcadores de respuesta al tratamiento con fármacos biológicos en la enfermedad inflamatoria intestinal mediante abordaje proteómico y de citometría de masas PI18/00622. ISCIII. 2019-2021.
- Chaparro Sánchez, María. Comprehensive study of mechanisms underlying inflammatory bowel disease: a multi-omic approach of a newly diagnosed cohort. PI19/01034. ISCIII. 2020-2022.
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- Pérez Gisbert, Javier. Predictive biomarkers for response to JAK-inhibitors and biologic therapies in ulcerative colitis by a multi-omic approach. Pfizer. 2019-2023.



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GROUP 39



Head of laboratory



Research interest



Madero López, Luis



Group members

- Aguado Bueno, Beatriz
- Bautista Sirvent, Francisco José
- Castillo Sanz, Andrés Gaspar
- Colmenero Blanco, Isabel
- Díaz Pérez, Miguel Ángel
- Gálvez de la Villa, Eva
- Gómez García, Ana María
- González Murillo, África
- González Vicent, Marta
- Izquierdo Delgado, Elisa Pilar
- Lassaletta Atienza, Álvaro
- Ramírez Orellana, Manuel
- de Rojas de Pablo, Teresa
- Sebastián Pérez, Elena
- Sevilla Navarro, Julián
- Vicuña Andrés, Isabel

Although more than half of children diagnosed with cancer survive, yet cancer remains the leading cause of death by disease in children under 14 years. The reality for patients with metastasis at diagnosis or those who have genetic markers of poor prognosis or in cases of relapsed / refractory tumors, is very negative. Therefore, new treatment options are much needed to bail out all these patients. Our interest is trying to develop treatment strategies for children with poor prognosis, based on strategies of immunotherapy against cancer.

We propose to develop treatment strategies for children with malignant tumors of poor prognosis, based on the use of immune cells, able to attack and kill the cancer cells. This is a project that has both a clinical aspect and a preclinical one, and which is oriented both towards hematological malignancies and solid tumors. For children with leukemia, we aim to evaluate the administration of NK cells from the donor 1 month after receiving a haploidentical transplantation. Our current experience has allowed us to identify that the reconstitution of an insufficient number of NK cells 1 month after transplant is a factor significantly associated with leukemic relapse, so that administration of NK cells in this group of children may increase the clinical benefit of transplantation. In the case of solid tumors, we aim at evaluating a treatment that is not experienced in childhood cancer, but it has proven antitumor capacity especially in melanomas. It is the use of tumor infiltrating lymphocytes (TILs) as an anti-tumor therapy. This clinical investigation plan is accompanied by a parallel experimental research plan, which aims to prepare a product of cellular immunotherapy able to overcome the barriers imposed by the tumor on the effector cells, known as tolerance. Of the various mechanisms known to produce tolerance, we will begin to address the soluble molecules that induce a

decrease in the cytotoxic capacity of both NK cells and TILs. We aim at making effector cells resistant to the action of these immunoregulatory molecules, and also setting up protocols that may have immediate clinical translation. These strategies of cell manipulation want to be a proof of concept, and therefore will be evaluated in preclinical models, serving as a “master protocol” to apply to other known molecules or from which new knowledge is generated. The results should serve for the design of new clinical trials for the continuation of the project.

The team is a multidisciplinary group, with proven experience in the diagnosis and treatment of childhood cancer, and in developing research projects in advanced therapies applied to refractory pediatric cancer, and the development of clinical trials in pediatric oncology. It also has all the technical means and infrastructure for the development of the project, ensuring their implementation to the patients who tries to deal with potential impact for all children Advanced therapies and individualized medicine being treated in any of the pediatric oncology units in Spain.

The group is focused in:

Pediatric Oncology. Immunotherapies strategies:

1. Celyvir.
2. Nanoimmune medicine.
3. Adoptive Cellular Immunotherapy. Tumor-infiltrating lymphocytes (TILs).
4. Childhood leukemias.
5. Haematopoietic progenitor cell transplantation.



Major grants

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- Ramirez Orellana, Manuel. Combination of nanomedicine and immunotherapy for the treatment of neuroblastoma. PI19/01758. ISCIII. 2020-2022.

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- Ramirez Orellana, Manuel. Phase I trial to assess the safety and clinical response of intra-arterial infusion of repeated doses of autologous mesenchymal cells in children and adolescents with autoimmune refractory epilepsies. IC120/00120. ISCIII. 2021-2024.

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GROUP 44



Head of laboratory



Steegmann Olmedillas, Juan Luis



Group members

- Alegre Amor, Adrián
- Arranz Muñoz, Eva María
- Arranz Sáez, María Reyes
- Benzo Callejo, Gonzalo
- Cannata Ortiz, María Jimena
- Figuera Álvarez, Ángela
- García-Noblejas Moya, Ana María
- Gómez García de Soria, Valle
- Jiménez Braña, Jimena
- Loscertales Pueyo, Javier
- Sanz de Benito, María Ángeles



Research interest

The Group of Advanced Therapies in Oncohematology of the Research Institute of the Hospital de la Princesa has the mission of promoting clinical, epidemiological and translational research in hematologic malignancies.

The scope of the group is broad, reflecting the variegated nature of each member's interests, and spans from genetic studies to the commitment in the development of new drugs.

The Group has a differential interest in:

- Epidemiological studies on chronic myeloid leukemia.
- Study of the efficacy and safety of new drugs in hematologic malignancies.
- Immunological and genetic studies in hematologic malignancies.
- Analysis of conditioning regimes in bone marrow transplants (BMT)
- Analysis of infectious complications of BMT.

During the past 5 years, Dr. Steegmann has focused his clinical research activity in two fields. The first, as Spanish IP of the European Leukemia Net EUTOS projects, in epidemiological studies and good clinical practice recommendations. Secondly, as president of the Spanish CML group (GELMC), to foster clinical research in this group. In the next 5 years, the targets are, on one hand, to follow this path. We have constructed a mobile app for IOS, Windows, and Android for exchanging information between GELMC members.

On the other hand, locally, our aim is to establish common projects which could cover all the hematologic malignancies cared by our group. In this regard the plan is to set studies of quality of life, comorbidities, and pharmacology.



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GROUP 45



Head of laboratory



Fernández Ruiz, Elena



Group members

- Carracedo Rodríguez, María Rosa
- Santos Roncero, Santa Matilde



Research interest

Chromosomal translocations and gene mutations are frequently associated with the etiology of hematologic neoplasms. The JAK family of non-receptor tyrosine kinases (which comprises four members: JAK1, JAK2, JAK3 and TYK2) are involved in cytokine signaling on immune and hematopoietic cells and are crucial to normal hematopoiesis through the recruitment of down-

stream effectors of cell proliferation and survival. Recently, it has been reported that 10% of high risk pediatric acute lymphoblastic leukemia (ALL) cases bear activated JAK2 mutations, and could be potential candidates for JAK2 inhibitor therapeutic intervention. Acute lymphoblastic leukemia (ALL) is the most common neoplasm in childhood and although most cases respond to treatment, 20% relapse, shortening survival. Therefore, we analyzed high risk ALL samples with next generation sequencing (NGS) to determine the percentage of JAK-family receptor mutations in the Spanish population. ALL samples were obtained from hospitals throughout the country. We found that mutations in TP53 and JAK2 are independent prognostic biomarkers in B-cell ALL. Furthermore, for TYK2, we provide evidence of naturally occurring catalytic loss-of-function TYK2 variants and reduced expression of TYK2 in B-ALL patients.

On the other hand, it has been reported that Tyk2 deficiency in mouse increases the susceptibility to develop Abelson-induced B lymphoid leukemia/lymphoma linked to a diminished cytotoxic capacity of CD8+T, NK and NKT cells as a consequence of IFN-gamma decreased production. Taken together, these data suggest that TYK2 deficiency in humans is clinically silent, but could predispose to tumor formation, and patients with leukemia might be a target population in which TYK2 deficiency is enriched. Given the importance of maintaining an accurate immunological response for appropriate tumor surveillance, and that those immune responses are based on a functional JAK-dependent signal transduction, knowing the role in this response of the complex formed by cytokine receptors, JAK proteins and their target genes is highly relevant. In this sense, it is necessary to know the role of TYK2 in the immune system, both in infection and neoplasia.



Major grants

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GROUP 46



Head of laboratory



Muñoz Calleja, Cecilia



Research interest

Lymphocyte migration is involved in the pathogenesis of many diseases. Its control constitutes a target for different forms of immunotherapy. Conversely, other forms of immunotherapy can affect lymphocyte migration, leading to secondary effects, either desirable or not. Chemokines mediate recirculation of lymphocytes. The chemokine receptor CCR7 is involved in the homing of lymphocytes through secondary lymphoid organs and mediates the ganglionic dissemination of lymphoid malignancies and inflammatory processes. CCR7 is highly expressed on different lymphoid malignancies and several proofs of concept have demonstrated the therapeutic benefit of targeting either the molecule or the downstream signaling.



Group members

- Cuesta Mateos, Carlos
- Pérez García, Yaiza

Immune recovery after stem cell transplantation is one of the most important factors conditioning the outcome of this therapeutic procedure since it affects the incidence of infections, graft versus host disease and relapse. However, little is known about the association between the



ent time points (30, 60, 90, 180 and 360 days). We are analyzing the association between the proportions and absolute numbers of such T subsets and different clinical variables like GVHD and overall survival.

pattern of immune reconstitution of different immune cells and overall survival.

Dasatinib is a tyrosin kinase inhibitor used for the treatment of chronic myeloid leukemia, which has immunomodulatory effects, including a lymphocytosis occurring in most patients which has been associated to a better outcome of the patients.

Our group aims at three objectives:

1. The efficacy of CCR7 immunotherapy.

We are testing humanized versions of anti-CCR7 antibodies to treat ex vivo different lymphoid cancers, including B and T cell leukemias. We are analyzing their cytolytic activity dependent on complement or cells. Animal models of primary human T cell leukemias or GVHD are being used to evaluate the in vivo efficacy of targeting CCR7.

2. Identification of biomarkers of immune reconstitution

In a cohort of 200 patients who were treated at our hospital with an allogeneic stem cell transplantation, we have measured different T cell subsets including naïve, stem-cell like memory, central memory and effector memory, at differ-

3. Characterization of the immunomodulatory effects of dasatinib.

Intravital microscopy experiments are being performed to address whether dasatinib has direct effects in the adhesive and migratory abilities of lymphocytes. Here, we follow the hypothesis that adhesion and/or transmigration of lymphocytes across the HEV barrier may be impaired after dasatinib treatment. We will also perform multiphoton intravital microscopy to examine luminal crawling and transendothelial migration of purified T and B cells.



Major grants

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GROUP 58



Head of laboratory



Alfonso Manterola, Fernando



Research interest

Cardiovascular diseases represent the leading cause of mortality in developed countries including Spain. Coronary artery disease constitutes the main disease burden for these patients and this explains why major preventive, diagnostic and therapeutic research efforts are being developed to address this highly prevalent and challenging clinical condition. Percutaneous coronary intervention, with stent implantation, remains the most widely used method of revascularization in these patients.

Our group pursues several lines of investigation.

"Stent failure" constitutes our main research interest. Stent failure includes both "in-stent restenosis" and "stent thrombosis". Recently it has been suggested that neoatherosclerosis might provide an elusive link between these conditions. Specifically, we sought to assess the value on novel generation drug-eluting stents in the treatment of patients with different clinical and anatomic characteristics. We are also developing strategies to optimize stent implantation. In these regard, head-to-head randomized clinical studies comparing different therapeutic devices are of major interest. In addition, we are deeply interested in the healing and vascular repair process after stent implantation. In this regard, a detailed assessment of the target coronary segment using sophisticated intracoronary imaging techniques (optical coherence tomography, intravascular ultrasound) and a functional evaluation of the physiology of the vessel wall (pressure wire and fractional flow reserve), are of major value. These techniques unravel novel information on vessel healing, endothelization, neointimal hyperplasia response, and may also disclose risk markers for stent thrombosis. We



Group members

- Bastante Valiente, Teresa
- Benedicto Buendía, Amparo
- Cuesta Cuesta, Francisco Javier
- Díez Villanueva, Pablo
- García Guimaraes, Marcos Manuel
- Moreno Carriles, Rosa María
- Reyes Copa, Guillermo
- Reyes García, Antonio
- Rivero Crespo, Fernando
- Seidelberger, Bernhard

are leading multicenter controlled initiatives in our country to establish the relative value of different coronary interventions for patients suffering from in-stent restenosis. Likewise, we are actively involved in several international initiatives focused on the dreadful problem of stent thrombosis.

On the other hand, new intracoronary diagnostic techniques provide novel insights on the "vulnerable plaque" and may also help to understand mechanisms implicated in the pathophysiology of acute coronary syndromes and in coronary atherosclerosis progression and regression. In this regard, our group is actively involved in research projects on disease progression and in establishing further criteria to define lesion severity.

The diagnosis and clinical management of patients with acute coronary syndrome represents a major work-load of our daily clinical activity and, therefore, also stimulates many of our research projects. Different strategies are being evaluated in patients with ST-segment elevation acute myocardial infarction. This includes studies assessing preventive strategies, diagnosis and management initiatives in these patients.

New and potent antiplatelet and antithrombotic drugs and lipid lowering agents are currently available and we are studying their value in several subsets of patients with coronary artery disease requiring coronary revascularization or just medical management.

Last but not least, structural heart disease is another important evolving field. We are deeply interested in defining the role of some emerging interventional techniques as transcatheter aortic valve implantation in elderly patients with severe aortic stenosis and the value of other new devices aiming to correct diverse structural heart diseases.



Major grants

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GROUP 48



Head of laboratory



Research interest



Jiménez Borreguero, Luis Jesús



Group members

- **Cecconi Duca, Alberto**
- **López Melgar, Beatriz**
- **Olivera Serrano, María José**
- **Ortega Rabbione, Guillermo José**
- **Pérez Romero, Miriam**
- **Sanz García, Ancor**

Our research work is developed in cardiovascular diagnostics technologies for clinical research, in coordination with physicists and basic scientists at La Princesa Hospital.

We are carrying out a research line in collaboration with physicist scientists at La Princesa Hospital focusing in machine learning of big data for the prediction of heart disease, based on an in-deep analysis of more than 250.000 ECGs raw data.

Another line of clinical research focuses on the characterization of the heart phenotype in patients with hypertrophic cardiomyopathy and its association with prognosis, by identifying new targets in cardiovascular imaging technology.



Major grants

Granted 2020:

- Ortega Rabbione, Guillermo / Jiménez Borreguero, Jesús. Detección de nuevos marcadores pronósticos sub-clínicos y precoces mediante inteligencia artificial de > 400.000 electrocardiogramas de la base de datos de un hospital terciario. PI20/00792. ISCIII. 2021-2023.
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GROUP 57



Head of laboratory



Suárez Fernández, Carmen



Research interest

Cardiovascular diseases (CVD) are the main cause of mortality in developed countries. The prevalence and incidence of CVD are increasing. There are a great variety of new cardiovascular drugs that are targeted to dyslipidaemia, arterial and venous thrombosis and diabetes, and can modify the natural history of CVD.

Age is an important determinant of arterial and venous outcomes. However, usual clinical practice in a general setting reveals a disproportionately low use of cardiovascular medications and intensive treatment in elderly patients that could otherwise benefit from their use. On the other hand, there probably is an excessive use of these medications in patients with cognitive impairment and short life expectancy. There is not enough information about cardiovascular therapies in very elderly patients with multiple comorbidities/diseases.



Group members

- Aguilar Mulet, Juan Mariano
- del Arco Galán, Carmen
- Caballero Sánchez-Robles, María Paloma
- Curbelo García, José Juan
- Frieria Reyes, Alfonso
- García Polo, Iluminada
- Gil Martínez, Paloma María
- González Molina, María del Pilar
- Ibáñez Sanz, Patricia
- Moldenhauer Díaz, Fernando
- Parra Caballero, Pedro
- Real de Asúa Cruzat, Diego
- Roy Vallejo, Emilia
- Ruiz-Giménez Arrieta, Nuria
- Vega González, María Gema
- Vinuesa Sebastián, María Mercedes
- Von Wernitz Teleki, Andrés Carlos

The purpose of this group is:

1. To investigate the efficacy of new cardiovascular treatments in different settings
2. To evaluate the risks and benefit obtained from antithrombotic treatment in elderly patients with venous thromboembolic disease and atrial fibrillation.
3. To describe the natural history of CVD in very elderly patients (over 90).



Major grants

- del Arco Galán, Carmen. Diseño y validación de un modelo predictivo de resultados adversos a corto plazo en los ancianos dados de alta de los servicios de urgencias hospitalarios. PI17/O1624. ISCIII. 2018-2020.

- Moldenhauer Diaz, Fernando. Estudio del sistema renina-angiotensina-aldosterona y su relación con la ausencia de aterosclerosis en adultos con Síndrome de Down. Fundación Española de Medicina Interna. 2017-2020.
- Moldenhauer Diaz, Fernando. Study of the renin-angiotensin-aldosterone system and its relation to the absence of atherosclerosis in adults with Down Syndrome. The Jerome Lejeune Foundation. 2017-2020.
- Moldenhauer Díaz, Fernando. Patterns and causes of hospital admission, comorbidities and mortality of Spanish adults with Down Syndrome 2005-2014. Fundación Lejeune. 2018-2020.
- Real de Asua Cruzat, Diego / Suarez Fernández, Carmen. Estudio de los mecanismos protectores frente al desarrollo de hipertensión arterial en adultos con síndrome de Down PI19/00634. ISCIII. 2020-2022.

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GROUP 49



Head of laboratory



Research interest



Novella Arribas, Blanca

Our investigation addresses the genesis of scientific evidence on RCV in general and specific population, as well as evaluating the transfer of evidence both professionals and population.

My research projects directed to this are "Development, implementation and evaluation of a guide clinical practice in global cardiovascular risk" with 2 publications and publishing the results of the primary endpoint and a doctoral thesis; "Evaluation in Terms of Morbimortality and control of CVRF implementation of an adaptation of a GPC RCV" under analysis and a doctoral thesis and "A Clinical Trial Of Two Educational Strategies In Cardiovascular Health In Child Population (SAVINHEARTS)" assessment received CAIBER number extramurales2010 10 projects and has generated two publications. In analysis of the primary endpoint and two doctoral theses.



Group members

- Cubillo Serna, Ana
- Fernández Luque, María Jesús
- Gabriel Sánchez, Rafael
- Gallego Arenas, Ángela
- González Gamarra, Amelia
- Loeches Belinchón, María del Pilar
- López González, Javier
- Mayayo Vicente, María Soledad
- Rodríguez Salvanés, Francisco José
- Ruiz Díaz, María Lourdes
- Ruiz López, Marta
- Sánchez Alcalde, Rosa María
- Sánchez Gómez, Luis María
- Sierra García, María Belén

Collaborate with other groups of the institute with the project "Effect of oral nitrates on pulse pressure and arterial elasticity in patients older than 65 years with isolated systolic hypertension refractory. Ministry funding for non-commercial clinical trials. "Launch and publication. Also in projects from other institutions related to the RCV. "Project Prevention of Early Complications of Diabetes in Europe. European Project e-PREDICT" Hospital La Paz as a member of node ISCIII Cardiovascular Diseases Network and the Hospital 12 October through "CARDIORISK / MAPA-PRES Project" and I am a member of the international group RISC (research in insulin resistance).

We promote the investigation of the other group members in these lines. Thus, we have participated in the project "Control of blood pressure in diabetic patients: a comparative study between treatment based on BP measured in the medical consultation



and based on self-measurement of BP in the patient's home" and Development from primary care model risk stratification in patients with heart failure for predicting disability and hospitalization" within the network of Health in Chronic Disease.

With the research network Diabetes AP (GEDAPS) with studies PREDIMERC and CHAMBS and the IASB in the FOCUS trial led to the fixed-dose combination of drugs for secondary prevention of IHD. Over the next five years, thanks to the experience gained in these projects, we plan to start a project assessment tool doctor-patient communication addressed to the measurement and control of RCV, besides analyzing and publishing the results of studies launched over the years and continue to cooperate with other groups of the Institute.



Major grants

- Novella Arribas, Blanca. Utilización de un modelo innovador basado en comunidad, para el manejo y el seguimiento por personal de salud no médico (PSNM) para mejorar la conciencia, el tratamiento y el control de la Hipertensión Arterial (HTA). AC19/00112. ISCIII. 2020-2022.



Publications (3)

Kozakova, Michaela, Gastaldelli, Amalia, Morizzo, Carmela, Hojlund, Kurt, Nilsson, Peter M, Ferrannini, Ele, Palombo, Carlo, RISC Investigators. **Gamma-glutamyltransferase, arterial remodeling and prehypertension in a healthy population at low cardiometabolic risk.** J Hum Hypertens. 2020. IF: 2,260. DOI: 10.1038/s41371-020-0337-1.

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GROUP 50



Head of laboratory



de los Santos Gil, Ignacio



Research interest

Our group has been working on the study of HIV infection for more than 20 years. We have participated in several clinical trials and international research projects. Currently, we continue working in the Research Network on AIDS (CoRIS) collecting data for epidemiological studies from HIV-infected patients who come to our clinic for the first time, and periodically sending blood samples to the Biobank Network of AIDS, for virological and immunological studies. This project will keep going for years, and we will also continue collecting the data necessary for these studies.

We are also involved in clinical trials of new drugs and new therapeutic strategies for HIV, including the combination of two drugs Dolutegravir and lamivudine for naive and experienced patients, and the new maturation inhibitor in a very early phase. These trials began in 2019 and will last two years.

We expect to start a new clinical trial this year with a therapeutic vaccine for early treated HIV patients.

In addition, another field of interest, in which we have more than ten years of experience, is HIV / HCV co-infection. This aspect of HIV infection is currently having a major projection, due to the appearance of new drugs to treat hepatitis C, i.e direct antiviral agents. These drugs have revolutionized treatment achieving the greatest effectiveness until now (more than 95%) with few side effects. We are collaborating with the HEPAVIR cohort of co-infected patients, along with various centres in the Spanish territory, where we have treated more than 600 patients so far. The study of new drugs in real life is very important because it can reveal side effects not seen before in clinical trials.



Group members

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In this sense, and also in a multicentre group, we are studying the impact of sustained viral response in cardiovascular risk and inflammation markers, as well as its impact in appearance of liver cancer and cancer survival.



Major grants

- Santos Gil, Ignacio de los. Red Española de Investigación en Sida (RIS). RD16/0025/0012. ISCIII. 2017-2021.

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GROUP 51



Head of laboratory



Aspa Marco, Francisco Javier

post-transcriptional inhibition of gene expression. Recent studies have also begun to reveal that altered miRNA expression profiles may be associated with pathological processes within the lung and lead to the development of various pulmonary diseases, ranging from inflammatory diseases to lung cancers. Also miRNAs are pivotal to both adaptive and innate immunity, with regulatory effects on cell differentiation and immunological function.

miRNAs and community acquired pneumonia:

Community acquired pneumonia (CAP) is an infectious disease with high prevalence and great morbimortality rate. Numerous strategies have been studied to improve the prediction of CAP prognosis, and thus help in decision-making for the management of these patients. Regarding CAP pathophysiology, miRNAs can influence the development and function of immune cells by blocking the translation of key proteins such as transcription factors or intermediate molecules in cell receptor signalling cascades. In addition, some miRNAs have been identified as key players in modulating the immune response to severe bacterial infection, by controlling neutrophil activation and recruitment and the chemotactic signal that initiates the inflammatory process. Moreover, several studies have established the utility of circulating miRNAs in the diagnosis of sepsis and in various specific infections (e.g. HIV, viral hepatitis or tuberculosis). However, there is limited scientific literature on the usefulness of these molecules as prognosis markers in CAP.

miRNAs and Lung cancer:

The search for a biomarker that enables optimizing the early diagnosis of lung cancer is a pend-



Group members

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- **Manzanaque Pradales, Marcos**
- **Ortega Gómez, María del Mar**
- **Rajas Naranjo, Olga**
- **Vega Piris, Lorena.**



Research interest

MicroRNAs (miRNAs) are a family of endogenous, small, noncoding RNA molecules that modulate physiological and pathological processes by

ing challenge. The adequate management of a potentially malignant solitary pulmonary nodule in early stages is especially important in fragile and elderly patients. It is also important to use non-aggressive techniques to obtain good quality samples of deep breath. Exhaled breath condensate (EBC) is a simple, non-aggressive technique that provides a biological sample where different markers can be determined.

Recent promising studies have analysed miRNA profiles in EBC as potential biomarkers for early diagnosis in lung cancer patients. We will focus our efforts on establishing the utility of miRNA determination in EBC samples as a first step in the building process of a molecular signature for EBC in lung cancer patients.



Major grants

- Ortega Gómez, María del Mar. Plataforma de Biobancos. PT17/0015/0050. ISCIII. 2018-2020.
- Aspa Marco, Francisco Javier. Análisis molecular del condensado de aire exhalado en el manejo del nódulo pulmonar solitario. Asociación Española contra el Cancer. 2019-2021.

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Publications (13)

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GROUP 52



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Research interest

A great interest in the role of human microbiome in health and disease exists due to the accessibility of high throughput sequencing methods. Several studies indicate that the human microbiome may contribute to the regulation of multiple neuro-chemical and neuro-metabolic pathways through a complex series of highly interactive and symbiotic host-microbiome signaling systems that mechanistically interconnect the gastrointestinal tract, skin, liver, and other organs with the central nervous system. Several studies suggest that the stomach contains an unexpected diversity of microorganisms but their relationship with *Helicobacter pylori*, and with other human diseases is not well established.



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- Yarcí Carrión, Ayla
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H. pylori infects 50% of the population worldwide and colonizes the gastric mucosa causing many gastrointestinal diseases such as severe gastritis, peptic ulcer disease, gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. It is identified as a Group I carcinogen by the International Agency for Research on Cancer of the World Health Organization. Several treatment regimens have been used to eradicate this microorganism. Resistance to antibiotics is considered the main cause of treatment failure.

Since the beginning of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) pandemic, a large quantity of studies has been performed to develop and validate real-time PCR (RT-PCR) techniques capable of providing an accurate diagnosis in respiratory samples. However, SARS-CoV-2 has also been detected in other types of samples such as blood. Assessment of commercial RT-PCR techniques in serum and plasma samples has been one of the aims of our group, which has provided satisfactory re-

sults. We performed a multidisciplinary study to assess detection of SARS-CoV-2 viremia as a marker to identify patients who are at risk of developing severe COVID-19 and mortality. This marker has shown better results than other biomarkers such as SEIMC score, interleukin-6, or lymphopenia.

This group includes members of the Microbiology Department with interest in diagnosis and treatment of several infectious diseases caused by pathogens such as fungi, Mycobacterium spp or CMV, as well as in infections in cystic fibrosis patients. Since March 2020, a huge interest in SARS-CoV-2 infection has emerged.

The main lines of research are: (1) Study of gastric microbiome and its relationship with H. pylori infection and other human diseases with potential therapeutic applications. (2) Detection of antimicrobial resistance in H. pylori (national and international surveys) and molecular methods for detection of clarithromycin resistance and heteroresistance. (3) Study of the in vitro activity of wine phenolic compounds against H. pylori. (4) Determination of the role of Non-Tuberculous Mycobacteria on the development of several diseases. (5) Detection of SARS-CoV-2 viremia as a marker to identify patients who are at risk of developing severe COVID-19 and mortality.



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Colomer Bosch, Ramón



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GROUP 40

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Research interest

Our line of clinical research is focused on the development of innovative cancer therapies. We have contributed to the clinical evaluation of neoadjuvant Pertuzumab, currently the standard of therapy in HER2+ breast cancer, or Neratinib in advanced HER2+ breast cancer. We have evaluated in phase I and phase II trials novel drugs such as Nintedanib or Dovitinib, and monoclonal antibodies such as Durvalumab. We have developed medical and surgical protocols for lung, breast and pancreatic cancers.

Our line of translational research is focused on the discovery of biomarkers for assessing the effects

of anticancer immunotherapy and biomarkers of cancer, including an immunophenotype profile in patients with advanced cancer and the rare double amplification of FGFR-1 and CCDN1 in breast cancer. By using a systems biology approach, we are clustering breast cancer into subtypes defined by biologic features that constitute therapeutic targets.



Major grants

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Publications (18)

di Martino M, Muñoz de Nova JL, Guijarro Rojas M, Alday Muñoz E, Martín-Pérez E. **Positive Resection Margins Detected by Standardized Study of a Pancreaticoduodenectomy Sample:**

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GROUP 53



Head of laboratory



Zapatero Laborda, Almudena



Group members

- Adrados de Llano, María Magdalena
- Arellano Gañan, Ramón Cristóbal
- Castro Tejero, Pablo
- Cruz Conde, José Alfonso
- Martin de Vidales Cervantes, María del Carmen
- Murillo González, María Teresa
- Pérez González, Leopoldo
- Roch González, María



Research interest

This group is focused on four research lines:

1. Identification of clinical and Biological Markers as risk and predictive factors in Prostate Cancer.

a. Cooperative projects with Fundación Centro Nacional de Investigaciones Oncológicas (CNIO) to determine the prognostic value of expression of molecular markers in patients with high-risk localized prostate cancer (REF CaPr-HLP-RT-01/ PI 197) and metastatic cancer (PROCURE platform).

b. We have just completed a project in collaboration with HU Santiago de Compostela and HU 12 de Octubre, Madrid, about the prognostic and predictive role of CTCs in high-risk non-metastatic prostate cancer (CaPr-RTCTC-01/PI 197). Results presented in abstract form in IJROBP 2019. Manuscript in preparation.

c. IRONMAN-ES: "Estudio prospectivo observacional de parámetros clínicos y biomarcadores en cáncer de próstata avanzado en hospitales de España"; in collaboration with CNIO (co-sponsor).

d. Collection of biological markers within the EORTC research project platform 1822 E2-RADlatE- OligoCare: A pragmatic observational cohort study to evaluate radical radiotherapy for oligo-metastatic cancer patients.

2. Advances in Prostate Cancer Treatment:

a. A phase III clinical trial to determine the optimum duration of androgen deprivation alongside high-dose radiotherapy in localized intermediate and high-risk PCa patients ("Phase III Trial comparing Long-Term Versus Short-Term Androgen Deprivation Combined With High-Dose Radiotherapy For Localized Prostate Cancer: GICOR Protocol DART01/05". EudraCT 2005-000417-36 ClinicalTrials.gov, number NCT02175212). 5-year data reported in Lancet Oncol 2015 and In J Radiat Oncol Biol Phys 2016. Substudy analysis of prognostic and predictive value of Testosterone nadir is ongoing.

b. Collaboration with the ICECaP Working Group, a multidisciplinary team of academic cancer researchers from the Dana-Farber Cancer Institute-Harvard Medical School:

- "Intermediate Clinical Endpoints In Cancer Of The Prostate (ICECaP) Initiative", a Meta-analysis. Published in JCO 2017.

- "Event-Free Survival, a PSA-Based Composite Endpoint, is Not a Surrogate for Overall Survival in Localized Prostate Cancer". Sent to publication.

c. Participation in 6 Randomized Phase III clinical trials in several treatment and disease scenarios: localized-high risk prostate cancer, prostate cancer without metastasis with biochemical failure after radical treatment, in M0 castration resistant prostate cancer and in metastatic prostate cancer (MDV3100-14, MDV3100-13, JNJ-56021927, TALAPRO-2 (C3441021) EORTC 1333 and EORTC 1531).

3. High Technology and Innovation:

a. Over the last 10 years we have actively worked in Intensity Modulated Radiation Treatment - Image Guided Radiotherapy (IM-RT-IGRT) versus three-dimensional conformal radiotherapy (3DCRT): comparative results on patients treated in a single institution, which demonstrate the significant reduction in acute and late genitourinary and rectal toxicity in patients with prostate cancer treated with IM-RT-IGRT. The results have been presented in international meetings and reported in indexed journals.

b. Implementation of the new technology VMAT (Volumetric Modulated Arc Therapy) and Stereotactic Body Radiation Therapy for the treatment of localized and oligometastatic PCa

- Design and implementation of a Phase II clinical trial: Dose Intensification With a Focal Boost to Dominant Intraprostatic Lesion Using Volumetric Modulated Arc Therapy /Image Guided Radiotherapy in Patients With Localized Prostate Cancer, Protocol ID: CaP-VMAT-DIL. ClinicalTrials.gov Identifier: NCT03030625. Active recruitment.

- Participation in a Phase II clinical trial: Tratamiento de las Oligo-metástasis de Cancer de Prostata Mediante SBRT- Código SBRT-SG 05. NCT02192788

STAGE: Recruitment completed.

- Participation in a Phase II clinical trial EC/2018/0130PEACE V/STORM: A randomized phase II trial for the Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM).PROMOTOR: Ghent University. GICOR

4. Multi-Institutional Data Base Register in PCa:

- National Register of Prostate Cancer Treated with Radiotherapy (RECAP)

- EORTC research project 1822 E²-RADlatE - Oligo-Care: A pragmatic observational cohort study to evaluate radical radiotherapy for oligo-metastatic cancer patients. Activation phase

5. BLADDER CANCER- BLADDER SPARING PROGRAM

a. Our team is one of the most active and successfully experienced groups in the conservative treatment of invasive bladder cancer. We continue to study the optimal sequence of treatment concerning tumor control, bladder preservation, quality of life and efficient delivery. The results have been presented in international meetings and reported in indexed journals.



b. Collaboration- inclusion in clinical trial of Radio.Immunotherapy in this context. "Eficacia del atezolizumab con radioterapia concomitante en pacientes con cáncer de vejiga músculo-invasivo."Code: SOGUG-2017-A-IEC(VEJ)-4EudraCT: 2018-004348-47



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GROUP 54



Head of laboratory



Cerezo Padellano, Laura



Group members

- Hinojar Gutiérrez, Adolfo Carlos
- López Elzaurdía, Consuelo
- López Rodríguez, Mario
- Manzanares Soler, Rafael
- Marín Palomo, Alicia
- Martín Martín, Margarita
- Muñoz Guerra, Mario Fernando
- Naval Gías, Luis
- Raboso García-Baquero, Eduardo
- Rodríguez Campo, Francisco José



Research interest

Advances in head and neck cancer include new knowledge on etiology and progress on organ preservation treatments modalities. Head and neck cancer (HNC) is mainly related to smoking, however, another risk factor, the human papillomavirus (HPV),

has emerged in recent years. HPV related carcinoma constitutes a distinct entity which presents in young adults, not heavy smokers, usually presenting as regionally advanced disease and with better prognosis, probably due to their different molecular profile. In the other hand, organ preservation with chemoradiation is feasible in locally advanced head and neck cancer without compromising survival.

Our group pursues four lines of investigation: 1) Monitor the evolving incidence of HPV-induced OPSCC in our region and identify new molecular mechanisms in these tumors, related to increased radiosensitivity. For the next years we are planning to expand this research, analyzing all patients with oropharyngeal cancer treated from 2011 to 2015 from six large hospitals in Madrid and studying the percentage of HPV positive. Thus, we will have a clear picture of the incidence of oropharyngeal cancer related to HPV infection in our region. We have applied for a grant to study the gene expression profile of HPV positive and HPV negative oropharyngeal cancer, with potential implications on treatment choices. 2) Advance in organ preservation treatment in locally advanced head and neck within a multidisciplinary approach of chemotherapy, radiotherapy and immunotherapy. We will participate in phase III, randomized, study of the effects of leukocyte interleukin injection plus radiotherapy in patients with advanced squamous cell carcinoma of the oral cavity. 3) Test new drugs that can reduce acute and late toxicity derived from chemoradiation, such as mucositis and xerostomia. Our multicentric phase III study on the benefit of Clonidine for the prevention of oral mucositis in head and neck cancer patients has completed accrual now and statistical analysis is planned for this year. Also, the study on intranasal Fentanyl for the treatment of pain associated with oral mucositis, has completed its accrual now. 4) We are also working in surgical rehabilitation, including dental implants and mandibular reconstruction in order to improve quality of

life of head and neck cancer patients. A review on neck dissection after chemoradiation for head and neck cancer has been done, in collaboration with the E.N.T. department, and the Radiology department to establish which patients undergoing a conservative treatment need to be operated.



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GROUP 59



Head of laboratory



Group members



Olivier Gómez, Carlos Manuel

- Acosta Reveles, Marco Antonio
- Albers Acosta, Eduardo Mariano
- Bocardo Fajardo, Gloria
- Brime Menéndez, Ricardo
- Celada Luis, Guillermo
- Cogorno Wasylkowski, Leopoldo
- Diego García, Victoria
- Fernández González, Inmaculada
- Galán Sánchez-Heredero, María José
- Otta Oshiro, Renan Javier
- San José Manso, Luis Alberto



Research interest

Our group focused on different research areas.

Erectile dysfunction: Endothelial dysfunction is one of the first symptoms of erectile dysfunction (ED) and is closely related to atherosclerosis and risk factors such as diabetes mellitus (DM), both of them characterized by inflammatory and oxidative advanced state. Vardenafil is one of the more effective 5-phosphodiesterase inhibitors in patients with ED and DM. We have determined plasma proteome of patients with DM and the effect of vardenafil administration in the expression of proteins related to inflammatory oxidative stress and cellular homeostasis. We have observed a significant negative correlation between plasma levels of betatropomyosin and IIEF-EF score. Elevated levels of beta-tropomyosin in plasma indicate cell damage and loss of cellular regenerative capacity.

Urothelial cancer: Exosomes extracellular vesicles are potent intercellular mediators containing membrane and cytosolic proteins, mRNA and specific miRNA, which in turn can be obtained from fluids such as urine. We have analyzed urinary exosomes, miRNA and protein content in order to find diagnostic markers for bladder urothelial cancer. Some of the miRNAs that are involved in tumor cell proliferation, inhibition of tumor suppressor genes, activation of EMT and metastatic state, are significantly reduced in urinary exosomes from patients with bladder urothelial carcinoma and may be useful as non-invasive diagnostic biomarkers in bladder cancer.

With regard to surgical techniques, we have optimized the diagnosis and therapeutic endourologic approach to the upper urothelial tract cancer.



Publications (2)

Angulo, Javier C., Virseda-Chamorro, Miguel, Arance, Ignacio, Ruiz, Sonia, Ojea, Antonio, Carballo, Manuel, Rodriguez, Andres, Pereira, Javier, Teyrouz, Antoine, Rebassa, Miguel, Escribano, Gregorio, Teba, Fernando, Celada, Guillermo, Madurga, Blanca, Martins, Francisco E., Mendes, Pedro A., Cruz, Francisco. **Long-term outcome of adjustable transobturator male system for stress urinary incontinence in the Iberian multicentre study.** Neurourol Urodyn 39 (6): 1737-1745. 2020. PMID: 32496606. IF: 2,037. DOI: 10.1002/nau.24410.

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