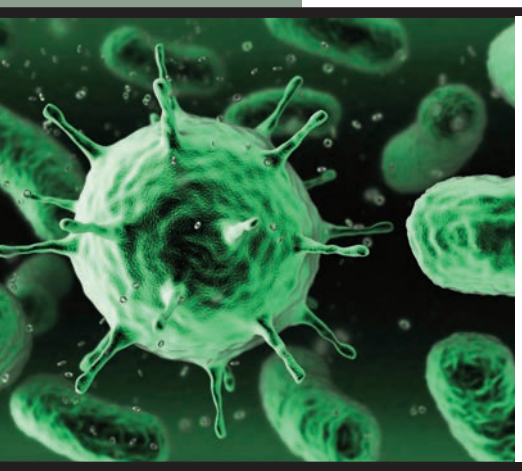
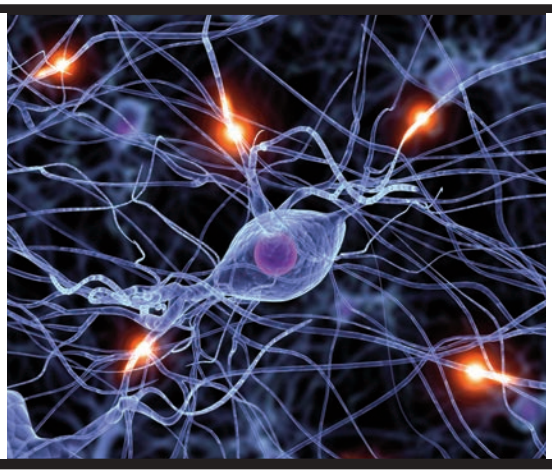
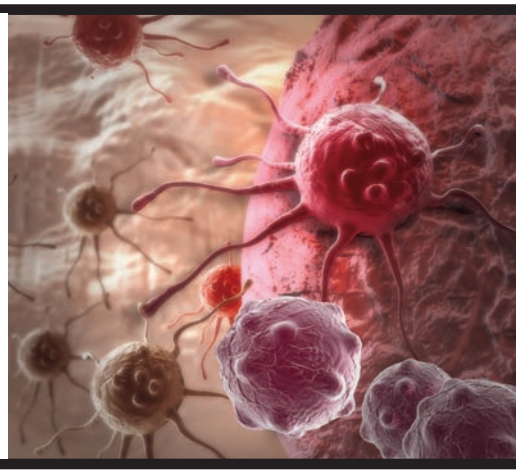
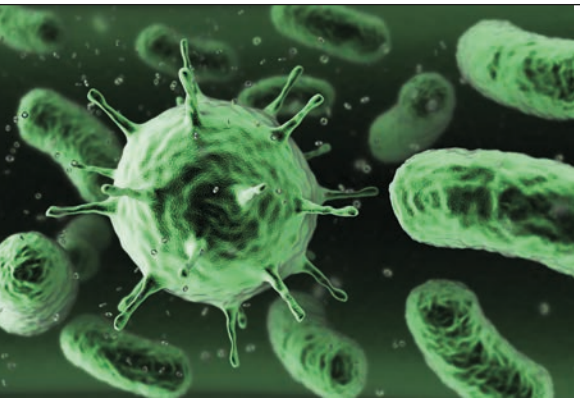




2017

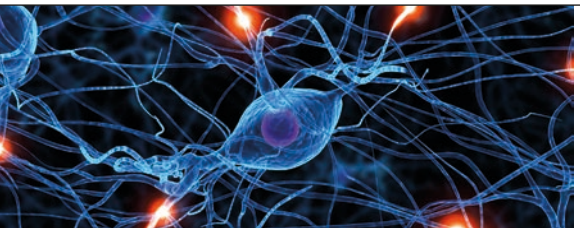
ANNUAL REPORT OF SCIENTIFIC ACTIVITY

AREA 1



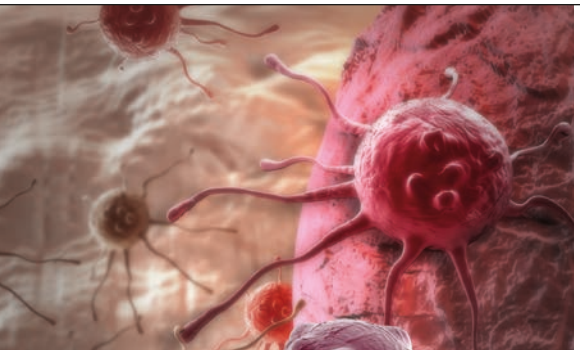
Line 1.1	Intercellular communication in the inflammatory response.
Line 1.2	Cellular and molecular responses to hypoxia.
Line 1.3	Animal models of inflammatory diseases and intercellular signalling.
Line 1.5	Cellular mechanisms and molecular determinants of allergy-based diseases.
Line 1.6	Inflammatory 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.

AREA 2



Line 2.1	Neuropharmacology and neuroprotection.
Line 2.2	Neurotransmission in the hippocampus.
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.

AREA 3



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.

INSTITUTO DE INVESTIGACIÓN SANITARIA
HOSPITAL UNIVERSITARIO DE LA PRINCESA

2017 ANNUAL REPORT OF SCIENTIFIC ACTIVITY

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2017 ANNUAL REPORT OF SCIENTIFIC ACTIVITY

Editing: Ibáñez&Plaza Asociados S.L.

INDEX

FOREWORD IP

IIS-Princesa 2017

Letter from the Scientific Director

After nine years of activity, the IIS IP has 51 research groups and more than 500 researchers and technicians who encompass almost all the Medical Services in several hospitals

The Health Research Institute of the University Hospital La Princesa (IIS IP) began its journey in 2009. At that time the Institute was formed by 400 members, distributed in 48 research groups. After nine years of activity, the IIS IP has 51 research groups and more than 500 researchers and technicians who encompass almost all the Medical Services in the hospitals La Princesa, Santa Cristina and the children´s hospital Niño Jesús, as well as several related departments at the Autonomous University of Madrid.

This increase in personnel has also been reflected in a very significant increase in the number of publications (in 2017, almost 150 more publications than in 2010), its cumulative impact factor (1,000 points higher) and its average impact factor (almost one point above). Although these data are very positive and are the result of the effort of our personnel and the quality of our research, we must aim to keep growing to maintain this upward trend in the future.

The year 2017 has also been very positive in terms of the number of research grants awarded. Twenty four new research grants have been awarded to IIS IP researchers in competitive public and private calls, national and international, and 15 people have joined the institute thanks to competitive funding obtained by our members through human resources calls. It is worth mentioning that we have renewed our participation in three of the ISCIII platforms -Innovation in Medical and Health Technologies, Biobanks and Clinical Research Units and Clinical Trials- which allow us to provide a quality and more personalized support to the researchers of our centre.

In the area of Clinical Trials we can also be proud of the work done with the 116 clinical trials and observational studies approved by the CEIm.

By subscribing the words of the late Steve Jobs “innovation distinguishes leaders from followers”, IIS IP has always bet - and will continue to bet in the future - on innovation as the engine of future growth. In this 2017, 11 patents have been

filed, of which 6 are national, 1 European, 2 PCT and two international, one in Canada and one in the USA. In addition, we have been beneficiaries of prestigious research grants such as Caixa Impulse and FIPSE.

In this year we have accomplished two milestones, which we are particularly proud of. The first was to obtain the "Human Resources Strategy for Researchers" (HRS4R) European recognition, which allows us to use its logo to be identified as a centre aligned with the principles of the European Charter of the Researcher Staff and the Code of Conduct for the Recruitment of Research Staff, thus becoming the first health research institute of the Community of Madrid to achieve this recognition. The second important achievement was to sponsor, together with ROCHE, the First research Call "Stop Brain drain", which received applications from 23 postdoctoral candidates of the different IIS of the Community of Madrid, supported by tutors with competitive projects, to obtain funding for an 18-month contract.

Continuing with the task of bringing science closer to society that we have developed in recent years, members of our Institute have participated for the second consecutive year in the call "Pint of Science", where science is brought to bars in an informal way to reach the general public. We have also participated in the Science Week with more workshops and with a greater number of participants than in previous years.

As in previous years, I would like to thank the outstanding work carried out by each and every member of this institute as well as the people who are not part of our institution, but also contribute to improve year after year the results we show you here.

Without anything else to add I leave you here with the Annual Scientific Report which presents detailed information of the activity carried out during this year, accompanied by the most relevant global data and a small presentation of our governing bodies, consultants, platforms, units and commissions.

In this year we have accomplished two milestones: to obtain the "Human Resources Strategy for Researchers" (HRS4R) European recognition; and to sponsor, together with ROCHE, the First research Call "Stop Brain drain"

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 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.

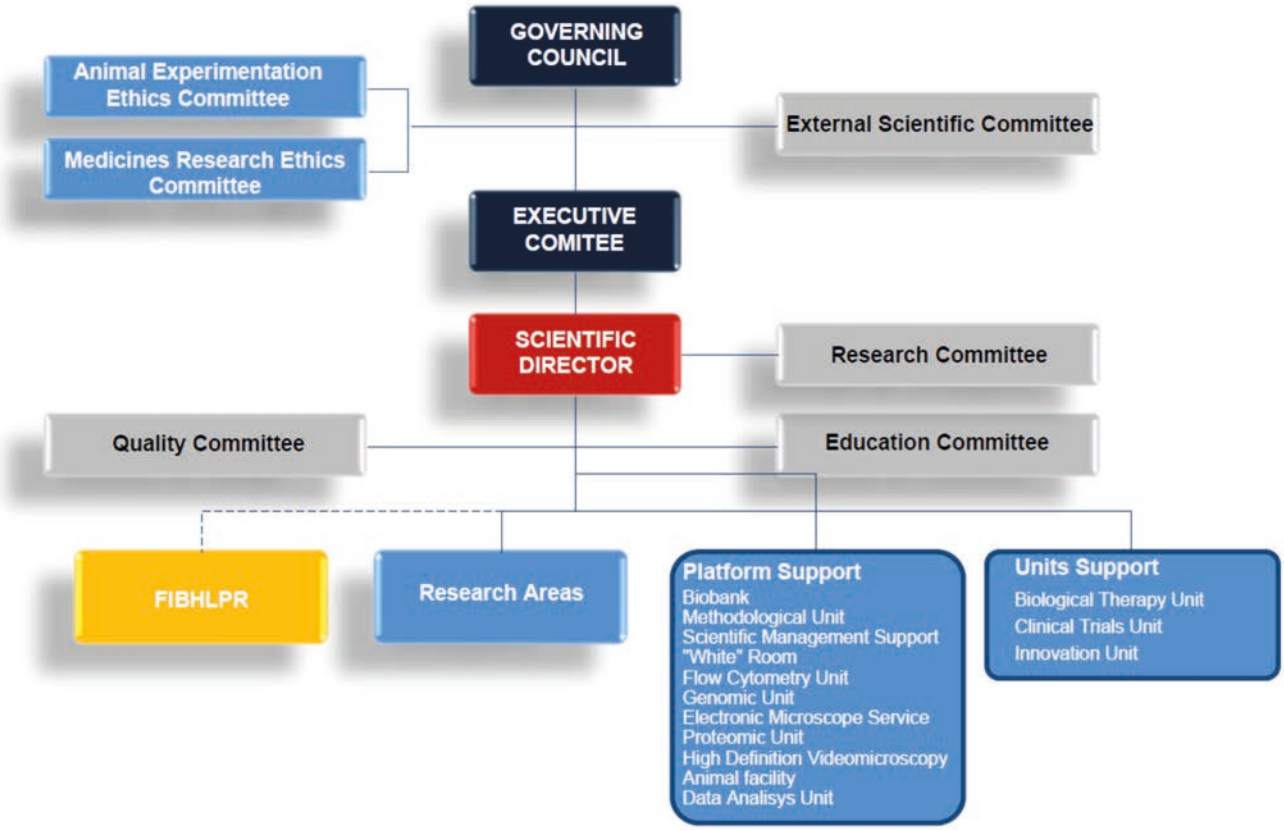
In 2013 the activity of the Agency of Training, Research and Health Studies of the Community of Madrid "Pedro Laín Entralgo" was finished, and its functions were assumed by the Ministry of Health of the Community of Madrid, in particular by its the General Directorate of Research, Training and Health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

SaludMadrid
Hospital Universitario de La Princesa
Hospital Universitario Santa Cristina
Hospital Infantil Universitario Niño Jesús
Dirección General de Planificación, Investigación y Formación
CONSEJERÍA DE SANIDAD
Comunidad de Madrid

UAM
UNIVERSIDAD AUTONOMA DE MADRID

FIB FUNDACIÓN DE INVESTIGACIÓN BIOMÉDICA
hospital universitario la princesa

ORGANIZATION CHART



GOVERNING COUNCIL

The Governing Council is the governing body which is responsible for the representation, management and administration of the Institute.

CHAIRMAN

Manuel Molina Muñoz
Deputy Minister of Health, Comunidad de Madrid

VICE-CHAIRMAN

Rafael Garesse Alarcón
Chancelor of Universidad Autónoma de Madrid

MEMBERS

Julio Ancochea Bermúdez
Head of Respiratory Department, Hospital Universitario La Princesa

Gustavo Casero Balboa
Management and general services Director, Hospital Universitario La Princesa
Cesar Gómez Derch
General Director, Hospital Infantil Universitario Niño Jesús
Fidel Illana Robles
General Director, Hospital Universitario La Princesa
Federico Mayor Menéndez
Centro de Biología Molecular Severo Ochoa, Madrid
César Pascual Fernández
Director of Health Care Coordinator, Comunidad de Madrid
Miriam Rabaneda Gudiel
Director of Planning, Research and Training, Consejería de Sanidad de la Comunidad de Madrid
Rosa María Ramos Pérez
General Director, Hospital Universitario Santa Cristina
Francisco Sánchez Madrid
Scientific Director of Instituto de Investigación Sanitaria Hospital Universitario La Princesa
Marta Sánchez-Celaya del Pozo
Manager of Atención Primaria, Servicio Madrileño de Salud
Alberto José Sebastián Palomino
Management, Hospital Universitario La Princesa

SECRETARY

Rosario Ortiz de Urbina Barba
Director of Fundación de Investigación Biomédica Hospital Universitario La Princesa

EXECUTIVE COMMITTEE

The Executive Committee is the executive organ of government of the Institute and is competent to implement research initiatives and project development.

CHAIRMAN

Fidel Illana Robles
General Director, Hospital Universitario La Princesa

VICE-CHAIRMAN

Antonio García García
Emeritus Professor, Universidad Autónoma de Madrid

MEMBERS

Francisco Javier Aspa Marco
Scientific Management Support Unit, Hospital Universitario La Princesa
Gustavo Casero Balboa
Management and general services Director, Hospital Universitario La Princesa
Manuel Fresno Escudero
Centro de Biología Molecular Severo Ochoa, Madrid
Luis Madero López
Head of Hematology Department, Hospital Infantil Universitario Niño Jesús
Francisco Sánchez Madrid
Scientific Director of Instituto de Investigación Sanitaria Hospital Universitario La Princesa
Alberto José Sebastián Palomino
Management, Hospital Universitario La Princesa

Emilio Ucar Corral
Medical Deputy Director, Hospital Universitario Santa Cristina

SECRETARY

Rosario Ortiz de Urbina Barba
Director of Fundación de Investigación Biomédica Hospital Universitario La Princesa

SCIENTIFIC DIRECTOR

The Scientific Director of the Health Research Institute Hospital Universitario de La Princesa is responsible for its scientific management. The main functions are to ensure the quality of research, promote relations between research groups, lead the scientific activities carried out in the Institute and to foster traslational research.

Francisco Sánchez Madrid
Scientific Director of Instituto de Investigación Sanitaria Hospital Universitario La Princesa

EXTERNAL SCIENTIFIC COMMITTEE

The External Scientific Committee is the main advisory board of the Health Research Institute. Its most relevant functions are to ensure a high quality of research activities in the center and to give advice to the Scientific Director. It is formed by 6 members from different National Centers, with an outstanding research career.

Xosé R. Bustelo
Chairman, Professor Centro de Investigación del Cáncer, CSIC, Salamanca
Jaume Bosch Genover
Professor Universidad de Barcelona. Hospital Clínico y Provincial de Barcelona
José López Barneo
Professor Universidad de Sevilla. Director of Instituto de Investigación Biomédica, Sevilla
Carlos López Otín
Professor Universidad de Oviedo. Deparment of Biochemistry and Molecular Biology.
Miguel López-Botet Arbona
Professor Universidad Pompeu Fabra. Scientific Director IMIM, Barcelona.
Felipe Rodríguez de Castro
Professor of Medical School, Universidad de Las Palmas de Gran Canaria

RESEARCH COMMITTEE

The IIS-Princesa has a Research Committee, responsible for promoting and coordinating scientific activity at the Institute. All members of the Research Committee are professionals of recognized scientific track that lead research groups, where it is represented all the institutions that make up the IIS.

CHAIRMAN

Francisco Sánchez Madrid
Scientific Director of Instituto de Investigación Sanitaria Hospital Universitario La Princesa

MEMBERS

Francisco Abad Santos
Clinical Pharmacology Department, Hospital Universitario La Princesa

Adrián Alegre Amor
Hematology Department, Hospital Universitario La Princesa
Julio Ancochea Bermúdez
Respiratory Department, Hospital Universitario La Princesa
Jesús Argente Oliver
Endocrinology Department, Hospital Infantil Universitario Niño Jesús
Francisco Javier Aspa Marco
Scientific Management Support Unit, Hospital Universitario La Princesa
Ramón Colomer Bosch
Medical Oncolgy Department, Hospital Universitario La Princesa
Antonio García García
Emeritus Professor, Universidad Autónoma de Madrid
Carmelo García Monzón
Internal Medicine Department, Hospital Universitario Santa Cristina
Isidoro González Álvaro
Rheumatology Department, Hospital Universitario La Princesa
Mónica Marazuela Azpiroz
Endocrinology Department, Hospital Universitario La Princesa
Federico Mayor Menéndez
Centro de Biología Molecular Severo Ochoa, Madrid
Francisco Javier Pérez Gisbert
Gastroenterology Department, Hospital Universitario La Princesa
Carmen Suárez Fernández
Internal Medicine Department, Hospital Universitario La Princesa
María Yáñez Mó
Research Unit, Hospital Universitario Santa Cristina

SECRETARY

Mª Ángeles Vallejo Rodríguez
Immunology Department, Hospital Universitario La Princesa

CLINICAL RESEARCH ETHIC COMMITTEE

Clinical Research Ethic Committee (CEIm) is responsible for assessing the ethical, methodological and legal aspects of clinical trials with medicines and those studies in which research is conducted on humans.

CHAIRMAN

Francisco Abad Santos
Clinical Pharmacology Department, Hospital Universitario La Princesa

VICE-CHAIRMAN

Dolores Ochoa Mazarro
Clinical Pharmacology Department, Hospital Universitario La Princesa

MEMBERS

Enrique Alday Muñoz
Anesthesiology Department, Hospital Universitario La Princesa
Carmen del Arco Galán
Emergency Department, Hospital Universitario La Princesa
Santos Castañeda Sanz
Rheumatology Department, Hospital Universitario La Princesa

Ramón Colomer Bosch
Medical Oncolgy Department, Hospital Universitario La Princesa
José María Galván Román
Internal Medicine Department, Hospital Universitario La Princesa
Andrés López Romero
Family and Community Medicine, Primary Care
Concepción Martínez Nieto
Pharmacy Department, Hospital Universitario La Princesa
Concepción Paloma Menéndez González
Patient representative
Pablo Montalvo Rebuelta
Lawyer, ASJUSA
José Luis Muñoz de Nova
General Surgery Department, Hospital Universitario La Princesa
Carolina Pozuelo González
Pharmacy Department, Primary Care
Amelia Rodríguez Nogueiras
Nurse, Hospital Universitario La Princesa
Eduardo Sánchez Sánchez
Internal Medicine Department, Hospital Universitario La Princesa
Alba Serrano Ruiz
Clinical Trials Department, FIB, Hospital Universitario La Princesa

TECHNICAL SECRETARY

Mara Ortega Gómez
Biobank, Hospital Universitario La Princesa

ADMINISTRATIVE SECRETARY

Julio González de Castro
Cecilia López García

FOUNDATION FOR BIOMEDICAL RESEARCH (FBR)

The foundation aims to manage programs and clinical research projects and other related activities in the field of biomedicine, to contribute to the promotion and protection of health of the population and the advancement and improvement of the health system of the Community of Madrid, ruled by Article 2 of Law 12/2001, of 21 December, of Health Planning of the Community of Madrid.

DIRECTOR

Rosario Ortiz de Urbina Barba

HUMAN RESOURCES DEPARTMENT

David Lafuente Alonso

PROJECTS MANAGEMENT DEPARTMENT

Jesús Santamaría Pérez
María del Carmen Barrio Fuentes

ACCOUNTING DEPARTMENT

Jorge Gómez Juan

CLINICAL TRIALS MANAGEMENT DEPARTMENT

Alba Serrano Ruiz
Olga Montes Romero

RESEARCH MANAGEMENT DEPARTMENT

Jesús Capa Algara

SECRETARY

Ana Aroca Martínez

WARD STAFF

José Corrochano de la Cruz

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

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

Sergio Luquero Bueno

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

TECHNICAL STAFF

Lorena Vega Piris

MEDICAL WRITER

Manuel Gómez Gutiérrez

SCIENTIFIC MANAGEMENT SUPPORT UNIT

The Scientific Management Support Unit of IIS-Princess 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.

TECHNICAL DIRECTOR

María Antonia Varela-Portas San Juan

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 Ramírez

HIGH DEFINITION VIDEOMICROSCOPY

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

COORDINATOR

Miguel Vicente Manzanares

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
Miriam Pérez-Romero

BIOLOGICAL THERAPY 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

José Mª Álvaro Gracia

MULTIDISCIPLINAR TEAM

Isidoro González Álvaro
Rheumatology Department
Esteban Daudén Tello
Dermatology Department
Francisco Javier Pérez Gisbert
Gastroenterology Department
Virginia Meca Lallana
Neurology 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

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

Carmen Suárez Fernández
Internal Medicine Department

INNOVATION COMMITTEE

Carmen del Arco Galán
Emergency Department
Elena Español Pueyo
Communication Cabinet
María Pilar Prieto Alaguero
Nursing Deparment
Ana Gago Veiga
Neurology Department

Fidel Illana Robles
General Director, Hospital Universitario La Princesa
Luis Jesús Jiménez-Borreguero
Cardiology Deparment
Alberto Morell Baladrón
Hospital Pharmacy Department
Ramón Moreno Balsalobre
Thoracic surgery Department
Rosario Ortiz de Urbina
Director of Fundación de Investigación Biomédica Hospital Universitario La Princesa
Francisco Redondo Montserrat
Nursing Deparment
Francisco Sánchez Madrid
Scientific Director of Instituto de Investigación Sanitaria Hospital Universitario La Princesa
Luis Sánchez-Urdazpal González
General and Digestive Surgery Department
Alberto José Sebastián Palomino
Management, Hospital Universitario La Princesa
Gema Vega González
Intensive Care Medicine Department
María Mercedes Vinuesa Sebastián
Quality Coordinator

SECRETARY INNOVATION COMMITTEE AND INNOVACION STAFF
Antonio Rodríguez Hita

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
Mª Angels Figuerola Tejerina
Preventive Medicine Deparment

QUALITY COMMITTEE
Arantzazu Alfranca González
Immunology Department
Francisco Javier Aspa Marco
Scientific Management Support Unit
Ramón Colomer Bosch
Medical Oncolgy Department
Mara Ortega Gómez
Biobank

SECRETARY

Jesús Capa Algara
Research Managment

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).

COORDINATOR

Francisco Javier Aspa Marco
Scientific Management Support Unit, Hospital Universitario La Princesa

EDUCATION COMMITTEE

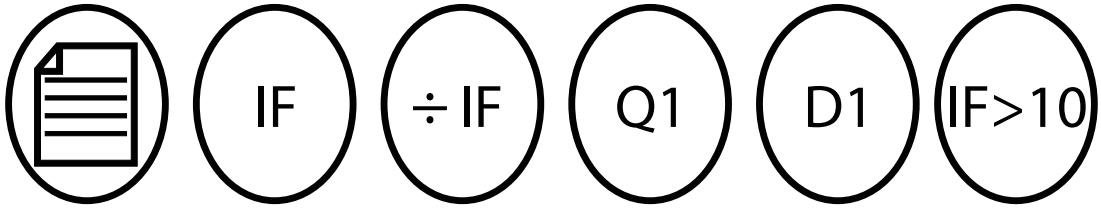
Elena Fernández Ruiz
Molecular Biology Department
Elena Martín Pérez
Head of studies Resident Doctor
Ramón Moreno Balsalobre
Thoracic Surgery Service
Mara Ortega Gómez
Biobank
Fernando Ramasco Rueda
Continuous Training coordinator
Francisco Rodríguez Salvanés
Diagnosis Training Unit
Jesús Sanz Sanz
Internal Medicine Department

SECRETARY

Jesús Capa Algara
Research Managment

SCIENTIFIC OUTPUT

PUBLICATIONS



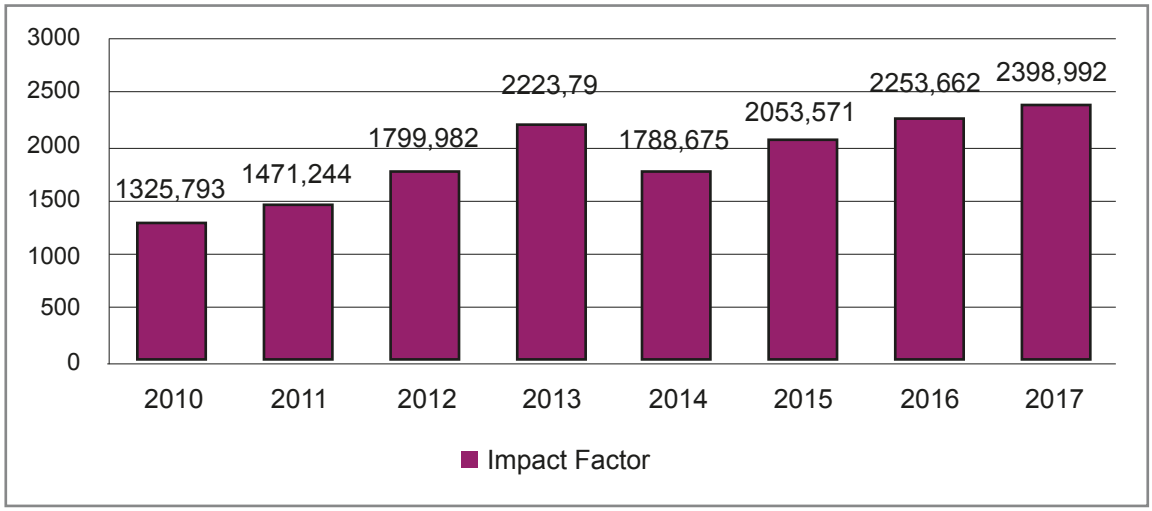
Biomedical research has become one of the most important elements of the scientific development of countries, which contributes to improve the welfare of the population. Publications are essential for the scientific activity contributing to disseminate scientific advances new processes and / or products within the scientific community, as well as allowing researchers to obtain recognition for their work.

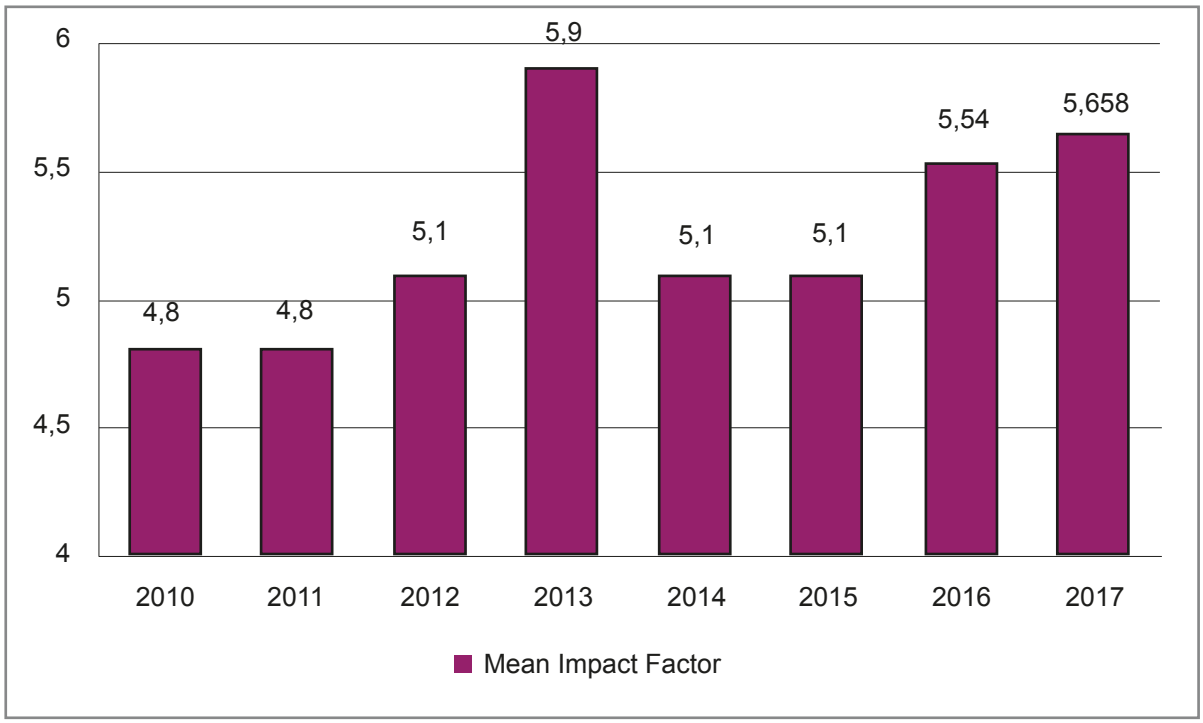
Quantitative bibliometric indicators -such as the number of citations- and impact indicators are used to measure scientific output. The "Journal Citation Report (JCR)" is an internationally recognized index which measures impact by determining the relative importance of journals, organized into thematic categories, assigning them a score called impact factor (IF). Considering this score, ordered from highest to lowest, first decile (D1) journals are those located in the group with the ten percent highest score, and first quartile (Q1) those that are framed within the twenty-five percent highest score.

Below is shown the most significant data obtained by evaluating the original articles, reviews and editorials registered in international databases, in which at least one of its authors has been part of the IIS during 2017. Data includes articles in journals whose impact factor is higher than 1 in the JCR 2016.

In total, in 2017 more than 400 articles were published, of which 25 percent were included in first decile. The cumulative impact factor was over 2000 points, and more importantly, the average impact factor was 5.7, which highlights the relevance of our research.

Below is a selection of the most relevant data of the scientific output of the IIS since 2010.

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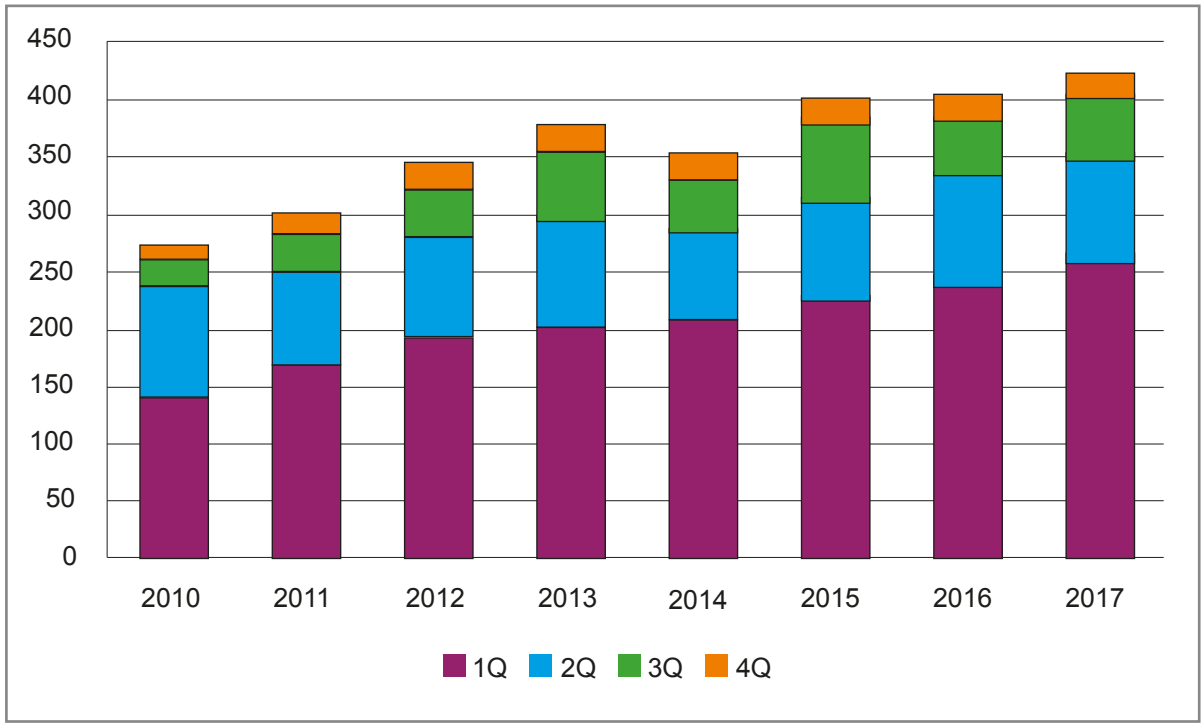
2011
2012
2013
2014
2015
2016
2017
Mean Impact Factor


450
400
350
300
250
200
150
100
50
0
2010
2011
2012
2013
2014
2015
2016
2017
1Q
2Q
3Q
4Q

PRODUCTIVITY AND IMPACT THE SCIENTIFIC OUTPUT OF THE SCIENTISTS

To asses the career output of scientists, the most recognized indicator is the h index, which combines the assessment of number of publications and number of citations throughout their careers.

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

	GROUP	DIRECTOR	H INDEX
Intercellular Communication in the Inflammatory Response	1	Francisco Sánchez Madrid	86
	2	Esteban Veiga Chacón	20
	3	María Yáñez Mó	37
	4	Miguel Vicente Manzanares	32
	14	María de las Nieves Navarro Lobato	10
	56	Ana Urzainqui Mayayo	16
Cellular and molecular responses to Hypoxia	9	Julián Aragonés López	24
	7	Antonio Martínez Ruiz	27
	8	María José Calzada García	13
	10	Susana Cadenas Álvarez	31
Animal models of inflammatory diseases and intercellular signalling	11	Federico Mayor Menéndez	41
	12	Manuel Fresno Escudero	45
	13	Petronila Penela Márquez	22
	17	Cristina Murga Montesinos	21
	18	Miguel Ángel Iñiguez Peña	27
Cellular mechanisms and molecular determinants of allergy-based diseases	20	Carlos Blanco Guerra	28
	15	María Dolores Ibáñez Sandín	17
Inflammatory processes in nephrological diseases	21	José Antonio Sánchez Tomero	19
Inflammatory mechanisms in pulmonary diseases	22	Julio Ancochea Bermúdez	27
Inflammatory response in hepatic diseases	24	Pedro Lorenzo Majano Rodríguez	26
	23	Luisa Consuelo García Buey	28
Mechanisms and mediators of endocrine diseases	25	Mónica Marazuela Azpiroz	31
Children´s development (obesity and growth)	26	Jesús Argente Oliver	48
Metabolic syndrome and vascular risk	5	Carmelo García Monzón	29

ÁREA 2: TRANSLATIONAL NEUROSCIENCE

	GROUP	DIRECTOR	H INDEX
Neuropharmacology and neuroprotection	28	Antonio García García	51
Pharmacological Neuroprotection in Neurodegenerative Diseases and Stroke	16	Manuela García López	42
Clinical pharmacology and pharmacogenetics	32	Francisco Abad Santos	17
Diagnostic and therapeutic advances in affective disorders	33	José Luis Ayuso Mateos	37
Neurosurgery of epilepsy	34	Rafael García de Sola	18
Cerebrovascular diseases	35	Jose Aurelio Vivancos Mora	29
	Asoc 1	Ignacio Lizasoain Hernández	52

AREA 3: ADVANCED THERAPIES AND INDIVIDUALIZED MEDICINE

	GROUP	DIRECTOR	H INDEX
Prognostic and predictor markers in autoimmune diseases	36	Isidoro González Álvaro	24
	37	Esteban Daudén Tello	19
Esophagogastrointestinal inflammatory diseases	38	Francisco Javier Pérez Gisbert	52
Progenitors and cell therapy	39	Luis Madero López	26
Advanced therapies in oncohematology	44	José Luis Steegmann Olmedillas	26
Biological, cellular and molecular monitoring in oncohematology	45	Elena Fernández Ruiz	16
	46	Cecilia Muñoz Calleja	13
New diagnostic and therapeutic advances in cardiovascular diseases	58	Fernando Alfonso Manterola	46
	48	Luís J. Jiménez Borreguero	17
	57	Carmen Suarez Fernández	20
	49	Blanca Novella Árribas	2
New therapies in infectious pathologies	50	Ignacio de los Santos Gil	12
	51	Francisco Javier Aspa Marco	15
	52	Teresa Alarcón Cavero	28
Individualized medicine in solid tumors	40	Ramón Colomer Bosch	47
	53	Almudena Zapatero Laborda	17
	54	Laura Cerezo Padellano	19
	59	Carlos M. Olivier Gómez	8
	Asoc 3	José Cordero Ampuero	13

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	EUROPEAN APPLICATIONS	PCT APPLICATIONS	APPLICATIONS IN OTHER COUNTRIES	TOTAL APPLICATIONS
6	1	2	2	**11**

GRANTED PATENTS	INTERNATIONAL PATENTS GRANTED	TOTAL GRANTED
2	0	**2**

NATIONAL APPLICATIONS OF PATENTS

Title: *Nuevos derivados de gramina con efecto protector de la actividad fosfatasa, y su aplicación en el tratamiento de enfermedades humanas*
Number: P201731196
Date of applicant: 10/10/2017
Owners/s: Fundación de Investigación Hospital Universitario de La Princesa (40%) Universidad Autónoma de Madrid (39%) y Fundación Teófilo Hernando (21%)
Inventors: Cristóbal de los Ríos Salgado, María Rocío Lajarín Cuesta, Antonio García García y Raquel López Arribas

Title: *Método de análisis multivariante en encefalografía*
Number: P201731458
Date of applicant: 22/12/2017
Owners/s: Fundación de Investigación Hospital Universitario de La Princesa (100%)
Inventors: Jesús Pastor Gómez y Lorena Carolina Vega Zelaya.

Title: *Método no invasivo para determinar la presión intracraneal mediante la actividad bioeléctrica del cerebro*
Number: P201730943
Date of applicant: 18/07/2017
Owners/s: Fundación de Investigación Hospital Universitario de La Princesa (100%)
Inventors: Guillermo José Ortega Rabbione, 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 y Cristina Virginia Torres Días.

Title: *Uso de CD81 como diana terapéutica para regular los niveles intracelulares de dNTPs*
Number: P201700345
Date of applicant: 30/03/2017
Owners/s: Fundación de Investigación Hospital Universitario de La Princesa (25%) y Universidad Autónoma de Madrid (75%).
Inventors: María Yáñez Mó, Henar Suarez Montero, Francisco Sánchez Madrid y Vera Pires Ferreira Rocha Perugini.

REGISTRY OF SOFTWARE IN SPAIN

Software title: *Método para determinar el nivel de activación del sistema trigémino-vascular"*
Number: M - 7702- 2017

Date of applicant: 30/11/2017
Owners/s: Fundación de Investigación Hospital Universitario de La Princesa (51%) y Universidad Complutense de Madrid (49%).
Inventors: Ana Beatriz Gago Veiga, Mónica Sobrado Sanz, José Aurelio Vivancos Mora, Josué Pagán Ortiz, José Luis Ayala Rodrigo y José Luis Risco Martín.

EUROPEAN APPLICATION OF PATENTS

Title: *Compounds derived from 3-alkylamine-1h-indolyl acrylate and their use in the treatment of neurodegenerative diseases*
Number: EP15851060.2
Date of applicant: 12/05/2017
Owners/s: Fundación de Investigación Biomédica del Hospital Universitario La Princesa (55%), Universidad Autónoma de Madrid (40%) y DNS Neuroscience SL (5%)
Inventors: Rafael León Martínez, Antonio García García, Manuela García López, Javier Egea Maiquez, Izaskun Buendía Abaitua, Elisa Navarro González de Mesa, Patrycja Michalska, Isabel María Gameiro Ros y Alicia López Vivo

APPLICATION OF PATENT IN CANADA

Title: *Compounds derived from 3-alkylamine-1h-indolyl acrylate and their use in the treatment of neurodegenerative diseases*
Number: 2,964,309
Date of applicant: 11/04/2017
Owners/s: Fundación de Investigación Biomédica del Hospital Universitario La Princesa (55%), Universidad Autónoma de Madrid (40%) y DNS Neuroscience SL (5%)
Inventors: Rafael León Martínez, Antonio García García, Manuela García López, Javier Egea Maiquez, Izaskun Buendía Abaitua, Elisa Navarro González de Mesa, Patrycja Michalska, Isabel María Gameiro Ros y Alicia López Vivo.

APPLICATION OF PATENT IN USA

Title: *Compounds derived from 3-alkylamine-1h-indolyl acrylate and their use in the treatment of neurodegenerative diseases*
Number: 15/518,223
Date of applicant: 10/04/2017
Owners/s: Fundación de Investigación Biomédica del Hospital Universitario La Princesa (55%), Universidad Autónoma de Madrid (40%) y DNS Neuroscience SL (5%)
Inventors: Rafael León Martínez, Antonio García García, Manuela García López, Javier Egea Maiquez, Izaskun Buendía Abaitua, Elisa Navarro González de Mesa, Patrycja Michalska, Isabel María Gameiro Ros y Alicia López Vivo.

APPLICATION OF INTERNATIONAL PCT PATENT

Title: *Distractor mandibular.*
Number: PCT/ES2017/070783
Date of applicant: 29/11/2017
Owners/s: Fundación de Investigación Biomédica del Hospital Universitario La Princesa (100%)
Inventors: Pilar Rubio Bueno

Title: *Método para determinar el nivel de activación del sistema trigémino-vascular.*
Number: PCT/ES2017/070004
Date of applicant: 03/01/2017

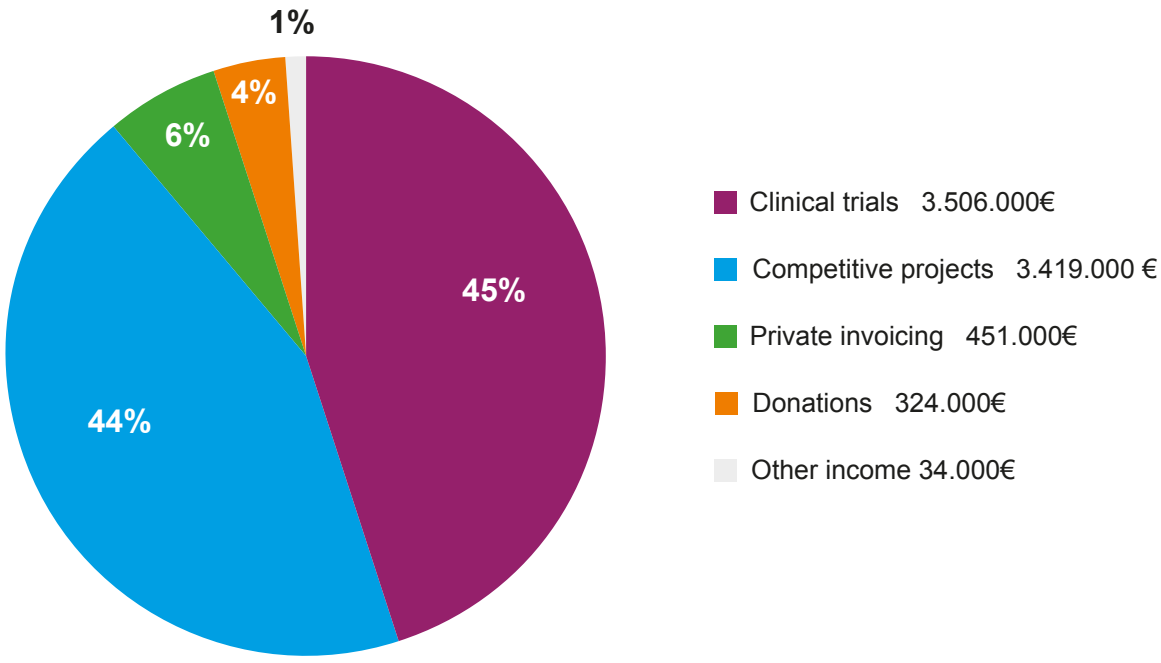
Owners/s: Fundación de Investigación Biomédica del Hospital Universitario La Princesa (51%) Y Universidad Autónoma de Madrid (49%)
Inventors: Ana Beatriz Gago Veiga, Mónica Sobrado Sanz, José Aurelio Vivancos Mora, Josué Pagán Ortiz, María Irene de Orbe Izquierdo y José Luis Ayala Rodrigo.

NATIONAL PATENTS GRANTED

Title: *Compuestos derivados de acrilato de 3-Alquilamino-1H-Indolilo y su uso en el tratamiento de enfermedades neurodegenerativas*
Number: ES2570452
Date of applicant: 10/04/2017
Owners: Fundación de Investigación Biomédica del Hospital Universitario La Princesa (55%), Universidad Autónoma de Madrid (40%) y DNS Neuroscience SL (5%)
Inventors: Rafael León Martínez, Antonio García García, Manuela García López, Javier Egea Maiquez, Izaskun Buendía Abaitua, Elisa Navarro González de Mesa, Patrycja Michalska, Isabel María Gameiro Ros y Alicia López Vivo.

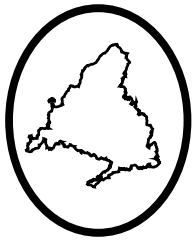
Title: *Nuevos derivados de (1H-Indol-3-Ilmetil) Dimetilamina con actividad bloqueador de los canales de Ca2+ dependientes de voltaje, preferentemente NO-L, y su aplicación en el tratamiento de enfermedades del sistema nervioso*
Number: ES2589599
Date of applicant: 08/08/2017
Owners/s: Fundación de Investigación Biomédica del Hospital Universitario La Princesa (44%), Universidad Autónoma de Madrid (43%) y Fundación Teófilo Hernando (13%)
Inventors: Rocío Lajarín Cuesta, Juan Alberto Arranz Tagarro, Carmen Pérez de Nanclares, Luis Gandía Juan, Antonio García García y Cristóbal de los Ríos Salgado.

FUNDING RECRUITMENT



NEW COMPETITIVE PROJECTS

Projects: 4



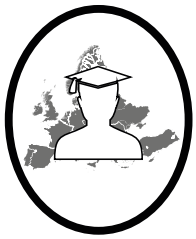
Projects: 2
Personnel: 5

Projects: 19
Personnel: 2

DEFENDED DOCTORAL THESES

The great dedication of IP to training is reflected in the large number of doctoral theses supervised by IP members. Within the IP, during the year 2015 a total of 16 national and 2 international theses have been defended. A list of them is shown below.

40



8

THESES

Trombocitopenia inmune primaria: factores evolutivos y cambios terapéuticos
Doctoral candidate: Sandra Fernández Plaza
Director/s: Julián Sevilla Navarro / Luis Madero López
Defense date: 17/01/2017

Aurora A shines on early cell activation
Doctoral candidate: Noelia Blas Rus
Director/s: Francisco Sánchez Madrid
Defense date: 20/01/2017

Inmunoterapia con veneno de himenópteros: estudio observacional prospectivo para identificar factores asociados a riesgo de reacciones sistémicas
Doctoral candidate: Aranzazu Vega Castro

Director/s: Manuel Rodríguez Zapata / Carlos Blanco Guerra
Defense date: 03/02/2017

In vivo phosphoproteomics reveals kinase activity profiles that predict treatment outcome in triple- negative breast cancer
Doctoral candidate: Ivana Zagorac
Director/s: Miguel Quintela-Fandino
Defense Date: 17/03/2017

Reacciones adversas cutáneas a telaprevir y boceprevir administrados en triple terapia en pacientes con hepatitis C crónica en práctica clínica
Doctoral candidate: Raquel Carrascosa de Lome
Director/s: Javier Sánchez Pérez
Defense Date: 29/03/2017

Capacidad de la calprotectina fecal para predecir la presencia de actividad endoscópica en pacientes con enfermedad inflamatoria intestinal
Doctoral candidate: Vanesa Jusué Irurita
Director/s: Javier Pérez Gisbert / María Chaparro Sánchez
Defense date: 29/03/2017

Tromboembolismo pulmonar : estudio de tomografía computarizada pulmonar . Análisis de hallazgos y factores pronósticos
Doctoral candidate: María Luz Parra Gordo
Director/s: Paloma Caballero Sánchez-Robles / Alfonsa Friera Reyes / Napoleón Pérez Farinós
Defense date: 04/04/2017

Reacciones psoriasiformes paradójicas asociadas a terapia anti-TNFα. Estudio clínico-patológico, fisiopatológico y genético
Doctoral candidate: Raquel Navarro Tejedor
Director/s: Esteban Daudén Tello
Defense Date: 18/04/2017

PSGL-1/P-selectin interaction: regulation of immune and vascular homeostasis
Doctoral candidate: Rafael González Tajuelo
Director/s: Ana Urzainqui Mayayo
Defense date: 18/04/2017

A regulatory motif in non-muscle myosin II-B regulates its assembly and determines its role in plasma membrane protrusion, adhesion dynamics and migratory polarization
Doctoral candidate: Alba Juanes García
Director/s: Miguel Vicente Manzanares
Defense date: 19/04/2017

Pathophysiology of hypoxia: Molecular mechanisms involved in pulmonary hypertension and renal carcinoma
Doctoral candidate: David Labrousse Arias
Director/s: María Josefa Calzada García
Defense date: 21/04/2017

Tratamiento radioterápico en el cáncer de pulmón: resultados y toxicidad
Doctoral candidate: Margarita Martín Martín
Director/s: Laura Cerezo Padellano
Defense date: 03/05/2017

Estudio de los factores de riesgo relacionados con la muerte súbita cardiaca en la provincia de Albacete
Doctoral candidate: Pedró José Lorente García

Director/s: María Gema Vega González / Carmen Suárez Fernández
Defense date: 05/05/2017

Enfermedad metabólica ósea en la colangitis biliar primaria (CBP): estudio descriptivo e implicación de nuevos biomarcadores del remodelado óseo
Doctoral candidate: Alicia Ruiz Rubí
Director/s: María Luisa García Buey y Santos Castañeda
Defense date: 17/05/2017

Monitorización Ambulatoria de la Presión Arterial (MAPA) en pacientes VIH. Impacto en la evaluación del riesgo vascular
Doctoral candidate: Ana Gómez Berrocal
Director/s: Carmen Suárez Fernández
Defense date: 22/05/2017

Detección del virus del papiloma humano en el cáncer de orofaringe: prevalencia y valor pronóstico
Doctoral candidate: Olga Liñán Díaz
Director/s: Laura Cerezo Padellano
Defense date: 26/05/2017

Estudio de la función tiroidea de los recién nacidos hijos de madres con tiroiditis crónica autoinmune
Doctoral candidate: María Magdalena Hawkins Solís
Director/s: Jesús Argente Oliver
Defense date: 01/06/2017

Descripción de la Transfagocitosis, una vía para la captura de bacterias y la presentación antigénica por parte de los linfocitos T CD4+: posibles aplicaciones en biomedicina
Doctoral candidate: Guillermo Ramírez Santiago
Director/s: Esteban Veiga Chacón
Defense date: 05/06/2017

Estudio descriptivo del proteoma plasmático de pacientes afectados de disfunción eréctil y diabetes mellitus tratados con vardenafilo
Doctoral candidate: Ricardo Brime Menéndez
Director/s: Carlos Manuel Oliver Gómez / Antonio López Farré
Defense date: 12/06/2017

Aplicabilidad clínica de la fibroendoscopia flexible de la deglución en una unidad de cuidados intensivos de un hospital de tercer nivel
Doctoral candidate: Jorge Prada Pendolero
Director/s: Eduardo Raboso García-Baquero / Esther Fernández Bermejo.
Defense Date: 22/06/2017

Función del motor molecular miosina no muscular II-B en la regulación mecánica de la activación de los linfocitos T y la sinapsis inmune
Doctoral candidate: Álvaro Ortega Carrión
Director/s: Miguel Vicente Manzanares
Defense date: 23/06/2017

Evaluación de la Técnica tomografía computarizada de 64 detectores (TCMD64) frente a la tomografía por emisión de positrones/tomografía computarizada (18FDG PET7TC) en el estudio clínico de pacientes con linfoma: estudio multicéntrico.
Doctoral candidate: Begoña López-Botet Zulueta
Director/s: Dra Nieves Gomez León
Defense date: 26/06/2017

Factores relacionados con la mortalidad a largo plazo de una cohorte de pacientes que sobreviven 28 días tras un IAM. Efecto de la aparición de diabetes mellitus durante el seguimiento
Doctoral candidate: Jesús Olmedo Llanes
Director/s: María Gema Vega González / Carmen Suárez Fernández
Defense date: 30/06/2017

La fosfatasa DUSP10 es un gen inducido por la Ciclooxigenasa-2, implicado a través de la regulación de YAP1 en el desarrollo del cáncer colorrectal
Doctoral candidate: Marta Jiménez Martínez
Director/s: Manuel Fresno Escudero / Konstantinos Stamatakis Andriani
Defense date: 06/07/2017

Relevancia y medida del bienestar subjetivo y su asociación con el estado de salud en el contexto europeo.
Doctoral candidate: Blanca Mellor Marsá
Director/s: Marta Miret García y Francisco Félix Caballero Díaz
Defense date: 07/07/2017

Nuevos mecanismos de regulación de las funciones celulares de la proteína contráctil miosina II no muscular
Doctoral candidate: Rocío Aguilar Cuenca
Director/s: Miguel Vicente Manzanares
Defense date: 10/07/2017

Microtubule associated protein-4 (MAP4) balances T cell activation through the regulation of positive and negative signals
Doctoral candidate: Eugenio Bustos Morán
Director/s: Francisco Sánchez Madrid
Defense date: 13/07/2017

Molecular characterization of the hypoxia-induced mitochondrial activity regulator Ndufa4l2
Doctoral candidate: Qilong Oscar Yang Li
Director/s: Julian Aragonés López
Defense date: 08/09/2017

Regulation of GRK2 by Mdm2 and the APC/C complex: a way to fine-tune dynamics and faithful progression of the cell cycle
Doctoral candidate: Clara Reglero Gómez
Director/s: Petronila Penela / Federico Mayor Menéndez
Defense date: 15/09/2017

Inmunoterapia sublingual: mecanismos inmunológicos
Doctoral candidate: Tania María Ramos García
Director/s: Dinubgi Barber Hernández / Carlos Blanco Guerra
Defense date: 18/09/2017

Marcadores predictivos de agresividad y supervivencia en tumores neuroendocrinos gastroenteropancreáticos
Doctoral candidate: Miguel Antonio Sampedro Núñez
Director/s: Mónica Marazuela Azpiroz
Defense date: 07/09/2017

Impacto del plan de atención al paciente con ictus de la Comunidad de Madrid en la mejora organizativa y asistencial de la enfermedad. Análisis del periodo 2008-2015
Doctoral candidate: Álvaro Ximenez-Carrillo Rico
Director/s: José Aurelio Vivancos Mora
Defense date: 01/09/2017

Estudio aleatorizado con grupo control de inmunoterapia con huevo en niños con alergia persistente mediada por IgE : desensibilización clínica y desensibilización de la respuesta inmunológica.
Doctoral candidate: Inmaculada Pérez Rangel
Director/s: María Dolores Ibáñez Sandín
Defense date: 05/09/2017

Evaluación de la combinación de sunitinib y ketoconazol: farmacocinética, búsqueda de dosis, seguridad y bioequivalencia
Doctoral candidate: María Ángeles Gálvez Múgica
Director/s: Francisco Abad Santos
Defense date: 12/09/2017

Desarrollo de un índice de gravedad en la artritis reumatoide
Doctoral candidate: Esther Toledano Martínez
Director/s: Isidoro González Álvaro
Defense date: 12/09/2017

Avances en el diagnóstico molecular y en el tratamiento de los gliomas de bajo grado en la edad pediátrica
Doctoral candidate: Álvaro Lassaletta Atienza
Director/s: Luis Madero López
Defense date: 12/09/2017

Características electrofisiológicas del núcleo centromediano talámico humano
Doctoral candidate: Lorena Carolina Vega Zelaya
Director/s: Jesús Pastor Gómez
Defense date: 15/09/2017

El linfoma de células del manto durante la última década: Una búsqueda de un estándar terapéutico y disponibilidad de nuevos agentes
Doctoral candidate: Ana María García-Noblejas Moya
Director/s: María Reyes Arranz Sáez
Defense date: 20/09/2017

Inmuno-quimioterapia en el linfoma indolente B. Resultados de dos estudios prospectivos multicéntricos: LNH- PRO y LNH- PRO- 05. Análisis a largo plazo del esquema CVP-IFN# 2b (Ensayo LNH-PRO). Resultados terapéuticos con doble inmunoterapia (R-CVP-IFN) en el Linfoma Folicular con FLIPI intermedio-alto y alto riesgo (Ensayo LNH-PRO-05)
Doctoral candidate: María Jimena Cannata Ortiz
Director/s: María Reyes Arranz Sáez
Defense date: 22/09/2017

Capacidad de esfuerzo, actividad física y estado nutricional en pacientes con EPOC
Doctoral candidate: Emma Vázquez Espinosa
Director/s: Rosa María Girón Moreno / Julio Ancochea Bermúdez
Defense date: 26/09/2017

EUROPEAN THESES

Deactive complex I triggers a superoxide signal through NCLX in acute hypoxia
Doctoral candidate: Pablo Hernansanz Agustín
Director/s: Antonio Martínez Ruiz
Defense date: 27/04/2017

Applications of Functional Magnetic Resonance Imaging in Drug Development for Paediatric Oncology
Doctoral candidate: Fernando Carceller Lechón
Director/s: Lucas Moreno / Lynley Marshall / Luis Madero
Defense Date: 25/05/2017

Identification of pmepa1 as a cyclooxygenase-2 induced gene and its potential implication in cancer progression
Doctoral candidate: Alba María Jiménez Segovia
Director/s: Manuel Fresno Escudero; Konstantinos Stamatakis
Defense date: 30/06/2017

Novel functional roles of G protein- coupled receptor kinase 2 (GRK2) in Squamous Cell Carcinomas
Doctoral candidate: Julia Palacios García
Director/s: Federico Mayor Menéndez / Catalina Ribas Núñez
Defense date: 21/07/2017

Influencia de la disfunción neurocognitiva, el estilo de afrontamiento y el ajuste premórbido en el pronóstico y funcionalidad de pacientes con diagnóstico de Esquizofrenia Paranoide
Doctoral candidate: María del Rosario Gutiérrez Labrador
Director/s: José Luis Ayuso Mateos
Defense date: 12/09/2017

Impacto de la soledad y las redes sociales sobre diferentes aspectos de la salud
Doctoral candidate: Laura Alejandra Rico Uribe
Director/s: José Luis Ayuso Mateos / Marta Miret García
Defense date: 21/09/2017

Undiagnosed Depression: an Epidemiologic study in the three European countries.
Doctoral candidate: Samir Mohamed Ahmed Zaki Youssef
Director/s: Francisco Félix Caballero Díaz y Pilar López García
Defense date: 21/11/2017

Resonancia magnética multiparamétrica previa a la radioterapia en el cáncer de próstata: Implicaciones clínicas
Doctoral candidate: Felipe Couñago Lorenzo
Director/s: Laura Cerezo Padellano

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 2016, IIS Princesa researchers have participated in the development of 13 clinical guidelines.

Panel de expertos de GeSIDA y Plan Nacional sobre el Sida, Sanz Sanz, Jesús .**Documento de consenso de GeSIDA/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2017).** http://gesida-seimc.org/wp-content/uploads/2017/02/gesida-guiasclinicas-2017-TAR.pdf. GESIDA.

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COMMUNICATION AND DISSEMINATION

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 IP 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 and other European initiatives such as "Pint of Science", which offers entertaining, interesting and important talks about the latest scientific research, in a format accessible to the public.

During the year 2017, the most outstanding news were:

JANUARY

The project "Monitoring and predictive modeling of migraine attacks" of the Neurology groups of the IIS Princesa and the UCM got the first prize for the "Best implemented health ICT project in 2015" in the "ad qualitatem" awards.

MAY

The IIS IP participates again in the scientific dissemination festival "Pint of Science" with two presentations: Biobanks and Science: "All together and for all", given by Mara Ortega-Gómez and Sergio Luquero Bueno (Head and technician of La Princesa Biobank, respectively) and "Hepatitis C: That famous great unknown" by Águeda González Rodríguez (Miguel Servet researcher of Santa Cristina Hospital).

JUNE

Roche together with the IIS IP sponsored the Fist Call "Stop Brain drain" Roche-IIS Princesa, for the hiring of a post-doctoral researcher in any of the Health Research Institutes of the Community of Madrid.

JULY

An innovative project led by Dr. Rafael León was selected in the Caixa impulse 2017 program.

NOVEMBER

For the fifth consecutive year, the IIS Princesa participated in the XVII edition of the Week of Science of the Community of Madrid, which was held between November 6 and 19, 2017

DECEMBER

The IIS Princesa was awarded the European emblem HRS4R that identifies research centres which support a favorable work environment, becoming the first IIS of the Community of Madrid to achieve this recognition.

HR EXCELLENCE IN RESEARCH

RESEARCH AREAS

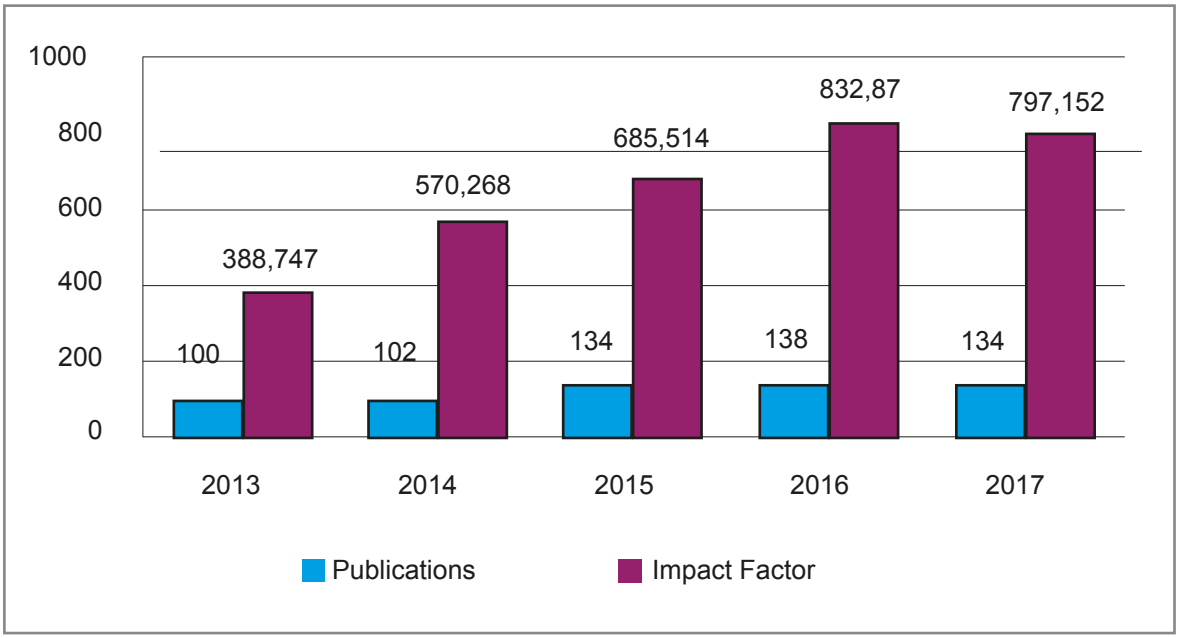
IIS Princesa is structured in 3 research areas, 24 lines and 50 research groups. A summary of the three research areas and their research lines is shown in this section. The evolution of their scientific output in the last five years is presented in a graph including the number of publications per area and their accumulated impact factor.

3 Areas | 24 Research lines | 50 groups | 310 women | 193 men

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

COORDINATOR

Francisco Sánchez Madrid

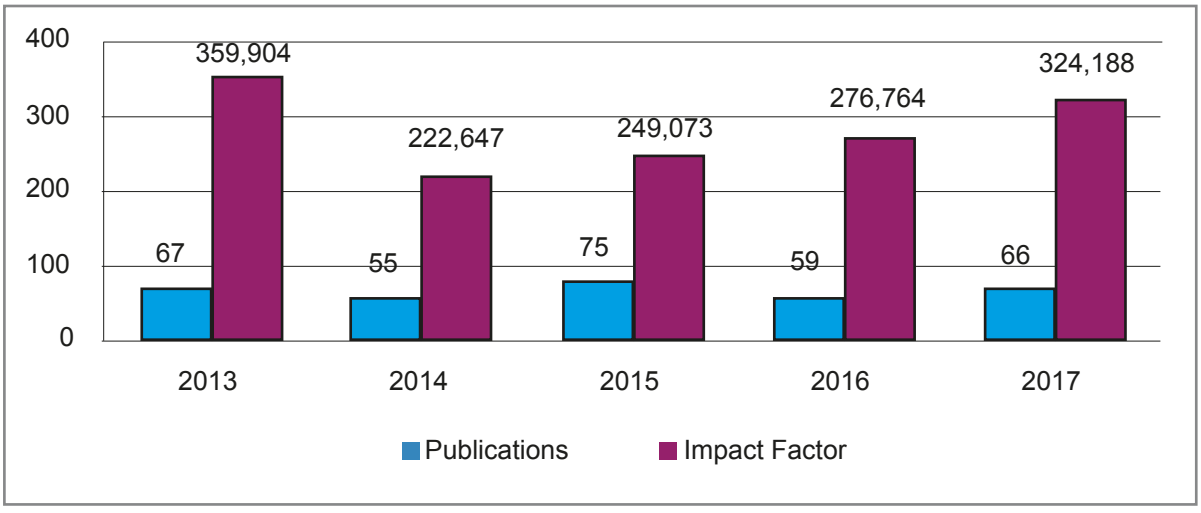


LINE	NAME	DIRECTOR
1.1	Intercellular Communication in the Inflammatory Response	Francisco Sánchez Madrid
1.2	Cellular and molecular responses to Hypoxia	Julián Aragonés López
1.3	Animal models of inflammatory diseases and intercellular signalling	Federico Mayor Menéndez
1.5	Cellular mechanisms and molecular determinants of allergy-based diseases	Carlos Blanco Guerra
1.6	Inflammatory processes in nephrological diseases	José Antonio Sánchez Tomero
1.7	Inflammatory mechanisms in pulmonary diseases	Julio Ancochea Bermúdez
1.8	Inflammatory response in hepatic diseases	Pedro L. Majano Rodríguez
1.9	Mechanisms and mediators of endocrine diseases	Mónica Marazuela Azpiroz
1.10	Children´s development (obesity and growth)	Jesús Argente Oliver
1.11	Metabolic syndrome and vascular risk	Carmelo García Monzón

AREA 2. TRANSLATIONAL NEUROSCIENCE

COORDINATOR

José Luis Ayuso Mateos

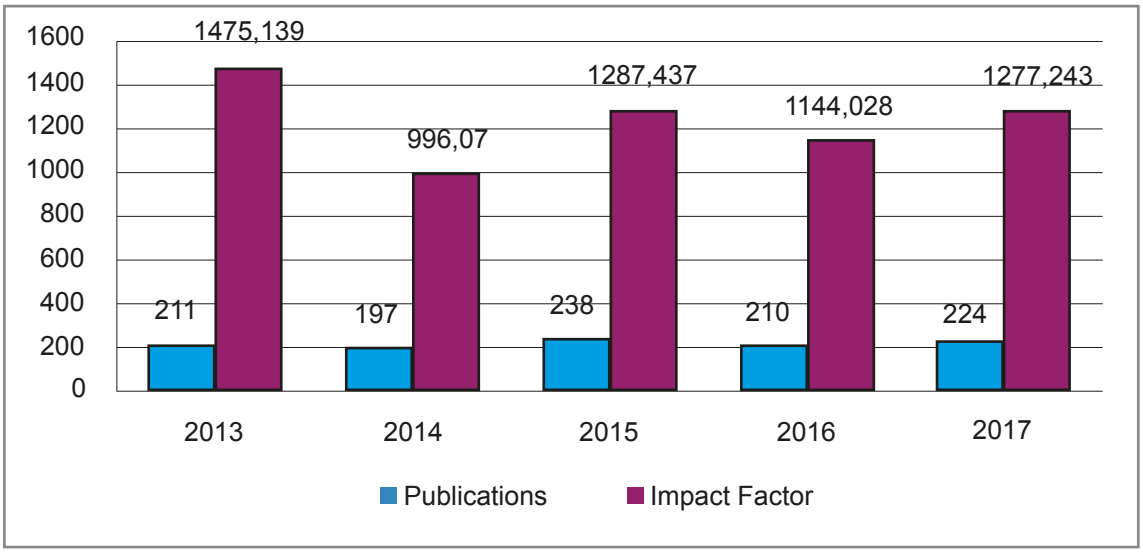


LINE	NAME	DIRECTOR
2.1	Neuropharmacology and neuroprotection	Antonio García García
2.2	Pharmacological Neuroprotection in Neurodegenerative Diseases and Stroke	Manuela García López
2.3	Clinical pharmacology and pharmacogenetics	Francisco Abad Santos
2.4	Diagnostic and therapeutic advances in affective disorders	José Luis Ayuso Mateos
2.5	Neurosurgery of epilepsy	Rafael García de Sola
2.6	Cerebrovascular diseases	José Aurelio Vivancos Mora

AREA 3. ADVANCED THERAPIES AND INDIVIDUALIZED MEDICINE

COORDINATOR

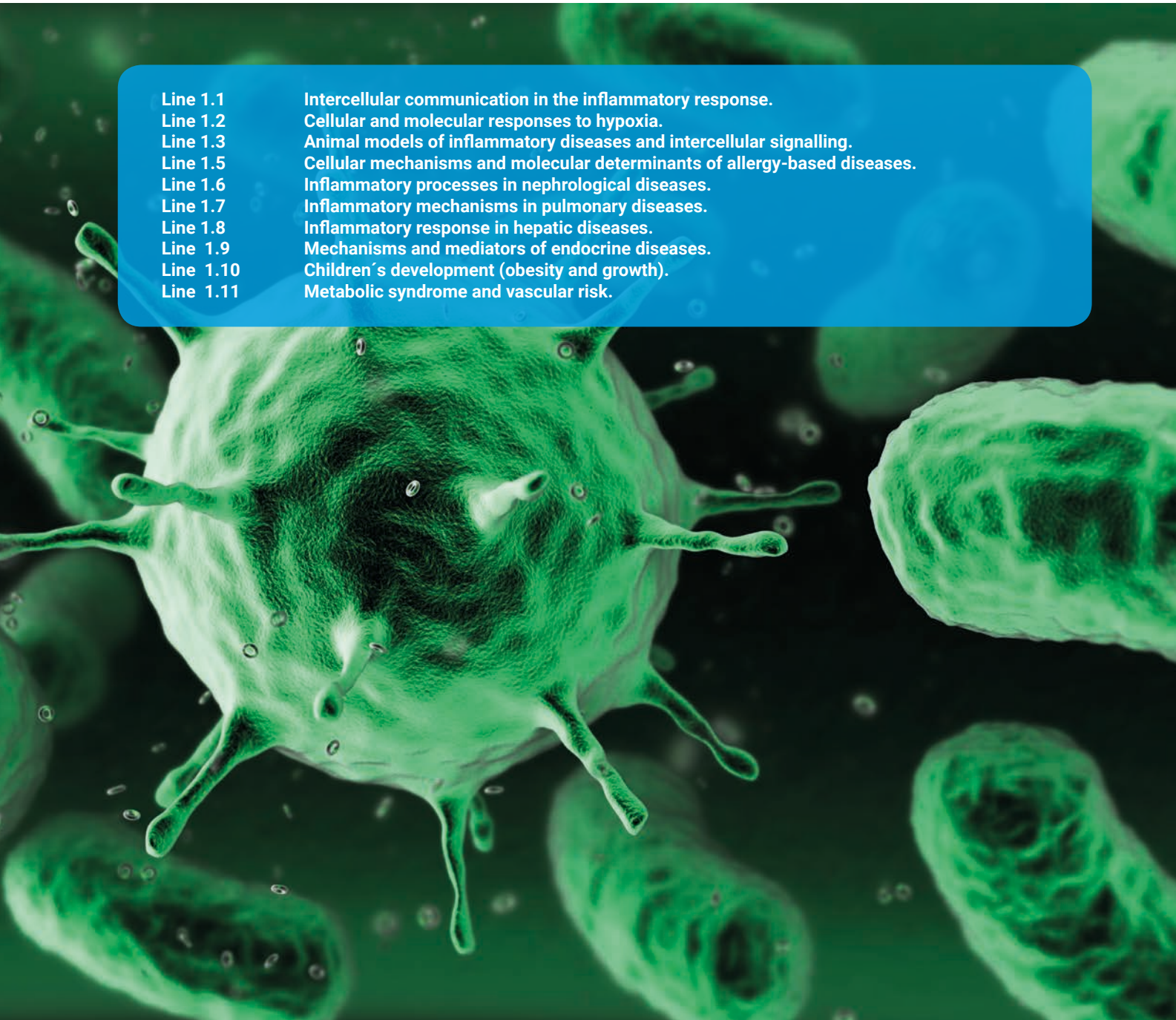
Isidoro González Álvaro



LINE	NAME	DIRECTOR
3.1	Prognostic and predictor markers in autoimmune diseases	Isidoro González Álvaro
3.2	Esophagogastrointestinal inflammatory diseases	Francisco Javier Pérez Gisbert
3.3	Progenitors and cell therapy	Luis Madero López
3.4	Advanced therapies in oncohematology	Juan Luis Steegmann Olmedillas
3.5	Biological, cellular and molecular monitoring in oncohematology	Elena Fernandez Ruiz
3.6	New diagnostic and therapeutic advances in cardiovascular diseases	Fernando Alfonso Manterola
3.7	New therapies in infectious pathologies	Ignacio de los Santos Gil
3.8	Individualized medicine in solid tumors	Ramón Colomer Bosch

AREA 1

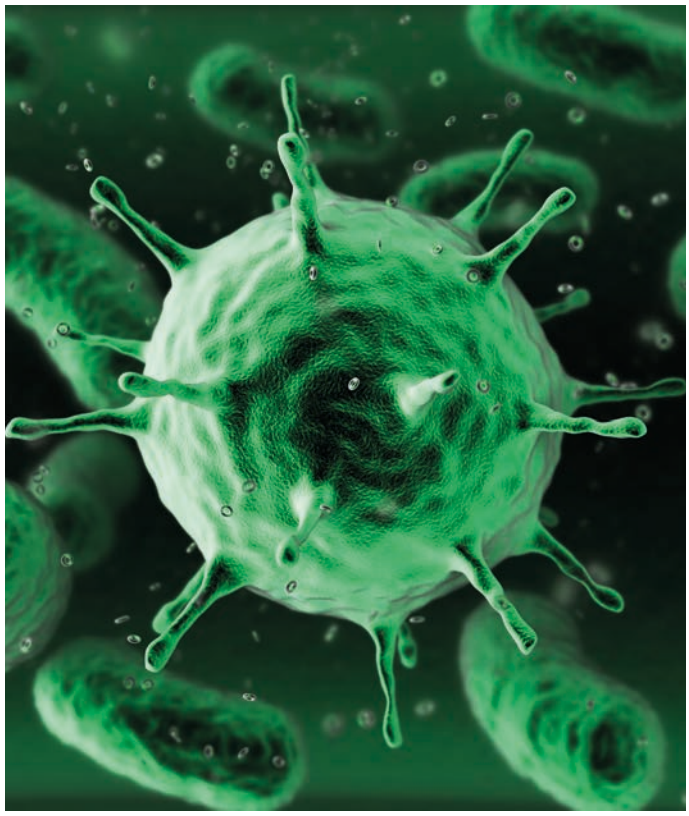
Cellular and molecular etiopathogenic mechanisms in inflammatory and autoimmune diseases



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.

AREA 1

Cellular and molecular etiopathogenic mechanisms in inflammatory and autoimmune diseases



LINE 1.1

Intercellular Communication in the Inflammatory Response

GROUP 1

HEAD OF LABORATORY

Francisco Sánchez Madrid

GROUP MEMBERS

- Arantzazu Alfranca González
- Francesc Baixauli Celda
- Noelia Blas Rus
- Eugenio Bustos Moran
- Danay Cibrián Vera
- Hortensia de la Fuente Flores
- Irene Fernández Delgado
- Lola Fernández Messina
- Cristina Gutiérrez Vázquez
- Noa Beatriz Martín Cofreces
- Olga Moreno Gonzalo
- Vera Pires Ferreira Rocha Perugini
- Marta Esther Ramírez Huesca
- María Laura Saiz Álvarez
- Daniel Torralba Grajales
- María Ángeles Ursa Pecharroman
- María Ángeles Vallejo Rodríguez
- Alicia Vara Vega
- Carolina Villarroya Beltri

RESEARCH INTEREST

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 molecular basis of these autoimmune diseases. These studies will open new avenues for vaccination strategies and novel therapies to treat autoimmune-related diseases.

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GROUP 2

HEAD OF LABORATORY

Esteban Veiga Chacón

GROUP MEMBERS

- Aránzazu Cruz Adalia
- Mónica Torres Torresano

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 infected 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 thousands-fold 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 remi-

niscent of innate immunity. Moreover, transinfected (ti) T cells secrete large amounts of proinflammatory cytokines (IL-6, interferon-γ and, TNF-α), 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. •1 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. •2 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. •3 We are expanding our knowledge in transinfection as a mechanism to capture/destroy/present bacterial antigens to B cells. •4 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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Granted 2017:

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PUBLICATIONS (1)

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GROUP 3

HEAD OF LABORATORY

María Yáñez Mó

GROUP MEMBERS

- Soraya López Martin
- Carla Mazzeo
- Henar Suarez Montero

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, focusing on the characterization of tetraspanins intracellular connections. Starting with a high throughput proteomic screen, we thereafter study the relevance of the molecular interactions found, in cellular models for fundamental processes of the biology of the immune system (leukocyte migration, immune synapse formation), HIV infection or tumor cell motility. Intracellular connections of tetraspaninenriched microdomains led us also to the field of extracellular vesicle (EV) research, since tetraspanin proteins are among the most abundant proteins on EV. Extracellular vesicles, including microvesicles, ectosomes, shedding vesicles, microparticles and exosomes, represent a novel mechanism of intercellular communication as vehicles for intercellular transfer of functional membrane and cytosolic proteins, lipids, and RNAs. In our group, we aim at profiting from all the tools against tetraspanin molecules and their associated partners (metaloproteinases and adhesion receptors) we have in the lab to study their functional role in the biogenesis, the regulation of their tropism, adhesion and uptake, and in the function of EVs in the target cells. This information will be critical for the optimization of those therapies based on EVs, since it will reveal novel therapeutic targets to block their secretion, diminish their metastatic or angiogenic capacities, or augment their stability and immunoregulatory potential. We are also pursuing the use of tetraspanin-based tools in the design of exosome detection devices and synthetic exosome mimetics.

MAJOR GRANTS

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Granted 2017:

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PUBLICATIONS (5)

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GROUP 4

HEAD OF LABORATORY

Miguel Vicente Manzanares

GROUP MEMBERS

- Rocío Aguilar Cuenca
- Cristina Delgado Arévalo
- Lidia Feo Lucas
- Alba Juanes García
- Álvaro Ortega Carrión

RESEARCH INTEREST

The actin cytoskeleton plays a fundamental role in cellular processes such as adhesion, migration and proliferation. Actin plasticity is organized by different actin-binding proteins with different kinetic and organizing properties. Our group is interested in the regulation of non-muscle myosin II as a major integrator of mechanical forces and organizer of actin in migrating cells. We have recently unveiled a role for novel phosphorylations of the myosin regulatory light chain in controlling the function of myosin II in the context of tumor cells. Since this phosphorylation directly depends on the expression and function of EGF receptors, this mechanism represents a paradigm shift in the control of mechanics in pathological scenarios in which EGF plays a role, e.g. breast cancer.

We have also elucidated a major role for NMII-B, a high-load and low-speed isoform of myosin II, in T cell activation. NMII-B controls the shape of the interaction between a T cell and an antigen-presenting cell and is expressed in an activation-dependent manner. Genetic removal of this isoform causes aberrant contact between the T cell and the antigen-presenting cell, leading to deficient T cell activation.

We have also collaborated with the group of Dr. Cecilia Muñoz to reveal the role of actomyosin contraction as a crucial mediator of the side effects (mainly bleeding and pleural effusion) of dasatinib in leukemic patients. Finally, we have collaborated with the Rheumatology service to unveil the role of NMII-B in ectopic activation of T cells. Our preliminary data suggest that NMII-B could be overrepresented in autoimmune T cells, suggesting a possible scenario in which NMII-B expression could be a diagnostic marker of severity or a prognostic marker of response to treatment.

MAJOR GRANTS

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GROUP 14

HEAD OF LABORATORY

María de las Nieves Navarro Lobato

GROUP MEMBERS

- Candelas Álvarez Salamero

RESEARCH INTEREST

The incidence of inflammatory and autoimmune diseases has increased in the last 30 years particularly among developed countries, creating a demand for development of new therapies to treat these diseases. Interleukin 23 (IL-23) is a pro-inflammatory cytokine that plays a fundamental role in several inflammatory diseases such as Crohn's disease, ulcerative colitis and psoriasis. Some of the pathological consequences of IL-23 have been associated with its ability to activate the JAK kinases and the STAT family of transcription factors, promoting the production of interleukin 17 (IL-17) in various subsets of lymphocytes, although the specific molecular mechanisms by which IL-23 contributes to the development of these diseases remain largely unknown. The interest of the laboratory is focused on the comprehensive study

of signalling pathways regulated by IL-23, particularly in phosphorylation events, in order to identify key molecular mechanisms in the development of IL-23-related diseases. The IL-23-regulated signalling cascade is being examined in the laboratory using a large-scale quantitative phosphoproteomics approach in a target population of IL-23 action: the Th17 CD4 T lymphocytes. This strategy allows the simultaneous identification and quantification of thousands of phosphorylations, and provides evidence of IL-23-regulated kinase-substrate networks. This global analysis will expose previously unknown IL-23-regulated phosphorylations whose function will be examined in different experimental systems, including animal models of IL-23-dependent psoriasis. Some of the evidences of the critical role of IL-23 in human disease derive from genomewide association studies (GWAS) showing that a polymorphic variant receptor IL-23 (IL-23R) confers strong protection against inflammatory bowel diseases and psoriasis. This polymorphism involves a single amino acid change in the coding sequence of IL-23R. The study of the impact of this allelic variant in the signalling cascade and the transcriptional program regulated by IL-23 will be used as a strategy to identify the molecular mechanisms involved in inflammatory diseases. The ultimate aim of our studies is to generate the knowledge about IL-23 signalling pathways required to identify novel therapeutic targets for the development of new treatments for IL-23-mediated diseases.

MAJOR GRANTS

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PUBLICATIONS (2)

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GROUP 56

HEAD OF LABORATORY

Ana Carmen Urzainqui Mayayo

GROUP MEMBERS

- Marina Espartero Santos
- Rafael González Tajuelo
- Javier Silván Montoya

RESEARCH INTEREST

P-Selectin Glycoprotein Ligand-1 (PSGL-1) is a leucocyte receptor that interacts with P-, E- and L-Selectins and is responsible for the initial steps of leukocyte extravasation to the sites of inflammation. Our lab 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 have recently described that PSGL-1 KO mice develop a progressive autoimmune disease similar to systemic sclerosis (SSc). In addition, we have observed that the absence of P-Selectin, main ligand of PSGL-1, develop an autoimmune syndrome similar to human-lupus, with generation of anti-dsDNA autoantibodies, deposits of immunecomplexes in skin and kidney and hypersensitivity to UV light, characteristics that could match with systemic lupus erithematosus (SLE). Interestingly, we have observed that P-Selectin and PSGL-1 KO aged females develop pulmonary arterial hypertension (PAH), the most severe form of connective tissue-related autoimmune diseases due to increased levels of AngiotensinII and endothelial dysfunction with low production of NO. 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 in SSc patients and that 95% or more circulating pDCs expressing ADAM8 associate with the presence of SSc. (Silván J et al, J Invest Dermatol, 2018, unswering to reviewers). Lupus patients have reduced expression of P-selectin in skin vessels and reduced expression of PSGL-1 in neutrophils, correlating with disease activity.

Main research lines:

1. Study of PSGL-1 signaling and functional role in neutrophils, B cells and monocytes of WT, PSGL-1 KO and P-Selectin KO mice. We will analyze the signals elicited by PSGL-1 engagement and their implication in the function of B cells, neutrophils and monocytes.
2. Study of PSGL-1 signaling and functional role in neutrophils, B cells and monocytes of healthy controls and patients of SSc and Lupus. We will analyze the implication of PSGL-1 in the function of B cells, neutrophils and monocytes and the possible alterations that could contribute to SSc and lupus pathogenesis.
3. Study of the pattern of microRNA expression in the serum of healthy donors and patients with SSc and lupus.

MAJOR GRANTS

- Urzainqui Mayayo, Ana Carmen. Interacción PSGL-1/p-Selectina: homeostasis del sistema inmune, vascular y reproductor en ratones. Relevancia en el desarrollo de HAP y enfermedades autoinmunes en humanos. PI14/01698. ISCIII. 2015-2017.

Granted 2017:

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PUBLICATIONS (2)

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LINE 1.2

Cellular and molecular responses to Hypoxia

GROUP 9

HEAD OF LABORATORY

Julián Aragonés López

GROUP MEMBERS

- Ainara Estibaliz Elorza Peregrina
- Esther Fuertes Yebra
- Florinda Meléndez Rodríguez
- Ángel Ordoñez Navadijo
- Manuel Ortiz de Landázuri Busca
- Inés Soro Arnaiz
- María del Mar Torres Capelli
- Qilong Oscar Yang Li

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 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 HIFs en patología pulmonar asociada a las vías respiratorias. SAF2016-76815-R. MINECO. 2017-2019.

PUBLICATIONS (1)

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GROUP 7

HEAD OF LABORATORY

Antonio Martínez Ruiz

GROUP MEMBERS

- Juan Daniel Cabrera García
- Pablo Hernansanz Agustín
- Tamara Oliva Taravilla

RESEARCH INTEREST

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

- Hypoxia signalling by reactive oxygen and nitrogen species
- Oxidative post-translational modifications and redox proteomics

1. Hypoxia signalling by reactive oxygen and nitrogen species

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 can function as a mitochondrial Na+/H+ antiporter, and that this functional shift of complex I is a key step in the superoxide burst. We continue investigating how mitochondrial Na^{+}/Ca^{2+} exchanger (NCLX) is involved in this superoxide burst, which proposes NCLX as a pharmacological target in the treatment of diseases in which hypoxia and reactive oxygen species production are present.

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 (manuscript in preparation), ebselen-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 normofunctional valves from heart donors.

MAJOR GRANTS

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GROUP 8

HEAD OF LABORATORY

María Josefa Calzada García

GROUP MEMBERS

- Cintia Fernández Pérez
- David Labrousse Arias

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 matricellular 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.

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

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GROUP 10

HEAD OF LABORATORY

Susana Cadenas Álvarez

GROUP MEMBERS

- Irene Álvarez Guerra
- Guillén Reyes, Jesús
- Patricia Sánchez Pérez

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 (H_2O_2) 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

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PUBLICATIONS (1)

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LINE 1.3

Animal models of inflammatory diseases and intercellular signalling

GROUP 11

HEAD OF LABORATORY

Federico Mayor Menéndez

GROUP MEMBERS

- Álvaro Caballero Lombraña
- Sofía Cabezudo Violero
- María Margarida Martins Neves
- Julia Palacios García
- Paula Ramos Barbeito
- Catalina Ribas Núñez
- Susana Rojo Berciano

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

MAJOR GRANTS

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GROUP 12

HEAD OF LABORATORY

Manuel Fresno Escudero

GROUP MEMBERS

- Ruth Álvarez Díaz
- Raquel Álvarez Velilla

- Alicia Arranz de Miguel
- Beatriz Barrocal López
- Francisco Callejas Hernández
- Natalia Cuesta Rubio
- María de los Ángeles de Chorro y de Villa-Ceballos
- Javier Galán Martínez
- Nuria Girones Pujol
- Pablo Gómez del Arco
- Marta Jiménez Martínez
- Alba María Jiménez Segovia
- María del Carmen Maza Moreno
- Cristina Poveda Cuevas
- Konstantinos Stamatakis Andriani

RESEARCH INTEREST

We are analysing the involvement of Toll-like receptors (TLR)/NFAT/Cyclooxygenase (Cox)-2/prostaglandins (PGs) in the immune system and inflammatory pathologies as Obesity, Cancer and Sepsis. PGs trigger activation and migration of T lymphocytes, controlling the duration of their interaction with antigen presenting cells. Macrophage migration is induced by PGs due to activation of p110-PI3K by PG receptors. PGF2α negatively regulates adipocyte differentiation through the transcription factor NFAT. Moreover, NFATc4 deficiency induces obesity in mice indicating a key role in obesity and fatty acid metabolism.

Cox2 Inhibitors reduce colorectal cancer but have cardiovascular risks. As an alternative therapeutic approach, we have analysed genes regulated by Cox2 and select those that could provide a protooncogenic advantage to form tumours and/or metastasize. Among those, we identified, mPGES1, PMEPA1 and DUSP10 as Cox2 induced molecules in ovarian or colon cancer. mPGES1 is involved in increased growth and induced through a PGF2α/Egr-1 mechanism. DUSP10 controls stress response to serum deprivation and confluence arrest whereas PMEP1A induces Epithelial Mesenchymal Transition. DUSP10 inhibits p38 mitogen activated protein kinase (MAPK) activation, whereas PMEPA1 inhibit phosphorylation of SMAD1,5,8 by TGFβ.

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 model that differ depending of 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- and play a negative role in the infection through repression of the NADPH oxidase.

In the near future, we will continue the studies on the role of Cox-2/PGF2α and different NFAT family members on the differentiation of adipocytes and how this translate into obesity and insulin resistance. Also, apart from finishing the DusP10 and PMEPA1 roles on ovarian and colon Cancer, we will analyze the role of other Cox-2/NFAT dependent genes we have already identifies on colon cancer and also in Intestinal inflammation. Finally in T. cruzi we will continue the work 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.

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GROUP 13

HEAD OF LABORATORY

Petronila Penela Márquez

GROUP MEMBERS

- Adolfo Javier Molejón García
- Clara Reglero Gómez
- Verónica Rivas Guerrero

RESEARCH INTEREST

Breast cancer is one of the most common and heterogeneous cancers, with ductal carcinomas representing 80% of breast tumors. Based on distinctive molecular profiling, ductal carcinomas are classified in order of worse prognosis as estrogen-positive luminal A and luminal B, ERBB2-positive or basal-like (ER-, PR-, ERBB2-negative) tumors. Besides oncogenic drivers underpinning breast ductal carcinomas (PI3K, Ras, mutations in p53), alteration of relevant signaling nodes can critically modulate cancer progression-related cellular networks to strength key tumoral hallmarks as aberrant proliferation, angiogenesis or invasion and metastasis. Some of these molecular nodes integrate multiple upstream inputs and elicit diverse downstream outputs through the modulation of posttranslational modifications, including phosphorylation, ubiquitination or acetylation of manifold regulatory and effector proteins. These nodes work as molecular switches that cooperate with oncogenic-signaling routes or act in normal signaling compensatory pathways in order to trigger transformation or to cope with intrinsic tumor-derived vulnerabilities. Our studies indicate that the serine/threonine kinase GRK2 is emerging as a relevant modulator of oncogenic signaling modules by its ability to impinge the ubiquitination and acetylation of manifold proteins in transformed cells. GRK2 stimulates the activity of the E3 ligase Mdm2 and the deacetylase HDAC6, which are key players in cellular transformation by means of the inhibition of tumor suppressors (p53) and modulation of molecules involved in cell-cycle control, angiogenesis, stress responses or metastatic progression. Indeed, concurrent up-regulation of GRK2, Mdm2 and HDAC6 emerges as a functional module characteristic of luminal breast cancer cells that contributes to cellular proliferation and survival. GRK2 also attenuates the ATM signaling cascade, a central sensor of DNA damage and metabolic stress, which is also engaged in the regulation of Mdm2 and p53. In addition, our data show that endothelial GRK2 downregulation is a relevant event in the angiogenic switch triggered by tumor cells by favoring a permissive microenvironment for tumor growth and metastasis.

Our main goals are to define the functional intertwinement of Mdm2/p53/HDAC6 in transformed epithelial cells and in the behavior of normal stromal cells (endothelial cells, fibroblasts), to characterize the regulation of this signaling module

by GRK2 under different tumor-environmental stresses and their consequences on breast tumor progression. Different integrated responses that contribute to tumor malignancy such as cellular invasiveness, cellular senescence, regulation of cell cycle dynamics or stromal remodelling are analyzed. We are addressing how the regulation of Mdm2/HDAC6 by GRK2 impacts on cell cycle progression and the metabolic homeostasis of breast cells when genome integrity is compromised by nutrient overload, genotoxic agents or oxidative stress. We are also characterizing the angiogenic response promoted by this signaling module and the molecular mechanisms involved in the concurrent and opposite changes of GRK2 in the epithelial (up-regulation) and vascular endothelial (down-modulation) components of breast tumors, responsible for the intra-tumor vascular remodeling.

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GROUP 17

HEAD OF LABORATORY

Cristina Murga Montesinos

GROUP MEMBERS

- Alba Concepción Arcones
- Marta Cruces Sande
- Rocío Vila Bedmar

RESEARCH INTEREST

Obesity and insulin resistance (IR) are major health problems that have reached epidemic proportions worldwide. The inflammatory components of these diseases are being recently unveiled as key factors in both the aetiology and the development of these diseases. Cell signalling pathways that serve as a nodal points interconnecting pathological insults and metabolic signals to inflammatory routes are thus a main focus of research for the mechanistic basis of these pathologies to be fully understood. In this line, the signaling hub of the G protein-coupled receptor kinase 2 (GRK2) emerges as a clear point of control in the metabolic, stress and inflammatory network of routes controlling the initiation and progress of these diseases. Given the lack of selective and potent inhibitors for this kinase, our group has focused on proof of concept studies in genetically-modified animal models.

In this context, our group pursues four main lines of investigation.

1. Preliminary evidence suggests that specific GRK2 effects in macrophages and other inflammatory cells may contribute to the control of insulin sensitivity, adiposity and obesity in human samples and animal models of these diseases. We will study the influence of changes in GRK2 expression levels specifically in macrophages infiltrating white adipose tissue and other insulin-sensitive organs during fat mass accretion in the development of obesity-associated weight gain, adiposity and IR.

2. We will work on the validation of GRK2 as a novel therapeutic target in the development of obesity and/or IR using a tamoxifen-inducible mice model that allows for the deletion of this protein once the pathology has been established. We will study whether GRK2 deletion not only prevents but can also revert weight gain and IR and characterize the main tissues and cellular functions by which GRK2 could exert these effects as well as the molecular mechanisms involved.

3. We will analyze the importance of the GRK2 signaling node and changes in its levels or activity in the development of hepatic steatosis in the form of non alcoholic steatohepatitis (NASH) and its further development into more complex pathologies such as non alcoholic fatty liver disease (NAFLD) that involve liver inflammation, dysfunction and fibrosis. We will use mice models of these diseases (including high fat diet feeding and hepatic damage models) in order to test the influence and importance of the GRK2 node in the genesis or progression of these pathologies paying particular attention to the inflammatory component (infiltrates, M1/M2 polarization, secretome,...).

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GROUP 18

HEAD OF LABORATORY

Miguel Ángel Íñiguez Peña

GROUP MEMBERS

- Ángel Bago Plaza
- Ana Renshaw Calderon

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, 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.

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LINE 1.5

Cellular mechanisms and molecular determinants of allergy-based diseases

GROUP 20

HEAD OF LABORATORY

Carlos Blanco Guerra

GROUP MEMBERS

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

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. Nowadays, allergen specific immunotherapy is the only way to modify the natural course of allergic respiratory diseases. Meanwhile, food allergy is a rising problem, due to both the potential severity of reactions and to its great impact on patient quality of life. In this context, 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. Results are now being analysed.
- 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 associated 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 the San Pablo C.E.U. University) and an original paper has recently been submitted to the Journal of Allergy and Clinical Immunology, the main journal on the field of allergic diseases. On the other side, a study focused on T-cell response repertoire to profilin, in collaboration with ALK-Denmark, has been performed and its results recently accepted for publication in Allergy (2017 Nov 9. doi: 10.1111/all.13351. PMID: 29121407).

- Finally, Dr. Daschner continues with its productive research lines on Anisakis allergy and allergen characterization. Application of Evolutionary Medicine and Bioinformatic studies has prompted insights into characteristics of Anisakis allergen recognition depending on phylogenetic analysis. Further, an evolutionary analysis of dampness and mold induced symptoms has facilitated interpretation of not only allergic symptoms, but also non-respiratory symptom complexes. These results have been published in several original articles in peer-reviewed journals. The edition of a new volume of Evolutionary Medicine includes also own research on general principles in this field as well as aspects of diet and inflammation from an evolutionary point of view.

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GROUP 15

HEAD OF LABORATORY

María Dolores Ibáñez Sandín

GROUP MEMBERS

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

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 SEAIC 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 ina paediatric populationclinical 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.

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LINE 1.6

Inflammatory processes in nephrological diseases

GROUP 21

HEAD OF LABORATORY

José Antonio Sánchez Tomero

GROUP MEMBERS

- Abelardo Isaac Aguilera Peralta
- Vicente Álvarez Chiva
- Guillermina Barril Cuadrado
- Carmen Bernis Carro
- Antonio Carlos Fernández Perpén
- Martín Giovanni Giorgi González
- Isabel Herráez Jiménez
- Almudena Núñez Sánchez
- Borja Quiroga Gili
- Pablo Ruano Suarez
- Laura Salanova Villanueva
- María Carmen Sánchez González

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, Tamoxifen, 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 disea-

se. 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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- Barril Cuadrado, Guillermina. Estudio del dializador de Triacetato de celulosa. Comportamiento in vivo en hemodiafitración on-line. Nipro S.A.

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González Mateo, Guadalupe, Gallardo, Juan Manuel, Sánchez Tomero, José Antonio, Majano Rodríguez, Pedro Lorenzo, Flores-Maldonado, Elizabeth, Paniagua, Ramón, Selgas, Rafael, López Cabrera, Manuel, Aguilera Peralta, Abelardo Isaac. Pharmacological Preservation of Peritoneal Membrane in Peritoneal Dialysis. Some Special Problems in Peritoneal Dialysis. ISBN: 978-95-3512-599-0

Salanova Villanueva, Laura, Pavone, Mario A, González Parra, Emilio, Sánchez Tomero, José Antonio, Aguilera Peralta, Abelardo Isaac. The FGF23-Klotho Axis and Cardiovascular Diseases in Peritoneal Dialysis Patients. Peritoneal Dialysis: Practices, Complications and Outcomes. pp. 97 - 128. ISBN: 978-15-3610-515-5

Riobó, Pilar, Ortiz, Alberto, Barril Cuadrado, Guillermina. Capítulo 53. Nutrición En Enfermedades Renales. Tratado de nutricion. ISBN: 978-84-9110-194-9

CLINICAL TRIAL

PRINCIPAL RESEARCHER: BARRIL CUADRADO, GUILLERMINA

Estudio doble ciego, aleatorizado, controlado con placebo para evaluar el efecto de SNF472 en la progresión de la calcificación cardiovascular además del tratamiento de referencia en pacientes con nefropatía terminal (NT) sometidos a hemodiálisis (HD). Laboratorios Sanifit SNFCT2015-05

EudraCT: 2016-002834-59

PRINCIPAL RESEARCHER: AGUILERA PERALTA, ABELARDO

Ensayo clínico cruzado y aleatorizado sobre el efecto de resincolestiramina en la absorción intestinal de nuevas

toxinas urémicas en pacientes con insuficiencia renal crónica en hemodiálisis. Resinfenol

EudraCT: 2017-001899-32

PRINCIPAL RESEARCHER: QUIROGA GILI, BORJA

Estudio posautorización de seguridad multicéntrico y no intervencionista de 6 años de duración realizado en pacientes a los que se ha recetado JINARC® debido a poliquistosis renal autosomática dominante. Otsuka Pharmaceuticals Europe Ltd 156-12-299 / OPE-TOL-2017-01

PRINCIPAL RESEARCHER: ALVAREZ CHIVAS, VICENTE

Estudio observacional y multicéntrico de farmacovigilancia (NI-PASS) para monitorizar las reacciones adversas relacionadas con el tratamiento entre los pacientes con insuficiencia renal crónica (IRC) que reciben, mediante administración subcutánea (s.c.), Binocrit® o Epoetin Alfa Hexal®. Hexal AG HX575-507/HEX-EPO-2017-01

LINE 1.7

Inflammatory mechanisms in pulmonary diseases

GROUP 22

HEAD OF LABORATORY

Julio Ancochea Bermúdez

GROUP MEMBERS

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

RESEARCH INTEREST

Inflammation and reparative process in lung diseases. Chronic obstructive pulmonary disease (COPD). Apnea-Hypopnea Syndrome. Idiopathic pulmonary fibrosis (IPF). Inmunopathogeny. 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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- Zamora García, Enrique Domingo. Estudio de los factores de respuesta a hipoxia (HIF) en enfermedad pulmonar obstructiva crónica (EPOC) para la identificación de biomarcadores no invasivos diagnósticos y pronósticos. SEPAR. 2014-2017.
- Girón Moreno, Rosa María. Estudio del papel de los glicosaminoglicanos celulares de epitelio pulmonar en el desarrollo de infecciones asociadas a fibrosis quística. SEPAR. 2015-2017.
- Soriano Ortiz, Joan B. TackSHS: Tackling secondhand smoke in Europe: assessment of SHS exposure according to policies, attributable disease and economic burden, and impact of interventions for reducing the exposure. TackSHS: 681040. Comisión Europea. 2015-2019.
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- Gómez Punter, Rosa Mar. Utilidad para valoración pronostica de mortalidad del handgrip en pacientes con enfermedad pulmonar obstructiva crónica. 2017-2019.
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- Gómez Punter, Rosa Mar. DECAF score como predictor de mortalidad y su relación con el cuestionario de calidad de vida CAT en pacientes con diagnóstico de EPOC. 2017.

Granted 2017:

- Ancochea Bermudez, Julio. 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.

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: VALENZUELA, CLAUDIA

Estudio aleatorizado, doble ciego y controlado con placebo para evaluar la eficacia y la seguridad del tratamiento con nintedanib durante 52 semanas en pacientes con enfermedad pulmonar intersticial fibrosante progresiva (EFI-FP). Boehringer Ingelheim International GMBH 1199.247

EudraCT: 2015-003360-37

PRINCIPAL RESEARCHER: VALENZUELA, CLAUDIA

Ensayo clínico doble ciego, aleatorizado, de grupos paralelos y de 24 se manas para evaluar la eficacia y seguridad de nintedanib oral administrado de forma concomitante con sildenafilo oral, en comparación con el tratamiento con nintedanib en monoterapia, en pacientes con fibrosis pulmonar idiopática (IPF) y afectación avanzada de la función pulmonar. Boehringer Ingelheim España, S.A. 1199.36

EudraCT: 2015-002619-14

PRINCIPAL RESEARCHER: VALENZUELA, CLAUDIA

Estudio retrospectivo para evaluar el perfil clínico de pacientes con fibrosis pulmonar idiopática, y no tratados, con pirfenidona en España; Estudio Aeras. Sociedad Española de Neumología y Cirugía Torácica SEP-PIR-2016-01 (ML30155)

PRINCIPAL RESEARCHER: LANDETE RODRIGUEZ, PEDRO

Estudio en fase III, multicéntrico, aleatorizado y doble ciego de una sola dosis de S-033188 en comparación con placebo o 75 mg de oseltamivir administrado dos veces al día durante 5 días a pacientes con gripe con alto riesgo de padecer complicaciones gripales. SHINOGI LTD 1602T0832 (VHP)

EudraCT: 2016-002688-32

PRINCIPAL RESEARCHER: LANDETE RODRIGUEZ, PEDRO

Estudio transversal para conocer las necesidades clínicas no cubiertas en asma grave. (Estudio ENEAS). Sociedad Española de Neumología y Cirugía Torácica SEP-COR-2017-01

PRINCIPAL RESEARCHER: CISNEROS SERRANO, CAROLINA

Nuevo Estudio observacional, longitudinal en pacientes con un diagnóstico o sospecha de diagnóstico de asma y/o EPOC para describir las características de los pacientes, patrones de tratamiento y carga de la enfermedad con el paso del tiempo para identificar fenotipos y endotipos asociados a resultados diferenciales que pueden respaldar el desarrollo futuro de estrategias de tratamiento personalizadas. Astrazeneca AB D2287R00103/AZA-SAL-2016-01

EudraCT: EPA-SP

PRINCIPAL RESEARCHER: CISNEROS SERRANO, CAROLINA

Estudio observacional para describir la prevalencia de asma grave en centros hospitalarios españoles. Glaxosmithkline España, S.A. PAGE

PRINCIPAL RESEARCHER: GIRON MORENO, ROSA-MARIA

Ensayo clínico con enmascaramiento doble, multicéntrico y controlado con placebo para investigar la eficacia y seguridad de 12 meses de terapia con Promixin® inhalado (colistimetato de sodio) para el tratamiento de pacientes con bronquiextasia no debida a fibrosis quística con infección crónica por Pseudomonas aeruginosa (P. aeruginosa). Zambon S.P.A. Z7224L01

EudraCT: 2015-002743-33

LINE 1.8

Inflammatory response in hepatic diseases

GROUP 24

HEAD OF LABORATORY

Pedro Lorenzo Majano Rodríguez

GROUP MEMBERS

- Andrea Cristina Garrido Guitart
- Francisca Molina Jiménez

RESEARCH INTEREST

Hepatotropic viruses, including Hepatitis C virus (HCV), chronically infect millions of people worldwide. Infection can lead to fibrosis, cirrhosis and hepatocellular carcinoma, and is the major reason for liver transplantation. Current standard-of-care therapy against chronic hepatitis C, pegylated IFN-α in combination with ribavirina and HCV NS3/4A protease inhibitor, is frequently not effective depending on viral and host factors.

In our group we are interested in understanding how HCV interacts with target cells, with particular emphasis on the role of the cellular factors implicated in different steps of the viral life cycle including entry, assembly, egress and spread. Our recently published studies have determined that HCV egress is a clathrin-dependent process. We are studying 1) cellular factors implicated in HCV entry in highly polarized cultures; 2) the role of apolipoproteins in HCV spread; 3) changes in hepatocyte proteome after HCV infection. Finally, we are also exploring whether dendrimer-based therapies could be used to inhibit HCV infection.

In overall, these studies may provide new insights for our understanding of virus-host interactions and the molecular mechanisms underlying hepatotropic viruses-related pathogenesis of progressive liver disease. We believe that this ambitious project could identify molecular targets involved in HCV infection and it could improve the management of the chronic infected patients.

MAJOR GRANTS

Granted 2017:

- Majano Rodríguez, Pedro Lorenzo / Cecilio Santander Vaquero. 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.

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Sepúlveda-Crespo, Daniel, Jiménez, José Luis, Gómez, Rafael, De La Mata, Francisco Javier, Majano Rodríguez, Pedro Lorenzo, Muñoz-Fernández, Ma Ángeles, Gastaminza, Pablo. **Polyanionic carbosilane dendrimers prevent hepatitis C virus infection; in cell culture.** Nanomed.-Nanotechnol. Biol. Med. 13(1):49-58. 2017. PMID: 27562210. IF: 5,720. DOI: 10.1016/j.nano.2016.08.018. http://dx.doi.org/10.1016/j.nano.2016.08.018.

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González Mateo, Guadalupe, Gallardo, Juan Manuel, Sánchez Tomero, José Antonio, Majano Rodríguez, Pedro Lorenzo, Flores-Maldonado, Elizabeth, Paniagua, Ramón, Selgas, Rafael, López Cabrera, Manuel, Aguilera Peralta, Abelardo Isaac. Pharmacological Preservation of Peritoneal Membrane in Peritoneal Dialysis. Some Special Problems in Peritoneal Dialysis. ISBN: 978-95-3512-599-0

GROUP 23

HEAD OF LABORATORY

Luisa Consuelo García Buey

GROUP MEMBERS

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- María Jesús Borque Iñurrita
- Leticia González Moreno
- Jorge Mendoza Jiménez-Ridruejo
- Ricardo Moreno Otero
- Yolanda Real Martínez
- María Paloma Sanz Cameno

RESEARCH INTEREST

During last years our research group has been particularly focused on identifying non-invasive prognostic biomarkers of chronic liver diseases (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. Therefore, 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, clue 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's 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 TEMs regulation can lead to important therapeutic advances. Interestingly, in the meantime, other authors described that TEMs might work as useful cellular diagnostic and prognostic biomarker for HCC.

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

MAJOR GRANTS

- García Buey, Luisa Consuelo. Estudios inmunológicos. Proyecto Hepatitis C: Impacto del tratamiento con nuevos antivirales. EHD15PE94B_/2016. CIBERehd. 2016-2017.

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: MENDOZA JIMENEZ-RIDRUEJO, JORGE

Registro informatizado de pacientes con patologías pancreáticas en España (Registro RIPPE). Asociación Española de Pancreatologia (AESPANC) REGISTRO RIPPE

LINE 1.9

Mechanisms and mediators of endocrine diseases

GROUP 25

HEAD OF LABORATORY

Mónica Marazuela Azpíroz

GROUP MEMBERS

- Marta Araujo Castro
- Sandra Campos Mena
- Elena Carrillo Lozano
- Carlos Ferrero Manauta
- Isabel Huguet Moreno
- Rebeca Martínez Hernández
- Carmen Melina Morencos Pinedo
- Andrés Pérez Casas
- Ana María Ramos Levi
- Ana Rodríguez Muñoz
- Miguel Antonio Sampedro Núñez
- Ana Serrano Somavilla

RESEARCH INTEREST

Our current and future work involves different research fields in endocrine diseases. We are studying the role of of immunoregulatory molecules in patients with autoimmune thyroid diseases (AITD) including Hashimoto's thyroiditis (HT), Graves' disease (GD) and Graves' ophtalmopathy (GO). During the last years, we have discovered that patients with AITD have altered populations of regulatory T cells (Treg), augmented Th17 cells, diminished levels of plasmacytoid dendritic cells, and a defective expression of theTr1 regulatory cells. We are also studying additional regulatory molecules such as VIP in these patients. These abnormalities in immunoregulatory molecules may contribute to the pathogenesis and/or auto perpetuation of AITD.

We are also studying the expression of miRNAs (miRNAome) in samples of thyroid in patients with AITD and healthy controls and the potential use of the selected miRNAs as biomarkers in serum samples of AITD patients. 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 (immuno-regulatory molecules) of IMID severity and responsiveness to biological therapies. We are developing novel approaches of analysis using exosomes as target containers of these relevant biomarkers. The aim of this study was to improve the selectivity and efficacy in the use of biological therapies in IMID.

Our last results in this field include 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. Furthermore,

we have developed a 5 miRNA signature that could be an independent risk factor for developing AITD and for predisposition of a worse clinical picture in GD patients. In 2016 we initiated a new project (PI16-02091) to identify new susceptibility genes and miRNA targets and to evaluate the use of microRNAs as possible therapeutical targets in AITD.

Another area of investigation of the group is the study of mechanisms resulting in evasion of immune attack in neuroendocrine gastroentero-pancreatic tumors. We are studying the role of CD69+ lymphocytes and the interaction of PD1 and PDL1 molecules in human samples of these tumors and we aim to correlate the results with clinical data of the patients. We will correlate these findings with the characteristics of the patients including clinical, pathological diagnosis, treatments received and prognosis.

Our group also leads the Spanish Molecular Registry of Pituitary Adenomas (REMAH) with 1400 patients registered. 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.

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 in these tumors will allow us for testing the effect of new treatments, thus increasing the range of adenomas that can be treated pharmacologically.

MAJOR GRANTS

- Marazuela Azpiroz, Mónica. Estudio de integración de miRNAS y mRNAS en las enfermedades tiroideas autoinmunes: análisis de vías de susceptibilidad y marcadores de la enfermedad. PI16/02091. ISCIII. 2017-2019.

Granted 2017:

- Marazuela Azpiroz, Mónica. Estudio del microambiente celular en tumores neuroendocrinos gastroenteropancreáticos. Caracterización de la respuesta inmunológica peritumoral y relación con el marcador de hipoxia/estrés tisular lat-1. Grupo Español de Tumores Neuroendocrinos (GETNE). 2017-2019.

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: MARAZUELA AZPIROZ, MONICA

Búsqueda de biomarcadores de enfermedades tiroideas autoinmunes mediante integración de microRNAs y mRNAs. LAIR 040517-MMA

PRINCIPAL RESEARCHER: MARAZUELA AZPIROZ, MONICA

Estudio ACROVAL: Estudio observacional, trasversal y multicéntrico para valorar el grado de actividad de la enfermedad de los pacientes acromegálicos en España según la escala ACRODAT (ACROmegaly Disease Activity Tool). Pfizer INC PFI-PEG-2017-01(A6291046) PFI-ACR-2017-01

PRINCIPAL RESEARCHER: RAMOS LEVI, ANA MARIA

Estudio europeo, observacional, de pasireotida LAR en acromegalia- Estudio ACRONIS. Novartis Farmaceutica, S.A. NOV-PAS-2016-01/SOM230CIC05

PRINCIPAL RESEARCHER: SAMPEDRO NUÑEZ, MIGUEL ANTONIO

Estudio retrospectivo y multicéntrico en práctica clínica habitual con iSGLT2 (dapagliflozina) y iDPP4 (sitagliptina) en pacientes con Diabetes Tipo 2 en España. Estudio DAPA-RWE. Fundación Pública Andaluza para la Gestión (FISEVI) FIS-DAP-2016-01

PRINCIPAL RESEARCHER: SAMPEDRO NUÑEZ, MIGUEL ANTONIO

Estudio para evaluar el uso de recursos y los costes asociados al síndrome carcinoide controlado y no controlado en pacientes con tumores neuroendocrinos (NETs) en España. Estudio RECOSY. Ipsen Pharma, S. A. IPS-SOM-2017-01

LINE 1.10

Children´s development (obesity and growth)

GROUP 26

HEAD OF LABORATORY

Jesús Argente Oliver

GROUP MEMBERS

- Pilar Argente Arizón
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- Alejandra Freire Regatillo
- Gabriel Ángel Martos Moreno
- María Teresa Muñoz Calvo
- Jesús Pozo Román
- Oscar Rubio Cabezas

RESEARCH INTEREST

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 affectation 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.

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- Argente Olivier, Jesús. Obesidad infantil grave de comienzo precoz al diagnóstico y tras pérdida ponderal: Fundamentos metabólicos, hormonales, genéticos, genómicos, metabolómicos y de microbiota. PI16/00485. ISCIII. 2017-2019.

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Mela, Virginia, Hernandez, Oskarina, Hunsche, Caroline, Díaz González, Francisca, Chowen King, Julie Ann, De la Fuente, Mónica. **Administration of a leptin antagonist during the neonatal leptin surge; induces alterations in the redox and inflammatory state in peripubertal; /adolescent rats.** Mol. Cell. Endocrinol. 454(C):125-134. 2017. PMID: 28641938. IF: 3,754. DOI: 10.1016/j.mce.2017.06.018. http://dx.doi.org/10.1016/j.mce.2017.06.018.

Frago Fernández, Laura María, Canelles Ortíz, Sandra, Freire Regatillo, Alejandra, Argente Arizón, Pilar, Barrios Sabedor, Vicente, Argente Oliver, Jesús, Garcia-Segura, Luis M., Chowen King, Julie Ann. **Estradiol Uses Different Mechanisms in Astrocytes from the Hippocampus; of Male and Female Rats to Protect against Damage Induced by Palmitic; Acid.** Front. Molec. Neurosci. 10:330-330. 2017. PMID: 29114202. IF: 5,076. DOI: 10.3389/fnmol.2017.00330. http://dx.doi.org/10.3389/fnmol.2017.00330.

LINE 1.11

Metabolic syndrome and vascular risk

GROUP 5

HEAD OF LABORATORY

Carmelo García Monzón

GROUP MEMBERS

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- Alfonso Jaime Casado Collado
- Elvira del Pozo Maroto
- Almudena García Carrasco
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- María Gloria Mateo Jiménez
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- Alicia Sáez Sáez
- Isabel Trijueque García
- Rodolfo Javier Vargas Castrillón

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 hepatocellular 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 noninvasive 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 acions. 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

- González Rodríguez, Águeda. Identificación de nuevos biomarcadores para el diagnóstico no invasivo de la enfermedad del hígado graso no alcohólico. Fundación Francisco Cobos. 2016-2017.
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- García Monzón, Carmelo / Ancochea Bermúdez, Julio. 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.

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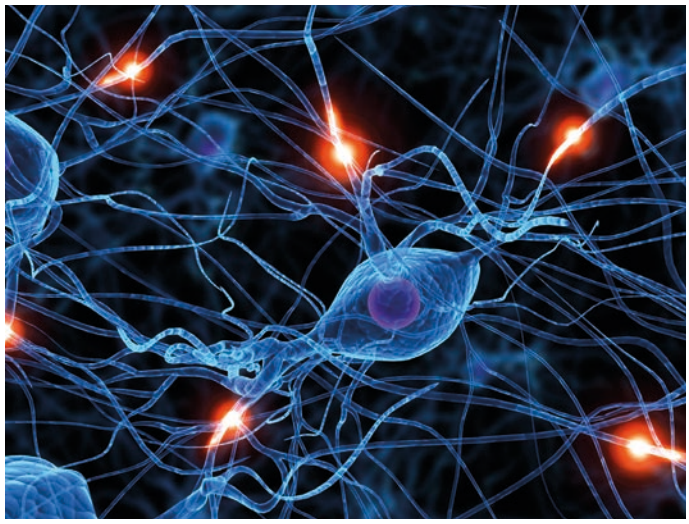
AREA 2
Translational Neuroscience

Line 2.1	Neuropharmacology and neuroprotection.
Line 2.2	Neurotransmission in the hippocampus.
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.

AREA 2

Translational Neuroscience



LINE 2.1

Neuropharmacology and neuroprotection

GROUP 28

HEAD OF LABORATORY

Antonio García García

GROUP MEMBERS

- Juan Alberto Arranz Tagarro
- Enrique Calvo Gallardo
- María Francisca Cano Abad
- Cristóbal de los Ríos Salgado
- Ricardo de Pascual y del Castillo
- Javier Garrosa Jiménez
- Juan Fernando Padín Nogueira
- Alejandro Palomino Bernal
- Ana Ruiz Nuño
- Aneta Iwona Wojnicz

RESEARCH INTEREST

1) Exocytosis-neurotransmission-calcium signalling. I am working since almost 40 years on basic ionic and receptor mechanisms involved in the regulation of exocytotic neurotransmitter release. I mostly use adrenal medullary chromaffin cell as a model to perform electrophysiological, pharmacological and neurosecretory studies, by the use of calcium imaging techniques with patch-clamp and amperometric techniques. I am particularly interested in going forward with my hypothesis that the functional triad formed by voltage-dependent calcium channels, the endoplasmic reticulum and the mitochondria, shape the cytosolic calcium signals required to regulate preexocytotic and exocytotic steps. I am trying to project this hypothesis into pathogenic mechanisms of three disorders, i.e. Alzheimer´s disease, amyotrophic lateral sclerosis and hypoxia survival in early life.

2) Design, synthesis and Pharmacology of neuroprotective compounds with potential therapeutic application in neurodegenerative diseases and stroke.

In 1994 I published my first paper, trying to link sodium and calcium channels to basic mechanisms of neuronal death, using the chromaffin cell as a model. In subsequent years, I developed this area, focusing on neurotoxicity mechanisms looking for targets to develop new chemical entities with potential neuroprotective effects and therapeutic applications to neurodegenerative diseases (particularly Alzheimer´s disease) and cerebrovascular diseases (stroke).

During the next 5 years I will focus on the understanding of neurotransmitter release, exocytosis and endocytosis in neurodegenerative diseases. Also, I will try to develop newly synthesised compounds as neuroprotective medicine for Alzheimer's disease.

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LINE 2.2

Pharmacological Neuroprotection in Neurodegenerative Diseases and Stroke

GROUP 16

HEAD OF LABORATORY

Manuela García López

GROUP MEMBERS

- Sheila Abril Comesaña
- Izaskun Buendía Abaitua
- Pablo Duarte Flórez
- Francisco Javier Egea Maiquez
- Cristina Fernández Mendivil
- Isabel María Gameiro Ros
- Vanessa Gómez Rangel
- Rafael León Martínez
- Enrique Luengo Martin
- Patrycja Michalska Dziama
- Esther Parada Pérez
- Paula Trigo Alonso

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 flu***x participate in neurodegeneration, in order to develop pharmacological interventions to regulate these pathological conditions.
2. Development of in vitro a 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.

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LINE 2.3

Clinical pharmacology and pharmacogenetics

GROUP 32

HEAD OF LABORATORY

Francisco Abad Santos

GROUP MEMBERS

- Carmen Belmonte Campillo
- María Eugenia Flores Ruiz
- Pedro Gil Divasson
- Esperanza González Rojano
- María José Hernández Martínez
- Samuel Martín Vilchez
- Gina Paola Mejía Abril
- María Dolores Ochoa Mazarró
- María del Carmen Ovejero Benito
- Concepción Pérez Hernández
- Ángela Rivas Acosta
- Irene Román Martínez
- Manuel Román Martínez
- Miriam Saiz Rodríguez
- María Talegón García
- Sarahi Elizabeth Valdez Acosta

RESEARCH INTEREST

The aim of the investigation performed in this group is to evaluate pharmacokinetics, pharmacodynamics and pharmacogenetics in order to predict the response of the patients to drugs, in terms of efficacy and safety.

Our group has wide experience conducting numerous phase I, II and III clinical trials. We have available a Clinical Trials Unit, with capacity for 14 subjects (7th floor, Hospital Universitario de la Princesa). The Clinical trials performed include safety, pharmacokinetics, pharmacodynamics, interaction and bioequivalence studies in healthy volunteers, and studies in patients to probe the efficacy of new drugs in collaboration with several specialists in the hospital and primary care. Our group performed more than 20 clinical trials each year, and this number is anticipated to increase due to the demand from the pharmaceutical industry.

Our pharmacogenetic research is related with various clinical diseases, trying to search for new pharmacogenetic markers to predict drug responses, both therapeutic and toxic, that could help physicians to decide the best treatment for every patient. In 2017, 247 patients benefited from pharmacogenetic testing. We are already increasing the number of pharmacogenetic tests performed in our Service to better support the physicians on the decision about therapeutic strategies. In addition, in 2017 we participated in 3 projects, one of them about epigenetic biomarkers

predicting response to biological drugs in psoriasis, which is the continuation of another project analyzing pharmacogenetic biomarkers.

MAJOR GRANTS

- Abad Santos, Francisco. Plataforma de Unidades de Investigación Clínica y Ensayos Clínicos. PT13/0002/0027. ISCIII. 2014-2017.
- Abad Santos, Francisco. TREATMENT: Training European Network: Metabolic Dysfunctions associated with Pharmacological Treatment of Schizophrenia. 674921. Comisión Europea. 2016-2020.

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- Abad Santos, Francisco. Plataforma de Unidades de Investigacion Clinica y Ensayos Clinicos. PT17/0017/0007. ISCIII. 2018-2020.
- Ovejero Benito, María del Carmen. Caracterización molecular, epigenética y estudio de tetraploidias en pacientes epilépticos fármaco resistentes del lóbulo temporal. PI17/02244. ISCIII. 2018-2020.

PUBLICATIONS (12)

Prieto-Pérez, Rocío, Llamas Velasco, María del Mar, Cabaleiro, Teresa, Solano-López, Guillermo, Márquez, Beatriz, Román Martínez, Manuel, Ochoa Mazarro, María Dolores, Talegón García, María, Daudén Tello, Esteban, Abad Santos, Francisco. **Pharmacogenetics of ustekinumab in patients with moderate-to-severe; plaque psoriasis.** Pharmacogenomics. 18(2):157-164. 2017. PMID: 27977334. IF: 2,350. DOI: 10.2217/pgs-2016-0122. http://dx.doi.org/10.2217/pgs-2016-0122.

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BOOKS

Ortega Gómez, María del Mar, Luquero Bueno, Sergio, Abad Santos, Francisco. Capítulo 11: Farmacogenómica y Biobancos. ENSAYOS CLÍNICOS EN ESPAÑA: Actualización en ética, normativa, metodología y nuevas tecnologías.. pp. 285 - 307. 01/05/2017. ISBN 9788469131161

Abad Santos, Francisco, Ochoa Mazarro, María Dolores, Ortega Gómez, María del Mar. Capítulo 4: CEIm. Composición. Funciones. ENSAYOS CLÍNICOS EN ESPAÑA: Actualización en ética, normativa, metodología y nuevas tecnologías.. pp. 111 - 136. 01/05/2017. ISBN 9788469131161

CLINICAL TRIALS

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico replicado, cruzado y aleatorizado de bioequivalencia de dos formulaciones de atorvastatina 80mg comprimidos recubiertos, tras su administración oral en dosis única a voluntarios sanos en ayunas. Galenicum Health S.L. GAL-ATO-09

EudraCT: 2017-002021-38

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico aleatorizado de biodisponibilidad comparada de dos formulaciones de comprimidos de mercaptopurina 50mg, tras su administración oral en dosis única a voluntarios sanos en ayunas en un diseño cruzado replicado. Laboratorios Silverfarma S.L. UECHUP-MER/17-1

EudraCT: 2017-000691-29

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico aleatorizado de bioequivalencia de dos formulaciones de amlodipino/valsartan/hidroclortiazida 10/160/25 mg comprimidos recubiertos, tras su administración oral en dosis única a voluntarios sanos en ayunas con diseño cruzado. Laboratorios Normon, S.A. N-AVH-17-227

EudraCT: 2017-000547-40

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico randomizado, doble ciego, controlado con placebo, para la evaluación de la seguridad, tolerabilidad y farmacocinética de la primera administración en humanos de acetato de contraloid con la administración de una dosis única, según un esquema de dosis ascendente, en sujetos sanos. Forschungszentrum Juelich GMBH NSC17001

EudraCT: 2017-000396-93

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo abierto, cruzado, aleatorizado, para el estudio de la biodisponibilidad comparada de dos formulaciones de hidrosmina en dosis múltiple, en voluntarios sanos. FAES Farma HID-0216/BA-SS

EudraCT: 2016-004714-10

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínica piloto aleatorizado cruzado de bioequivalencia de dos formulaciones test de atorvastatina 80mg comprimidos recubiertos, tras su administración oral en dosis única a voluntarios sanos en ayunas. Galenicum Health S.L. GAL-ATO-12

EudraCT: 2016-004636-37

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico, aleatorizado, de bioequivalencia de tres formulaciones de rececadotrilo cápsulas de 100mg, tras su administración en dosis única a voluntarios sanos en ayunas con un diseño cruzado. Galenicum Health S.L. GAL-RAC-03

EudraCT: 2016-000415-33

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico cruzado, aleatorizado de bioequivalencia de una formulación de dutasterida/tamsulosina 0.5mg/0.4mg cápsulas duras versus duodart® 0.5mg/0.4mg cápsulas duras, tras su administración en dósis úni-

ca a voluntarios sanos con comida con un diseño en dos etapas. Galenicum Health S.L. GAL-DUT-TAM-08

EudraCT: 2017-001592-23

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico cruzado, aleatorizado de biodisponibilidad comparada de dos formulaciones de ambrisentan de 10mg comprimidos recubiertos con película, tras su administración oral en dosis única a voluntarios sanos en ayunas. Laboratorios Kern Pharma S.L. KP-AMB-89

EudraCT: 2016-002631-14

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico aleatorizado de bioequivalencia de dos formulaciones de amlodipino/valsartan/hidroclorotiazida 10/160/12.5mg comprimidos recubiertos, tras su administración oral en dosis única a voluntarios sanos en ayunas con diseño cruzado replicado. Laboratorios Normon, S.A. N-AVH-17-229

EudraCT: 2017-001716-10

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico aleatorizado de bioequivalencia de dos formulaciones de amlodipino/valsartan/hidroclorotiazida 10/320/25mg comprimidos recubiertos, tras su administración oral en dosis única a voluntarios sanos en ayunas con diseño cruzado replicado. Laboratorios Normon, S.A. N-AVH-17-230

EudraCT: 2017-001757-14

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico cruzado y aleatorizado de bioequivalencia de dos formulaciones de fentanilo 300 microgramos comprimidos sublinguales, tras su administración oral en dosis única a voluntarios sanos en ayunas. Laboratorios Kern Pharma S.L. KP-FNT-72

EudraCT: 2016-001939-13

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico aleatorizado, abierto y cruzado de tres vías de bioequivalencia de tres formulaciones de ibuprofeno 400mg (ibuprofeno suspensión 40mg/ml e ibuprofeno suspensión 20mg/ml versus brufen 20mg/ml oral suspensión) tras su administración oral en dosis única a voluntarios sanos. ITF Research Pharma S.L.U. RES-6014

EudraCT: 2017-001442-94

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico cruzado, aleatorizado de bioequivalencia de una formulación de dutasterida/tamsulosina 0.5mg/0.4mg cápsulas duras versus duodart® 0.5mg/0.4mg cápsulas duras, tras su administración en dosis múltiple a voluntarios sanos con comida. Galenicum Health S.L. GAL-DUT-TAM-11

EudraCT: 2017-003244-21

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico cruzado y aleatorizado de bioequivalencia de dos formulaciones de atorvastatina 80mg comprimidos recubiertos con película, tras su administración oral en dosis única a voluntarios sanos en ayunas con diseño replicado. Laboratorios Normon, S.A. N-ATO-16-224

EudraCT: 2016-002759-39

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico cruzado, aleatorizado de bioequivalencia de dos formulaciones de eslicarbazepina acetato com-

primidos de 800mg, tras su administración en dosis única a voluntarios sanos en ayunas. Laboratorios Cinfa S.A. CFA-1009-1-17

EudraCT: 2017-003116-40

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico piloto aleatorizado cruzado de bioequivalencia de dos formulaciones de atorvastatina 80mg comprimidos recubiertos versus Cardyl®80mg comprimidos recubiertos, tras su administración oral en dosis única a voluntarios sanos en ayunas. Galenicum Health S.L. GAL-ATO-12

EudraCT: 2017-003917-25

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico aleatorizado y cruzado para determinar la biodisponibilidad relativa de ranitidina 15mg/ml solución oral, comparada con zantac syrup® tras la administración de una dosis única a voluntarios sanos en ayunas. Farmalider S.A. FMLD-RAGUSA-41

EudraCT: 2017-004623-75

PRINCIPAL RESEARCHER: OCHOA MAZARRO, DOLORES

Ensayo clínico cruzado y aleatorizado de bioequivalencia de dos formulaciones de sitagilptina/metformina 50mg/100mg comprimidos recubiertos con película, tras su administración oral en dosis única a voluntarios sanos con comida. Laboratorios Alter, S.A. UECHUP-SIT-MET/17-2

EudraCT: 2017-004727-73

LINE 2.4

Diagnostic and therapeutic advances in affective disorders

GROUP 33

HEAD OF LABORATORY

José Luis Ayuso Mateos

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- María Cabello Salmerón
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- María Provencio Ortega
- Laura Alejandra Rico Uribe
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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 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 Wellbeing 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.

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- Ayuso Mateos, José Luis. MARATONE: Mental health training through research network in Europe. 31795. Comisión Europea. 2013-2017.
- Ayuso Mateos, José Luis. PATHWAYS: PArticipation To Healthy Workplaces And inclusive Strategies in the Work Sector. 663474. Comisión Europea. 2015-2017.
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- Ayuso Mateos, José Luis. Trayectoria de salud mental, salud física y funcionamiento: tercera evaluación de una cohorte población adulta. PI16/00218. ISCIII. 2017-2019.

- Miret García, Marta. Fluctuación Emocional en el Día a Día. Análisis ecológico de la sintomatología depresiva en población general (FEDD). PI16/00177. ISCIII. 2017-2019.
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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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Kamenov Kamenov, Kaloyan, Cabello Salmerón, María, Nieto, Mónica, Bernard, Renaldo, Kohls, Elisabeth, Rummel-Kluge, Christine, Ayuso Mateos, José Luis. **Research Recommendations for Improving Measurement of Treatment; Effectiveness in Depression.** Front. Psychol. 8:356-356. 2017. PMID: 28337167. IF: 2,323. DOI: 10.3389/fpsyg.2017.00356. http://dx.doi.org/10.3389/fpsyg.2017.00356.

Caballero Díaz, Francisco Félix, Soulis, George, Engchuan, Worrawat, Sánchez-Niubó, Albert, Arndt, Holger, Ayuso Mateos, José Luis, Haro, Josep Maria, Chatterji, Somnath, Panagiotakos, Demosthenes B. **Advanced analytical methodologies for measuring healthy ageing and its; determinants, using factor analysis and machine learning techniques: the; ATHLOS project.** Sci Rep. 7:43955-43955. 2017. PMID: 28281663. IF: 4,259. DOI: 10.1038/srep43955. http://dx.doi.org/10.1038/srep43955.

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LINE 2.5

Neurosurgery of epilepsy

GROUP 34

HEAD OF LABORATORY

Rafael García de Sola

GROUP MEMBERS

- Ángela Adgyan de Abreu Arvelo
- Eva de Dios Tomas
- Luis Domínguez Gadea
- Eduardo García Navarrete
- Oscar Garnés Camarera Estruch
- José Luis Martínez-Chacón Crespo
- María Luisa Meilan Paz
- Marta Navas García
- Guillermo José Ortega Rabbione
- Jesús Pastor Gómez
- Miriam Pérez Romero
- Miguel Pintor Zamora
- Paloma Pulido Rivas
- Ancor Sanz García
- Cristina Virginia Torres Díaz
- Lorena Carolina Vega Zelaya
- Rybel Wix Ramos

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.

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 electrophisiological 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

- Ortega Rabbione; Guillermo José. Utilidad diagnóstica y predictiva de la monitorización mediante EEG cuantificado en pacientes con traumatismo craneoencefálico severo. Fundación Mutua Madrileña. 2015-2018.

Granted 2017:

- Pastor Gómez, Jesús. Monitorización neurofisiológica funcional intraoperatoria dellenguaje en pacientes con sedación. PI17/02193. ISCIII. 2018-2020.
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LINE 2.6

Cerebrovascular diseases

GROUP 35

HEAD OF LABORATORY

José Aurelio Vivancos Mora

GROUP MEMBERS

- Teresa Carreras Rodríguez
- María de Toledo Heras
- Ana Beatriz Gago Veiga
- María de las Mercedes Gallego de la Sacristana López-Serrano
- Lydia López Manzanares
- Virginia Meca Lallana
- Noemí Mora Pérez
- Florentino Nombela Merchán
- Gemma Reig Rosello
- Mónica Sobrado Sanz
- Aránzazu Vázquez Doce
- Álvaro Ximenez-Carrillo Rico
- Gustavo Enrique Zapata Wainberg

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

Movement Disorders

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

Cephaleas.

- Prediction of migraine crisis
- Study of the response variables to botulinum toxin

- Glutamate and headaches.
- Psychological aspects and headaches.

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

MAJOR GRANTS

- Vivancos Mora, José Aurelio. Monitorización ambulatoria no invasiva de variables biométricas y biofísicas y como método para la predicción de una crisis de migraña. PI15/01976. ISCIII. 2016-2018.
- Vivancos Mora, José Aurelio. REgenerative Stem cell therapy for STroke in Europe –Therapeutic efficacy of allogenic adipose tissue derived mesenchymal stem cells for enhancing functional outcome in stroke patients. 681044. Comisión Europea. 2015-2020.

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- Vivancos Mora, José Aurelio. MULTI-TARGET&VIEW-CM: imagen multimodal de la respuesta terapéutica a estrategias multidiana en enfermedades neurológicas. B2017/BMD-3688. Comunidad de Madrid. 2018-2021.

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: GAGO VEIGA, ANA BEATRIZ

Evaluación de las variables más predictoras de la respuesta del paciente con migraña al tratamiento con toxina botulínica (OnabotA). PROYECTO BIGDATA-BOTOX

PRINCIPAL RESEARCHER: GAGO VEIGA, ANA BEATRIZ

La carga de la migraña en centros de cefalea especializados que tratan pacientes que han fallado a tratamientos preventivos (Estudio BECOME). Novartis Farmaceutica, S.A. CAMG334A3301

PRINCIPAL RESEARCHER: GAGO VEIGA, ANA BEATRIZ

Estudio aleatorizado, con doble enmascaramiento, de inicio diferido, en el que se evalúa LY3314814 (AZD3293) en la Enfermedad de Alzheimer en fase temprana (ampliación del estudio AZES, el estudio AMARANTH). Lilly, S.A. I8D-MC-AZFD

EudraCT: 2016-003440-36

PRINCIPAL RESEARCHER: MECA LALLANA, VIRGINIA

Estudio multicéntrico, aleatorizado, doble ciego y controlado, con placebo en sujetos con esclerosis múltiple recurrente para evaluar la eficacia y la seguridad de BIIB033 como tratamiento adicional a los tratamientos antiinflamatorios modificadores de la enfermedad. Biogen Ma Inc. 215MS202

EudraCT: 2017-001224-22

PRINCIPAL RESEARCHER: MECA LALLANA, VIRGINIA

Evaluación de las necesidades de información de pacientes con esclerosis múltiple en Espala: preocupaciones, preferencias y nivel de satisfacción según su personalidad y características clínicas y funcionales (infoseek-ms). Roche Farma, S.A. ML39780

PRINCIPAL RESEARCHER: MECA LALLANA, VIRGINIA

Preferencias de los pacientes y neurólogos por las características de los tratamientos de segunda línea para la esclerosis múltiple. Merck & Co., Inc MER-NAT-2017-01

PRINCIPAL RESEARCHER: MECA LALLANA, VIRGINIA

Estudio aleatorizado, doble ciego, doble enmascarado, de grupos paralelos para comprar la eficacia y seguridad de ofatumumab frente a teriflunomida en pacientes con esclerosis múltiple que cursa brotes. Novartis Farmaceutica, S.A. COMB157G2302

EudraCT: 2015-005419-33

PRINCIPAL RESEARCHER: MECA LALLANA, VIRGINIA

Estudio multicéntrico, abierto, de un solo brazo, antes y después del cambio para evaluar la eficacia, la seguridad y la tolerabilidad de alemtuzumab en pacientes pediátricos con esclerosis múltiple recurrente remitente (EMRR) con actividad de la enfermedad en la terapia previa modificadora de la enfermedad (TME). Genzyme Corporation EFC13429

EudraCT: 2016-003100-30

PRINCIPAL RESEARCHER: VAZQUEZ DOCE, ARANZAZU

Eficacia y seguridad del tratamiento con lidocaína tópica en la tendinitis anserina. PROYECTO VERSATIS

PRINCIPAL RESEARCHER: VIVANCOS MORA, AURELIO

Detección de fibrilación auricular escondida en Atención Primaria en población categorizada por riesgo con un sistema de banda de registro el electrocardiográfo de larga duración: Estudio DEScuuBRE-FA. Fundación de Investigación Biomédica HUP ESTUDIO DESCUUBRE-FA

PRINCIPAL RESEARCHER: LOPEZ MANZANARES, LYDIA

Estudio en fase II de 52 semanas, aleatorizado, con doble enmascaramiento y controlado con placebo, para evaluar la eficacia de RO7046015(PRX002) intravenoso en participantes con Enfermedad de Parkinson incipiente, con una extensión con enmascaramiento de 52 semanas (PASADENA). HOFFMAN-LA ROCHE BP39529

EudraCT: 2017-000087-15

PRINCIPAL RESEARCHER: LOPEZ MANZANARES, LYDIA

Estudio de fase II, aleatorizado, doble ciego, controlado con placebo y con administración flexible durante 15 semanas para estudiar la eficacia seguridad y tolerabilidad de PF-06649751 en pacientes con Enfermedad de Parkinson en estadio inicial. Pfizer Inc B7601011

EudraCT: 2016-001575-71

PRINCIPAL RESEARCHER: LOPEZ MANZANARES, LYDIA

Estudio clínico, observacional y transversal de prevalencia de la asimetría facial en la Enfermedad de Parkinson. ESTUDIO PARKMIM

PRINCIPAL RESEARCHER: LOPEZ MANZANARES, LYDIA

Un estudio multicéntrico, internacional y abierto de la seguridad de ND0612, una solución de levodopa/crbidopa administrada mediante un sistema de bomba como perfusión subcutánea continua en sujetos con Enfermedad de Parkinson avanzada (BeyoND). Neuroderm Ltd ND0612H-012

EudraCT: 2015-005814-31

PRINCIPAL RESEARCHER: LOPEZ MANZANARES, LYDIA

A multicenter, open-label study to evaluate the safety and tolerability of tozadenant as adjunctive therapy in levadopa-treated patients with parkinsons disease experiecing end of dose wearing off. Biotie Therapies TOZ-CL06

EudraCT: 2016-003961-25

PRINCIPAL RESEARCHER: LOPEZ MANZANARES, LYDIA

Efecto de la safinamida sobre los síntomas depresivos en la Enfermedad de Parkinson: estudio abierto, multicéntrico, longitudinal, retrospectivo. EST-SAF-2017-01

GROUP ASSOCIATED 1

HEAD OF LABORATORY

Ignacio Lizasoain Hernández

GROUP MEMBERS

- María Isabel Cuartero Desviat
- Macarena Hernández Jiménez
- Olivia Hurtado Moreno
- María Ángeles Moro Sánchez

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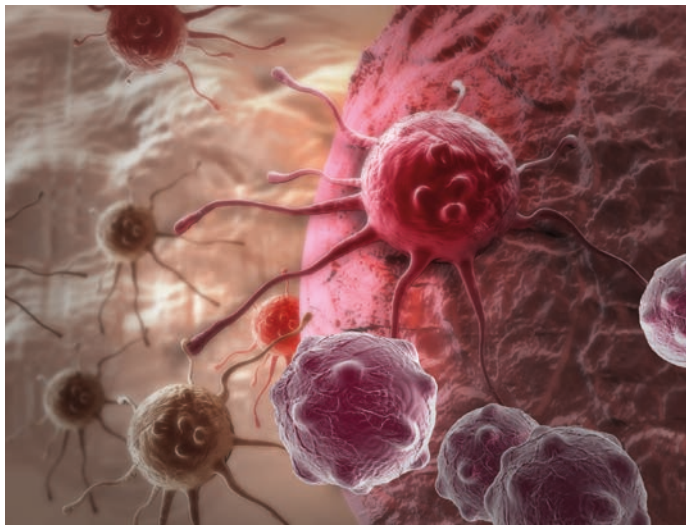
AREA 3
Advanced therapies and individualized medicine

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.

AREA 3

Advanced therapies and individualized medicine



LINE 3.1

Prognostic and predictor markers in autoimmune diseases

GROUP 36

HEAD OF LABORATORY

Isidoro González Álvaro

GROUP MEMBERS

- José María Álvaro-Gracia Álvaro
- Amada Elia Beltrán Núñez
- Santos Castañeda Sanz
- Rosario García de Vicuña Pinedo
- Jesús Alberto García Vadillo
- María de las Nieves Gómez León
- Amalia Lamana Domínguez
- Nuria Montes Casado
- Ana María Ortiz García
- Eva Gloria Tomero Muriel
- Ana Triguero Martínez
- Miren Uriarte Ecenarro
- Teresa Velasco Ripoll
- Esther Francisca Vicente Rabaneda

RESEARCH INTEREST

The main goal for our group is personalized medicine in the field of autoimmune/inflammatory rheumatic disorders (mainly rheumatoid arthritis, spondyloarthritis, systemic lupus erythematous, 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 BioIMID 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 Biobank, 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 from the ISCIII. Our research is 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. However, many other rheumatologic diseases such as scleroderma, systemic lupus erythematosus, systemic vasculitis, osteoporosis, osteoarthritis, are objectives of the research work conducted by our researchers. As a result of the intense activity of the group, some of its members have been called to participate in several documents to establish 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. In addition, members of the group have developed two patents.

For the next years, our efforts will continue to focus on discovering new biomarkers allowing us to treat patients more efficiently. The main objective is to find applications for the findings protected by our patents and transfer them to the industry. Thus, we could offer to the society some tools that may help to establish more efficient therapeutic schedules for the diseases of our interest.

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: ALVARO-GRACIA ALVARO, JOSE M.

Estudio en fase II, multicéntrico, aleatorizado, doble ciego y controlado con placebo para evaluar la seguridad y la eficacia de RO7123520 como tratamiento complementario en pacientes con artritis reumatoide activa moderada o grave y con respuesta inadecuada a los inhibidores de TNF-alfa. F. Hoffmann-La Roche Ltd BP39261
EudraCT: 2016-002126-36

PRINCIPAL RESEARCHER: ORTIZ GARCIA, ANA-MARIA

Estudio observacional transversal para evaluar la adherencia al tratamiento en pacientes con artritis reumatoide en España. Fundación Ramón Domínguez FRD-ART-2017-01

GROUP 37

HEAD OF LABORATORY

Esteban Daudén Tello

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- María del Mar Llamas Velasco
- Abilio Javier Sánchez Pérez
- Fátima Tudelilla Fernández

RESEARCH INTEREST

The investigation activity of the Group at present and for the following 5 years is focused on:

1. Immune-mediated inflammatory diseases (IMID), particularly psoriasis. 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 moderate-to-severe psoriasis. 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) Factors associated with receiving biologics or classic systemic therapy for moderate to severe psoriasis. g) Study of paradoxical psoriasiform reactions with change of morphology induced by biologics in patients with psoriasis. Determination of the prevalence, clinical and histopathological features, possible trigger or associated factors. Assessment of the therapeutic management. h) Identification of Copy-Number Variants associated with the risk to develop psoriasis and psoriatic arthritis, using a genome-wide analysis approach. i) Study of optimization strategies (dose reduction, increase of the administration interval) in the treatment of moderate-to-severe psoriasis with systemic agents; j) Regulation of CXCL12 and RAPTOR by novel miRNAs and their role during the inflammatory process in Psoriasis.

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 on solar urticaria

MAJOR GRANTS

- Daudén Tello, Esteban. Identificación de microRNAs como biomarcadores de gravedad y respuesta al tratamiento en pacientes con Psoriasis. PI14/01751. ISCIII. 2015-2017.

Granted 2017:

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

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: SANCHEZ PEREZ, ABILIO JAVIER

Ensayo fase III, aleatorizado, doble ciego, controlado con placebo, para evaluar la eficacia y seguridad de tralokinumab en monoterapia en pacientes con dermatitis atópica moderada a grave que sean candidatos para un tratamiento sistémico VHP1076 (2017045). Leo Pharma A/S LP0162-1325

EudraCT: 2016-004200-65

PRINCIPAL RESEARCHER: SANCHEZ PEREZ, ABILIO JAVIER

Registro de dermatitis de contacto de la AEDV. Fundación Piel Sana FAE-DER-2017-01

PRINCIPAL RESEARCHER: DAUDEN TELLO, ESTEBAN

Secukinumab, ixekizumab y apremilast en el tratamiento de la psoriasis moderada-grave. Análisis de efectividad y seguridad. EDT-SIA-2017-01

PRINCIPAL RESEARCHER: DAUDEN TELLO, ESTEBAN

Búsqueda de marcadores genéticos predictores de respuesta a nuevos fármacos en el tratamiento de la psoriasis. EDT-SIA-2017-02

PRINCIPAL RESEARCHER: ARGILA FERNANDEZ-DURAN, DIEGO DE

Estudio aleatorizado, multicéntrico para evaluar el efecto de secukinumab 300mg por vía s.c. administrado durante 52 semanas en pacientes con psoriasis en placas moderada a grave de nueva aparición como intervención temprana en comparación con el tratamiento estándar con UVB de banda estrecha (Estudio STEPIn). Novartis Pharma Services AG CAIN457A2322

EudraCT: 2015-002423-26

PRINCIPAL RESEARCHER: LLAMAS VELASCO, MARIA DEL MAR

Estudio clínico abierto para evaluar la eficacia y la seguridad a largo plazo de dimetilfumarato en adultos con psoriasis crónica en placas de moderada-grave en la práctica clínica (Estudio DIMESKIN 1). Almirall S.A. M-41008-41
EudraCT: 2017-001368-40

LINE 3.2

Esophagogastrointestinal inflammatory diseases

GROUP 38

HEAD OF LABORATORY

Javier Pérez Gisbert

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- Alba Díaz-Guerra Peñalba
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- María García Donday
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- Alicia Carmen Marín Gómez
- Adrián Gerald Mcnicholl
- Ana Montalbán Arques
- Irene Mora Gutiérrez
- Olga Raquel Pérez Nyssen
- Cecilio Santander Vaquero

RESEARCH INTEREST

The Gastrointestinal Inflammatory Disease Group, focuses on the understanding and management of *Helicobacter pylori* infection and Inflammatory Bowel Disease (IBD). Clinical and epidemiological projects are performed coordinating networks of gastroenterologists from over 30 Spanish hospitals. Different projects have been developed in collaboration with the Pathology service, the Immunology service and the Clinical Pharmacology service of La Princesa Hospital, the Biochemistry and Molecular Biology Department of Alcalá de Henares University, the Pharmacology Department of Valencia University, the Oncology Institute of Catalunya, 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) and several digestive services throughout Spain.

Prominent lines

1) Clinical Investigation in IBD

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

- Direction and coordination of the "Epidemiological study of the incidence of inflammatory bowel disease in Spain", with approximately 200 participating centers P-FIS (FI17/00143)
- Direction and coordination of the clinical trial "Withdrawal of anti-TNF treatment in patients with inflammatory bowel disease: Multicenter, prospective and randomized clinical trial" FIS15 / 00560
- Direction and coordination of the "Prospective and multicentric study on the epidemiology and "omic" characteristics of newly diagnosed inflammatory bowel disease in Spain" FIS16 / 01296
- Direction and coordination of the study "Long-term safety of anti-TNF treatment in children exposed to these drugs during pregnancy", involving 30 centers in several European countries.
- Direction and coordination of the study predicting short- and long-term response to treatment with anti-TNF drugs in patients with Crohn's disease. Predicrohn Study. FIS12 / 02557

2) AEG-REDCap Platform

- Direction and coordination of the Online Platform for collaborative Reesearch AEG-REDCap with over 50 projects and 1,000 researchers.
- Management of the AEG-REDCap Strategic Line at CIBERehd

3) H. pylori infection

- International coordination of the European Registry on H. pylori management, prospective study of clinical practice including 240 hospitals of 27 European Countries.
- In situ and in vivo detection and treatment with multifunctional nanomaterials.
- Effect of eradication treatment on intestinal microbiota.
- Validation of new diagnostic methods.
- Prevalence, transmission, resistance, and sociosanitary factors of infection.

4) Angiogenesis and lymphangiogenesis in IBD

- Ulcerative colitis vs. Crohn's disease
- Correlation with clinical and disease course variables
- Effect of the therapy (immune suppressors and biologic treatments)

5) Immunity in IBD

- Vaccination optimization in IBD patients.
- Immunological alterations after Hepatitis B virus (HBV) vaccination
- Predictive variables to HBV vaccination response.
- Mechanisms of production of antibodies against anti-TNF treatments, and their relation with treatment response.
- Characterization of circulating dendritic cells and monocytes and intestinal dendritic cells and macrophages in IBD patients with different affected tissues
- Identification of the mechanisms mediating the recruitment of circulating dendritic cell and monocyte subsets towards the inflamed mucosa in IBD patients.
- Proteomic characterization of microvesicles in the serum of IBD patients.
- Identification and characterization of novel bioactive peptides secreted by the commensal microbiota with immunomodulatory properties over the intestinal mucosa in IBD patients.

6) 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,
- Long and short-term safety of biological drugs during pregnancy and breats-feeding in IBD patients

7) Eosinophilic Esophagitis (EoE)

- Analysis of the changes in both genes and proteins expression in esophageal biopsies of adult patients with 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.

8) New diagnostic methods

- Serologic diagnosis of Duodenal Ulcer
- Clinical utility of biological markers like fecal calprotectin and lactoferrin as well as azathioprine metabolites
- Genetic/Pharmacogenetics and individualized medicine in IBD
- Improved diagnosis of concomitant diseases in IBD
- Characterization of circulating dendritic cell and monocyte subsets as novel biomarkers in IBD
- Circulating antibodies against microbiota peptides as novel biomarkers in IBD

9) New therapies

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

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Banales, Jesús M, Díaz-Hernández, Laura, Argüelles-Arias, Federico, López-Díaz, Javier, Pérez-Martínez, Isabel, García-Talavera, Noelia, Nuevo-Siguairo, Olivia Karina, Riestra, Sabino, Pérez Gisbert, Francisco Javier. **Prevalence of Malnutrition and Nutritional Characteristics of Patients; With Inflammatory Bowel Disease.** J. Crohns Colitis. 11(12):1430-1439. 2017. PMID: 28981652. IF: 5,813. DOI: 10.1093/ecco-jcc/jjx102. http://dx.doi.org/10.1093/ecco-jcc/jjx102.

CLINICAL TRIALS

PRINCIPAL RESEARCHER: SANTANDER VAQUERO, CECILIO

FLUTicasona en la esofaguitis eosinofílica (FLUTE): estudio de mantenimiento, aleatorizado, doble ciego, controlado con placebo y de búsqueda de dosis de APT-1011 en sujetos con esofaguitis eosinofílica. Adare Pharmaceutical SP-1011-002

EudraCT: 2016-004749-10

PRINCIPAL RESEARCHER: SANTANDER VAQUERO, CECILIO

Registro nacional en trastornos funcionales digestivos, acalasia y otros trastornos motores esofágicos, incontinencia fecal, Síndrome de intestino irritable y estreñimiento crónica. Proyecto Integra

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio en fase IIb, doble ciego, aleatorizado, controlado con placebo, con grupos paralelos y búsqueda de dosis de PF-06651600 y PF-06700841 por vía oral como tratamiento de inducción y tratamiento crónico en pacientes con colitis ulcerosa moderada o grave. Pfizer Ltd B7981005

EudraCT: 2016-003708-29

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio de estrategias de mantenimiento comparando práctica clínica habitual frente a "treat to target" en pacientes con Enfermedad de Crohn tratados con ustekinumab (STARDUST). Janssen-Cilag International NV CNTO-1275CRD3005

EudraCT: 2016-002918-43

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio en fase II, doble ciego, aleatorizado y controlado con placebo para evaluar la eficacia y la seguridad de filgotinib en el tratamiento de la Enfermedad de Crohn de intestino delgado (ECID). Gilead Sciences, Inc GS-US-419-4015

EudraCT: 2016-003179-23

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio de fase III, multicéntrico, aleatorizado, doble ciego y controlado con placebo para investigar la eficacia y la seguridad de Mongersen (GED-0301) en el tratamiento de sujetos adultos y adolescentes con Enfermedad de Crohn activa. Celgene Corporation GED-0301-CD-003

EudraCT: 2015-001924-40

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio de fase 2, aleatorizado, controlado con placebo, multicéntrico para investigar la eficacia y la seguridad de GED-0507-34-Levo (GED0507) para el tratamiento de pacientes con colitis ulcerosa activa. PPM Services SA GED0507-UC-001

EudraCT: 2016-001684-36

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudios combinados de fase III, aleatorizados, doble ciego y controlados con placebo, para evaluar la eficacia y la seguridad de filgotini en la inducción y el mantenimiento de la remisión en pacientes con Enfermedad de Crohn de actividad moderada a intensa. Gilead Sciences, Inc GS-US-419-3895

EudraCT: 2016-001367-36

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudios combinados de fase IIb/III, aleatorizados, doble ciego y controlados con placebo, para evaluar la eficacia y la seguridad de filgotinib en la inducción y el mantenimiento de la remisión en pacientes con colitis ulcerosa de actividad moderada a intensa. Gilead Sciences Incorporated GS-US-418-3898

EudraCT: 2016-001392-78

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio de extensión a largo plazo para evaluar la seguridad de filgotinib en sujetos con Enfermedad de Crohn. Lead Sciences Incorporated GS-US-419-3896

EudraCT: 2016-002763-34

PRINCIPAL RESEARCHER: 06024 PEREZ GISBERT, FRANCISCO JAVIER

Estudio de extensión abierto para evaluar la seguridad de filgotinib en pacientes con Colitis Ulcerosa. Gilead Sciences Incorporated GS-US-418-3899

EudraCT: 2016-002765-58

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio en fase I abierto, aleatorizado, de grupos paralelos para evaluar la farmacocinética, la eficacia y la seguridad de CT-P13 subcutáneo y CT-P13 intravenoso en pacientes con enfermedad activa de Crohn y pacientes con colitis ulcerosa activa. Celltrion Inc. CT-P131.6

EudraCT: 2016-002124-89

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Análisis de la efectividad y seguridad del Switch de infliximab original a biosimilar en los pacientes con Enfermedad Inflamatoria Intestinal. GIS-2017-SWITCH / JPG-INF-2017-01

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Registro de exposición a largo plazo prospectivo y observacional de pacientes adultos con colitis ulcerosa moderada a grave. Registro OPAL. Janssen Biotech Inc. CNTO148UCO4001/JAN-GOL-2016-01

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio de fase IV, aleatorizado, con doble enmascaramiento, para evaluar la seguridad y la proporción de sujetos con curación de una o más fístulas en dos regímenes de dosis de entyvio (vedolizumab i.v.) en el tratamiento de la Enfermedad de Crohn fistulizante. Takeda Development Centre Europe VEDOLIZUMAB-4003

EudraCT: 2015-000852-12

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio fase 3 multicéntrico, de extensión abierta, para evaluar la seguridad y eficacia a largo plazo de ABT-494 en pacientes con colitis ulcerosa. Abbvie Deutschland GMBH & Co. KG M14-533

EudraCT: 2016-000674-38

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio en fase 3, aleatorizado, doble ciego, controlado con placebo y de grupos paralelos para evaluar la eficacia y la seguridad de SHP647 como tratamiento de inducción en sujetos con colitis ulcerosa moderada o grave (FIGARO UC 302). Shire Human Genetic Therapies Inc. SHP647-302

EudraCT: 2017-000572-28

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio de fase 3, aleatorizado, doble ciego, controlado con placebo y de grupos paralelos sobre la eficacia y la seguridad de SHP647 como tratamiento de mantenimiento en sujetos con colitis ulcerosa de moderada a grave (FIGARO UC 303). Shire Human Genetic Therapies Inc. SHP647-303

EudraCT: 2017-000573-37

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Estudio de fase 3, de extensión de seguridad a largo plazo de SHP647 en sujetos con colitis ulcerosa de moderada a grave (AIDA). Shire Human Genetic Therapies Inc. SHP647-304

EudraCT: 2017-000574-11

PRINCIPAL RESEARCHER: PEREZ GISBERT, FRANCISCO JAVIER

Efecto modulador ex-vivo del péptido 5-mer sobre la mucosa de los pacientes con enfermedad inflamatoria intestinal. GIS-PEPIBD-2017

LINE 3.3

Progenitors and cell therapy

GROUP 39

HEAD OF LABORATORY

Luis Madero López

GROUP MEMBERS

- Beatriz Aguado Bueno
- Francisco José Bautista Sirvent
- Andrés Gaspar Castillo Sanz
- Isabel Colmenero Blanco
- Miguel Ángel Díaz Pérez
- Ana María Gómez García
- África González Murillo
- Marta González Vicent
- Álvaro Lassaletta Atienza
- Lucas Moreno Martín Retortillo
- Manuel Ramírez Orellana
- Julián Sevilla Navarro
- Isabel Vicuña Andrés

RESEARCH INTEREST

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.

MAJOR GRANTS

- Ramirez Orellana, Manuel. GENEGRAFT: Phase I/II ex vivo gene therapy clinical trial for recessive dystrophic epidermolysis bullosa using skin equivalent grafts genetically corrected with a COL7A1-encoding SIN retroviral vector. 261392. Comisión Europea. 2012-2017.
- Ramírez Orellana, Manuel. Papel de BMP4 en Leucemia Linfoblástica Aguda Infantil: factor pronóstico y función en la recaída. Fundación uno entre cien mil. 2015-2017.
- Ramirez Orellana, Manuel. VISION: Visual privacy management in user centric open environments. 653642. Comisión Europea. 2015-2017.
- Ramirez Orellana, Manuel. Búsqueda de biomarcadores asociados a la respuesta clínica en niños con cáncer tratados con Celyvir. PI16/02008. ISCIII. 2017-2019.
- Moreno Martín, Lucas Retortillo. Desarrollo de nuevos fármacos y biomarcadores para alteraciones moleculares recurrentes de ALK, RAS/RAF/MAPK/MEK, TERT y CHK1 en neuroblastoma de alto riesgo. PI16/02114. ISCIII. 2017-2019.

Granted 2017:

- Madero López, Luis. Ensayo clínico fase II de CELYVIR en combinación con quimioterapia para niños y adolescentes con tumores sólidos refractarios o en recaída. PI17/02105. ISCIII. 2018-2020.

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Cormenzana Carpio, María, Nehme Álvarez, Daniel, Hernández Marqúes, Carmen, Pérez Martínez, Antonio, Lassaletta Atienza, Álvaro, Madero López, Luis. **Tumores germinales intracraneales: revisión de 21 años.** An Pediatr (Barc). 86(1):20-27. 2017. PMID: 27068071. IF: 1,140. DOI: 10.1016/j.anpedi.2016.03.005. http://dx.doi.org/10.1016/j.anpedi.2016.03.005.

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Jerome, Neil P., Miyazaki, Keiko, Collins, David J., Orton, Matthew R., d'Arcy, James A., Wallace, Toni, Moreno Martín Retortillo, Lucas, Pearson, Andrew D. J., Marshall, Lynley V., Carceller, Fernando, Leach, Martin O., Zacharoulis, Stergios, Koh, Dow-Mu. **Repeatability of derived parameters from histograms following non-Gaussian diffusion modelling of diffusion-weighted imaging in a paediatric oncological cohort.** Eur. Radiol. 27(1):345-353. 2017. PMID: . IF: 3,967. DOI: 10.1007/s00330-016-4318-2. http://dx.doi.org/10.1007/s00330-016-4318-2.

Carceller, Fernando, Jerome, Neil P, Miyazaki, Keiko, Collins, David J, Orton, Matthew R, d'Arcy, James A, Wallace, Toni, Moreno Martín Retortillo, Lucas, Pearson, Andrew D J, Zacharoulis, Stergios, Leach, Martin O, Marshall, Lynley V, Koh, Dow-Mu. **Feasibility and applicability of diffusion-weighted and dynamic contrast-enhanced magnetic resonance imaging in routine assessments of children with high-grade gliomas.** Pediatr Blood Cancer. 64(2):279-283. 2017. PMID: 27615273. IF: 2,513. DOI: 10.1002/pbc.26216. http://dx.doi.org/10.1002/pbc.26216.

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Forero-Castro, Maribel, Robledo, Cristina, Benito, Rocío, Bodega Mayor, Irene, Rapado, Inmaculada, Hernández-Sánchez, María, Abáigar, María, Maria Hernández-Sánchez, Jesús, Quijada-Álamo, Miguel, María Sánchez-Pina, José, Sala-Valdés, Mónica, Araujo-Silva, Fernanda, Kohlmann, Alexander, Luis Fuster, José, Arefi, Maryam, de Las Heras, Natalia, Riesco, Susana, Rodríguez, Juan N, Hermosín, Lourdes, Ribera, Jordi, Camos Guijosa, Mireia, Ramírez Orellana, Manuel, de Heredia Rubio, Cristina Díaz, Barragán, Eva, Martínez, Joaquín, Ribera, José M, Fernández Ruiz, Elena, Hernández-Rivas, Jesús-María. **Mutations in TP53 and JAK2 are independent prognostic biomarkers in B-cell precursor acute lymphoblastic leukaemia.** Br J Cancer. 117(2):256-265. 2017. PMID: 28557976. IF: 6,176. DOI: 10.1038/bjc.2017.152. http://dx.doi.org/10.1038/bjc.2017.152.

Moreno Martín Retortillo, Lucas, Pearson, Andrew D J, Paoletti, Xavier, Jimenez, Irene, Geoerger, Birgit, Kearns, Pamela R, Zwaan, C Michel, Doz, Francois, Baruchel, Andre, Vormoor, Josef, Casanova, Michela, Pfister, Stefan M, Morland, Bruce, Vassal, Gilles, Innovative Therapies for Children with Cancer (ITCC) Consortium. **Early phase clinical trials of anticancer agents in children and adolescents - an ITCC perspective.** NAT REV CLIN ONCOL. 14(8):497-507. 2017. PMID: 28508875. IF: 20,693. DOI: 10.1038/nrclinonc.2017.59. http://dx.doi.org/10.1038/nrclinonc.2017.59.

Moreno Martín Retortillo, Lucas, Caron, Hubert, Geoerger, Birgit, Eggert, Angelika, Schleiermacher, Gudrun, Brock, Penelope, Valteau-Couanet, Dominique, Chesler, Louis, Schulte, Johannes H, De Preter, Katleen, Molenaar, Jan, Schramm, Alexander, Eilers, Martin, Van Maerken, Tom, Johnsen, John Inge, Garrett, Michelle, George, Sally L, Tweddle, Deborah A, Kogner, Per, Berthold, Frank, Koster, Jan, Barone, Giuseppe, Tucker, Elizabeth R, Marshall, Lynley, Herold, Ralf, Sterba, Jaroslav, Norga, Koen, Vassal, Gilles, Pearson, Andrew Dj. **Accelerating drug development for neuroblastoma - New Drug Development; Strategy: an Innovative Therapies for Children with Cancer, European; Network for Cancer Research in Children and Adolescents and; International Society of Paediatric Oncology Europe.** Expert. Opin. Drug Discov. 12(8):801-811. 2017. PMID: 28604107. IF: 3,876. DOI: 10.1080/17460441.2017.1340269. http://dx.doi.org/10.1080/17460441.2017.1340269.

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Bautista Sirvent, Francisco José, Moreno Martín Retortillo, Lucas, Marshall, Lynley, Pearson, Andrew D J, Geoerger, Birgit, Paoletti, Xavier. **Revisiting the definition of dose-limiting toxicities in paediatric oncology phase I clinical trials: An analysis from the Innovative Therapies for Children with Cancer Consortium.** Eur J Cancer. 86:275-284. 2017. PMID: 29055843. IF: 6,029. DOI: 10.1016/j.ejca.2017.09.015. http://dx.doi.org/10.1016/j.ejca.2017.09.015.

Bautista Sirvent, Francisco José, Fioravantti, Victoria, de Rojas, Teresa, Carceller, Fernando, Madero López, Luis, Lassaletta Atienza, Álvaro, Moreno Martín Retortillo, Lucas. **Medulloblastoma in children and adolescents: a systematic review of; contemporary phase I and II clinical trials and biology update.** Cancer Med. 6(11):2606-2624. 2017. PMID: 28980418. IF: 3,362. DOI: 10.1002/cam4.1171. http://dx.doi.org/10.1002/cam4.1171.

Illade, Laura, Fioravantti, Victoria, Andion, Maitane, Hernandez-Marques, Carmen, Madero López, Luis, Lassaletta Atienza, Álvaro. **Dicentric translocation (9;12) in acute lymphoblastic leukemia: a chromosomal abnormality with an excellent prognosis?.** TUMORI. 103(Suppl. 1). 2017. PMID: 28967092. IF: 1,233. DOI: 10.5301/tj.5000683. http://dx.doi.org/10.5301/tj.5000683.

Izquierdo, Elisa, Yuan, Lina, George, Sally, Hubank, Michael, Jones, Chris, Proszek, Paula, Shipley, Janet, Gatz, Susanne A, Stinson, Caedyn, Moore, Andrew S, Clifford, Steven C, Hicks, Debbie, Lindsey, Janet C, Hill, Rebecca M, Jacques, Thomas S, Chalker, Jane, Thway, Khin, O'Connor, Simon, Marshall, Lynley, Moreno Martín Retortillo, Lucas, Pearson, Andrew, Chesler, Louis, Walker, Brian A, De Castro, David Gonzalez. **Development of a targeted sequencing approach to identify prognostic, predictive and diagnostic markers in paediatric solid tumours.** ONCOTARGET. 8(67):112036-112050. 2017. PMID: 29340109. IF: 5,168. DOI: 10.18632/oncotarget.23000. http://dx.doi.org/10.18632/oncotarget.23000.

CLINICAL TRIALS

PRINCIPAL RESEARCHER: MIGUEL ÁNGEL DÍAZ PÉREZ

Estudio adaptativo y aleatorizado de fase 3 para comparar la eficacia y la seguridad de Defibrotide frente al mejor tratamiento de soporte en la prevención de la enfermedad venooclusiva hepática en pacientes adultos y pediátricos sometidos a un trasplante hematopoyético de células madre. Jazz Pharmaceuticals 15-007

EudraCT: 2016-002004-10

PRINCIPAL RESEARCHER: FRANCISCO JOSÉ BAUTISTA SIRVENT

Estudio Fase I-II de Vinblastina en Combinación con Nilotinib en Niños, Adolescentes, y Adultos jóvenes con Glioma de bajo grado Refractario o Recurrente. Gustave Roussy IGR 2012 /1883

EudraCT: 2012-003005-10

PRINCIPAL RESEARCHER: ALVARO LASSALETTA ATIENZA

Ensayo clínico fase Ib/II de nivolumab en monoterapia y nivolumab en combinación con ipilimumab en pacientes pediátricos con neoplasias malignas primarias del SNC de alto grado. Bristol Myers CA209-908

EudraCT: 2016-004441-82

PRINCIPAL RESEARCHER: MIGUEL ÁNGEL DÍAZ PÉREZ

Estudio de extensión fase II de linfocitos T con CaspaCide (BPX-501) de un donante emparentado parcialmente compatible respecto al HLA tras selección negativa de linfocitos T TCR αβ+ en pacientes pediátricos afectados de trastornos hematológicos. Bellicum Pharmaceuticals BP-004

EudraCT: 2014-000584-41

PRINCIPAL RESEARCHER: LUCAS MORENO MARTIN RETORTILLO

Estudio clínico de fase 2 de pomalidomida (CC-4047) en monoterapia para niños y adultos jóvenes con tumores cerebrales primarios recurrentes o progresivos. Celgene CC-4047-BRN-001

EudraCT: 2016-002903-25

PRINCIPAL RESEARCHER: MIGUEL ÁNGEL DÍAZ PÉREZ

Estudio de un solo grupo para evaluar la eficacia de UVADEX® (metoxsaleno) solución estéril en conjunto con el sistema de fotoféresis CELLEX® de THERAKOS® en pacientes pediátricos con enfermedad del injerto contra el huésped aguda (EICHa) refractaria a esteroides. Therakos, Inc. TKS-2014-001

EudraCT: 2014-004806-14

PRINCIPAL RESEARCHER: MIGUEL ÁNGEL DÍAZ PÉREZ

Incidence and outcomes associated with the management of adenovirus infections in allogeneic hematopoietic cell transplant recipients: advance. Chimerix CHI-ADE-2016-01

LINE 3.4

Advanced therapies in oncohematology

GROUP 44

HEAD OF LABORATORY

Juan Luis Steegmann Olmedillas

GROUP MEMBERS

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

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 variegate 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.

PUBLICATIONS (24)

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: STEEGMANN OLMEDILLAS, JUAN-LUIS

Estudio observacional, internacional, multicéntrico, sobre el uso de ruxolitinib en el tratamiento de pacientes con policitemia vera que presentan resistencia o intolerancia a la hidroxiurea. Novartis Farmaceutica, S.A. CINC424BIC04

PRINCIPAL RESEARCHER: GOMEZ GARCIA-SORIA, VALLE

Estudio de fase III aleatorizado, abierto y multicéntrico de ruxolitinib frente a la mejor terapia disponible en pacientes con Enfermedad de Injerto contra huésped crónica refractaria a corticosteroides tras trasplante alogénico de células madre. Novartis Farmaceutica, S.A. CINC424D2301

EudraCT: 2016-004432-38

PRINCIPAL RESEARCHER: FIGUERA ALVAREZ, ANGELA

Estudio de fase IIIb, abierto y multicéntrico, para evaluar la seguridad y eficacia de midostaurina (PKC412) en pacientes adultos con leucemia mieloide aguda (LMA) con mutación FLT3 de nuevo diagnóstico, que son candidatos a quimioterapia "7+3" o "5+2". Novartis Pharma Services AG CPKC412A2408

EudraCT: 2016-004440-12

PRINCIPAL RESEARCHER: LOSCERTALES PUEYO, JAVIER

Estudio de fase III, internacional, abierto y aleatorizado de BGB-3111 en comparación con bendamustina más rituximab, en pacientes con leucemia linfocítica crónica o linfoma linfocítico de células pequeñas no tratados previamente. Beigene Ltd. BGB-3111-304

EudraCT: 2017-001551-31

PRINCIPAL RESEARCHER: ALEGRE AMOR, ADRIAN

Estudio de fase 3, aleatorizado, comparativo, sin enmascaramiento, en el que se compara melfluen/dexametasona con pomalidomida/dexametasona, en pacientes con mieloma múltiple recidivante y resistente al tratamiento, que no responden a lenalidomida. Oncopeptides AB OP-103

EudraCT: 2016-003517-95

PRINCIPAL RESEARCHER: FIGUERA ALVAREZ, ANGELA

Estudio observacional prospectivo sobre la supervivencia global y la calidad de vida en pacientes mayores de 60 años diagnosticados de leucemia mieloide aguda en España, tratados según la práctica clínica habitual. Estudio SvLMA. Celgene, S.L. CEL-LMA-2017-01

PRINCIPAL RESEARCHER: LOSCERTALES PUEYO, JAVIER

Estudio para la medición de la longitud telomericia y actividad telomerasa como biomarcadores de pronóstico asociado al registro regional puesto en marcha para el diagnóstico, seguimiento y tratamiento de la leucemia linfocítica crónica (LLC). Life Length_LL-RLLC-ONC001

PRINCIPAL RESEARCHER: LOSCERTALES PUEYO, JAVIER

Registro regional para evaluar la práctica médica con observación longitudinal para el diagnóstico, seguimiento y tratamiento de la leucemia linfocítica crónica. Asociación Madrileña de Hematología_REG-LLC/ REGISTRO LLC

PRINCIPAL RESEARCHER: ALEGRE AMOR, ADRIAN

Estudio en fase III para comparar la administración de pomalidomida y dexametasona con o sin daratumumab en pacientes con mieloma múltiple recurrente o resistente que han recibido al menos una línea de tratamiento previo con lenalidomida y con inhibidor del proteasoma: Estudio Apollo. European Myeloma Network (EMN)_EMN14/54767414MMY3013

EudraCT: 2017-001618-27

PRINCIPAL RESEARCHER: FIGUERA ALVAREZ, ANGELA

Estudio de fase III, aleatorizado, doble ciego, multicéntrico y controlado con placebo, de pracinostat en combinación con azacitidina en pacientes >= 18 años con leucemia mieloide aguda de diagnóstico reciente no aptos para la quimioterapia de introducción habitual. Helsinn Healthcare SA PRAN-16-52/MEI-009

EudraCT: 2016-004724-34

PRINCIPAL RESEARCHER: FIGUERA ALVAREZ, ANGELA

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EudraCT: 2016-001466-28

PRINCIPAL RESEARCHER: ALEGRE AMOR, ADRIAN

Estudio de fase IB/II de cobimetinib administrado en monoterapia y en combinación con venetoclax, con o sin atezolizumab, en pacientes con mieloma múltiple recidivante y refractario. F. Hoffmann-La Roche Ltd. BO39813

EudraCT: 2017-000830-68

PRINCIPAL RESEARCHER: STEEGMANN OLMEDILLAS, JUAN-LUIS

Estudio fase 3, multicéntrico, abierto, aleatorizado, de ABL001 oral frente a bosutinib, en pacientes con leucemia mieloide crónica en fase (LMC-FC) previamente tratados con 2 o mas inhibidores de la tirosina quinasa. Novartis Farmaceutica, S.A. CABL001A2301

EudraCT: 2016-002461-66

PRINCIPAL RESEARCHER: LOSCERTALES PUEYO, JAVIER

Estudio multicéntrico, no aleatorizado y abierto, para evaluar la eficacia y seguridad de ibrutinib seguido por consolidación con ofatumumab en pacientes con Leucemia Linfocítica Crónica (LLC) o Linfoma Linfocítico de células Pequeñas (LLCP) sin tratamiento previo. Fundacion Pethema GELLC-7

EudraCT: 2016-004937-26

PRINCIPAL RESEARCHER: ALEGRE AMOR, ADRIAN

Ensayo clínica en fase III, aleatorizado, abierto y multicéntrico para comparar isatuximab (SAR650984) en combinación con pomalidomida y dosis bajas dedaxametasona frente a pomalidomida y dosis bajas de dexametaxona en pacientes con mieloma múltiple refractario o recidivante y refractario. Sanofi-Aventis Recherche et Development EFC14335

EudraCT: 2016-003097-41

LINE 3.5

Biological, cellular and molecular monitoring in oncohematology

GROUP 45

HEAD OF LABORATORY

Elena Fernández Ruiz

GROUP MEMBERS

- Irene Bodega Mayor
- Santa Matilde Santos Roncero
- Edgar Alejandro Turrubiartes Martínez

RESEARCH INTEREST

Chromosomal translocations and gene mutations are frequently associated with the etiology of hematologic neoplasm. The JAK family of non-receptor tyrosine kinases (which comprises four members: JAK1, JAK2, JAK3 and TYK2) are involved in cytokine signalling on immune and hematopoietic cells and are crucial to normal hematopoiesis through the recruitment of downstream 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 have found two patients (3%) each of them with a mutation not previously described (TYK2mut), and twelve patients (18%) with non-synonymous polymorphisms, some of which have already been demonstrated to result in a loss-of-function of the protein.

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 to maintain an accurate immunological response for appropriate tumor surveillance, and that those immune responses are based on a functional JAK-dependent signal transduction, it is of high relevance to know the role of the complex formed by cytokine receptors, JAK proteins and their target genes in this response. In this sense, it is necessary to know the role of TYK2 in the immune system.

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GROUP 46

HEAD OF LABORATORY

Cecilia Muñoz Calleja

GROUP MEMBERS

- Beatriz Colom Fernández
- Carlos Cuesta Mateos
- Yaiza Pérez García

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 ganglionar 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.

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 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 different 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.

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.

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LINE 3.6

New diagnostic and therapeutic advances in cardiovascular diseases

GROUP 58

HEAD OF LABORATORY

Fernando Alfonso Manterola

GROUP MEMBERS

- Amparo Benedicto Buendía
- Rosa María Moreno Carriles
- Guillermo Reyes Copa
- Antonio Reyes García
- Fernando Rivero Crespo
- Bernhard Seidelberger

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 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 co-

ronary 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.

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PRINCIPAL RESEARCHER: ALFONSO MANTEROLA, FERNANDO

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PRINCIPAL RESEARCHER: ALFONSO MANTEROLA, FERNANDO

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GROUP 48

HEAD OF LABORATORY

Luis Jesús Jiménez Borreguero

GROUP MEMBERS

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- María José Olivera Serrano

RESEARCH INTEREST

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.

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GROUP 57

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Carmen Suárez Fernández

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- José Juan Curbelo García
- Carmen del Arco Galán
- Alfonsa Friera Reyes
- Iluminada García Polo
- Paloma María Gil Martínez
- Patricia Ibáñez Sanz
- Fernando Moldenhauer Díaz
- Nuria Ruiz-Giménez Arrieta
- María Gema Vega González
- María Mercedes Vinuesa Sebastián
- Andrés Carlos Von Wernitz Teleki

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 venoues 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.

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).

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: SUAREZ FERNANDEZ, CARMEN

Registro informatizado de pacientes de edad avanzada con Enfermedad Vascular. Fund.Esp.M.Interna(FEMI)y Soc. Esp. M.Interna(SEMI). NONAVASC 2

PRINCIPAL RESEARCHER: SUAREZ FERNANDEZ, CARMEN

Estudio de fase III, internacional, multicéntrico, aleatorizado y abierto, para evaluar la eficacia en la reducción de cLDL y presión arterial y la seguridad de Trinomia® versus tratamiento habitual en pacientes de muy alto riesgo cardiovascular sin evento previo: Estudio VULCANO. Ferrer Internacional FMD-TRI-2016-01

EudraCT: 2016-004015-13

PRINCIPAL RESEARCHER: ARCO GALAN, CARMEN

Ensayo clínico fase IIIb, aleatorizado, abierto, para evaluar el alivio del dolor con metoxifluorato inhalado, en comparación con el protocolo actual para el tratamiento del dolor de origen traumático, en adultos atendidos en unidades de urgencias españolas. Mundipharma Pharmaceuticals, S. L. INMEDIATE

EudraCT: 2017-000338-70

GROUP 49

HEAD OF LABORATORY

Blanca Novella Arribas

GROUP MEMBERS

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

RESEARCH INTEREST

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.

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 / MAPAPRES 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.

PUBLICATIONS (4)

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LINE 3.7

New therapies in infectious pathologies

GROUP 50

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Ignacio de los Santos Gil

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- Ana María Isabel Salas Aparicio
- Jesús Sanz Sanz
- María Cristina Sarria Cepeda

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 from patients with HIV infection who come to our clinic for the first time, for epidemiological studies, and sending blood samples periodically to the Biobank Network of AIDS, for virological and immunological studies. This project will keep going for years, and will also continue collecting the data necessary for these studies.

We are also involved in clinical trials of new drugs for HIV, including the combination of Darunavir and cobicistat and the new nonnucleoside, Doravirine, both drugs for naive and pretreated patients. These trials began in 2015 and will last three years.

In addition, another field of interest, in which we have more than ten years of experience, is the HIV / HCV coinfection. This aspect of the HIV infection is currently having a major projection, due to the appearance of new drugs to treat hepatitis C, direct antiviral agents, that have revolutionized the treatment, with the greatest effectiveness until now (more than 90%) and few side effects. We are collaborating with the HEPAVIR cohort of coinfected patients, along with various centres in the Spanish territory, where we have a number of more than 600 patients treated 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.

In this sense, and also in a multicentre group, we are studying the impact of sustained viral response in cardiovascular risk and inflammation markers, and look forward to the first data in late 2018.

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CLINICAL TRIALS

PRINCIPAL RESEARCHER: SANTOS GIL, IGNACIO DE LOS

Ensayo clínico fase IV, abierto, aleatorizado y piloto diseñado para evaluar la potencial neurotoxicidad de dolutegravir/lamivudina/abacavir en pacientes VIH neurosintomáticos y su reversibilidad tras el cambio a el vitegravir/cobicistat/emitricitabina/tenofovir alafenamida. ESTUDIO DREAM. FUNDACION SEIMC-GESIDA GESIDA 9016

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PRINCIPAL RESEARCHER: SANTOS GIL, IGNACIO DE LOS

Estudio observacional del uso concomitante de los fármacos ledipasvir/ sofosbuvir y tenofovir disoproxil fumarato + potenciadores farmacocinéticos en adultos coinfectados por hepatitis C crónica y VIH-1. Estudio Heaven. Gilead Sciences Europe Limited GS-EU-337-1820

PRINCIPAL RESEARCHER: SANTOS GIL, IGNACIO DE LOS

Estudio en fase III, controlado con placebo, aleatorizado, con evaluación ciega por terceros, para evaluar la eficacia, la seguridad y la tolerabilidad de una vacuna de clostridium difficile en adultos de 50 años de edad o mayores. Pfizer Inc B5091007

EudraCT: 2016-003866-14

PRINCIPAL RESEARCHER: SANTOS GIL, IGNACIO DE LOS

Estudio piloto de fase 2a aleatorizado, doble ciego, controlado con placebo para investigar la actividad antiviral, los resultados clínicos, la seguridad, la tolerabilidad y la farmacocinética de dos dosis de JNJ- 53718678 en pacientes adultos no hospitalizados infectados por el virus respiratorio sincital. Janssen Research Development LLC 53718678RSV2004

EudraCT: 2017-003252-24

PRINCIPAL RESEARCHER: CAMARA LLANZA, JOSE-RAFAEL

Estudio de fase 3, multicéntrico, aleatorizado, doble ciego, con doble simulación, con controla activo para evaluar la eficacia y la seguridad de maribavir en comparación con valganciclovir para el tratamiento de la infección por citomegalovirus (CMV) en receptores de un trasplante de células madre hematopoyéticas. Shire Viropharma Incorporated SHP620-302

EudraCT: 2015-004726-34

PRINCIPAL RESEARCHER: CAMARA LLANZA, JOSE-RAFAEL

Estudio sobre las complicaciones clínicas directas e indirectas derivadas de la detección de la infección por citomegalovirus (CMV) en pacientes con trasplante alogénico de células progenitoras hematopoyéticas (ALO-TPH). Estudio CMV-ALOTPH. Merck Sharp & Dohme de España, S.A. MSD-CMV-2017-01

GROUP 51

HEAD OF LABORATORY

Javier Aspa Marco

GROUP MEMBERS

- Guillermo Fernández Jiménez
- José María Galván Román
- Ángel Lancho Sánchez
- Sergio Luquero Bueno
- María del Mar Ortega Gómez
- Olga Rajas Naranjo
- Lorena Vega Piris

RESEARCH INTEREST

Community acquired pneumonia (CAP) is an infectious disease with high prevalence and great morbid-mortality rate. Our group has been working on different collaborative research lines.

Our current research project aims at the incidence of cardiovascular events following hospitalization for CAP in adults, and its association with different markers of inflammation. In this project we try to quantify the incidence of cardiovas-

cular disease in adult patients, in the year after hospital admittance due to CAP, and to establish its possible relationship with mortality. Moreover, we will try to describe the distribution of a wide spectrum of immune response mediators upon the admittance to and release from hospital. This will allow characterizing an inflammatory profile for these patients and determining a possible relationship with the incidence of cardiovascular disease.

The preliminary results are very promising: we have found a link between long-term mortality and occurrence of cardiovascular events. We have also been able to select some biomarkers to improve prognosis scores at admission. We need a longer time monitoring to ensure the relationship between biomarkers and development of cardiovascular events.

MicroRNAs (miRNAs) are a family of endogenous, small, noncoding RNA molecules that modulate physiological and pathological processes by 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. The expression of different miRNAs in patients with cardiovascular events had also been published recently. We propose to explore the role of different miRNAs in the development of heart failure in patients with CAP and the regulation of the inflammatory response in CAP patients.

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Ortega Gómez, María del Mar, Luquero Bueno, Sergio, Abad Santos, Francisco. Capítulo 11: Farmacogenómica y Biobancos. ENSAYOS CLÍNICOS EN ESPAÑA: Actualización en ética, normativa, metodología y nuevas tecnologías. pp. 285 - 307. 01/05/2017. ISBN 9788469131161

Abad Santos, Francisco, Ochoa Mazarro, María Dolores, Ortega Gómez, María del Mar. Capítulo 4: CEIm. Composición. Funciones. ENSAYOS CLÍNICOS EN ESPAÑA: Actualización en ética, normativa, metodología y nuevas tecnologías. pp. 111 - 136. 01/05/2017. ISBN 9788469131161

GROUP 52

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- Carmen María Serrano Morago
- Tamara Soler Maniega
- Verónica Bernadette Valdez Blanco
- Nelly Daniela Zurita Cruz

RESEARCH INTEREST

A great interest in the role of human microbiome in health and disease exists due to the accesible 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 signalling 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 the relationship with H. pylori, and with other human diseases are not well established.

Helicobacter 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 from the World Health Organization. Several treatment regimens have been used to eradicate this microorganism. Resistance to the antibiotics is considered the main cause of treatment failure.

This group includes members of the Microbiology Department with interest in diagnosis and treatment of several infectious diseases such as fungi, Mycobacterium spp or CMV infection, as well as infections in cystic Fibrosys patients.

The main lines of research at present time and for the near future are: (1) the study of gastric microbiome and its relationship with H. pylori infection but also with other human diseases with potential therapeutic applications. The role of human microbiome in H. pylori infections but also in other diseases is going to be an exciting research area for the nextfew years. (2) We are interested in antimicrobial resistance in H. pylori (national and international surveys) and in molecular methods for detection of clarithromycin resistance and heteroresistance. (3) We are also interested in the in vitro activity of wine phenolic compounds against H. pylori. (4) The role of phages and CRISPR in H. pylori strains and their relationship with the transfer of resistance genes is an area of interest.

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LINE 3.8

Individualized medicine in solid tumors

GROUP 40

HEAD OF LABORATORY

Ramón Colomer Bosch

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- Nuria Romero Laorden
- José Miguel Sánchez Torres
- Natalia Torres Waldhaus
- Erich Alberto Vargas Diez
- Francisco Eduardo Viamontes Ugalde
- Ivana Zagorac

RESEARCH INTEREST

Our line of clinical research is focused on the development of new cancer therapies. We have contributed to the clinical evaluation of three-weekly Trastuzumab and neoadjuvant Pertuzumab, both drugs currently the standard of therapy in HER2+ breast cancer, or the HER2 tyrosine kinase inhibitor Neratinib in advanced breast cancer. We have evaluated novel drugs such as Nintedanib or Dovitinib in phase I and phase II trials, 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 breast cancer, including the rare double amplification of FGFR-1 and CCDN1. By using a systems biology approach, we are clustering breast cancer into subtypes defined by biologic features that constitute therapeutic targets. We have also studies the interactions of fatty acids and oncogenes.

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Mondejar Solis, Rebeca, Collazo Lorduy, A, Viñas Villaró, G., Colomer Bosch, Ramón. Los agentes antimicrotúbulo: taxanos, alcaloides de la vinca, epotilonas y halicondrinas. Oncomecum. 22/09/2017. ISBN 9788499269962

CLINICAL TRIALS

PRINCIPAL RESEARCHER: SANCHEZ TORRES, JOSE MIGUEL

Ensayo clínico fase II, exploratorio y multicéntrico, de quimioterapia neo-adyuvante para el tratamiento del cáncer de pulmón no microcítico estadio III operable. Grupo Español de Cáncer de Pulmón (GECP) NADIM(GECP 16/03)

EudraCT: 2016-003732-20

PRINCIPAL RESEARCHER: SANCHEZ TORRES, JOSE MIGUEL

Estudio fase III multicéntrico, abierto, randomizado para evaluar la eficacia y seguridad de atezolizumab comparado con quimioterapia en pacientes con cáncer no microcítico de pulmón avanzado o recurrente (estadio IIIB no tratable con múltiples modalidades terapeúticas) o metastásico (estadio IV), no tratados previamente y que no se consideran aptos para recibir quimioterapia que contiene platino. F. Hoffmann-La Roche Ltd MO29872

EudraCT: 2015-004105-16

PRINCIPAL RESEARCHER: SANCHEZ TORRES, JOSE MIGUEL

Ensayo clínico aleatorizado fase II de terapia combinada de osimertinib y bevacizumab frente al uso de osimertinib en monoterapia como tratamiento de segunda línea en pacientes con cáncer de pulmón no microcítico estadío IIIb-IVb con EGFRm y T790m confirmadas. Grupo Español de Cáncer de Pulmón (GECP) ETOP 10-16 BOOSTER

EudraCT: 2016-002029-12

PRINCIPAL RESEARCHER: SANCHEZ TORRES, JOSE MIGUEL

Gio-Tag: Estudio de datos de la vida real sobre la terapia secuencial con Gi(l)otrif®/afatinib como tratamiento de primera línea seguido de osimertinib en pacientes con cáncer de pulmón no microcítico avanzado con mutación del EGFR. Boehringer Ingelheim International GMBH 1200-0286/BII-AFA-2017-01

PRINCIPAL RESEARCHER: COLOMER BOSCH, RAMON

Estudio en fase III, multicéntrico, aleatorizado, doble ciego y controlado con placebo para evaluar la eficacia y seguridad de ribociclib con tratamiento endocrino como tratamiento adyuvante en pacientes con cáncer de mama hormonal positivo, HER" negativo, temprano y de alto riesgo. Novartis Farmaceutica, S.A. CLEE011G2301

EudraCT: 2014-001795-53

PRINCIPAL RESEARCHER: COLOMER BOSCH, RAMON

Estudio en fase III, multicéntrico, doble ciego y controlado con placebo para evaluar la eficacia y seguridad de ribociclib con tratamiento endocrino como tratamiento adyuvante en pacientes con cáncer de mama receptor hormonal positivo, HER" negativo, temprano y de riesgo intermedio. Novartis Farmaceutica, S.A. CLEE011H2301

EudraCT: 2016-005135-33

PRINCIPAL RESEARCHER: COLOMER BOSCH, RAMON

Estudio en fase 3 aleatorizado, abierto, de abemaciclib en combinación con tratamiento endocrino adyuvante estándar, en pacientes con cáncer de mama en estadios iniciales, de alto riesgo, con afectación ganglionar, receptores hormonales positivos, Her2 negativo. Eli Lilly & Company I3Y-MC-JPCF

EudraCT: 2016-004362-26

PRINCIPAL RESEARCHER: GARCIA FERNANDEZ, JOSE LUIS

Osteosíntesis de pared torácica. Grupo de trabajo SECT. Sociedad Española de Cirugía Torácica (SECT) ESTUDIO GEOPT

PRINCIPAL RESEARCHER: BALLESTEROS GARCIA, ANA-ISABEL

COMPLEEMENT-1: Estudio de fase IIIb, abierto, multicéntrico, para evaluar la seguridad y la eficacia de ribociclib (LEE011) en combinación con letrozol en el tratamiento de hombres y mujeres pre/postmenopáusicas con cáncer de mama avanzado (CMA) con receptor hormonal positivo (HR+) y HER 2 negativo (HER2-) que no hayan recibido tratamiento hormonal para la enfermedad avanzada. Novartis Farmaceutica, S.A. CLEE011A2404

EudraCT: 2016-003467-19

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio Proradium. Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de próstata resistente a la castración tratados con RADIUM-223; Estudio Proradium. Instituto de Investigación Biomédica de Málaga IBIMA-CNIO-CP-01-2016/CNI-RAD-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Identificación de factores biológicos asociados a la progresión metastásica precoz en pacientes con cáncer de próstata resistente a la castración MO con elevación del PSA (JPV-CP); Estudio MO. JPV-CP-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PRÓStata resistente a la castración tratados con ABIraterona; (Versión 2.0: 16-01-15).Estudio Prosabi. Centro Nacional de Investigación Oncológica (CNIO) CNIO-CP-03-2014/CNI-ABI-2014-02

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PRÓStata resistente a la castración tratados con ENZAlutamida; (Versión 1.0:01-02-16) Estudio Prosenza. Instituto de Investigación Biomédica de Málaga BIMA-CNIO-CP-01-2016/CNI-ENZ-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PROstata resistente a la castración tratados con doceTaxel o Cabazitaxel; (Versión 3.0: 16-01-15).Estudio Prostac. Centro Nacional de Investigación Oncológica (CNIO) CNIO-CP-02-2014/CNI-DOC-2014-02

GROUP 53

HEAD OF LABORATORY

Almudena Zapatero Laborda

GROUP MEMBERS

- María Magdalena Adrados de Llano
- Ramón Cristóbal Arellano Gañan
- Pablo Castro Tejero
- José Alfonso Cruz Conde
- Feliciano García Vicente
- María del Carmen Martín de Vidales Cervantes
- Leopoldo Pérez González
- María Roch González

RESEARCH INTEREST

This group is focused on four lines of investigation:

1) The identification of clinical and biological markers as risk and predicitive factors in Prostate cancer.

- We have worked in a cooperative project with the CNIO to determine the prognostic value of the expression of molecular markers (hif1a, pak-6, and psmb4) in the biopsy specimens of intermediate- and high-risk localized prostate cancer patients treated with androgen deprivation and dose escalation radiation therapy. We also participate in an international project with a cell cycle progression (CCP) gene panel, a test for risk assessment of localized prostate cancer (PCa) patients. The test combines the gene expression levels of 31 genes related to cell cycle progression and 15 housekeeping genes into a cell cycle progression (CCP) score that is used to predict 10-year prostate cancer specific disease progression and mortality. Finally, we have an active project in collaboration with HU Santiago de Compostela and HU 12 de Octubre, Madrid, regarding the prognostic and predictive role of CTCs in high –risk non-metastatic prostate cancer.

2) Prostate cancer treatment:

- A phase III clinical trial to determine the optimum duration of androgen deprivation alongside high-dose radiotherapy in localized intermediate and high-risk PCa patiens (:“ 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 2005-000417-36ClinicalTrials.gov, number NCT02175212).
- 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.
- Participation in another 4 International Randomized Phase III clinical trials (MDV3100-14, MDV3100-13, JNJ-56021927 and EORTC 1333)

3) High Technology and Innovation:

- Over the last 10 years we have actively worked in Intensity Modulated Radiation Treatment – Image Guided Radiotherapy (IMRT-IGRT) versus three-dimensional conformal radiotherapy (3DCRT): comparative results on 671 patients treated in a single institution, that demonstrate the significant reduction in acute and late genitourinary and rectal toxicity in patients with prostate cancer treated with IMRT-IGRT.
- Implementation of the new technology VMAT (Volumetric Modulated Arc Therapy) and its application in

the treatment of patients with localized and metastatic PCa. Participation on SBRT of Oligometastases, phase II national trial (GICOR SBRT).

- Design and implementation of a Phase II clinical trial on "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

4) National Register of Prostate Cancer Treated with Radiotherapy (RECAP): We participate in the design of this ambitious project whose most relevant work is the construction of nomograms for predicting the development of metastases and biochemical failure in cancer of prostate treated with radiation therapy.

5) BLADDER CANCER- BLADDER SPARING PROGRAM The optimal management of muscle-invasive bladder cancer remains a continuous subject of controversy. Although trimodality treatment, including transurethral resection of bladder tumour (TURBT) and radio-chemotherapy (RCT), has proven to be an alternative to primary cystectomy, the optimal regimen and combination of RT and chemotherapy remains to be established.

- 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.

PUBLICATIONS (2)

Zapatero Laborda, Almudena, Roch González, María, Büchser, D, Castro Tejero, Pablo, Fernández-Banda, L, Pozo, G, Liñán, O, Martín de Vidales Cervantes, María del Carmen, Cruz Conde, José Alfonso, García Vicente, Feliciano. **Reduced late urinary toxicity with high-dose intensity-modulated; radiotherapy using intra-prostate fiducial markers for localized; prostate cancer.** Clin. Transl. Oncol.. 19(9):1161-1167. 2017. PMID: 28374321. IF: 2,353. DOI: 10.1007/s12094-017-1655-9. http://dx.doi.org/10.1007/s12094-017-1655-9.

Xie, Wanling, Regan, Meredith M, Buyse, Marc, Halabi, Susan, Kantoff, Philip W, Sartor, Oliver, Soule, Howard, Clarke, Noel W, Collette, Laurence, Dignam, James J, Fizazi, Karim, Paruleker, Wendy R, Sandler, Howard M, Sydes, Matthew R, Tombal, Bertrand, Williams, Scott G, Sweeney, Christopher J, ICECaP Working Group, Zapatero Laborda, Almudena. **Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer.** J Clin Oncol. 35(27):3097-3104. 2017. PMID: 28796587. IF: 24,008. DOI: 10.1200/JCO.2017.73.9987. http://dx.doi.org/10.1200/JCO.2017.73.9987.

BOOKS

Zapatero Laborda, Almudena, Cruz Conde, José Alfonso, Büscher, David, Fernández Banda, Laura. Papel de la radioterapia en el cáncher de próstata de alta riesgo N0. Controversias en cáncer de próstata III. pp. 98 - 115. ISBN 9788461777846

CLINICAL TRIALS

PRINCIPAL RESEARCHER: ZAPATERO LABORDA, MARIA-ALMUDENA

Registro Español de Cáncer de Próstata (RECAP): tratamiento radioterápico en pacientes con cáncer de próstata conforme a la práctic a clínica habitual en los servicios de oncología radioterápica españoles. SEOR-FEOR SEO-RAD-2017-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio Proradium. Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de próstata resistente a la castración tratados con RADIUM-223; Estudio Proradium. Instituto de Investigación Biomédica de Málaga IBIMA-CNIO-CP-01-2016/CNI-RAD-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Identificación de factores biológicos asociados a la progresión metastásica precoz en pacientes con cáncer de próstata resistente a la castración MO con elevación del PSA (JPV-CP); Estudio MO. JPV-CP-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PRÓstata resistente a la castración tratados con ABIraterona; (Versión 2.0: 16-01-15).Estudio Prosabi. Centro Nacional de Investigación Oncológica (CNIO) CNIO-CP-03-2014/CNI-ABI-2014-02

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PRÓstata resistente a la castración tratados con ENZAlutamida; (Versión 1.0:01-02-16) Estudio Prosenza. Instituto de Investigación Biomédica de Málaga BIMA-CNIO-CP-01-2016/CNI-ENZ-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PROstata resistente a la castración tratados con doceTaxel o Cabazitaxel; (Versión 3.0: 16-01-15).Estudio Prostac. Centro Nacional de Investigación Oncológica (CNIO) CNIO-CP-02-2014/CNI-DOC-2014-02

GROUP 54

HEAD OF LABORATORY

Laura Cerezo Padellano

GROUP MEMBERS

- Adolfo Carlos Hinojar Gutiérrez
- Consuelo López Elzaurdia
- Mario López Rodríguez
- Rafael Manzanares Soler
- Alicia Marín Palomo
- Margarita Martín Martin
- Mario Fernando Muñoz Guerra

- Luis Naval Gías
- Eduardo Raboso García-Baquero
- Francisco José Rodríguez Campo

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 distint 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 inmunotherapy. 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.

PUBLICATIONS (2)

Rubio Bueno, Pilar, Landete Rodríguez, Pedro, Ardanza, B, Vázquez, L, Soriano Ortiz, Joan B., Naval Gías, Luis, Capote Moreno, Ana Laura, Zamora García, Enrique Domingo, Ancochea Bermúdez, Julio, Naval Gías, Luis. **Maxillomandibular advancement as the initial treatment of obstructive; sleep apnoea: Is the mandibular occlusal plane the key?.** Int. J. Oral Maxillofac. Surg. 46(11):1363-1371. 2017. PMID: 28760319. IF: 1,918. DOI: 10.1016/j.ijom.2017.07.003. http://dx.doi.org/10.1016/j.ijom.2017.07.003.

Sánchez, Pedro, Meca Lallana, Virginia, Barbosa, Antonio, Manzanares Soler, Rafael, Palmí, Itziar, Vivancos Mora, José Aurelio. **Tumefactive demyelinating lesions of 15 patients: Clinico-radiological; features, management and review of the literature.** J. Neurol. Sci. 381:32-38. 2017. PMID: 28991707. IF: 2,295. DOI: 10.1016/j.jns.2017.08.005. http://dx.doi.org/10.1016/j.jns.2017.08.005.

CLINICAL TRIAL

PRINCIPAL RESEARCHER: CEREZO PADELLANO, LAURA

Estudio del RECTO. Estudio multicéntrico de escalada de dosis de radioterapia, en pacientes diagnosticados de carcinoma de recto localmente avanzado. Hospital Ramón Y Cajal RTRC--001

GROUP 59

HEAD OF LABORATORY

Carlos Manuel Olivier Gómez

GROUP MEMBERS

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

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 exosomas, 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)

Farina-Gomez, Noemi, Barrabes, Silvia, Gomez-Lopez, Jorge E, Gonzalez, Monica, Puerta, Angel, Navarro-Calderon, Diana, Albers-Acosta, Eduardo, Olivier Gómez, Carlos Manuel, Diez-Masa, Jose C, Peracaula, Rosa, de Frutos, Mercedes. **Sample preparation of serum to allow capillary electrophoresis analysis; of prostate specific antigen isoforms.** J. Pharm. Biomed. Anal. 134:220-227. 2017. PMID: 27918991. IF: 3,255. DOI: 10.1016/j.jpba.2016.11.045. http://dx.doi.org/10.1016/j.jpba.2016.11.045.

Fernández González, Inmaculada, Brime Menéndez, Ricardo, Celada Luis, Guillermo, Acosta Reveles, Marco Antonio, Albers Acosta, Eduardo Mariano, Mejia Celemin, Pilar, San José Mansó, Luis Alberto, Casado Varela, Javier. **Tratamiento de la litiasis con laparoscopia. Técnicas combinadas.** Arch Esp Urol. 70(1):235-244. 2017. PMID: 28221158. IF: 0,323.

CLINICAL TRIAL

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de próstata resistente a la castración tratados con RADIUM-223; Estudio Proradium. Instituto de Investigación Biomédica de Málaga IBIMA-CNIO-CP-01-2016/CNI-RAD-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Identificación de factores biológicos asociados a la progresión metastásica precoz en pacientes con cáncer de próstata resistente a la castración MO con elevación del PSA (JPV-CP); Estudio MO. JPV-CP-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PRÓstata resistente a la castración tratados con ABIraterona; (Versión 2.0: 16-01-15).Estudio Prosabi. Centro Nacional de Investigación Oncológica (CNIO) CNIO-CP-03-2014/CNI-ABI-2014-02

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PRÓstata resistente a la castración tratados con ENZAlutamida; (Versión 1.0:01-02-16) Estudio Prosenza. Instituto de Investigación Biomédica de Málaga BIMA-CNIO-CP-01-2016/CNI-ENZ-2016-01

PRINCIPAL RESEARCHER: ROMERO LAORDEN, NURIA; SAN JOSE MANSO, LUIS ALBERTO; ZAPATERO LABORDA, MARIA-ALMUDENA

Estudio prospectivo multicéntrico de factores pronósticos en pacientes con cáncer de PROstata resistente a la

castración tratados con doceTaxel o Cabazitaxel; (Versión 3.0: 16-01-15).Estudio Prostac. Centro Nacional de Investigación Oncológica (CNIO) CNIO-CP-02-2014/CNI-DOC-2014-02

PRINCIPAL RESEARCHER: SAN JOSE MANSO, LUIS ALBERTO; FERNANDEZ ARJONA, MANUEL

Estudio Identifica: Estudio observacional y transversal para la optimización del diagnóstico de metástasis en fase de CPRC M0 en práctica clínica habitual en España. Janssen-Cilag, S.A. JAN-CPR-2017-01// 212082PCR4046

PRINCIPAL RESEARCHER: COGORNO WASYLKOWSKI, LEOPOLDO; OLIVIER GOMEZ, CARLOS

Identificación de las bases genéticas de susceptibilidad al cáncer testicular familiar mediante secuenciación del exoma: Aplicación clínica. Centro Nacional de Investigación Oncológica (CNIO) CNIO-GH-001-2015

PRINCIPAL RESEARCHER: OLIVIER GOMEZ, CARLOS

Estudio prospectivo no intervencional poscomercialización para evaluar los criterios sobre que renovación del tratamiento con análogos de la LHRH se realiza en pacientes con cáncer de próstata localmente avanzado o metastásico (Estudio Anaren). Ipsen Pharma, S. A. IPS-TRI-2016-02/A-ES-52014-224

GROUP ASSOCIATED 3

HEAD OF LABORATORY

José Cordero Ampuero

GROUP MEMBERS

- Enrique Alday Muñoz
- Vicente Jesús Casa de Pantoja
- Francisco Clement Fernández
- Esther Fernández Bermejo
- Juan Jacobo González Guijarro
- Emilio Marín Araez
- Mar Orts Rodríguez
- Antonio Planas Roca
- Fernando Ramasco Rueda
- Fernando Teba del Pino

PUBLICATIONS (2)

Ferrando, Carlos, Soro, Marina, Unzueta, Carmen, Canet, Jaume, Tusman, Gerardo, Suarez-Sipmann, Fernando, Librero, Julian, Peiró, Salvador, Pozo, Natividad, Delgado, Carlos, Ibáñez, Maite, Aldecoa, César, Garutti, Ignacio, Pestaña, David, Rodríguez, Aurelio, García Del Valle, Santiago, Diaz-Cambronero, Oscar, Balust, Jaume, Redondo, Francisco Javier, De La Matta, Manuel, Gallego, Lucía, Granell, Manuel, Martínez, Pascual, Pérez, Ana, Leal,

Sonsoles, Alday Muñoz, Enrique, García, Pablo, Monedero, Pablo, Gonzalez, Rafael, Mazzinari, Guido, Aguilar, Gerardo, Villar, Jesús, Belda, Francisco Javier, iPROVE-O2 Network Group. **Rationale and study design for an individualised perioperative open-lung; ventilatory strategy with a high versus conventional inspiratory oxy-gen; fraction (iPROVE-O2) and its effects on surgical site infection: study; protocol for a randomised contro-lled.** BMJ OPEN. 7(7). 2017. PMID: 28760799. IF: 2,369. DOI: 10.1136/bmjopen-2017-016765. http://dx.doi.org/10.1136/bmjopen-2017-016765.

Planas Roca, Antonio, Ramasco Rueda, Fernando. **Search for biomarkers to identify surgical patients at high cardiovascular and perioperative mortality risk.** Rev Esp Anestesiol Reanim. 64(10):547-547. 2017. PMID: 29102403. DOI: 10.1016/j.redar.2017.09.002. http://dx.doi.org/10.1016/j.redar.2017.09.002.

CLINICAL TRIALS

PRINCIPAL RESEARCHER: ALDAY MUÑOZ, ENRIQUE

Reducción de la infección de la herida quirúrgica con una estrategia perioperatoria individualizada de ventilación de protección pulmonar con fracción inspiratoria de oxígeno elevada. Estudio comparativo, prospectivo, multicéntrico, aleatorizado y controlado. I-PROVE O2

EudraCT: 2016-002936-34

PRINCIPAL RESEARCHER: ALDAY MUÑOZ, ENRIQUE

Postoperative outcomes within an enhanced recovery alter surgery protocol. POWER AUDIT

PRINCIPAL RESEARCHER: CORDERO AMPUERO, JOSE

Ensayo clínica multicéntrico, abierto, randomizado que compara dos dosis diferentes de células madre mesenquimales autólogas, de médula ósea, expandidas y combinadas con biocerámica frente al autoinjerto de cresta ilíaca, en la curación de fracturas de huesos largos sin consolidación. Universidad Autónoma de Madrid (UAM) ORTHOUNION

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GROUP PLATFORM

HEAD OF LABORATORY

Alberto Morell Baladrón

PUBLICATIONS (1)

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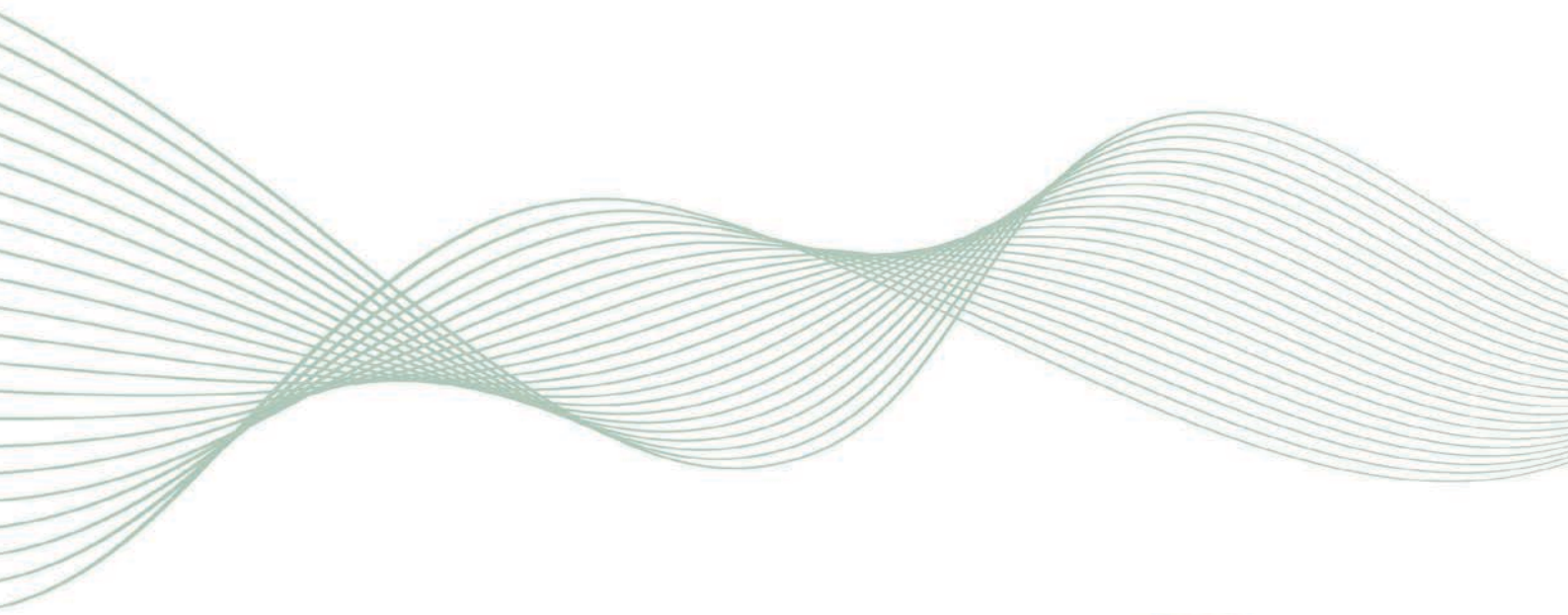

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