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FOREWORD BY

THE DIRECTOR
With the arrival of anti-COVID vaccines and the implementation of a highly efficient vaccination campaign by the Valencia Health ministry, the CIPF returned to a normal level of activity in 2021. Nevertheless, we are ever mindful that the pandemic is not entirely over, that infection with new variants of Sars-CoV-2 virus remains a threat for the vulnerable members of our society.

In April, we opened the exposition “Living to be a 100 years old”, an interactive, audiovisual project dedicated to the biological, psychological, cultural, and economic aspects of human ageing. As the world confronts the health and economic challenges of an ageing population, there has been dramatically increased interest in the science and social aspects of ageing. We are grateful to the CSIC Foundation for the loan of this very timely exhibit. During the spring and summer, many members of the public visited the exhibit in our center. We closed this event with a multidisciplinary workshop on Healthy Ageing which coincided with the International Day for Older Persons.

The development of more international collaborations is a priority in our strategic plan as these agreements permit us to enhance the visibility of the CIPF in the global scientific community. This year we created our first international joint unit with Dr. Toni Vidal-Puig of the University of Cambridge. Dr. Vidal-Puig is a prestigious investigator in the field of diabetes and obesity and his presence in the CIPF will enrich the research and competitiveness of our center. He currently is principal investigator of the ERC grant STEMAT.

In summer of 2021, we welcomed two new Ramón y Cajal investigators as junior group leaders. Dr. Juan Rodríguez-Vita comes to us from the German Cancer Research Center. Juan has an extensive background in immunology and metabolism which he now uses to pursue questions in the field of tumor biology. Dr. Vicente Perez Garcia performed his postdoctoral training at the University of Cambridge’s Trophoblast Center and will now direct a group dedicated to the cellular and molecular basis of implantation. Dr. Stefania Carobbio, a recipient of the GenT fellowship, joined the CIPF as a junior group leader from the Sanger Institute and brings extensive expertise in adipose biology. Additionally, Dr. Víctor Gómez is the new director our animal facility after spending more than 10 years as head vet in the clinical hospital of Oslo. We were also very fortunate to recruit Cristina Rajo as head of our new Research Support Unit. Cristina has an excellent track record as a scientific project management and we look forward to working with her to further develop our funding portfolio.

As we welcomed the arrival of new colleagues, we were saddened to say farewell to our long-time collaborator, the eminent pathologist Dr. Jerónimo Forteza who passed away in April. Dr. Forteza inspired many of us not only with his passion for cancer research but also with his determination to remain active and productive despite his struggle with Parkinson’s disease. We paid our tribute to the many contributions of Dr. Forteza by placing his name on our large conference room and thus, a part of Jerónimo remains with us for our seminars and events.

Although the confinement and other measures to control COVID in 2020 altered the rhythm of the center in 2021, 2021 was a stellar year for our scientific results. More than 80% of all our publications were in Q1 or higher journals. This is an excellent result for the CIPF and brings us closer to our goal of becoming a Severo Ochoa center. Dr. Rosa Farràs applied successfully to coordinate a COST Action project from the EU program. Dr. Vicky Moreno was awarded a grant from the very prestigious Synergy program of the EU. In addition to our success in these very competitive international calls, 6 of our principal investigators submitted successful applications to the annual call from the Ministry of Science. Finally, congratulations to Dr. María Jesús Vicent who received the Concepción Aleixandre Prize for Women in Science from the local city of Picanya.

Many thanks to all of you for your patience and your strength as we resume our seminars, lab meetings, courses, and other activities that are best done in person. The success of the anti-COVID vaccines has revealed to the public what we already know: with ample funding and sufficient collaboration and support, scientists can solve the most urgent medical problems. More research, better health.

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*In the Board meeting celebrated on the 13th of December 2021, Carmelina Pla and Antonio Pellicer were relieved of their position. Mónica Almiñana joins as new member.
OVERVIEW

Our investigation based on pre-clinical and clinical approaches to unveil diet-host-microbe interactions underlying metabolic health have permitted us to advance in the understanding of how our microbes modulate our physiology under certain nutritional environments. We are also actively working on developing and formulate innovative symbiotics products using next generation potential probiotics strains in combination with novel plant-origin ingredients. The main group outcomes in 2021 consisted of a relevant clinical assessment to unveil sex-associated response to a caloric restriction regime with fiber supplementation to ameliorate metabolic dysfunction in obese subjects. New clinical studies have started in our laboratory to improve the characterization of microbial communities towards defining composition at species and strain level using cost-effective and cutting-edge sequencing technology.

SELECTED PUBLICATIONS


During 2021, we have continued to pursue our aim of expanding basic knowledge about the role(s) of insulin receptor substrate (IRS) proteins in diabetes and obesity. Understanding the mechanisms that underlie β-cell dysfunction is crucial for designing therapeutic approaches for both type 1 and type 2 diabetes. Development of this strategy for clinical consideration requires a thorough knowledge of the regulatory pathways that govern β-cell development and their survival in adults. Deletion of Irs2 in mice causes diabetes owing to a reduced β-cell mass and peripheral insulin resistance. IRS2 signals are required for β-cell compensation under conditions of metabolic stress such as high fat feeding. To investigate the role of IRS-2 signaling in pancreatic progenitor cells, we use a multi-disciplinary approach that combines a novel reporter mouse model with in vitro human experimental models. We are using the reporter mouse to define the spatial and temporal expression of IRS2 during stages of embryonic pancreas development and during the normal ageing of adult mice using a new reporter model where GFP and luciferase are driven by the Irs2 promoter. Completion of these aims will not only improve our understanding of how IRS2 signaling regulates β-cell development and survival but will provide new insights into the etiology of diabetes and may identify new markers for the early diagnosis and treatment of β-cell failure. IRS2 represents a rationale target for protecting existing β-cells in the adult pancreas. The reporter mouse is also an excellent tool for defining the role of IRS2 signals in other insulin-sensitive tissues including liver and adipose tissue.

**SELECTED PUBLICATIONS**

Immunological response against SARS-CoV-2 following full-dose administration of Comirnaty® COVID-19 vaccine in nursing home residents.

Our laboratory is unveiling cellular and molecular mechanisms underlying cognitive function. Using mice as animal models, we recently revealed specific neural circuits expressing serotonin that regulate the formation of social and fear memories (Barettino, Ballesteros-González et al., 2021 Frontiers in Cell and Developmental Biology).

In addition, our work contributed to a better understanding of the efficacy of antiepileptic drugs in the treatment of neurodevelopmental disorders characterized by severe cognitive and motor function such as the CDKL5 deficiency disorder (Aledo-Serrano et al., 2021, Epilepsy behavior). Thanks to this interdisciplinary work, we have started to unveil molecular targets that will be leveraged during the design of new therapeutic strategies aimed to improve cognitive symptoms in a wide range of neurological and neurodevelopmental disorders of known genetic etiology. Finally, we highlight advances of new diagnostic strategies used in those patients suffering of neurological disorders with uncertain genetic etiology (Aledo-Serrano et al., 2021 J Transl Genet Genom).

SELECTED PUBLICATIONS


**OVERVIEW**

Our group develops new therapeutic cell-based treatments for neurodegenerative diseases by using adult stem cells or pluripotent stem cells which include human embryonic stem cells (hESCs) and induced human pluripotent stem cells (hiPSCs). We develop clinically acceptable protocols for neural differentiation and test them in different animal models as potential therapeutic tools to help treat spinal cord injuries and different types of ataxias. We also apply combinatorial approaches using small molecules in order to increase the success of cell-based therapies.

Hereditary retinal dystrophies are another research line in our laboratory. In particular, we are focusing on creating new human cell models using patient-specific hiPSCs, and especially, retinal pigment epithelial (RPE) cells and optic-cup organoids. These can then be used to investigate the mechanisms driving these diseases, develop treatments, perform toxicity screens, and model development in cells affected by these diseases.

Moreover, we intend to correct the gene mutations in these cells using Crispr/Cas9 technology and to optimize the derivation of RPE and photoreceptors from corrected hiPSCs as a cell source for transplantation therapies in animal models with retinal degeneration diseases. In collaboration with other laboratories, we are developing new tools for maintaining high cell viability while delivering RPE and photoreceptor cells into degenerated retina in small and large animal models.

**SELECTED PUBLICATIONS**


OVERVIEW

We investigate rare neurodegenerative diseases, specifically, movement disorders (dystonia, parkinsonism, tremor), ataxia, Wilson's disease, and childhood epilepsy. The studies focus mainly on two objectives: (1) establish the molecular basis and the disease mechanisms of this group of rare disorders, and (2) characterize useful diagnostic/prognostic biomarkers for orphan drug monitoring. We generated a cerebellum Purkinje cell (CPC) model for the study of an ultra-rare condition, PLAN (PLA2G6-associated neurodegeneration).

After its characterization, we demonstrated that the CPC-PLAN model shows impairment in mitochondrial dynamics, lipid peroxidation and ferroptosis, as the PLAN patients. We investigated four cohorts of patients with different types of infantile epilepsy (focal, structural, generalized and encephalopathy) in order to determine the microRNA signature of each of these epilepsies. The preliminary findings revealed that the analysis of five miRNAs in plasma allowed us to obtain a differential signature between the epilepsy groups studied.

SELECTED PUBLICATIONS


OVERVIEW
Rev-erba, a repressor of mitochondrial function in Melanoma cells. Rev-erba is a nuclear receptor and component of the endogenous circadian clock that timely coordinates the circadian metabolic response. Rev-erba modulates mitochondria function in muscle by interfering with Ampk-Sirt1-Ppargc1-α signaling. However, the direct role of Rev-erba in mitochondria has not yet been explored. We have found that Rev-erba is within mitochondria from Melanoma cells and acts as a repressor of mitochondrial function. Moreover, Rev-erba influences the migratory and invasion capacities of these tumor cells.

Small viral non-coding RNAs in COVID19. We studied the role of two SARS-cov2-encoding small RNAs in down-regulating the expression of a host restriction factor with multiple antiviral activities, SERINC5. The anti-correlative expression between these two svRNAs and SERINC5 was found in different biological samples, including patient samples from COVID19 patients. Silencing of these svRNAs with anti-sense oligonucleotides recovers SERINC5, alters viral gene expression and reduces the expression of certain cytokines.

SELECTED PUBLICATIONS
OVERVIEW

Despite great advances, lung cancer remains the leading cause of cancer-related death in developed countries. Metastasis and drug resistance are the main factors contributing to relapse and death. The developmental program known as mesenchymal epithelial transition (EMT), has become a possible candidate mechanism to explain tumor metastasis. TGF-beta signalling has been shown to play an important role in EMT.

Our research focuses on studying the changes induced by the TGF-beta signalling pathway at two different levels. First, at the transcriptional level through the activity of AP-1 transcription factors. Dysregulation of AP-1 can promote cell invasion and metastatization, contribute to angiogenesis or stimulate inflammatory responses facilitating cancer development. Second, we also study alterations at the translational level through the activity of eIF5A translation factor which promotes EMT in non-small cell lung cancer. Understanding the EMT process will help define new treatment strategies to counteract tumor progression and drug resistance.

To investigate lung tumour biology, we generate in vivo cancer experimental models that can adequately represent tumour heterogeneity and predict drug sensitivity in vivo. Through our expertise in protein degradation our group coordinate the COST ProteoCure Action dedicated to the study of protein homeostasis in health and disease.

SELECTED PUBLICATIONS


OVERVIEW

Our group studies the development of the cerebral cortex and investigates innovative strategies to promote the regeneration of cortical neurons upon brain injury.

We found that Nrg1 intracellular signaling regulates neuronal development and that the Nrg1 intracellular signaling is neuroprotective upon stroke both in vitro and in vivo. In addition, we developed a new model of Nrg1 haploinsufficiency to mimic the alteration in Nrg1 expression found in human Schizophrenic patients.

Our multidisciplinary study revealed that relatively subtle decrease in Nrg1 expression may results in significant deficits in the inhibitory circuits. These deficits provoke a decrease in GABAergic transmission and in the distribution of specific subtypes of cortical interneurons (Navarro-Gonzalez et al.; 2021).

Overall, this study provides new insights into the molecular basis of Schizophrenia.

Besides, we developed a new methodology to investigate the role of different genes in neuroprotection and development in vitro. This powerful tool will be important for translational research in neurons (Rodriguez-Prieto et al.; 2021).

SELECTED PUBLICATIONS


Overview

The Neurobiology Laboratory performs basic and translational research on the mechanisms, diagnostic and treatment of cognitive and motor impairment in animal models of hyperammonemia and minimal hepatic encephalopathy (MHE). We study in rats the mechanisms responsible for cognitive and motor impairment in MHE patients. We analyze the role of peripheral inflammation, how it induces neuroinflammation, how neuroinflammation alters neurotransmission and how this leads to cognitive and motor impairment. Once we identify the mechanisms involved, we design and test new therapeutic treatments to reverse neuroinflammation and restore neurotransmission and cognitive and motor function.

In the Joint Unit with INCLIVA on Neurological Impairment we perform studies in cirrhotic patients with MHE to analyze the cognitive and motor alterations, the cerebral alterations (by magnetic resonance, neurophysiology and neuropathology) and the role of changes in the immune system in triggering these alterations. We look for new, early and more sensitive procedures to diagnose MHE.

Selected Publications


The Bioinformatics and Biostatistics Unit aims to develop innovative methods and tools for integrative data analysis from different sources in Biomedicine, which allow us a better characterization of human diseases and their treatments. The main lines of work are focused on 1) the generation of clinical predictors based on high throughput technologies and artificial intelligence methods, 2) the detection and understanding of the molecular mechanisms associated with spinal cord injuries, and 3) the study of gender and sex differences in biomedical studies using computational approaches based on omic data meta-analysis, that allow the detection and characterization of the specific molecular mechanisms of male and female in several disease groups: (i) cardiovascular diseases (aortic stenosis and ischemic heart disease), (ii) neurodegenerative diseases (Parkinson's, Alzheimer's and multiple sclerosis), (iii) autoimmune diseases (rheumatoid arthritis, dermatitis, psoriasis), (iv) liver diseases, (v) metabolic diseases and (vi) different tumor groups (ovarian, breast, lung, pancreatic cancer).

SELECTED PUBLICATIONS


OVERVIEW

Adolescence is a brain maturation developmental period during which remodeling and changes in synaptic plasticity and neural connectivity take place in some brain regions. Changes in synaptic plasticity and its regulation by mTOR have been suggested to play a role in the behavioral dysfunction of binge ethanol drinking in adolescence. Using adolescent female and male mice (PND30) treated intermittently to ethanol, we show that binge ethanol treatment alters the density and morphology of dendritic spines, effects that are associated with learning and memory impairments along with changes in the CREB phosphorylation and miRNAs. Inhibition of mTOR by rapamycin administration, restores ethanol-induced changes in both plasticity and behavior dysfunctions in adolescent mice. These results support the role of mTOR/autophagy in the dendritic spines alterations and cognitive dysfunction associated with binge drinking (see Fig).

In an adult mice model of chronic alcohol intake we have also demonstrated that administration of a polypeptide-based nanoconjugate of a curcuminoid (StClPr-BDMC-ANG) capable to pass the blood-brain-barrier, downregulated microRNAs that negatively modulate inflammation ameliorating alcohol-induced neuroinflammation and brain damage.

SELECTED PUBLICATIONS


OVERVIEW

The vision is the most important sense in humans since the majority of information of our environment is obtained through sight. Therefore, the loss of vision results in the most debilitating sensorial disorders. Approximately 25% of vision loss is due to retinal dystrophies. The retina is light sensitive tissue that converts light into electrical signals that are sent to the brain for further processing. Retinal dystrophies are progressive disorders that end up with blindness and currently have no cure.

Our aim is to understand retinal function during development and in homeostasis and disease. Using state-of-the-art in vitro techniques, we aim to design new and more effective strategies for therapeutic intervention. Our efforts are focused on the following aims:

1. Understand the hereditary retinal degeneration by developing patient specific retinal models
2. Develop therapeutic strategies based on human pluripotent stem cells
3. Decipher the molecular mechanism of retinogenesis, especially photoreceptor specification via pluripotent stem cells directed differentiation

SELECTED PUBLICATIONS


NEURONAL AND TISSUE REGENERATION LABORATORY

TEAM MEMBERS
Victoria Moreno Manzano, Principal investigator
Esther Giraldo Reboloso, Ana Alastrue Agudo, Marina Sánchez Petidier, Pablo Bonilla Villamil, Beatriz Martínez Rojas, Sonia Hingorani Jai Prakash, Mª del Mar Sánchez Martín, Neus Torres Hernández, Maravillas López Mellado, Eric López Mocholi

OVERVIEW
In the Neuronal and Tissue Regeneration laboratory we aim to tackle currently incurable spinal cord injuries (SCI) by the implementation of novel combinatorial strategies that harnesses multiple independent mechanisms involving the use of biomaterials, cells transplantation, pharmacological treatments or genetic modifications for optimal functional regeneration. Among those, last year, we described a new rationally-designed bioresponsive polymer-fasudil conjugate, with enhanced Rho/ROCK inhibitory activity (PGA-SS-F) capable to induce neurite elongation and axon growth in vitro. The intrathecal administration of PGA-SS-F after SCI prevented early apoptosis and induced the expression of axonal growth- and neuroplasticity-associated markers to a higher extent than the free form of fasudil. Moreover, the combination treatment comprising the acute transplantation of NPCs pre-treated with PGA-SS-F leads to enhanced cell engraftment and reduced cyst formation with neuroprotective effects after SCI (Figure 1) (Giraldo et al, Biomaterials. 2021 Sep; 276:121052).

SELECTED PUBLICATIONS


NEURONAL AND TISSUE REGENERATION LABORATORY
SCIENCE

METABOLIC GROWTH SIGNALS AND REGENERATIVE MEDICINE

TEAM MEMBERS

Luke A Noon, Principal investigator
Matilde D’Angelo, Alberto Sánchez Almira, Ignacio Frances Castillo

OVERVIEW

We recently identified a novel mechanism by which insulin signals drive wound healing in liver – called the “IRS2/FGF7-axis”. Our discovery provides proof-of-concept that insulin signals reduce scarring, whilst simultaneously improving paracrine communication between scar tissue and progenitors, whose job it is to promote regeneration. In 2021, we were awarded a 3-year “Plan Nacional” grant by the Spanish government to explore this pathway further and expose the cellular mechanisms underlying our discovery. We have made significant progress towards this aim by identifying a novel mediator of insulin receptor substrate 2 (IRS2) actions. We have also worked with researchers at CISIC Alberto Sols to establish a method to activate the IRS2/FGF7-axis to improve liver repair. We have also begun an exciting collaboration with researchers at UCL (UK) and Hospital La Fe (Valencia) after identifying a new cell type within the hepatic stroma with enormous potential to participate in liver physiology and disease.

SELECTED PUBLICATIONS

Manzano-Núñez, Fatima; JoseArambul-Anthony, Maria; GalanAlbinana, Amparo; et al; Noon, LA. 2019. Insulin resistance disrupts epithelial repair and niche-progenitor Fgf signaling during chronic liver injury. PLOS BIOLOGY. PUBLIC LIBRARY SCIENCE. 17:1. ISSN 1545-7885.


Lee, Youngmin A.; Noon, LA.; Akat, Kemal M.; et al; Friedman, Scott L. 2018. Autophagy is a gatekeeper of hepatic differentiation and carcinogenesis by controlling the degradation of Yap. NATURE COMMUNICATIONS. NATURE PUBLISHING GROUP. 9. ISSN 2041-1723.
TARGETED THERAPIES ON CANCER AND INFLAMMATION

TEAM MEMBERS
Mª del Mar Orzáez, Principal investigator
Mónica Sancho Medina, Federico Lucantoni, Diego Leiva Yuste, Paula Soriano Teruel, Milagros Buffa, Alicia García Jareño, Estefanía Barrero, Iván Fernández Pérez, Víctor Caurín Perpiñá

OVERVIEW
The Targeted Therapies Laboratory works on the identification and preclinical development of new modulators for cell death and inflammation.

In cell death projects, our main targets are the transmembrane interactions between proteins of the Bcl-2 family. Deregulation of the Bcl-2 interactome is associated with tumour development and acquisition of chemotherapy resistances. We work to solve the mitochondrial Bcl-2 transmembrane interactions responsible for cancer resistances and to develop new drugs targeting these interactions and triggering cancer cell death.

The main goal of our inflammation projects is to develop new inflammasome modulators. The inflammasome is one of the main components of the pro-inflammatory signalling pathway that protects our body from injury and infections. Deregulation of this protein complex is associated with the pathophysiology of autoimmune disorders, inflammatory diseases, and cancer. We work on the characterisation of new inflammasome inhibitors both as therapeutic agents and as chemical tools to understand how the inflammasome contributes to the molecular mechanisms responsible for these diseases.

SELECTED PUBLICATIONS
OVERVIEW

The group of Pathophysiology and Therapies for Visual Disorders is focused on searching pharmacological therapies for inherited retinal dystrophies (IRDs). We pay particular attention to cellular processes related to oxidative stress and neuroinflammation that may exacerbate IRD progression. In inflammation, we have described the relationship between retinal inflammation and IRD progression. Pharmacological manipulation with anti-TNFα agents downregulates these processes. Based on previous findings, we started a clinical trial together with the Manises hospital. The clinical trial, called ADARET, will evaluate the safety and effectiveness of intravitreal anti-TNF agents on the progression of retinitis pigmentosa, the most common form of IRDs. In oxidative stress, we have evaluated the effect of antioxidant nutraceuticals in rd10 mice and patients with retinitis pigmentosa. We published that nutraceuticals ameliorated retinal dysfunction (electroretinogram recordings), retinal degeneration and neuroinflammation. Currently, we are analyzing the delivery of anti-inflammatory or antioxidant drugs to the retina with different types of nanocarriers.

SELECTED PUBLICATIONS


OVERVIEW

The Polymer Therapeutics Lab develops nanopharmaceuticals as solutions for unmet clinical needs, including metastasis and neurodegeneration. Our interdisciplinary strategy begins with controlled polymer chemistry, supramolecular assembly, optimized conjugation, and physico-chemical characterization, but extends to in vivo preclinical evaluation. The ERC-Co-MyNano project, which aims to develop anticancer combination nanoconjugates, has established a family of self-assembled polypeptidic carriers. We characterized patient-derived three-dimensional breast cancer models and identified optimal personalized polypeptide-based combination nanoconjugates:functional biomarkers.

We strengthened research efforts in immuno-oncology by designing lymphotropic nanoconjugates that enhance immunomodulation in melanoma (ERC-PoC-Polymmune) and pancreatic cancer (La Caixa HR-NanoPanTher) as single agent and multivalent nanovaccines. Furthermore, exhaustive characterization approaches by LC-MS and AF4 have been implemented. Research supported by MICINN and AECC-CV demonstrated how polypeptide-based nanoconjugates bypass the blood-brain barrier after intravenous or intranasal administration to provide treatment opportunities for disorders including Alzheimer’s disease, multiple sclerosis, pediatric tumors, and brain metastases; these studies are now reinforced with the recently awarded ERC-PoC-PolyBraint project. Finally, newly developed polypeptide-based nanoconjugates for local administration have demonstrated their benefits as single agents and combination therapies in spinal cord injury (Marató TV3, AV1).

SELECTED PUBLICATIONS


PATENT

NEW CIPF RESEARCH GROUPS 2021

OBESITY, DIABETES AND COMORBIDITIES

TEAM MEMBERS
Stefania Carobbio, Principal investigator
Carmen Navarro Gonzalez, Jaime Navarro Perez, Elena Pérez Navarro

OVERVIEW

In 2021 we just started to set up the lab. Our research is mainly focusing on healthy expansion of white adipose tissue (WAT). WAT is a critical metabolic organ that contributes to energy storage, endocrine homeostasis and metabolic flexibility by efficiently storing the surplus of fuel and quickly mobilising lipids/energy to supply peripheral organs. In the context of the current obesity epidemic, the demands imposed on the expandability and functionality of WAT are paramount, overwhelming WAT capacity to store and mobilise fat, promoting the development of metabolic comorbidities.

Whereas most research aims to understand why obese people develop comorbidities, we will study the opposite paradigm, why some obese people are resilient and do not develop comorbidities.

Our question is not why obese patients develop comorbidities but how to make them resilient, and we hypothesise that this depends on the mechanisms that keep their adipose tissue healthy irrespectively of its size.

SELECTED PUBLICATIONS

Carobbio S.; Guenantin AC.; Bahri M.; et al; Vidal-Puig A. 2021. Unravelling the developmental roadmap towards human brown adipose tissue. Stem Cell Reports.
Huang LO.; Rauch A.; Mazzaferro E.; et al Carobbio S.; Loos RJF. 2021. Genome-wide discovery of genetic loci that uncouple excess adiposity from its comorbidities implicates new biology Nature Metabolism.

Picture of immunofluorescence of mature adipocytes. Green: lipid staining; blue: DAPI staining; red: nuclear stain.
Hyaluronic acid is a master regulator of tumor stroma. Tumor cells use signals to communicate and educate the tumor stroma. Tumor cells use hyaluronic acid (HA) to modify their stroma in order to generate a more immunosuppressive environment. HA can be synthesized as low molecular mass-HA (LMM-HA) or high molecular mass-HA (HMM-HA). In our group try to understand the mechanisms that regulated the actions of HA on stromal cells. We have uncovered that CD44-mediated HMM-HA detection by TAMs, depletes cholesterol from their plasma membranes. Cholesterol depletion alters IL-4 signaling and amplifies its responses. We have discovered that tumor cells activate the Notch signaling in ECs, which leads to the upregulation of the HA receptor CD44 in TAMs in ovarian cancer. Mechanistically, Notch signaling increases the expression of CXCL2 in ECs. CXCL2 recruits monocyte-derived macrophages. CXCL2 also increases the presence of CD44 on the membrane of TAMs, which facilitates their education by tumor cells.

SELECTED PUBLICATIONS
NEW CIPF RESEARCH GROUPS 2021

MOLECULAR MECHANISMS OF PLACENTAL INVASION

TEAM MEMBERS
Vicente Pérez García, Principal investigator
Maravillas Mellado López, Paula Borrell, Claudia Alemán, Érica Pedrera Alcócer, Andrea Álvarez Sánchez, Maria Moya Navamu, Javier Montes Torres

OVERVIEW

The placenta is a transient organ that connects the embryo to the mother during pregnancy and mediates nutrient and oxygen supply to sustain normal growth. Functionality of the placenta depends on the earliest steps during placentation when trophoblast cells, the building block of the placenta, invade into the endometrium to establish the definitive maternal-fetal interface. Several pregnancy complications such as miscarriage and preeclampsia are caused by defects in the process of trophoblast invasion.

Intriguingly, trophoblast cells share some key similarities with carcinomas. These similarities include the ability to invade healthy tissues, the formation of new vessels and the promotion of an immunotolerant environment. A key biological question remains: do tumour cells repurpose the same genes and mechanisms that are critical for trophoblast invasion?

By using CRISPR/Cas9 genome editing systems, we will genetically manipulate trophoblast stem cells and organoids to:

- Identify the molecular signatures characteristics of invasive placental cells.
- Unravel the common molecular pathways between trophoblast invasion and cancer metastasis.

Our results will provide fundamental insights into the cellular invasive mechanisms that coordinate placentation and the potential implication of these same mechanisms in tumour metastasis.

SELECTED PUBLICATIONS


The Mixed Unit TRIAL is a translational unit whose purpose is to promote and develop oncological research focused in the search of new therapeutic approaches and biomarkers in the field of cancer immunotherapies.

During 2021 TRIAL has made significant contributions in the field of tumor immunology and tumor microenvironment in lung tumors in collaboration with national and international researchers.

We have characterized the TCR repertoire in peripheral blood of non-small cell lung cancer patients demonstrating that it may provide information about clinical outcome in the context of immune-based therapeutic approach (Dong et al, Cancers 2021).

In the area of tumour immunology and the analysis of immune-related markers, we described the role of the gut microbiota as an important factor involved in the modulation of tumor-immune interactions (Zang F et al., 2021; Dong N., 2021).

Regarding 3D models in lung cancer, the group has carried out an exhaustive characterization spheroids and organoids (Herreros-Pomares et al., 2019; Herreros-Pomares et al., 2021) and has a collection of samples obtained from patient’s tumours to carry out translational studies.

SELECTED PUBLICATIONS


OVERVIEW
The group is part of the UPV-CIPF Joint Unit, established in 2016 to promote scientific collaborations between researchers in both institutions in the fields of pathophysiology and nanomedicine. We use Drosophila melanogaster to study the basic biological mechanisms underlying development and disease.

We are using Drosophila to generate models to study rare diseases, with an especial interest in rare epileptic encephalopathies. Our ultimate goals are to understand the disease mechanisms involved and to generate new tools for biomarker and drug discovery. We have published the first Drosophila knock-out model for Dravet syndrome and we are currently developing another model for CDKL5 deficiency disorder. To achieve these goals, we have a network of collaborators that include groups working in Drosophila genetics, physiology and rare diseases, clinicians; and most important, a close partnership with the patient associations.

SELECTED PUBLICATIONS
OVERVIEW

Our group is interested in the origin and consequences of biological variability. Phenotypic heterogeneity is inherent to all biological populations. This phenomenon is especially important in pathologies such as cancer, where genetically identical cells show completely different phenotypes. This phenomenon can have important consequences in human pathology. In the case of cancer, it means that when we treat tumours, not all cells respond to treatment, and those cells that survive are responsible for relapses and the generation of treatment-induced metastasis.

One of the factors contributing to this heterogeneity is the mitochondrial content, which is segregated asymmetrically and stochastically during mitosis. This asymmetric division ensures cells with different mitochondrial content, and because mitochondria are modulators of gene expression, they facilitate different gene expression between genetically identical cells. We are now studying how perturbations of mitochondrial function may contribute to variability in gene expression, as well as other factors that contribute to cellular heterogeneity and plasticity.
OVERVIEW

Prof. Ramón Martínez-Máñez’s group (IDM-UPV) works on the development of new treatments from a multidisciplinary point of view and apply the latest advances in nanomedicine to solve health problems. This multidisciplinary research includes from the synthesis of molecular probes and nanoparticles, their physico-chemical characterization as well as their evaluation in vitro and in vivo preclinical models of cancer and senescence, among others. During 2021, the group has continued with an intense scientific activity publishing 22 articles that described the development of different systems applied to both diagnosis and therapy in different diseases. In the context of the joint research unit, we can highlight our research in the arisen field of chemical communication between nanosystems. In addition, to point our work related to the development of targeted-lung nanoparticles for the treatment of devastating acute lung injury as well as the development of new self-propelled nanosystems for cancer therapy.

SELECTED PUBLICATIONS


OVERVIEW

In 2021 our team has four main research lines for rare diseases: inherited retinal dystrophies (IRD) including the Usher syndrome (USH), Huntington’s disease (HD), spinal muscular atrophy (SMA) and primary ciliary dyskinesia (PCD). We follow the main objectives of the International Research for Rare Diseases Consortium (IRDiRC): to investigate to improve diagnosis and to develop therapies.

Our strategies allow to resolve the molecular diagnosis of over 80% of the USH syndrome patients and about 60% of IRDs. We are sequencing whole exomes and whole genomes to find novel genes or novel molecular defects in the unsolved cases of IRD, USH and PCD.

We have started the newborn screening of SMA and we aim to screen all the babies born in the Valencian Community in one year (estimation of 35,000-40,000). The emergence of treatments for this devastating disease that are effective when they are administrated very early, preferably in asymptomatic children prompted us to develop this screening.

We have also started a therapeutical approach for autosomal dominant IRDs based in camelid’s nanobodies.

Finally, we are looking for therapeutical targets for HD and we have also started a clinical trial in patients with HD.

SELECTED PUBLICATIONS


Starvation-generated cilia in human fibroblasts. In red, TAP11 marking the basal body. In green acetylated tubulin marking the axoneme.
The Joint Unit on Neurological Impairment CIPF-INCLIVA performs basic and translational research on cognitive and motor alterations in patients with liver diseases: cirrhotic patients showing minimal hepatic encephalopathy (MHE) and patients with non-alcoholic fatty liver disease showing mild cognitive impairment (MCI).

The aims are:

- In animal models
  - Unveil the molecular mechanisms leading to neurological impairment
  - Identify new therapeutic targets for its treatment
  - Design and assess new therapeutic procedures to reverse neurological impairment

- In patients
  - Study the mechanisms, diagnosis and treatment of neurological impairment.
  - Identify early diagnostic procedures for neurological impairment.
  - Bring to the clinic the diagnostic procedures identified.

We focus in understanding the role of hyperammonemia and peripheral inflammation in the induction of cognitive and motor impairment, analysing the shift in peripheral inflammation associated to the triggering of MHE and MCI. We also analyse how changes in peripheral inflammation are transmitted to brain to induce neuroinflammation, alterations in neurotransmission and cognitive and motor impairment.

We have shown that rifaximin improves MHE in many patients. We try to understand the underlying mechanisms to increase the number of patients recovering neurological function.

### OVERVIEW


The joint unit between Universitat de València and CIPF focuses its activity in biomedicine, particularly in the cellular functional study in Immunopathology and Regenerative Medicine, and the development of in vitro cytomic assays predictive of acute and chronic toxicity in humans and animals. Main lines of research:

- Search for biomarkers related to oxidative stress and inflammation in patients with eye and olfactory pathologies.
- Study by flow cytometry of immunological alterations in patients with Idic-15 Syndrome, a rare disease of the Autism Spectrum.
- Development of flow cytometry methods for immunological monitoring in marine mammals.
- Study by flow cytometry of the immunophenotype in patients with liver disease.
- Development of an immunoassay based on miniaturized microscopy for the detection of soluble antigens.

In 2021 the Unit continued its main scientific line related to the application of Cytomics to discover immunophenotypic biomarkers useful for risk prediction or for monitoring immune function both in humans and marine mammals. Advanced cytomic analysis of our data on young patients of Idic-15 syndrome, a neurological rare disease, showed that specific alterations in T-cell and B-cell subpopulations were stronger predictors of infection risk than genetic lesion parameters. These observations were suggestively associated to gender- and behavioural descriptors. On the other hand, we accomplished our study on developing and applying methods for immune monitoring in marine mammals, as highlighted by the presentation of the results in a Ph.D. defense in September 2021. Our Unit has started successfully new lines of scientific collaboration with groups in external institutions (Fisabio, Incliva) related to the discovery of oxidative-stress and inflammation biomarkers in patients with ophthalmic and olfactory diseases. In addition, our Unit has continued its significant involvement in educational activities in the field of Cytometry and Cytomics.

SELECTED PUBLICATIONS

OVERVIEW

The FISABIO-CIPF Joint Unit of Biomedical Imaging is expert in the anonymisation, curation, and processing of medical image data through the application of artificial intelligence and radiomics techniques. Our work involves the creation of medical imaging data lakes, and application of anonymisation, segmentation, and data curation techniques for medical images. We apply various artificial imaging techniques to study biomarkers in these images.

In 2021 we have developed various tools in this area, through participation in the European project Deep-Learning and HPC to boost biomedical applications for health (DeepHealth) and the start of two major national projects: IMPaCT-DATA consisting of the development of a data integration and analysis environment that includes the ability to both answer questions from clinical groups and TARTAGLIA: Federated network to accelerate the application of artificial intelligence in the Spanish Health System. Participation includes research in the fields of Alzheimer's disease, lumbar spine, and pulmonary conditions.

SELECTED PUBLICATIONS

OVERVIEW

We are currently working on several research lines:

- Pathophysiology of Friedreich's ataxia and other neuromuscular diseases
- Development of new therapeutic strategies for Friedreich's ataxia
- Development of new biomarkers in both adult and neonatal sepsis
- Pathophysiology of epileptic disorders
- Epigenetic regulation in the pathophysiology of rare diseases
- Epigenetic regulation of immunosuppression events in patients from Intensive Care Units.

SELECTED PUBLICATIONS


Friedreich ataxia (FRDA) is caused by mutations in the FXN gene, which results in loss of the mitochondrial protein frataxin.
The mission of the Joint Research Unit in Cancer IVO-CIPF is to translate the basic research performed at the CIPF into clinical scenarios and vice versa. We mainly focus on the discovery of new molecules that could play a role as prognostic or predictive biomarkers. In addition, we explore the design of new drugs as well as new therapeutic combinations which we test in appropriate cell and animal models. One of our tasks is also to develop new diagnostic tools based on next generation sequencing.

SELECTED PUBLICATIONS

Before the confinement due to the COVID-19 pandemic, we organised and hosted several conferences, seminars, and events, while in the months subsequent to the lockdown we moved all of these activities online. We were able to adapt to the situation very quickly thanks to our IT team and the technology available at the CIPF, allowing our scientists to carry on with this important aspect of their careers: collaborating, networking, and sharing knowledge. Nonetheless, we recognize that although technologies represent interesting tools for scientific events, in-person meetings create so many other opportunities that virtual meetings cannot replicate.

CIPF in the media

Total visits to the CIPF website www.cipf.es 152,421

SOCIAL MEDIA FOLLOWERS

Twitter_ 4,998
Facebook_ 2,278
LinkedIn_ 5,425
Youtube Views_ 34,580
Instagram_ 298
Seminars

June 4th
Paula Soriano
INFLAMMATORY TUMOR MICROENVIRONMENT AS TARGET IN THE DESIGN OF NANOCONJUGATES FOR THE TREATMENT OF ADVANCED BREAST CANCER
Carlos Manuel Cuesta
METAGENOMIC ANALYSES OF CHRONIC ALCOHOLIC MICE AND THE IMPACT OF TOLL-LIKE RECEPTOR 4 IN GUT MICROBIOTA AND INTESTINE

June 18th
Marina Sánchez Petidier
TOLL-LIKE RECEPTORS IN SPINAL CORD DERIVED NEURAL PRECURSOR CELLS: IMPLICATIONS ON SPINAL CORD INJURY AND CELL TRANSPLANTATION
Teresa Rubio Martínez-Abcoa
MULTI-OMIC ANALYSIS TO IDENTIFY IMMUNE SYSTEM ALTERATIONS ASSOCIATED WITH THE APPEARANCE OF MINIMAL HEPATIC ENCEPHALOPATHY IN CIRRHOTIC PATIENTS.

July 14th
Ana Sánchez Monteagudo
CIRCULATING MiRNAs PROFILING IN PLASMA AS BIOMARKERS IN WILSON DISEASE
Candela Machuca Arellano
MULTI-OMIC ANALYSIS TO IDENTIFY IMMUNE SYSTEM ALTERATIONS ASSOCIATED WITH THE APPEARANCE OF MINIMAL HEPATIC ENCEPHALOPATHY IN CIRRHOTIC PATIENTS. CEREBELLAR PURKINJE CELL MODEL GENERATION BASED IN IPSCS TECHNOLOGY FOR THE STUDY OF TWO RARE NEURODEGENERATIVE DISEASES: AUTOSOMAL RECESSIVE SPASTIC ARSACS AND PLAN

July 22nd
Alexandre Medina
EFFECTS OF DEVELOPMENTAL ALCOHOL EXPOSURE ON SENSORY PROCESSING

September 17th
Anna Labernadie
MECHANOBIOLOGY OF THE TUMOUR MICROENVIRONMENT DRIVING CANCER SPREADING AND IMMUNE CELLS TRAFFICKING
September 24th
Paz Boix
OPTIMIZATION OF ACCURATE BREAST CANCER MODELS FOR THE ADVANCED PRECLINICAL EVALUATION OF POLYMER THERAPEUTICS
Francisco Ibañez
ROLE OF EXTRACELLULAR VESICLES DURING ETHANOL INDUCED NEUROINFLAMMATION IN ADOLESCENCE

October 29th
Sheyla Velasco
ANTI-INFLAMMATORY THERAPIES FOR THE TREATMENT OF RETINITIS PIGMENTOSA
Arantxa Martinez
ROLE OF THE POLYAMINE-HYPUSINE-EIF5A IN CANCER PROGRESSION

November 26th
Isabel Hinarejos
MOLECULAR BASIS OF NEURODEGENERATION WITH BRAIN IRON ACCUMULATION AND RELATED SYNDROMES
Mª José Arambul
REGULATION OF PARACRINE TISSUE REPAIR SIGNALS BY INSULIN

December 17th
Inés Domingo
USING NMR-MEDIATED METABOLOMICS TO CHARACTERIZE BREAST CANCER-ASSOCIATED ALTERATIONS TO VITAL BIOCHEMICAL PATHWAYS
Amparo Andrés
EPILEPSY STUDY: SEARCH FOR DIAGNOSIS/PROGNOSTIC BIOMARKERS.

Maria José Arambul _ Seminar
Sheyla Velasco and Arantxa Martinez _ Seminars
Isabel Hinarejos _ Seminar
Inés Domingo and Amparo Andrés _ Seminars
DOCTORAL THESIS

Molecular Genetics and Biomarkers of Wilson's Disease
Ana Sánchez Monteagudo, Doctoral Student
Carmen Espínos, Vincenzo Lupo, Directors

MesoPorous Silica and Gold-Based Nanodevices: New Controlled Delivery Platform for Biomedical Applications
Gema Vivó Llorca, Doctoral Student
Mar Orzáez, Ramón Martínez, José Ramón Murguía, Directors

Molecular Approaches for the Identification of New Biomarkers and Therapeutic Targets of Non-Small Cell Lung Cancer: Tumor Stem Cells, Epithelial-Mesenchymal Transition and Patient-Derived Xenograft Models
José Miguel Pardo Sánchez, Doctoral Student
Rosa Farías Rivera, Director
José Ramón Murguía Ibáñez, Tutor

Role of Extracellular Vesicles in the Propagation and Maintenance of Neuroinflammation Induced by Alcohol Consumption in Adolescence
Francesc Ibañez Cabanes, Doctoral Student
Consuelo Güerri Sirera, María Pascual Mora, Directors

Alterations in Neurotransmission in the Hippocampus of Hyperammonaemic Rats. Role of Neuroinflammation, Modulation by Extracellular GMPC
María Sancho Alonso, Doctoral Student
Vicente Felipo, Andrea Cabrera Pastor, Marta Llansola, Directors

078/079
CIPF Dissemination and outreach events

Since October 2020, the CIPF belongs to the Unit of Scientific Culture and Innovation (UCC+i) Network as a member accredited by the FECYT in recognition of our activities in scientific dissemination, communication, outreach and training.

CIPF disseminates and shares science to improve and increase scientific culture and knowledge of citizens. To do so, there are many different initiatives throughout the year in which CIPF laboratories in collaboration with different partners carry out activities for different audiences.
Outreach

18/02/2021
Toy collections for Fundación Colegios Siglo XXI

28/04/2021
Opening of the Exhibition “A vivir que son 100 años”

11/06/2021
Clothes collect for KOOPERA

28/09/2021
International Science Culture Day: Chemistry is Cool. Invisible but real nanopharmaceuticals

CIPF Visits

05/03/2021
GENERALITAT VICE-PRESIDENT
RUBÉN MARTÍNEZ DALMAU

19/07/2021
ALICIA ROMERO LLANO,
FROM CATALONIA PARLIAMENT, PSC GROUP
IMPACT OF THE COVID19 PANDEMIC ON WOMEN IN RESEARCH. ONLINE CONFERENCE TO CELEBRATE THE 11TH OF FEBRUARY, INTERNATIONAL DAY OF WOMEN AND GIRLS IN SCIENCE. WITH JAVIER S. BURGOS, PALMIRA MUÑOZ, DEBORAH BURKS, MARIA TERESA RUIZ CANTERO AND ELENA MARBÁN.

MEETING AT CIPF TO RENEW THE AGREEMENT BETWEEN CIPF AND CACSA. WITH FRANCESC COLOMER, DEBORAH BURKS, ENRIQUE VIDAL AND ENRIQUE FONTES.

FLOW CYTOMETRY COURSE, TECHNICAL BASIS. COORDINATED BY ALICIA MARTÍNEZ AND JOSÉ ENRIQUE O’CONNOR. WITH THE PARTICIPATION OF GUADALUPE HERRERA AND BEATRIZ JAVEGA. THIS COURSE IS CERTIFIED BY EYES AND THIS EDITION CELEBRATED BETWEEN THE 4TH AND THE 8TH OF OCTOBER WAS SPONSORED BY JANSSEN SPAIN.
MARIA JESUS VICENT AWARDED BY PICANYA TOWN HALL WITH THE SCIENTIFIC WOMEN PRIZE CONCEPCIÓN ALEIXANDRE.

SCIENTIFIC RETREAT, CIPF PRINCIPAL INVESTIGATORS MEETING CELEBRATED THE 24TH OF NOVEMBER AT DRASSANES 52, EL CABANYAL, VALENCIA.

OPENING OF THE FUNDACIÓN GENERAL CSIC EXHIBITION “A VIVIR QUE SON 100 AÑOS”. WITH ANA BARCELÓ AND MAVI MESTRE.

VISITS TO THE FGCSIC EXHIBITION AT CIPF “A VIVIR QUE SON 100 AÑOS”
WE CELEBRATED THE INTERNATIONAL DAY OF SCIENTIFIC CULTURE THE 28TH OF SEPTEMBER AT THE MUSEU DE LES CIÈNCIES. CIPF AND THE MUSEU DE LES CIÈNCIES ORGANISED AND COORDINATED INTERACTIVE SCIENTIFIC WORKSHOPS ON THIS DAY. CIPF POLYMER THERAPEUTICS LABORATORY TEAM OFFERED IN THE MUSEUM TWO SURPRISING AND AMUSING ACTIVITIES AND EXPERIMENTS FOR YOUNG STUDENTS AND GENERAL PUBLIC.

ON DECEMBER 16TH WE HOSTED AT CIPF THE III CONFERENCE ON PRECISION ONCOLOGY MANAGEMENT IN THE VALENCIAN COMMUNITY "ONE STEP CLOSER TO EQUITY". PRESENTED BY CARLOS CAMPS, ANA LLUCH AND DEBORAH BURKS. THE INAUGURATION OF THE CONFERENCE WAS CONDUCTED BY AMPARO GARCÍA LAYUNTA FROM CONSELLERIA DE SANITAT UNIVERSAL I SALUT PÚBLICA.
OCTOBER 1ST INTERNATIONAL DAY OF OLDER PERSONS CONFERENCE AT CIPF WITH DEBORAH BURK, ALVARO BONET, Mª AMPARO GARCÍA LAYUNTA, SACRAMENTO PINAZO, FERNANDO FLORES, ISABEL DEL PINO, AMPARO OLIVER, ÁNGEL BARCO, CAROLINA MIR, TERESA MIRALLES, ROSA MARTÍNEZ, MIREIA LÓPEZ AND PILAR HUERTA.

THE 19TH OF NOVEMBER CIPF ORGANISED AN EVENT IN MEMORY OF JERÓNIMO FORTEZA BOVER WITH HIS FAMILY AND FRIENDS AND WITH THE PARTICIPATION OF CARLOS CAMPS, JUAN SAUS AND SANTIAGO RAMÓN Y CAJAL. CIPF CONFERENCE ROOM IS CALLED SINCE THIS DAY JERÓNIMO FORTEZA CONFERENCE ROOM IN HIS HONOR.
The CIPF and the UPV investigate Dravet syndrome with Drosophila flies

30/12/2021 AlicantePress
Researchers investigate a rare childhood disease with a genetically modified fly model

30/12/2021 Infosalus
The CIPF and the UPV investigate a pediatric rare disease with a genetically modified fly model

30/12/2021 Europa Press Comunitat Valenciana
The Spanish Association Against Cancer of Valencia committed to young talent to develop new treatments for lung and breast cancer

30/12/2021 PharmaMarket
Four projects to fight cancer

28/12/2021 Las Provincias
The AECC allocates €352,000 to scientific projects to improve the response to lung and breast cancer treatment

27/12/2021 Europa Press Comunitat Valenciana
The AECC allocates €352,000 to scientific projects to improve the response to lung and breast cancer treatment

20/12/2021 20minutos
A step closer to equity in oncology

01/12/2021 Saó
CIPF leads a European COST Action to develop therapies based on the regulation of protein levels

25/11/2021 Europa Press Comunitat Valenciana
CIPF and the University of Cambridge will develop new therapies for diabetes and its associated complications

18/11/2021 Infodiabético
The CIPF and Cambridge University collaborate in the investigation of new therapies in diabetes and associated complications

16/11/2021 Europa Press Comunitat Valenciana
Description of Hereditary Retinal Dystrophies, Regina Rodrigo

04/11/2021 RadioLibertad FM
Adaret clinical trial: researchers test whether a new drug is effective against retinosis pigmentary

28/10/2021 Vision Num. 59
Debate on new ways to end pancreatic cancer

27/10/2021 La Razón
Pancreatic cancer, new treatments for the most lethal cancer

22/10/2021 La Vanguardia
Researchers identify a mechanism that controls the onset of puberty

18/10/2021 Genotipia
Spanish researchers identify ‘the switch’ of sexual maturation

15/10/2021 Alimente+Salud El Confidencial

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HEALTH RESEARCH FOUNDATIONS PARTICIPATE IN A PREDICTIVE MEDICINE AND DATA SCIENCE PROJECT WITH MORE THAN 100 INSTITUTIONS

METABOLIC ALTERATIONS IN RED BLOOD CELLS ASSOCIATED WITH AGING

VALENCIAN BIOMEDICAL RESEARCH FOUNDATIONS CREATE THE ANA LLUCH GRANT TO PROMOTE TRANSLATIONAL RESEARCH IN ONCOLOGY

BARCELÓ: “THERE ARE MANY FACTORS THAT INFLUENCE HOW WE AGE AND WE CAN PARTICIPATE ACTIVELY”

THE CIPF PARTICIPATES IN A EUROPEAN PROJECT THAT STUDIES A BIOHYBRID IMPLANT TO REGENERATE THE SPINAL CORD

NEW PHARMACOLOGICAL THERAPIES TO REDUCE RETINAL DEGENERATION ARE INVESTIGATED

A TREATMENT FOR ALZHEIMER’S BASED ON POLYPEPTIDE NANOCONJUGATES IS SUCCESSFULLY TESTED IN ANIMALS

A TEAM FROM CIPF AND CH NAVARRA IDENTIFIES A NEW FORM OF NON-PROGRESSIVE CONGENITAL ATAXIA

THE CIPF INVESTIGATES THE MOLECULAR BASES OF DIFFERENT TYPES OF CANCER, NEW TARGETED THERAPIES AND ADVANCED DIAGNOSTIC TOOLS

CIPF RESEARCHERS ADVANCE IN A PRECLINICAL MODEL OF SCHIZOPHRENIA

THE CIPF LEADS A EUROPEAN COST ACTION TO DEVELOP NEW THERAPIES BASED ON THE REGULATION OF PROTEIN LEVELS

THE CIPF AND THE UNIVERSITY OF CAMBRIDGE SIGN A COLLABORATION AGREEMENT TO INVESTIGATE NEW THERAPIES IN DIABETES AND ASSOCIATED COMPLICATIONS

A TEAM FROM THE CIPF AND THE UPV TESTS A BIOCOMPOSITE FOR ACUTE SPINAL CORD INJURIES

RESEARCHERS DETECT 15 GENES EXPRESSED DIFFERENTLY IN MEN AND WOMEN WITH PARKINSON’S

NEW LUNG CANCER XENOGRAFT MODELS

RESEARCHERS IMPROVE SUSTAINED RELEASE AND REDUCE HARMFUL SIDE EFFECTS IN PROSTATE CANCER TREATMENT

A MULTIDISCIPLINARY TEAM FROM CIPF HAS IDENTIFIED COMMON UNDERLYING PATTERNS IN BREAST, KIDNEY AND LUNG CANCERS

A CIPF TEAM ADVANCES IN THE KNOWLEDGE OF THE RECEPTORS INVOLVED IN NEUROINFLAMMATION, NEURODEGENERATION AND BRAIN DAMAGE DUE TO ALCOHOLISM

THE CIPF RESEARCHER, Mª JESÚS VICENT, WINS THE CONCEPCIÓ ALEIXANDRE AWARD FOR THE VALENCIAN SCIENTIFIC WOMAN OF PICANYA

CIPF DEVELOPS A NEW MODEL OF DRAVET SYNDROME IN DROSOPHILA FLY

RESEARCHERS REVEAL THAT ERBB4 DEFICIENCY CAUSES BEHAVIOURAL DEFICITS AND AFFECTS MEMORY

A TEAM FROM CIPF AND FISABIO DEVELOPS A TOOL THAT IMPROVES THE INTERPRETATION OF SPINAL CORD MRIS

METAFUN: META-ANALYSIS OF FUNCTIONAL MECHANISMS OF DISEASE

A TEAM FROM CIPF AND THE UPV TESTS A BIOCOMPOSITE FOR ACUTE SPINAL CORD INJURIES

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Inflammation and oxidation, possible targets to delay retinal degeneration
14/10/2021 Diario Médico

Researchers investigate new pharmacological therapies to reduce retinal degeneration
27/09/2021 Infosalus

CIPF and the City of Arts and Sciences celebrate the Day of Scientific Culture
27/09/2021 Las Provincias

Erwin Knecht—the intelligent and mad, funny and grumpy man of autophagy
23/09/2021 Autophagy, Taylor&Francis Online

Scientists find molecular changes linked to schizophrenia
17/08/2021 Diario Sanitario

Advances in the mechanisms involved in the development of schizophrenia
16/08/2021 Agencia EFE

Researchers find molecular alterations involved in the development of schizophrenia
16/08/2021 ConSalud

Researchers discover new alterations of cortical circuits related to schizophrenia
16/08/2021 Diario Médico

“Cancer will become a chronic and non-lethal disease”
31/07/2021 El Mundo

Dolors Corella, Marta Benet y Mª Jesús Vicent, premios Concepción Aleixandre a la Mujer Científica Valenciana
28/05/2021 UV Noticias

María Jesús Vicent Docón, Marta Benet Giménez and Dolors Corella, winners of the Picanya Valencian Scientific Woman Awards
27/05/2021 HortaNoticias

Mª Jesús Vicent Docón, head researcher of the CIPF, receives the Concepción Aleixandre de Picanya award
26/05/2021 Comarcal CV

Which factors influence alcohol addiction in adolescence?
18/05/2021 CadenaSer

European cooperation in a new project to regenerate the spinal cord
18/05/2021 IMMédico

Centro Príncipe Felipe participates in a European project to create a biohybrid implant that regenerates the spinal cord
17/05/2021 Infosalus

Fisabio’s and CIPF researchers design an algorithm that anonymizes “sensitive” information in medical records
15/05/2021 Europa Press Comunitat Valenciana

Inauguration in Valencia of the exhibition “Live up to 100 years”
07/05/2021 madrimasd

Fundaluce Award Ceremony
06/05/2021 Visión Num. 58

A total of 27 Valencian Dual Vocational Training students selected for the Sanec health research program
19/04/2021 Europa Press

A total of 27 Valencian Dual Vocational Training students selected for the Sanec health research program
19/04/2021 20 minutos

New nanomedicine treatment for Alzheimer’s successfully tested
15/04/2021 Diario de Navarra

Nanomedicine-based treatment for Alzheimer’s successfully tested on animals
15/04/2021 ConSalud

Nanomedicine treatment for Alzheimer’s successfully tested on animals
15/04/2021 CadenaSer

Nanomedicine treatment for Alzheimer’s successfully tested on animals
15/04/2021 LevanteEMV

The head of microbiology of the clinical hospital of Valencia scientific coordinator of vaccination
18/03/2021 La Vanguardia

Covid-19 is likely to be with us for years to come
17/03/2021 El Periódico de Aquí

A research team in which the CIPF participates identifies a new form of non-progressive congenital ataxia
12/03/2021 Diario de Navarra

Bankia Foundation launches the SANEC call
02/03/2021 Noticias Bancarias

C. Valenciana creates ProVaVac to investigate and “improve the effectiveness” of vaccination against covid-19
01/03/2021 DiarioFarma

Open the SANEC call to promote medical research in Dual Vocational Training students
01/03/2021 Éxito Educativo

The Generalitat creates a research program on vaccination to improve its effectiveness
01/03/2021 ValenciaPlaza

Women scientists: when breaking the “glass ceiling” is not a utopia
11/02/2021 Cevipyme

The Valencian biomedical research foundations create the Ana Lluch scholarship for Oncology
11/02/2021 Saforguia.com

Valencian biomedical research foundations create the Ana Lluch scholarship
10/02/2021 La Vanguardia

Impact of the COVID19 pandemic on women scientists in biomedical research
01/02/2021 tdefebrero.org

Health research foundations participate in a Predictive Medicine and Data Science project with more than 100 institutions
07/01/2021 El Periódic
The Nuclear Magnetic Resonance (NMR) Unit provides advanced applications for the identification, characterisation, and quantification of small molecules and macromolecules, offering tools to elucidate the molecular mechanisms underlying their biological activity. The Unit offers access to three NMR spectrometers with different field strengths (300, 500, and 600 MHz), equipped with a variety of probes and automation systems, including a probe for intact tissue analysis (HRMAS), a cold probe with enhanced sensitivity, and a SampleJet robot system for up to 500 samples. As support to its users, the Unit offers its extensive experience to help in the interpretation of NMR spectra and the characterisation and structural analysis of different chemical compounds and macromolecules.

Furthermore, the Unit can perform metabolic profiling of a broad range of biofluid samples, including plasma, serum, urine, amniotic fluid, cerebrospinal fluid, or tear fluid. The quantification of metabolites in different tissue and organ samples from patients and model animals, as well as in cellular models, can also be carried out. As a result, NMR technology has been applied to study the alterations of the metabolic profiles associated with different biochemical, pharmacological, or pathological processes, including cancer, diabetes, Alzheimer, or rare diseases. The Unit has worked in close partnership with research groups and hospitals on several of these projects. On the other hand, the NMR Unit also provides its equipment and experience for screening drug libraries to search for hits for specific protein targets, as well as to characterise the geometry of the interaction between drug molecules and protein or RNA macromolecules.

The NMR Unit has developed a protocol for the determination of the metabolic profile in mitochondria and nuclei of tissues or cultures, in collaboration with the Polymer Therapeutics Research Group. This methodology can be applied to tissue samples obtained from animal models or human biopsies, and could provide very useful information in biomedical projects or clinical studies focused on the evaluation of new drugs (e.g., efficacy, toxicity, etc.), particularly those ones targeting mitochondria or nuclei.

SELECTED ARTICLES


The CIPF Cytomics Facility provides technological solutions for high-speed polychromatic analysis, fluorescence activated cell sorting, and high-content screening assays. It offers high-quality experimental support applied to biomedicine, biotechnology, translational medicine, microbiology, and environmental sciences.

During 2021 we have collaborated with the CIPF research labs, CIPF collaborators and another external groups. A Final Degree Project and a PhD Thesis were the result of this collaboration. Final Degree Project: Development of an experimental model for in vitro drug research based on cell painting assays, Biotechnology UPV, ETSIAMN UPV by Alicia Ibíñez de las Heras, with Alicia Martínez Romero as tutor. PhD Thesis: Characterization of immune and platelet function in marine mammals and their alterations induced by stress, pathologies or environmental contaminants, by Mar. Felipo Benavent, University of Valencia, directed by José Enrique O’connor Blasco, Alicia Martínez Romero and Consuelo Rubio Guerri. Antonio Iradi Casal was the UV tutor.

Moreover, the course “Flow Cytometry: Technical Bases”, accredited by the Comisión de Formación Continuada de las Profesiones Sanitarias, was celebrated in October 2021. The Cytomics Core Facility also have participated in the University Certificate in Flow Cytometry: Fundamentals, Techniques and Applications, 1st Edition, Virtual Course University of Valencia, January-March 2021 (Online).

SELECTED ARTICLES
Electron microscopy uses an accelerated electron beam which, upon impacting the sample, generates different signals that provide information about its atomic structure. In Transmission Electron Microscopy (TEM), transmitted electrons are detected to generate conventional, dark-field, high-resolution transmission images. Due to its high resolution power, TEM allows the development of useful applications in the fields of biomedical research, biotechnology and diagnostics.

The Electron Microscopy Core Facility at CIPF collaborates with internal and external research groups offering an invaluable tool to address some scientific questions. The Unit provides technological support for many electron microscopy techniques: ultrastructural studies of tissues and cell cultures, negative staining of viruses and extracellular vesicles, some immunogold techniques and CryoTEM.

One of the most demanded techniques is the processing of extracellular vesicles and exosomes. Due to their size and composition, electron microscopy is one of the main tools that allow the morphological characterization of these particles. A remarkable technique is the detection of surface markers on the external membrane of extracellular vesicles by immunogold.

Also, in the line of developing new techniques, we are working jointly with the Advanced Light Microscopy Unit on the implementation of Correlative Light and Electron microscopy techniques (CLEM). We have developed correlation techniques in both cell culture and histological tissues.

In 2021, the large volume of samples processed from different national and international institutions has been highlighted. In addition to the service offered as a core facility, efforts are being made to exploit the knowledge of the technical staff in the field of research, for which scientific collaborations have been initiated with some research group. These collaborations cover both conventional electron microscopy and CLEM techniques.

The facility has not been oblivious to the pandemic we are experiencing and has tried to contribute knowledge to the fight against the Sars-Cov-2 virus. We have processed cell culture samples infected with the virus to study the mechanism of infection in the cells and in which cell compartments it establishes itself.

SELECTED ARTICLES

The Advanced Light Microscopy Facility (ALMF) is located in more than 100 square meters of space where the CIPF offers efficient access to a wide variety of microscopes for users, from conventional to state-of-the-art light microscopy equipment. The ALMF assists CIPF users and also external users in their research with key techniques and tools in the field of biomedical research (for live cells, fixed samples, model organisms, small animals or at most points in between) and also in other scientific areas such as nanoscience and nanotechnology, new materials, etc.

The facility is currently equipped with three laser scanning confocal microscopes, a multiphoton/intravital microscope, a wide-field fluorescence microscope with structured illumination (pseudo confocal microscope), five wide-field fluorescence microscopes, a slide scanner for whole slide imaging and a PALM laser microdissection system for non-contact sample cutting and capture. Live cell imaging can be performed at two workstations surrounded by environmental chambers to maintain constant temperature and CO₂ levels. An offline workstation can be used for image processing, visualization and user data analysis. In addition, the ALMF provides user training and ongoing support, including assistance with experimental design, visualization and image processing, and quantitative analysis.

Despite the pandemic situation, 2021 has been a year with a great scientific activity for the ALMF. Our equipment has been used by more than 60 users from more than 20 laboratories with a total of more than 9000 hours of use.

The evaluation of biological tissues in three dimensions is becoming increasingly popular. This trend coincides with the emergence of a wide variety of tissue clearing protocols and advances in two-photon microscopy. In 2021, we started combining both techniques, and have obtained excellent results that have provided us with more structural information than traditional optical sectioning.

On the other hand, in 2021, the ALMF, working closely with the electron microscopy service of the CIPF, has optimized and improved the CLEM technique by introducing the use of the laser microdissector. We have achieved that the technique is perfectly protocolized and we are currently collaborating in some research projects implementing this technique.
The CIPF Screening Platform supports the evaluation of biological and pharmacological compound libraries, including in-house libraries and those from external agencies (e.g. EU-OpenScreen). CIPF Screening facility is an accredited specialist site on complex cellular assays with the ERIC EU-OpenScreen. We aim to identify and characterize novel bioactive agents for cancer treatment, regenerative medicine, and infectious diseases, among other conditions.

We have validated an HTS approach to identifying exosome biogenesis/release inhibitors by AlphaScreenTM, which may improve diagnostic and therapeutic approaches in cancer, neuroinflammation, and many other diseases. Cancer research represents a crucial area; to this end, we have performed screenings that compare traditional 2D with advanced 3D breast cancer cell models and developed combination assays for various cancer types, including sarcoma, to develop personalized treatment approaches. We also undertook massive differential screening to detect drugs that induce breast cancer cell death through Gasdermin B.

Thanks to a European project (H2020-DRIVE) coordinated by EU-OpenScreen, we successfully conducted a massive screening of 100,000 compounds, which accelerated the development of an associated MedChem project. Other platform-involved projects include neurodegenerative diseases (e.g., Parkinson's disease) and infectious diseases such as SARS-COV-2; the latter includes an optimization for a high-density assay to identify drug-RNA (virus) interaction.

Finally, we collaborate broadly with the CIPF Cytomics and Advanced Light Microscopy services, where we are currently working towards implementing Cell Painting technology in 3D cell models.

The unit participates in: ERIC-EU-OpenScreen, SDDN, Geivex, and other networks of excellence such as REDEFAR, ES-OpenScreen and Tentacles.

SELECTED ARTICLES


Our main objective is to provide support and scientific advice to the different research groups, whether they are CIPF or external institutions; hospitals, OPIs and companies. To achieve this goal, the service integrates the scientific advances of the CIPF with advanced technology equipment, in the fields of human genetics, genomics and bioinformatics, also enriched with the knowledge generated through different collaborative projects. We focus on helping all our users in their next generation sequencing (NGS), qPCR, Sanger and microarray experiments and, therefore, our services range from the extraction of nucleic acids from tissue, cell cultures or biological liquids until the delivery of the data analyzed using bioinformatics tools.

Some of the most used applications were targeted resequencing, RNASeq, small genome sequencing, metagenomics, targeted gene expression profiling, miRNAs, aCGH, differential expression, interindividual genetic variation, and epigenetic profiling, among others.
TECHNOLOGY

ANIMAL MODELS PLATFORM

TEAM MEMBERS
Preclinical Models Platform Director: Víctor Gómez García
Tomás García Robles, Amparo Moragón Carretero, Melisa Vera Abarca

OVERVIEW
Advances in biomedical research often require the use of in vivo models and the consistency and reproducibility of data can only be achieved with high-quality standardised models, facilities, and procedures. At the CIPF, we are committed to the highest standard of animal welfare. The Animal Facility provides CIPF scientists with high-quality animal care services and facilities to improve animal research and ensure the health, well-being, and humane treatment of animals used in research and teaching.

Despite of the pandemic situation, the activity has been increasing during 2021. Some important changes have been done through the months securing a better service without losing any quality aspect of the service we provide to all our users. The Animal Models Platform has been up and running all year long making possible to keep the research animals housed in the department with the best standards of health, well-being and microbiological status.

Our skilled and experienced staff is always trying to find better ways to get better and implementing improvements which will be reflected even more in coming years results.
### CIPF Economic Figures

<table>
<thead>
<tr>
<th>Category</th>
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<td>Funds with a non-competitive origin</td>
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<td>Direct funds from Generalitat Valenciana</td>
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CIPF_ Publications

AVERAGE IMPACT FACTOR

6,15

JCR PUBLICATIONS

122

1Q PUBLICATIONS

97

1Q

79%

NUMBER OF PUBLICATIONS

PUBLICATIONS IN 1ST QUARTILE

IMPACT FACTOR
In 2021, the CIPF continued the Action Plan established to implement the European Commission’s Human Resources Strategy for Researchers (HRS4R) to promote research careers in accordance with the principles established by the European Charter for Researchers and the Code of Conduct. Since April 2021, as part of our strategic plan and commitment to the HRS4R program, the CIPF is offering its staff the Nature Masterclasses Training in areas such as Scientific Writing and Publishing, Effective Collaboration in Research, Managing Research Data to Unlock its Full potential, Data Analysis planning, Peer Review and Grant Writing among other courses. These courses give our researchers the opportunity to learn techniques and strategies to develop their skills and confidence in a variety of essential research activities. They will be able to apply these skills to their daily professional life, but also take advantage of them to develop their scientific career.

In recent years, several courses, conferences, seminars, workshops, FBR and thesis readings have been given for the personal researcher with the aim of equipping them with skills and training to improve their research development. The CIPF has offered courses focused on professional development. These trainings are carried out continuously in the workplace. Besides, English courses are also offered annually at various levels to improve writing and scientific presentation.

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<th>CIPF Research Personnel</th>
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CIPF_ Competitive Research Funding

ACTIVE PROJECTS 2021

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FUNDING ACTIVE PROJECTS 2021

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NEW PROJECTS AWARDED IN 2021

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FUNDING NEW AWARDS 2021

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CIPF_ Non Competitive Research Funding

ACTIVE PROJECTS 2021

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NEW PROJECTS AWARDED IN 2021

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</table>

CIPF Research Support Unit

TEAM MEMBERS

From left to right Zaira Alfonso, Mayra Pilar Rubio, María José Moreto, Cristina Rajo and Laetitia Poidevin.

Cristina Rajo Anadon joined CIPF in 2021 as Grants Support and Management Coordinator.
### H2020-EU

<table>
<thead>
<tr>
<th>GRANT TYPE</th>
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<tbody>
<tr>
<td>H2020-ERC-2014-Advanced Grant</td>
<td>New players in human BAT differentiation and activation</td>
<td>Antonio Vidal-Puig</td>
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<td>H2020-INFRADEV-03-2018-2019</td>
<td>Ensuring long-term sustainability of excellence in chemical biology within Europe and beyond</td>
<td>Mª Jesús Vicent</td>
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<td>H2020-MSCA-ITN-2019</td>
<td>Molecular Machines Functioning in Cells</td>
<td>Mª Jesús Vicent</td>
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<tr>
<td>COST. European Cooperation in Science and Technology</td>
<td>A sound proteome for a sound body: targeting proteolysis for proteome remodeling.</td>
<td>Rosa Farràs</td>
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### MCIN - Ministry of Science and Innovation

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<td>Development of a gene therapy platform for kidney genetic diseases</td>
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<td>Excellent Networks</td>
<td>Spanish network for ion channels</td>
<td>Victoria Moreno</td>
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<td>Excellent Networks</td>
<td>TENTACLES Translational Network for the clinical application of Extracellular Vesicles</td>
<td>Mª Jesús Vicent</td>
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<tr>
<td>Excellent Networks</td>
<td>REDEFAR Spanish Drug Discovery Network</td>
<td>Mª Jesús Vicent</td>
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<td>Excellent Networks</td>
<td>Consolidation and strategic positioning of the Spanish node in the ERC EU-OPENSCREEN network</td>
<td>Mar Orzáez</td>
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<td>Excellent Networks</td>
<td>Molecular mechanisms of neurological alterations (motor and cognitive) in hyperammonemia and hepatic encephalopathy. Therapeutic implications.</td>
<td>Vicente Felipo</td>
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<td>Excellent Networks</td>
<td>Deciphering the molecular mechanisms regulated by BAP1 PR-DUB complex of cell invasion shared between human trophoblast and cancer cells.</td>
<td>Vicente Pérez</td>
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<td>R&amp;D+i Projects Research Challenges</td>
<td>NRG1 Signaling in cortical circuits: Molecular basis of Schizophrenia</td>
<td>Pietro Fazzari</td>
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<tr>
<td>R&amp;D+i Projects Research Challenges</td>
<td>Phenotypic variability: origins and consequences</td>
<td>Francisco Ibomma</td>
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<tr>
<td>R&amp;D+i Projects Research Challenges</td>
<td>Synergistic Approach for Metastatic Tumor and Neurodegenerative Disorder Treatments using Versatile PolyPeptide-based Conjugates</td>
<td>Mª Jesús Vicent</td>
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<td>R&amp;D+i Projects Research Challenges</td>
<td>Channelopathies underlying prefrontal cortex dysfunction in Alzheimer’s disease</td>
<td>Isabel del Pino</td>
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<td>R&amp;D+i Projects Research Challenges</td>
<td>Targeting Nuclear Receptor REV-ERV-alpha in inflammatory bowel disease</td>
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<td>R&amp;D+i Projects Research Challenges</td>
<td>The membrane interactome of BCL-2 proteins as an antimutator target</td>
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<td>R&amp;D+i Projects Research Challenges</td>
<td>IRS2/fgf7 axis in the liver</td>
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<td>R&amp;D+i Projects Research Challenges</td>
<td>New bio-active biomaterial for the regeneration of spinal cord injuries</td>
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<td>R&amp;D+i Projects Research Challenges</td>
<td>The Role of Neurphilin-2 in the regulation of myeloid-derived suppressor cells</td>
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<td>NRG1 Signaling in axonal growth growing and regeneration in the cerebral cortex</td>
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<td>R&amp;D+i Projects Proof of Concept</td>
<td>Valorization of a first-in-class MCL-1 inhibitor</td>
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<td>Ramón y Cajal Programme</td>
<td>The role of genes involved in brain pathologies</td>
<td>Pietro Fazzari</td>
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<td>Hypothalamic immune-metabolism</td>
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<td>Trophoblast and cancer biology</td>
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<td>Tumor-stroma communication</td>
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<td>Researchers Training</td>
<td>Mª del Mar Sánchez new bio-active biomaterial for the regeneration of spinal cord injuries</td>
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<td>Researchers Training</td>
<td>Yolanda Arenas Molecular bases of neurological disorders and therapeutic implications</td>
<td>Vicente Felipo</td>
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<td>Researchers Training</td>
<td>María Ibáñez Synergistic Approach for Metastatic Tumor and Neurodegenerative Disorder Treatments using Versatile PolyPeptide-based Conjugates</td>
<td>Mª Jesús Vicent</td>
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### MEyFP - Ministry of Education and Vocational Training

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<td>FPU</td>
<td>Inés Domingo Development of new procedures to characterise biochemical routes altered in breast cancer in vitro and in vivo using metabolic profiles obtained by NMR spectroscopy</td>
<td>Mª Jesús Vicent</td>
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<td>FPU</td>
<td>Paz Boix Development of polymeric combination therapy for the treatment of triple-negative metastatic breast tumors</td>
<td>Mª Jesús Vicent</td>
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<td>FPU</td>
<td>Paula Izquierdo Molecular mechanisms of cognitive and motor disorders in hyperammonemia and hepatic encephalopathy. Therapeutic implications.</td>
<td>Vicente Felipo</td>
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<tr>
<td>FPU</td>
<td>Gergana Yvaylova Molecular mechanisms of cognitive and motor disorders in hepatic encephalopathy. Therapeutic implications.</td>
<td>Vicente Felipo</td>
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<tr>
<td>FPU</td>
<td>Mª de les Neus Torres Educating the cell therapy for the treatment of spinal cord injuries</td>
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<td>FPU</td>
<td>Irene Solar Caracterización de las diferencias de sexo en la enfermedad de esclerosis múltiple mediante el metaanálisis y la integración de estudios de imagen biomédica, transcriptoma y microbioma.</td>
<td>Francisco García</td>
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### MS - Ministry of Health

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<td>National Drug Plan</td>
<td>Neuroinflammation and alterations in brain plasticity in adolescents with alcohol abuse: gender differences, biomarkers and therapies</td>
<td>Consuelo Guerri</td>
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### ISCIII - ES Instituto de Salud Carlos III

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<td>FIS Project</td>
<td>Personalized treatment against activated AP-1 pathway in lung and breast cancer.</td>
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<td>FIS Project</td>
<td>Patient specific disease models as a tool toward effective therapies for hereditary retinal dystrophies.</td>
<td>Dunja Lukovic</td>
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<td>FIS Project</td>
<td>Clinical studies, genetic bases and prognostic biomarkers in rare neurodegenerative diseases.</td>
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<td>FIS Project</td>
<td>Preclinical study of the regenerative powers of stem-cell derived astrocytes in the treatment of mouse spinal injury.</td>
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<td>Development of anti-inflammatory nanotherapies in retinitis pigmentosa.</td>
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### CIUCSID - GVA Valencia Regional Health Ministry

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<td>CDEIGENT</td>
<td>Local insulin-induced paracrine signalling (LiiPS) in regenerative medicine and cancer</td>
<td>Luke Noon</td>
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<td>AMPER</td>
<td>Grants to finance HR activities to promote research and training in healthcare, biomedical and public health research, with 30 beneficiaries at CIPF in 2021</td>
<td>Cristina Rajo</td>
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### CIUCSID-GVA Valencia Regional Innovation, University, Science and Digital Society Ministry

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<td>From genes to therapy in neurogenerative and neuromuscular diseases</td>
<td>Carmen Espinós, Maximo Ibo Galindo</td>
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<td>Regenerative medicine of the human uterus: from cell therapy to organ creation through bioengineering</td>
<td>Deborah J. Burks</td>
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<td>MEMBDATH: Cell death and membranes: a new niche in the fight against cancer.</td>
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<td>Molecular and cerebral mechanisms of cognitive and motor disorders in hyperammonemia and hepatic encephalopathy. Therapeutic and diagnostic implications</td>
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<td>PROMETEO Programme</td>
<td>Novel therapeutic strategies in the developing and injured brain</td>
<td>Pietro Fazzari</td>
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<td>lRNAs mitochondrial fragments biomarkers and new therapeutic targets in mitochondrial diseases</td>
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<td>Mª de las Neus Torres Neural precursor cells and electrical stimulation for spinal cord injury</td>
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<td>Iván Atienza Mechanisms of peripheral inflammation, hyperammonemia and neurological impairment</td>
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<td>Beatriz Martínez Optogenetic and pharmacological stimulation of neural stem cells for the treatment of spinal cord injuries</td>
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<td>Sheyla Velasco. Anti-inflammatory nanotherapies for retinitis pigmentosa treatment</td>
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<td>Antonio Serrano Identification of new biomarkers and development of combination polymeric conjugates in metastatic prostate cancer</td>
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<td>María Sancha. Mechanisms by which cyclic GMP and neuroinflammation modulate neurotransmission and cognitive motor function</td>
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<td>Esther Martínez. Use of Intranasal Polypeptide Based Nanotherapeutics for the Treatment of Glioblastoma Multiforme (GBM)</td>
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<td>Sonia Prakash. Neural stem cells from inducible pluripotent stem-cells and PA-Curcumin combinatorial treatment for spinal cord injury regeneration</td>
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<td>CIDEGENT 2021</td>
<td>Molecular basis of healthy obesity: understanding pathology through paradoxical phenotypes</td>
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<td>Cytoskeletal dynamics in cell migration and cancer invasion</td>
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<td>Subsidies to support the hiring of doctoral research staff from the Ramón y Cajal grants</td>
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<tr>
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<td>Ana Sánchez Monteaquido: Genetic bases and prognostic biomarkers for Wilson and Wilson-like diseases</td>
<td>Carmen Espinós</td>
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<td>Functional study of photoreceptors in retinal organoids derived from patients with hereditary retinopathies</td>
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<td>ONCE Foundation</td>
<td>Development and optimization of anti-inflammatory nanotherapies in hereditary retinal dystrophies</td>
<td>Regina Rodrigo</td>
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<tr>
<td>BBVA Foundation</td>
<td>Role of the leak ion channel NALCN in neurodevelopmental diseases</td>
<td>Isabel Rodrigo</td>
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<td>Ramón Areces Foundation</td>
<td>Identification and modelling of molecular and cellular events of the immune response associated to the appearance of minimal hepatic encephalopathy in cirrhotic patients</td>
<td>Vicenta Felipo</td>
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<td>Generation of models in Drosophila melanogaster by knock-in of patient mutations</td>
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<td>Young IBRO</td>
<td>International collaboration between Del Pino Lab in Spain and Di Cristo Lab in Canada</td>
<td>Isabel del Pino</td>
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AFM Téléthon The cell therapeutic strategy for hereditary retinal dystrophies in small and large animals, MERTK associated Retinitis pigmentosa

EMBO Exchange Grant Identification of mechanisms by which hyperammonemia alters GABAergic synapses in primary cultures of cerebellum containing Purkinje neurons

EASI-Genomics Molecular basis of NBIA and NBIA-mimic

IDBAPS Implication of the specific cutaneous immune profile determined in peripheral blood in the prognosis and responsiveness to immunotherapy in melanoma

INDACEA Precision medicine in Dravet syndrome

María Sancho Mechanisms by which cyclic GMP and neuroinflammation modulate neurotransmission and cognitive and motor function

RESEARCH NETWORKS AND PLATFORMS

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<th>ENTITY</th>
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<td>UBIRED</td>
<td>UBIRed is a network committed to improve the quality, productivity and impact of the research groups in Spain specialised in the study of ubiquitin and UBL proteins and their roles in cell proliferation, differentiation and cancer.</td>
<td>Rosa Farràs</td>
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<tr>
<td>PROTEOSTASIS</td>
<td>European network with members from almost all countries in Europe. Its main objective is to facilitate research and collaborations in the fields of Ubiquitin/Proteasome, Ubiquitin-likes, autophagy and lysosomal systems in health and diseases.</td>
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<td>NANOMED</td>
<td>Spanish Nanomedicine Platform as an application to the development of new diagnostic systems and therapy, as well as the improvement of existing ones.</td>
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<td>TENTACLES</td>
<td>Translational NetWork for the Clinical application of Extracellular Vesicles, TcTACLES</td>
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<td>RD-Connect</td>
<td>Integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research</td>
<td>Francisco García</td>
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<td>EU OPENSSCREEN</td>
<td>European high capacity screening network</td>
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Platforms and Networks

COMUNITAT VALENCIANA PRECISION MEDICINE STRATEGY.
Therapeutic treatments aimed at individual patients based on their biomarkers, genetic, phenotypic or psychosocial characteristics. Coordinated by INCLIVA. Participants: CIPF, IIS La Fe, ISABIAL, FISABIO (Hospital Dr. Peset, Hospital Arnau de Vilanova).

COMUNITAT VALENCIANA STRATEGY OF COGNITIVE IMPAIRMENT.
Cognitive and functional deterioration associated with aging and chronic diseases. Coordinated by ISABIAL. Active members: CIPF, INCLIVA, IIS La Fe, FISABIO, FIHGUV.

COMUNITAT VALENCIANA RARE DISEASES STRATEGY.
Description of new genes causing RRSE, identify, develop and validate biomarkers that contribute to improve their diagnosis, prognosis and treatment. Coordinated by INCLIVA. Participants: CIPF, IIS La Fe, FISABIO.

COMUNITAT VALENCIANA STRATEGY OF INNOVATIVE MEDICINE.
New approaches to accelerate and enhance drug development and increase the efficiency and effectiveness of this process. Coordinated by IIS La Fe. Participants: CIPF, INCLIVA, FISABIO.

GOVERNMENTAL REGIONAL STRATEGY FOR ARTIFICIAL INTELLIGENCE AND BIG DATA IN HEALTH.
Development of Big Data and Artificial Intelligence projects in Health. Coordinated by INCLIVA. Participants: CIPF, FISABIO, IIS La Fe.

GOVERNMENTAL REGIONAL STRATEGY FOR EARLY MOLECULAR DETECTION OF CANCER.
New approaches to accelerate and enhance drug development and increase the efficiency and effectiveness of this process. Coordinated by FIHGUV. Fundación Investigación Hospital General Universitario de Valencia. Participants: CIPF, INCLIVA, FISABIO.

RETICS, THEMATIC NETWORKS OF COOPERATIVE RESEARCH IN HEALTH.
Addictive Disorders Network, RTA ISCIII.

PRB3 ISCIII, PROTEOMICS, GENOMICS AND CELL LINES.
BNLC, National Bank of Cellular Lines, Valencia node. Network structure with several coordinated nodes with the objective of guaranteeing the availability of human embryonic stem cell lines for biomedical research.

TRANSBIOMET.
UBIRED.
Network to improve the quality, productivity and impact of research groups in Spain specialized in the study of ubiquitin and UBL proteins and their role in the cell proliferation, differentiation and cancer.

PROTESTOSTASIS.
Collaboration network supported by the European Union (EU), made up of more than 100 laboratories of companies, universities and research centers from 20 European countries, to promote the research on protein life cycle, protein degradation and modification in the cell.

TENTACLES.
Translational NeTwork for the CLinical application of Extracellular Vesicles (EV) involves highly competitive researchers in the study of EVs and the development of new tools for effective use in the clinical setting.

REDEFINE.
Spanish Drug Discovery Thematic Network that seeks to speed up the drug discovery process discovery of new drugs in direct and innovative connection with the market and according to the requirements of the pharmaceutical and biotechnological industry.

SDDN.
Spanish Drug Discovery Network (SDDN), a network of Spanish professionals who work in the discovery and development of new drugs.

NANOMED.
Spanish Platform of Nanomedicine as an application to the development of new systems of diagnosis and therapy, as well as the improvement of existing ones.

RD-CONNECT.
Multidisciplinary project that unifies participants from the EU and other countries to create a global infrastructure for rare disease research.

EUROPEAN INNOVATION PARTNERSHIP.
Platform for the promotion of an active and healthy lifestyle throughout life and for healthy ageing.

COST.
European Cooperation in Science and Technology, organization for the creation of networks of research, offering spaces for collaboration between researchers from all over Europe.