"la Caixa" Foundation

CaixaResearch
Health Meeting

CAP ROIG 2024

Research for the future of health

WHO IS WHO

CaixaResearch

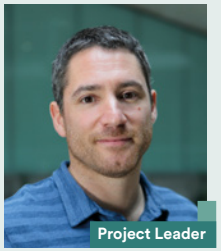
CARDIOVASCUAR AND METABOLLIC RELATED DISEASES

New therapeutic targets for diabetes

Function of a novel program of islet microexons in beta cell development, insulin secretion and diabetes (ENDOMICS)

Manuel *Irimia*

Centre de Regulació Genòmica (CRG), Barcelona



Our research is centered on two major questions: How does a single genome sequence encode the information to build the enormous complexity of cell types and structures of an adult organism? How are changes in this sequence translated into morphological novelties during evolution? We approach these topics by focusing on cell and tissue type specific transcriptomes.

→ manuel.irimia@crg.eu

PROJECT DESCRIPTION:

His group studies beta-pancreatic cells, crucial in diabetes, to understand insulin regulation and genetic risk factors. Damages in beta cells lead to diabetes, a significant public health challenge. Investigating the role of microexons within the disease will help to predict diabetes risk and to identify therapeutic targets. Understanding these mechanisms offers hope not only for innovative diabetes treatments, but also for the benefit of many people worldwide.

INTERIM RESULTS:

- Multi-level functional characterisation of the IsletMICs, a conserved programme of alternative microexons regulated by the SRRM3 gene in islet cells, that regulate glucose homeostasis.
- Changes in the activity of SRRM3 and its microexon targets potentially contribute to type 2 diabetes susceptibility.
- Several human variants have been identified to play a role in the glycaemic control and type 2 diabetes.
- Some of the IsletMICs would have potential as therapeutic targets through ASO (Antisense oligonucleotide) manipulation.

CARDIOVASCUAR AND METABOLLIC RELATED DISEASES

The search for new markers and therapeutic targets in atherosclerosis

Flow-driven inflammation and arterial wall remodeling in atherosclerosis: mechanisms and therapeutic potential (AtheroConvergence)

PROJECT DESCRIPTION:

Atherosclerosis, the top global cause of death, results from cholesterol buildup and arterial inflammation. Risk factors like diet and smoking contribute, especially where blood flow is irregular. Current therapies slow but don't reverse it. *AtheroConvergence* aims to understand disease progression comprehensively, using advanced tech and multidisciplinary approaches. Precision medicine and genetic markers are sought for intervention and risk prediction.

INTERIM RESULTS:

- A novel Deep Learning algorithm for the localisation and analysis of caveolae in electron microscopy images has been developed.
- They have provided RNA sequencing data for the murine inner curvature of the aortic arch after short-term hypercholesterolemia, which is also very useful for the researcher community studying initial processes in atherogenesis.
- They have generated an in vitro model demonstrating that Cav1 forms a variety of domains with different sizes and different buffering abilities and constitutes a versatile mechanoadaptation system, specifically contributing responsiveness to mild mechanical force.


Project Leader

Miguel Ángel *del Pozo Barriuso*

Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid

Our research focuses on caveolae, investigating their structural, molecular and cellular biology. Through quantitative methods we analyse their architecture and dynamic interactions. Also, we explore signalling networks downstream of mechanosensation, aiming to understand their role in coordinating cellular functions at a systems level.

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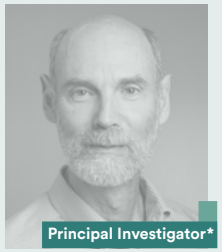
Principal Investigator*

Martin A. *Schwartz*

Professor of Medicine and Cell Biology - Yale University School of Medicine, New Haven

Interested in integrin signalling and mechanotransduction in the vasculature to understand the pathways governing cell function, and how these effects regulate development and disease in animal models.

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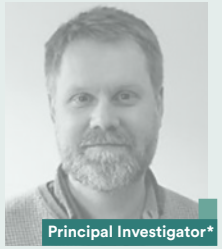
Principal Investigator*

Jacob *Fog Bentzon*

Professor in Experimental Atherosclerosis - Aarhus University, Aarhus

Investigates the mechanisms of atherosclerosis' formation aiming to understand how local smooth muscle cells of the artery wall transform their phenotype and build the fibrotic and calcified tissue of developing lesions.

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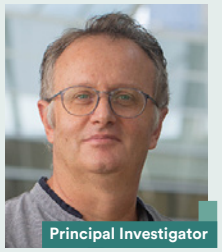
Principal Investigator

Jesús *Ruiz-Cabello*

CIC biomaGUNE, San Sebastián

Focuses on pulmonary hypertension and cardiovascular diseases aiming to identify new imaging, biosignals and system biology markers for early diagnosis and treatment monitoring.

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*Not attending the meeting

CARDIOVASCUAR AND METABOLLIC RELATED DISEASES

Improving diagnosis and treatment of sudden death

RNA mis-splicing in hypertrophic cardiomyopathy: opportunities for diagnosis and therapy (spliceHCM)

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PROJECT DESCRIPTION:

Hypertrophic cardiomyopathy, a prevalent hereditary cardiovascular disorder, is a leading cause of sudden death, particularly among young athletes. Genetic tests often miss mutations in a significant percentage of cases. Recently categorised as an orphan disease due to its severe impact on a small population, only one out of three developed drugs has shown some effectiveness. This project aims to enhance genetic diagnosis, prevention and therapeutic approaches, focusing on addressing the underlying genetic causes rather than solely managing symptoms.

INTERIM RESULTS:

- They have described new pathophysiological mechanisms underlying familial hypertrophic cardiomyopathy (HCM).
- The best five performer tools in discriminating HCM-associated variants have been identified: ClinPred, MISTIC, FATHMM, MPC and MetaLR. The combination of these tools would help to detect unknown HCM missense variants to be closely monitored in the clinics.
- Two induced pluripotent stem cell (iPSC) lines were derived from peripheral blood mononuclear cells obtained from two unrelated individuals with previously reported nonsense mutations in the MYBPC3 gene. The generated iPSCs exhibit appropriate expression of pluripotency markers, trilineage differentiation capacity and a normal karyotype. This resource contributes to gaining deeper insights into the pathophysiological mechanisms that underlie HCM.

Maria Carmo-*Fonseca*

Instituto de Medicina Molecular de la Universidad de Lisboa, Lisbon

Her research aims to unravel mechanisms of gene regulation controlled by RNA molecules. To do so, her laboratory uses a multidisciplinary approach that combines live-cell microscopy, computational modelling, molecular biology, biochemistry and bioinformatics.

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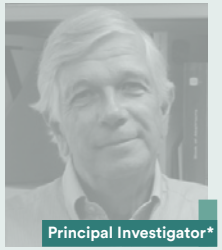

Joaquim *Cabral*

Associação do Instituto Superior Técnico para a Investigação e Desenvolvimento, Lisbon

His research interests are focused on the study of stem cells for tissue engineering and regenerative medicine, and stem cell bioprocessing and manufacturing for the development of novel bioreactors and advanced bioseparation and purification processes.

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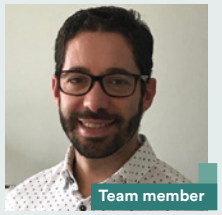
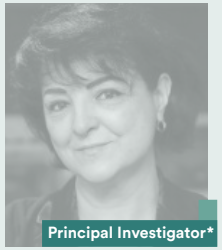


Simao José *T. Rocha*

Instituto de Medicina Molecular, Lisbon

Attending on behalf of the PI Joaquim Cabral.



Dulce *Brito*

Associação para Investigação e Desenvolvimento da Faculdade de Medicina, Lisbon

She is a researcher at the Cardiovascular Center of the University of Lisbon (CCUL) and a research team leader in the areas of heart failure and cardiomyopathies.

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*Not attending the meeting

CARDIOVASCUAR AND METABOLLIC RELATED DISEASES

New gut-tissue brain-adipose metabolic connection as a therapeutic target to combat obesity and diabetes

Succinate/SUCNR1 axis: a novel target for anti-obesity therapies (METASUCC)

PROJECT DESCRIPTION:

Obesity and related metabolic diseases like type 2 diabetes are escalating despite known preventive measures. This strains public health systems with profound psychosocial impacts. Cost-effective treatments are lacking. Identifying new weight and glucose control mechanisms is crucial. This project proposes a comprehensive approach, studying from animal models to patients at their bedside. It explores a gut-brain-adipose circuit regulated by succinate, offering potential for novel therapeutic strategies.

INTERIM RESULTS:

- The current project's results suggest that SUCNR1 deficiency modulates energy expenditure via a BAT-dependent mechanism. They are generating conditional mouse models targeting SUNCR1 in hypothalamic neuronal populations to explore this hypothesis.
- A protocol for the in vitro isolation and culture of mature adipocytes and white adipose tissue explants from humans and mice has been described.
- They have identified hepatocytes as target cells of extracellular succinate during non-alcoholic fatty liver disease progression and uncovered an unknown function for SUCNR1 as a regulator of hepatocyte glucose and lipid metabolism. Their clinical data highlight the potential of succinate and hepatic SUCNR1 expression as markers to diagnose fatty liver and NASH.

Sonia *Fernández Veledo*

Fundació Institut d'Investigació Sanitària Pere Virgili de l'Hospital Universitari de Tarragona Joan XXIII, Tarragona

She leads the Diabetes and Metabolic Associated Diseases Research Group (DIAMET), a multidisciplinary and dynamic research group focused on the study of metabolic disorders associated with diabetes mellitus and obesity morbidities.

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Miguel *López*

Universidad de Santiago de Compostela, Santiago de Compostela

His group studies obesity, in particular, the hypothalamic regulation of energy balance. Their main expertise is hypothalamic neuropeptides (especially orexins), hypothalamic lipid metabolism/AMPK and ER stress.

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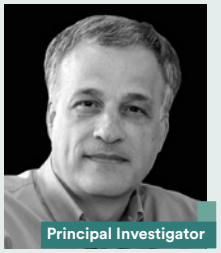

José Manuel *Fernández-Real*

Institut d'Investigació Biomèdica de Girona (IDIBGI), Girona

His research group studies innate immunity, inflammation and metabolic diseases, alongside genomic/genetic factors in type 2 diabetes and obesity. They study adipose tissue biology, iron's role in inflammation and metabolism, microbiota's influence on obesity and diabetes, non-alcoholic fatty liver diseases and brain metabolism, and develop computational tools for glycaemic control optimisation.

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Lidia *Cedó*

Institut d'Investigació Sanitària Pere Virgili (IISPV), Tarragona

Attending on behalf of the PL Sonia Fernández Veledo.

*Not attending the meeting

INFECTIOUS DISEASES

Attacking HIV reservoirs to eliminate the infection

Enhancing tissue-specific immune microenvironments for the cure of HIV (ETI-CureHIV)

PROJECT DESCRIPTION:

HIV remains incurable despite antiretroviral therapy. Viral reservoirs in tissues persist, evading immune recognition. Lymphoid and mucous organs harbour these reservoirs, impeding cure efforts. This project aims to understand local immunological mechanisms in tissues like intestines, tonsils and cervix, to devise strategies restricting or eliminating HIV presence.

INTERIM RESULTS:

- The preliminary results support the potential use of immunotherapy against the KLRG1 receptor to impact the viral reservoir during HIV persistence.
- They have observed that T cell immunoglobulin and ITIM domain (TIGIT) could be a target for T-cell exhaustion precision immunotherapies in patients living with HIV at all antiretroviral therapy stages.

María José *Buzón*

Vall d'Hebron Institut de Recerca (VHIR), Barcelona

Expert in virology and immunology and strong interest in translational research. She is dedicated to the study of new therapies aimed at curing HIV, with special emphasis on the characterisation of new cellular HIV reservoirs and the development of strategies that enhance the immune system. Recently part of her research has been focused on the study of SARS-CoV-2.

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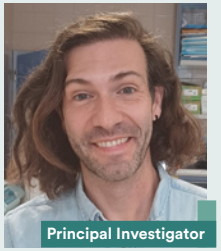

Enrique *Martin Gayo*

Universidad Autónoma de Madrid (UAM)-CSIC, Madrid

Interested in the characterization and manipulation of innate immune cell subsets in the context of infectious disease (HIV-1) and autoimmune disorders to develop novel preventive and therapeutic approaches to combat disease.

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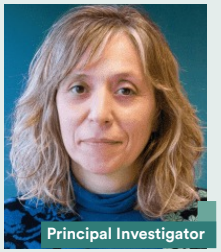

Julia *García*

IrsiCaixa, Barcelona

An expert in virology and immunology, her research interests focus on understanding the mechanism of "T cell immune exhaustion" as a significant barrier to curing HIV-1 and its implications for the development of novel immunotherapies. Currently, she has applied her knowledge of antiviral immunity to study T-cell responses in SARS-CoV-2, aiming to understand immune protection or dysregulation, particularly in relation to long-Covid sequelae.

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*Not attending the meeting

INFECTIOUS DISEASES

New strategies to treat sleeping sickness

Mechanism and function of epitranscriptomic poly(A) tail modifications in African trypanosomes (TrypM6A)

PROJECT DESCRIPTION:

Sleeping sickness, caused by tsetse fly-transmitted parasites, lacks treatment and is fatal in most cases. Researchers aim to uncover the parasite's genetic regulation mechanisms for potential therapeutic targets. Identifying factors essential for transmission via flies is crucial, with significant health and socio-economic implications in endemic regions of Sub-Saharan Africa.

INTERIM RESULTS:

- The project has demonstrated for the first time that poly(A) tails at the end of messenger RNAs can harbour chemical modifications. Methylation of adenosine resulted in very stable RNAs, which were protected from deadenylase activity.
- This is the first identification of an RNA modification in the poly(A) tail of any eukaryote, uncovering a post-transcriptional mechanism of gene regulation.

Luisa *Figueiredo*

Instituto de Medicina Molecular João Lobo Antunes, Lisbon

Interested in host-pathogen interactions, with a special focus on African trypanosomes, unicellular parasites that cause sleeping sickness in humans and nagana in cattle, respectively, in Sub-Saharan Africa. Her research focuses on the cellular and molecular mechanisms employed by trypanosomes to adapt to the tissue environment and to evade the host immune defences.

→ lmf@medicina.ulisboa.pt

INFECTIOUS DISEASES

Understanding and blocking the adaptation mechanism of the malaria parasite in order to eradicate the disease

Coping with unpredictability: regulatory plasticity as an adaptation strategy in the human malaria parasite (ADAPTORDIE)

PROJECT DESCRIPTION:

Pathogens face unpredictable changes in their host environment, requiring rapid adaptation mechanisms to survive. Blocking these mechanisms poses a significant challenge to global health. Malaria parasites, for instance, rapidly adapt to diverse mosquito species, crucial for their survival and disease transmission. This project examines epigenetic mechanisms enabling parasite adaptation, vital for developing treatments to eradicate malaria and combat evolving pathogens in a changing world.

INTERIM RESULTS:

- Deciphered mechanisms of adapting to rapid environmental change.
- Epigenetic determinants of rapid adaptation in vivo have been discovered.
- Novel tool designed: ILRA (Improvement of Long Read Assemblies). Novel pipeline to assist in the post-assembly process and finishing of genome sequences by filtering contigs, reordering, decontaminating, correcting sequencing errors, circularising organellar DNA and performing quality control.

Elena *Gómez-Díaz*

Instituto de Parasitología y Biomedicina López Neyra (CSIC), Granada

Interested in understanding how epigenetic processes are implicated in host-parasite interactions by regulating gene expression in response to changing environments, and how those processes impact adaptation in parasites.

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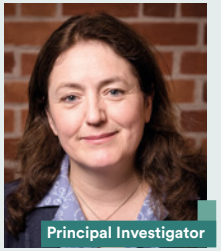

Lisa *Ranford-Cartwright*

University of Glasgow - Schools - School of Biodiversity, One Health & Veterinary Medicine, Glasgow

Her work focus is to apply information on genetic differences between parasites to develop new tests to predict disease severity in people, or the likelihood of mosquito-based transmission.

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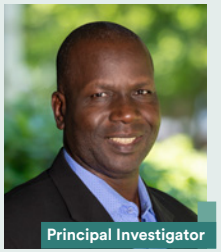

Mahamadou *Diakite*

USTTB, Malaria Research and Training Center, Bamako

His main interest is in the genomic epidemiology of infectious diseases in Africa and community-based interventions, particularly focused on malaria.

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INFECTIOUS DISEASES

New approaches to combatting Chagas disease and leishmaniasis

Discovery of new antiparasitic drug candidates and innovative modes of actions from Microbial Natural Products (NP4NTD)

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PROJECT DESCRIPTION:

Chagas and leishmaniasis, tropical diseases transmitted by insects, cause numerous deaths in impoverished nations. Global population movement and climate change drive increasing cases worldwide, including in developed countries, where effective treatments are unavailable or cannot be used due to resistance or side effects. This project, in collaboration with DNDi and Pasteur Institute of Korea, innovatively seeks natural compounds to accelerate discovery of new therapies against these diseases.

INTERIM RESULTS:

- NP4NTD is exploring the chemical diversity of MEDINA's vast microbial natural products libraries, using the whole-cell phenotypic screening assays of Institut Pasteur Korea.
- A new image-based "parasite painting" assay with cutting-edge cell imaging technology is being developed to identify new modes of action of novel compounds and to select the most promising for further development.
- Madurastatin D3 has been identified as a new compound of natural origin with potential application against Chagas disease.


Project Leader

Olga *Genilloud*

Centro de Excelencia en Investigación de Medicamentos Innovadores en Andalucía (Fundación MEDINA), Granada

Extended academic, clinical and pharmaceutical research experience in microbial natural products. Her main research interests are focused on the production and biosynthesis of novel products, the exploration of novel microbial diversity to deliver novel chemistry, and the development of molecular and chemical tools to support natural products drug discovery and the identification of potential new therapeutics.

→ olga.geniolloud@medinaandalucia.es


Principal Investigator*

Jean-Robert *Ioset*

Drugs for Neglected Diseases Initiative (DNDi), (not-for-profit research and development organisation), Geneve

Great expertise in natural product chemistry and drug discovery. His current mission is to identify, progress and deliver novel lead series to the DNDi preclinical programmes for visceral leishmaniasis and Chagas disease.

→ jrioset@dndi.org


Principal Investigator*

Joo *Hwan No*

Institut Pasteur Korea

His present activity focuses on:

- Identification of inhibitors of protozoan parasites utilizing HCS/HTS
- Mode of anti-parasitic action studies on generated inhibitors
- Development of diagnostics for leishmaniasis
- Macrophage-Leishmania interactions using NGS
- Modulation of macrophage function with small molecules

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*Not attending the meeting

INFECTIOUS DISEASES

The dialogue between neurons and defenses opens the door to new therapies against infections

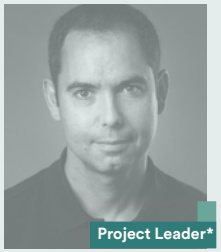
Unravelling pulmonary neuroimmune circuits during infection (Neurimm KISS)

PROJECT DESCRIPTION:

The immune system traditionally defends against pathogens, but recent discoveries highlight the role of the nervous system in infection response – the neuroimmune system. This system regulates organ function and protects against poorly understood illnesses lacking effective treatments. This project investigates neuroimmune interactions in animal models, focusing on pulmonary circuits during respiratory infections. Insights could lead to new therapies, crucial for combating antibiotic resistance.

INTERIM RESULTS:

- Neurimm KISS has described not only specific neuroimmune interactions during pulmonary infection but also in peripheral tissues and how neuroimmune interactions maximise sensing and integration of environmental aggressions, modulating immune function in health and disease.
- The current results show that type 2 immune responses drive a broad range of biological processes including defence from large parasites, immunity to allergens and non-immunity-related functions, such as metabolism and tissue homeostasis.



Henrique *Veiga-Fernandes*

Champalimaud Foundation, Lisbon

His group are working on defining lymphocyte sensory mechanisms in health and disease. They use an integrative across-level approach aiming to elucidate the principles of lymphocyte sensing and communication, within, across and beyond the organism.

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Maria *Aliseychik*

Champalimaud Foundation, Lisbon

Attending on behalf of the project.

*Not attending the meeting

NEUROSCIENCE

Cellular reprogramming to repair the brain's sensory circuits

Restoration of sensory circuits based on glia-to-neuron reprogramming (SENSORY-REPROGRAM)

PROJECT DESCRIPTION:

Sensory information shapes brain development, influencing neuronal connection formation and plasticity. The thalamus receives external stimuli, while the cerebral cortex processes them. Reduced sensory input leads to diminished neurons and circuits in these areas. This project aims to transform astrocytes into sensory neuron subpopulations, offering potential therapies for damaged cerebral circuits, including blindness.

INTERIM RESULTS:

- They have been working to reveal the rules of tissue-specific molecular signatures in astrocytes, assess their molecular plasticity in sensory-deprived mice and reprogramme brain circuits in vivo.
- They have elucidated that shared landmarks within each nucleus are partly explained by a nucleus-specific allocation of clonal cells, astrocytes and neurons.

Guillermina *López-Bendito*

Instituto de Neurociencias, centro mixto del CSIC y la Universidad Miguel Hernández, Alicante

Interested in studying the development and plasticity of brain circuits, exploring the molecular mechanisms that govern these processes and the role of spontaneous activity during early development. Specifically, we aim to uncover the principles underlying sensory circuits wiring, maintenance, and eventual rewiring of connections through an integrated and innovative experimental program. This knowledge will pave the way for designing strategies to restore defective neuronal connections in patients with sensory deficits, such as blindness or deafness.

→ g.lbendito@umh.es

NEUROSCIENCE

How does the brain classify stimuli as positive or negative?

Encoding reward and aversion in the mammalian brain: he overlooked role of endogenous opioids (RewAve)

Ana Joao *Rodrigues*

Universidade do Minho, Braga

Intrigued to unravel how our brain encodes rewarding and aversive events to drive motivated behaviours. How do our brains compute stimulus as “good” or “bad”? How is valence represented in the mammalian brain? What are the neural substrates underlying a rewarding or an aversive experience? What lies between the stimulus and the behavioural response?

She is also exploring how early life stress in specific developmental windows can imprint long-lasting marks in these processes, leading to maladaptive behaviours (depression, addiction).

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PROJECT DESCRIPTION:

The mammalian brain processes external stimuli, categorising them as positive or negative, influencing motivated behaviors. Neurons in the nucleus accumbens play a role in this classification, yet, the mechanism remains unknown. This project aims to unravel how the brain assigns valence to stimuli, shaping mammalian behaviour. Insights may inspire novel therapies for addiction and depression in the future.

INTERIM RESULTS:

- The project has identified patterns of nucleus accumbens medium spiny neurons activity encoding reward and aversion in freely behaving animals.
- The stimuli that induce opioid release in vivo by medium spiny neurons are being defined.
- The results obtained suggest that the different subpopulations of medium spiny neurons responding to positive and negative stimuli cannot be segregated by dopamine receptor D1- or D2- expression alone. The project is working to identify which features segregate these neural populations.

NEUROSCIENCE

New treatments for schizophrenia and ictus

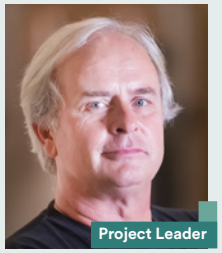
Amino acid transporter structure to target glutamate transmission in neuro diseases

PROJECT DESCRIPTION:

Both stroke and schizophrenia involve malfunctioning glutamate receptors, crucial for neuronal function. Schizophrenia posits limited transmission leading to cognitive deficits, while stroke entails excessive transmission causing neuronal toxicity. This project delves into the atomic structure of an amino acid transporter protein regulating these receptors. The goal is to design compounds targeting this transporter, activating receptors for schizophrenia or inhibiting them for conditions like stroke.

INTERIM RESULTS:

- Heteromeric amino acid transporters (HATs) of neutral amino acids participate in a variety of processes such as modulation of glutamatergic neurotransmission and synaptic plasticity, auditory function and promotion of brain development and tumour growth by supporting mTORC1 activity.
- The project has identified substrate specificity determinants of neutral amino acids HATs within the substrate-binding cavity and in a nearby region that holds the conformation of the substrate-binding site. The results suggest that LAT2 mutations in this scaffold region are associated with the molecular mechanisms of neurological disorders.
- The project has also determined the structure and the mechanisms of transport of the transporter human Asc1/CD98hc.



Manuel *Palacín*

Institut de Recerca Biomèdica (IRB Barcelona), Barcelona

His work focuses on the regulation and pathology of cellular membrane transport mechanism specifically in amino acid transporters.

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Oscar *Llorca*

Centro Nacional de Investigaciones Oncológicas Carlos III (CNIO), Madrid

His work focuses on the study of macromolecular complexes using electron microscopy (EM) and the applicability of single-particle 3D-electron microscopy to macromolecular complexes involved in DNA repair and RNA degradation, as well as exploring the prospect of cryo-EM advances to help in drug discovery.

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NEUROSCIENCE

In search of therapies for mitochondrial diseases

Mitochondrial transcription as a trigger for neurodegeneration (Mito Trigger)

Albert *Quintana*

Universitat Autònoma de Barcelona (UAB), Barcelona

He is intrigued by the molecular mechanisms defining why some neuronal populations are particularly affected by mitochondrial disease, with the overarching goal of identifying novel targets that lead to improved treatments for mitochondrial disease patients.

→ albert.quintana@uab.cat

PROJECT DESCRIPTION:

Mitochondrial diseases, rare genetic disorders affecting 1 in 5000 children, result from mitochondrial dysfunction. Currently untreatable, they are degenerative and often fatal. These diseases primarily impact high-energy-consuming tissues like the brain and neurons. The project uncovers basal ganglia neuron vulnerability, suspecting mitochondrial involvement in triggering cell death signals. Researchers aim to reverse these signals, paving the way for novel mitochondrial disease therapies.

INTERIM RESULTS:

- The project has established a novel animal model to study human pathology associated with Leigh syndrome, a mitochondrial disorder characterised by the degeneration of the central nervous system.
- The current results show that daily cannabidiol administration significantly extends lifespan and ameliorates pathology in Leigh syndrome mouse models, and cellular function in fibroblasts obtained from patients.

NEUROSCIENCE

Understanding the origin of Parkinson's disease

A cortical pathogenesis of Parkinson's disease (CORPARK)

Guglielmo *Foffani*

HM CINAC, Fundación de Investigación HM Hospitales, Madrid

Integrating expertise in brain stimulation, neural signal analysis and neurobiological mechanisms in humans and animal models, his main research interest is to understand and develop new treatments for neurodegenerative disorders, particularly Parkinson's disease.

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PROJECT DESCRIPTION:

Parkinson's disease, the second most common neurodegenerative disorder, is characterized by the degeneration of neurons in the substantia nigra, leading to motor symptoms like slowness of movement, stiffness, and tremor. The cause remains unknown, with the prevailing hypothesis suggesting that the disease spreads from the peripheral nervous system to the brain. This project explores a new theory proposing that the cerebral cortex itself may drive neurodegeneration in the substantia nigra, potentially explaining the focal motor onset of the disease.

INTERIM RESULTS:

- New mouse models developed in the project demonstrate that corticostriatal hyperactivity and alpha-synuclein overexpression induce striatal astrogliosis, supporting the relevance of early cortical alterations for the pathogenesis of Parkinson's disease and related synucleinopathies (unpublished data).
- Subthalamic oscillatory beta activity in patients with Parkinson's disease correlates with the rate of motor progression, which is consistent with the postulated pathogenic role of corticostriatal activity (Pardo-Valencia, J Physiol 2024).
- As a translational step, transcranial static magnetic field stimulation (tSMS) can noninvasively modulate corticostriatal activity in humans, validated through the novel ISAAC analysis framework and resting-state fMRI (Caballero-Insaurriaga *et al*., PNAS 2023).

NEUROSCIENCE

Diamond nanosensors to detect Parkinson's disease

Diamond photonics platforms for synaptic connectivity assessment in healthy and parkinson disease neuronal models (Diamond4Brain)

PROJECT DESCRIPTION:

Parkinson's disease affects over a million Europeans, diminishing quality of life. Limited diagnostic and therapeutic options exist. This project employs quantum mechanics technology with diamond nanosensors to measure neuron activity and connectivity changes sensitively. Testing in brain organoids aims to validate the technique, advancing Parkinson's understanding, enabling early diagnosis, and enhancing treatments.

INTERIM RESULTS:

- Diamond4Brain has explored pluripotent stem cells as a tool for the development of a dopaminergic neuron model by means of directed differentiation. The project has showed the biocompatibility of differentiated neurons with functionalized fluorescent nanodiamonds that may serve as a novel imaging tool for the dysfunction of dopaminergic neurons.
- Nanodiamond have served as sensors of intracellular parameters such as temperature and magnetic field. Physical parameters that can inform of disease progression and may allow the development of novel diagnostic tools.
- The project has designed 3D diamond photonic platform and 3D scaffolds to host brain organoids.

Jana B. *Nieder*

Laboratorio Ibérico Internacional de Nanotecnologia, Braga

She focuses on three interconnected photonics research areas: 1) advanced bioimaging and sensing, 2) integrated photonics, and 3) quantum photonics.

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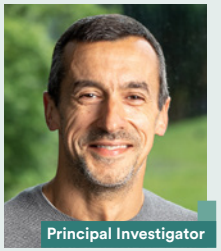

António *Salgado*

Universidade do Minho, Braga

His main areas of research are: 1) Development of ECM like hydrogels for the transplantation of mesenchymal stem cells into the injured CNS; 2) Role of the secretome of MSCs in neuroprotection and repair, particularly the establishment of novel therapies based on the sole use of MSCs secretome.

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Ramiro *Almeida*

Universidade de Aveiro, Aveiro

His research is focused on the molecular and cellular mechanisms that regulate neuronal development and regeneration. They combine molecular, genetic, imaging and microfluidic tools.

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NEUROSCIENCE

Epilepsy and neurodevelopmental disorders share mechanisms that may inspire new therapies

Potassium channel dysfunction in models of neurodevelopmental disorders (MStar)

PROJECT DESCRIPTION:

Currently, nearly half of individuals with intellectual disabilities have epilepsy. People with schizophrenia face double the risk of seizures compared to the general population. Epilepsy and neurodevelopmental disorders share genetic elements and underlying mechanisms, such as mutations in genes regulating neuronal excitability. This project explores these pathways as potential targets for more effective treatments.

INTERIM RESULTS:

- Mutations in the CACNG2 gene are associated with intellectual disability and schizophrenia.
- Stargazin, encoded by the CACNG2 gene, regulates synaptic activity and the nanoscale organization and function of potassium channels.
- Disease-associated mutations in CACNG2 impair potassium channel function and increase seizure susceptibility.
- These results open doors for targeting the stargazin-potassium channel complex to treat epilepsy.

Ana Luisa *Carvalho*

Centro de Neurociencias y Biología Celular de la Universidad de Coimbra, Coimbra

The aim of her research is to uncover cellular and molecular mechanisms at the basis of neuronal communication in the brain, excitability and synaptic function, and how they are impaired in brain diseases, since this modulation underlies complex brain processes such as learning, memory and development.

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Joana *Ferreira*

MIA-PORTUGAL, University of Coimbra, Coimbra

Her research is focused on the nanoscale architecture of the synapse, trans-synaptic signalling and its implications for neurological diseases. She has extensive and recognised experience in molecular imaging of NMDARs and their interactors and a broad background in molecular neuroscience, with specific training in super-resolution microscopy techniques.

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NEUROSCIENCE

Non-invasive test for amyotrophic lateral sclerosis (ALS)

Brain Liquid Biopsy for neurodegenerative disorders (Amyotrophic Lateral Sclerosis and Alzheimer disease) (BIOP-ALS)

PROJECT DESCRIPTION:

ALS and neurodegenerative diseases lack early diagnosis due to central nervous system (CNS) inaccessibility. A new non-invasive liquid biopsy detects genetic material in blood, potentially serving as a biomarker. This project aims to identify epigenetic markers in neuronal DNA fragments from blood plasma, offering real-time CNS insights. Findings may apply to other neurodegenerative diseases, aiding in early diagnosis and treatment development.

INTERIM RESULTS:

- Changes in DNA methylation in one gene involved in energy balance regulation (PRLHR) has an important role in the brain and is related to Alzheimer's disease.
- The liquid biopsy provides access to AD-specific epigenetic information in a non-invasive way during patient´s lifetime.
- They are building a clinical dataset for further studies in larger and independent cohorts in ALS patients.

Maite *Mendioroz*

Fundación Miguel Servet, Navarrabiomed, Pamplona

Her goal is to describe the DNA methylation pattern and how it affects the development of neurological diseases. Her unit wish to find epigenetic biomarkers that could be used for diagnosis, prognosis and treatment. They are particularly interested in epigenetic modifications in certain rare monogenic disorders associated with neurological disorders like laminopathies.Additionally, they aim at describing how environmental factors or targeted activities affect methylation patterns in healthy individuals.

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ONCOLOGY

Disabling immunosuppression mechanisms in melanoma

Immunomodulatory drivers in melanoma progression and therapy response (IMMUMELANOMA)

Marisol *Soengas*

Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid

The main objective of her team is to translate basic research in melanoma to the clinic by identifying novel markers of this disease and targets for drug development.

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PROJECT DESCRIPTION:

Melanoma, the most aggressive skin cancer, spreads rapidly even from small lesions. Metastasis is the primary cause of death, yet molecular markers for prognosis prediction are lacking. This project aims to identify genes driving melanoma progression, focusing on immune system modulation mechanisms to understand metastasis better.

INTERIM RESULTS:

- Definition of immunocompetent and immunodeficient mouse models for live imaging of Vegfr3-driven neolymphangiogenesis, as a versatile platform for drug screening in vivo.
- An alternative strategy has been proposed for targeting the tumour cell-lymphatic crosstalk and underscore the power of Vegfr3-lymphoreporters for pharmacological testing in otherwise aggressive cancers.
- Novel research tools have been developed such as different animal models for the study of melanoma and its metastasis and in vitro cell lines.

ONCOLOGY

Better understanding of the mutations present in T-lymphocyte lymphomas to improve their diagnosis and treatment

A new functional paradigm for RHOA gene mutations in peripheral T cell lymphoma: functional and clinical implications (UNCHARTED RHOADS)

PROJECT DESCRIPTION:

Cancer harbours numerous genetic alterations, yet only a fraction of their roles is understood. T-lymphocytes, crucial in immune response, can undergo cancerous genetic changes, leading to lymphomas with poor survival rates and limited treatments. This project investigates frequent genetic alterations in the RHOA gene in T-lymphocyte-derived lymphomas. Understanding tumour origins and uncovering new insights may improve patient stratification and treatment.

INTERIM RESULTS:

- The reason for the unexpected detection of gain- and loss-of-function mutations in the RHOA gene has been elucidated using biochemical, signaling, and adoptive T cell transfer experiments.
- Results indicate that these two antagonistic subset of RHOA mutants can in fact activate a common pathway in T cells that is critically involved in T cell lymphoma development
- These new protumorigenic functions are neomorphic, given that they are not elicited by the wild-type versions of the protein or other mutant versions not present in T cell lymphomas.
- Upon the functional characterization of 50 mutations of RHOA mutations found in tumors, we have found that the neomorphic ones are exclusively detected in T cell lymphomas, which further links this neomorphic pathway in T lymphomagenesis.
- The pharmacological targeting of this neomorphic pathway blocks the growth and survival of both mouse-generated T cell lymphomas and human derived tumor cells.

Xose R. *Bustelo*

Centro de Investigación del Cáncer de Salamanca, Salamanca

His research line focuses on the functional characterisation of molecules involved in signal transduction that have oncogenic capacity, with special emphasis on oncoproteins that connect the stimulation of membrane receptors with signalling routes involved in cytoskeletal and mitogenic changes.

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ONCOLOGY

Exploring blood production to understand the most aggressive forms of leukaemia

Gene regulatory NETworks in NORmal and MALignant Hematopoiesis-Identification and Targeting (GR-NET NORMAL-HIT)

PROJECT DESCRIPTION:

Acute myeloid leukaemia (AML) originates in bone marrow and quickly infiltrates the blood. Blood cells serve various functions, controlled by complex mechanisms involving transcription factors and chromatin remodelling factors. Understanding their alterations in leukaemia is crucial for developing targeted treatments. This project aims to identify such alterations by studying mice models and human leukaemia cells. Insights may lead to novel therapies.

INTERIM RESULTS:

- The project, aiming to decipher the transcription and chromatin orchestration for haematopoietic development and their corruptions in leukaemia, has demonstrated that single cell technologies combined with computational tools enable the study of a variety of cellular mechanisms involved in early haematopoiesis and can be used to dissect perturbed differentiation trajectories associated with ageing and malignant transformation.
- They have also identified the DDIT3 transcription factor as a driver of dyserythropoiesis, and a potential therapeutic target to restore the inefficient erythroid differentiation characterising myelodysplastic syndromes in patients.

Felipe *Prósper*

Universidad de Navarra, Pamplona

His principal research interest and key discoveries have been focused on specific areas: (I) epigenetic changes in haemato-oncological patients, mainly multiple myeloma and leukaemia-MDS; (II) identification of new epigenetic targets and design of new molecules; (III) stem cell biology and stem cell therapy for human diseases; (IV) clinical trials in patients with multiple myeloma and leukaemia-MDS.

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Jesús *San Miguel*

Fundación para la Investigación Médica Aplicada (FIMA/CIMA), Pamplona

His main research areas of interest are: (I) multiple myeloma, (II) minimal residual disease, and (III) development of new anti-tumour drugs.

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David *Gomez-Cabrero*

Fundación Miguel Servet Navarrabiomed, Pamplona

He specialised in bioinformatics and data integration analysis and has been collaborating with clinical groups that investigate in multiple sclerosis, rheumatoid arthritis, COPD and cancer among other diseases.

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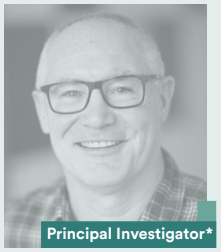

Brian *Huntly*

University of Cambridge

Interested in understanding how normal stem and progenitor cell function is subverted during the step-wise evolution of haematological malignancies, particularly on transcriptional and epigenetic alterations that cause acute myeloid leukaemia and malignant lymphomas.

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*Not attending the meeting

ONCOLOGY

Personalised therapy against a rare childhood cancer

Virtual patient derived xenografts for tumor treatment (vPDX)

—

PROJECT DESCRIPTION:

Brain stem glioma, a rare and aggressive tumour, predominantly affects children with poor prognosis and no effective treatment. Tumour cell heterogeneity complicates treatment discovery. This project innovatively proposes 3D multicellular reconstruction of patient-specific tumours in mice (PDX-patient derived xenograft). These models offer a platform for testing personalised treatments, potentially revolutionising therapeutic approaches for brain stem glioma.

INTERIM RESULTS:

- vPDX has described the utility of novel single-molecule tools to visualise the dynamic interplay between oncohistones and epigenetic pathways, thus revealing functional mechanisms by which tumorigenesis occurs. These tools are of significant value for the development and testing of new epigenetic therapeutic approaches.
- Lysine to methionine substitution H3-K27M oncohistone has a direct effect and highlights the capability of single-molecule tools to reveal new mechanisms of chromatin deregulation in cancer.
- The BRG1–BAF complex is a critical regulator of enhancer and transcription factor landscapes. It maintains H3K27M glioma in its progenitor state, precluding glial differentiation. Targeting the BAF complex could be a novel treatment strategy for paediatric H3K27M glioma.

Luciano *Di Croce*

Centre de Regulació Genòmica, Barcelona

Di Croce's group has focused its research efforts on understanding how epigenetic modifications and chromatin changes are established and, once in place, how they affect gene expression, stem cell differentiation and transformation.

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Jaume *Mora*

Fundació Sant Joan de Déu, Barcelona

His group aims to generate a knowledge base on developmental sarcomas and Langerhans cell histiocytosis (LCH) with a view to improving diagnosis, prognosis and treatment.

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*Not attending the meeting

ONCOLOGY

Fluorescent sensors to study physical forces in tumours

Enabling technologies to map nuclear mechanosensing: from organoids to tumors (Mech4Cancer)

PROJECT DESCRIPTION:

Malignant tumours spread by exerting mechanical forces, impacting surrounding tissue and facilitating invasion and dissemination. Limited technology hinders visualising these forces within the cell nucleus, crucial for gene expression and cancer progression. This project aims to develop fluorescent sensors to visualise nuclear forces during tumour invasion and metastasis, offering new diagnostic and treatment avenues.

INTERIM RESULTS:

- Demonstration of a new mechanosensing mechanism for plasma membrane cell shape homeostasis. Cancer-associated fibroblasts (CAFs) accumulate in tumours and produce an excessive extracellular matrix, forming a capsule that enwraps cancer cells and acts as a barrier, restricting tumour growth but increasing intratumoural pressure.
- Genetic and physical manipulations in vivo together with microfabrication and force measurements in vitro have shown that CAFs capsule actively compresses cancer cells using actomyosin contractility. Also, CAFs coordination is achieved through fibronectin cables that serve as scaffolds allowing force transmission.
- Nuclear mechanosensing can be observed in cancer cells through fluorescent sensors that translocate to the nucleus with force.
- Mech4Cancer reveals that the contractile capsule actively compresses cancer cells, modulates their mechanical signalling, and reorganises tumour morphology.

Xavier *Trepat*

Institut de Bioenginyeria de Catalunya, Barcelona

His research at IBEC focuses on integrative tissue dynamics and cytoskeletal mechanics.

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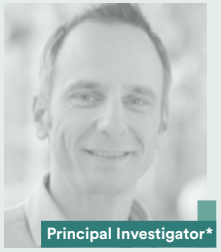

Jacco *van Rheenen*

Netherlands Cancer Institute, Amsterdam

His group studies the identity, behaviour and fate of cells that drive the initiation and progression of cancer. To study these dangerous cells, they developed microscopy techniques to visualise individual cells in real-time in whole bodies. By these techniques, they revealed multiple important factors within the single cell heterogeneity that are crucial in the processes of tissue homeostasis, tumour initiation and tumour progression.

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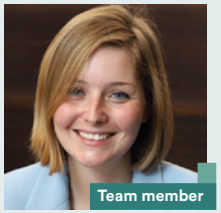

Valeria *Venturini*

Institute for Bioengineering of Catalonia-IBEC, Barcelona

Attending on behalf of the project.

*Not attending the meeting

ONCOLOGY

Artificial intelligence, a new ally against leukaemia

Deep learning to dissect the interaction between leukemic cells and the ageing niche (DeepAgeNiche)

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PROJECT DESCRIPTION:

Survival rates for elderly acute myeloid leukaemia (AML) patients on chemotherapy are low, urging new treatment approaches. Artificial intelligence offers potential by analysing complex datasets for innovative therapeutic insights. This project aims to develop deep learning algorithms to understand tumour-cell interactions in aged bone marrow. This understanding will identify new therapeutic targets to inhibit tumour growth, potentially improving outcomes for elderly AML patients.

INTERIM RESULTS:

- DeepAgeNiche has described new computational tools to investigate the ageing of the bone marrow microenvironment.
- The implementation of deep learning, by integrating various data sets, is a novel approach to understand how the niche (a specialised microenvironment, where a complex and dynamic network of interactions takes place across multiple cell types) regulates the haematopoietic stem cell function and its role in the development of AML.

M. Carolina *Florian*

Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona

Her lab focuses on understanding cellular and molecular mechanisms of somatic stem cell ageing, supporting the development of new therapeutic strategies to preserve the regenerative capacity of stem cells over time and to limit or prevent the development of age-related disorders and extend lifespan.

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Medhanie *Mulaw*

Universität Ulm, Ulm

He aims to develop personalised anti-ageing clinical interventions that will attenuate ageing-driven immune remodelling and haematopoietic disorders.

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ONCOLOGY

3D bioprinting, a new tool to improve cancer survival rates

BioPrinted hydROgel MicrofluidicS to mimic patient-specific tumor mEtastatic microenvironment (PROMISE)

PROJECT DESCRIPTION:

Metastatic colorectal cancer poses challenges in treatment response prediction. 3D bioprinting creates physiologically relevant cell models for testing therapeutic strategies. Liquid biopsy monitors therapeutic response in real time by studying circulating tumour cells. This project integrates 3D bioprinting and advanced liquid biopsy in an organ-on-a-chip device to aid in understanding and monitoring disease progression. Improved tools may enhance survival rates for metastatic colorectal cancer patients.

INTERIM RESULTS:

- The project combines bioengineering solutions such as bioprinting biomaterials and microfluidics to mimic the tumour microenvironment (TME) of metastatic sites in patients with metastatic colorectal cancer.
- The project has developed a novel bioprinted hydrogel-based microfluidic device that recapitulates TME, a successful ex-vivo, in vitro and dynamic model that permits a better understanding of the metastatic process in patients with metastatic colorectal cancer, from the intravasation to extravasation of circulating tumour cells to the better multiomic characterisation of circulating tumour cells and circulating tumour DNA.

Elena *Martínez*

Institut de Bioenginyeria de Catalunya, Barcelona

Her research activities focus on the development and application of new artificial systems that mimic tissue micro- and nanofeatures for biomimetic in vitro assays.

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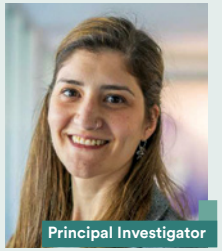

Lorena *Diéguez*

Laboratorio Ibérico Internacional de Nanotecnología, Braga

She is dedicated to translational medical research in close collaboration with hospitals. Her lab focus on the development of tools and solutions based on microfluidics, biosensors and nanotechnology towards early diagnosis and better understanding of diseases.

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Elena *Élez*

Fundació Institut Investigació Oncològica Vall Hebrón (VHIO), Barcelona

She aims to find new therapies and the identification of colon cancer biomarkers. She has contributed to the development of the typing and molecular classification of colorectal cancer based on a gene expression analysis and the mutational profile of the tumour.

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ONCOLOGY

Understanding the role of fatty acids in cancer regulation

Heterogeneous protein acylation and cancer (FAT&CURIOUS)

PROJECT DESCRIPTION:

Proteins play crucial roles in human physiology, often binding fatty acids like palmitic acid, abundant in palm oil, to interact with cell membrane proteins. However, cells contain over 1,000 lipid types, including 40 fatty acids, potentially influencing protein functions, particularly in cancer regulation. This project aims to analyse how fatty acids regulate cancer-involved proteins, enhancing disease prevention and treatment strategies

INTERIM RESULTS:

- FAT&CURIOUS has profiled the heterogeneity in protein lipidation, more specifically in S-acylated proteins, providing new insights into the role of these modifications.
- Protein palmitoylation or S-acylation has emerged as a key regulator of cellular processes. Increasing evidence shows that this modification is not restricted to palmitate but it can include additional fatty acids, raising the possibility that differential S-acylation contributes to the fine-tuning of protein activity. However, methods to profile the acyl moieties attached to proteins are scarce. We have reported a method for the identification and quantification of lipids bound to proteins that relies on hydroxylamine treatment and mass spectrometry analysis of fatty acid hydroxamates. This method has enabled unprecedented and extensive profiling of the S-acylome in different cancer and non-cancer cell lines and tissues, and has shed light on the substrate specificity of some S-acylating enzymes. Moreover, we could extend it to quantify also the acyl-CoAs, allowing us to establish, for the first time, a direct correlation between the endogenous levels of acyl-CoAs in a certain tissue and the S-acylation profile of its proteome.
- These results indicate that the composition of the S-acylome is tissue-dependent and suggest the existence of certain substrate specificities of the enzymes involved in their installation or removal. Future works will be directed to investigate potentially new mechanisms of crosstalk between lipid composition and protein function and to the identification of new targets relevant to cancer therapy.

Gemma *Triola*

Institut de Química Avançada de Catalunya (IQAC-CSIC), Barcelona

Lipid attachment to proteins plays an essential role in the regulation of protein trafficking, localization, stability, conformation, interactions and signal transduction. Since a cell can contain more than a thousand different lipid species, this huge diversity, if translated to proteins, can provide an additional layer of protein regulation. Consequently, her main goal is the use of chemical tools to study and characterize diseases, and improve the knowledge of important biological phenomena, with a special focus on lipid-modified proteins and lipid-protein interactions. As a result, her scientific interests span chemical biology, medicinal chemistry, biochemistry, cellular biology, and the use of mass-spectrometry techniques for lipid characterization.

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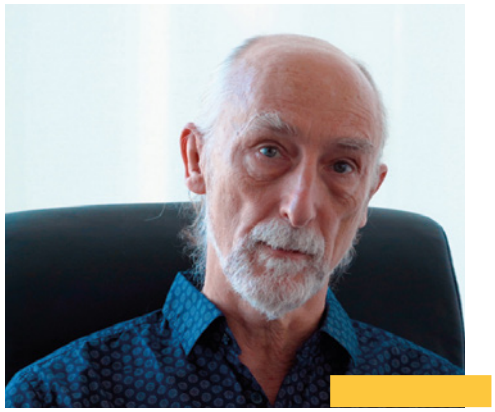
Moderators

Quentin *Cooper*

Quentin Cooper is a renowned science journalist and facilitator. He hosted BBC Radio 4's Material World from 1999 to 2013, and contributes to various science festivals and organizations, including the Royal Society and British Council. Cooper holds a BSc in psychology and AI from the University of Edinburgh and a Postgraduate Diploma in Journalism from Cardiff. His broadcasting career spans across BBC Radio, including work as a film critic and presenter of numerous arts and science programs. He holds honorary degrees for his contributions to science communication.



Alfonso *Valencia*

Prof. Alfonso Valencia is the Director of the Spanish National Bioinformatics Institute (INB-ISCIII) and leads a research group specializing in AI and machine learning for Personalized Medicine. His team develops advanced software for big data extraction and integration in genome projects. They actively participate in international consortia, including ENCODE, ICGC, BLUEPRINT, and RD-Connect. Under his leadership, INB represents Spain as a key node in the European ELIXIR bioinformatics infrastructure, providing cutting-edge bioinformatics solutions globally.

Paula *Adam*

Paula Adam is the Director of the Research Lab at the Agency of Health Quality and Assessment of Catalonia, co-founder of the International School on Research Impact Assessment (ISRIA) and former economist at the OECD in Paris. She is an expert in research impact assessment from the perspective of public policy, implementation and change management. In addition to research impact assessment in biomedicine, Paula has experience as a practitioner in gender policies, new research assessment models and open science. Paula is member of the Research Impact Assessment Advisory Board (RIAAB) of iCERCA, member of the expert group for the Strategy of Gender Equity in Science of the Department of Research and Universities of the Government of Catalonia and has been coordinator of the Commission for the accreditation of the biomedical research institutes of the "Instituto de Salud Carlos III" (ISCIII). She is currently collaborating with expert teams of INGENIO-CSIC-UPV.

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