CIBB

ANNUAL REPORT 2021

CENTRE FOR INNOVATIVE
BIOMEDICINE
AND BIOTECHNOLOGY

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INTRODUCTION

CIBB is a Research Center of excellence in the domains of Biomedicine and Biotechnology created by merging CNC and iCBR (previously IBILI) institutes. With cutting edge equipment and facilities, and the largest critical mass of researchers in the Portugal Centre Region, internationally experienced and linked to the Faculties of Pharmacy, Medicine, Sciences and Technology and Economics, as well as to the Institute of Interdisciplinary Research and CHUC, CIBB has a high-level of scientific production and attracts talent and funding at national and international levels.

This multidisciplinary structure, composed of 30 research groups, has a 5-year mission to understand how and why diseases develop (particularly age-associated ones) and to transform knowledge into clinical application and technological innovation. CIBB is organized in 3 lines: Neuroscience and Disease, that aims to decipher brain functioning and dysfunction in neurodegenerative, neuropsychiatric and vision disorders; Metabolism, Aging and Disease, which studies the cellular and molecular bases of metabolic dysfunction and aging and their impact on the progress of age-associated diseases; and Innovative Therapies that uses stem cells, genes and drugs to implement new therapies for neurodegenerative, cardiovascular, oncological and infectious diseases.

CIBB will reinforce its strong tradition in international training at Masters and PhD levels, and in the career development of young researchers supporting their progress into scientific leadership positions with emphasis on Portuguese institutions. CIBB researchers will also connect with society, through communication and public engagement, advanced courses on continuing education, production of science content for multiple audiences and evaluation of the socio-economic impact of fundamental and translational research, promoting public awareness of science.

In addition to a strong investment in fundamental research, the close link with CHUC and its Clinical Academic Center provides CIBB with privileged conditions to translate basic knowledge into clinical practice, stimulating researchers to transform scientific discoveries into new diagnosis and treatment.

CIBB will also promote the transformation of scientific innovations in intellectual property, and the transfer of technology and creation of added economic value, taking advantage of Biocant Park and its biotechnology companies, as well as of the direct relationship with companies with intervention in the area of Biomedicine and Biotechnology. Advanced training in industrial environment will be fostered so as to give young scientists the opportunity to create new enterprises and secure their own future employability.

CIBB is thus at the heart of an organized network of high-level valences, ranging from fundamental to translational clinical research and to creation of added value, with a strong component of advanced training, that make it an international reference Research Center

LUÍS PEREIRA DE ALMEIDA

CIBB Coordinator

FACTS & FIGURES

From Year 2021

RESEARCH STAFF

Members holding Ph.D. 295

PhD Students 186

MSc Students 60

Grant Technicians 35

PUBLICATIONS

International publication 695

National Publications 90

Book chapters & Book Edition 41

THESIS CONCLUDED

Ph.D. thesis 33

MSc thesis 155

RESEARCH LINES AND RESEARCH GROUPS

CIBB is organized in 3 research lines gathering the research groups according to their research focus: The "Neuroscience and Disease" line that aims to decipher brain functioning and dysfunction in neurodegenerative, neuropsychiatric and vision disorders; the "Metabolism, Aging and Disease" line, which will study the cellular and molecular basis of metabolic dysfunction and aging and their impact on the evolution of age-associated diseases; and the "Innovative Therapies" line that will use stem cells, genes and drugs to implement new therapies for neurodegenerative, cardiovascular, oncological and infectious diseases.
These areas intersect with 2 major domains, Biomedicine and Biotechnology, and are spaces of preferential interaction and flagship projects between research groups with scientific affinity. In addition, CIBB strongly promotes transdisciplinary projects crossing in a comprehensive and cohesive manner different areas aiming at breaking down barriers between disciplines, and integrating knowledge gained from studies at molecular, cellular, organ, whole organism and patient levels. CIBB also promotes collaborative projects with other research institutions in a continuous search for excellence.

Neuroscience and Disease Line

Ana Luísa Carvalho

Synapse Biology Group (Head: Ana Luísa Carvalho)
Neuromodulation Group (Head: Rodrigo Cunha)
Neurotrophin Signaling and Synaptic (Dys)Function Group (Head: Carlos Duarte)
Neuronal Circuits and Behavior Group (Head: João Peça)
Redox Biology and Brain Sensing Group (Head: João Laranjinha)
Mitochondria and Neurodegenerative Disorders Group (Head: A. Cristina Rego)
Vision Diseases Group (Head: Francisco Ambrósio)
Neuroendocrinology and Aging Group (Head: Cláudia Cavadas)
Biomarkers in Neuropsychiatric Disorders: from Molecules to Diagnosis and Intervention Group (Head: Isabel Santana)

Metabolism, Aging and Disease Line

Paulo Oliveira

Mitochondria, Metabolism and Disease (Head: Paulo Oliveira)
Metabolism control (Head: John Jones)
Cell Signaling and Metabolism in Disease Group (Head: Teresa Cruz)
Insulin Resistance and Diabetic Angiopathy Group (Head: Flávio Reis)
Biology of Reproduction & Stem Cell Group (Head: João Ramalho-Santos)
Molecular Mechanisms of Cardiovascular Diseases Group (Head: Henrique Girão)
Microbiomes, Metabolism and Omics Group (Head: Conceição Egas)
Human Genome Variation and Environment in Health and Disease Group (Head: Isabel Marques Carreira)
Healthy Living and Active Ageing Group (Head: João Malva)
Health, Management and Economics Group (Head: Pedro Ferreira)

Innovative Therapies

Lino Ferreira

Advanced Therapies Group (Head: Lino Ferreira)
Vectors, Gene and Cell Therapy Group (Head: Luis Almeida)
Tumor Microenvironment and Targeted Therapies Group (Head: João Nuno Moreira)
Cell Reprogramming and Developmental Hematopoiesis Group (Head: Carlos Filipe Pereira)
Medicinal Chemistry & Drug Discovery Group (Head: Jorge Salvador)
Molecular Biotechnology and Protein Engineering Group (Head: Isaura Simões)
Functional Genomics and RNA-based Therapeutics Group (Head: Miguel Mano)
RNA & Infection Group (Head: Ana Eulálio)
Molecular Microbiology and Microbiome Group (Head: Nuno Empadinhas)
Medical Microbiology Group (Head: Teresa Gonçalves)

CIBB External Advisory Board: John Greenwood (United Kingdom), Inna Slutsky (Israel), Kendall Wallace (USA), Matthijs Verhage (The Netherlands), Thomas von Zglinicki (United Kingdom)

RESEARCH ACTIVITY

NEUROSCIENCE AND DISEASE

COORDINATOR: ANA LUÍSA CARVALHO

GENERAL OBJECTIVES

The research activities in this line are focused on understanding at the molecular, cellular and circuit levels mechanisms that underlie neuronal and circuit function in physiological conditions, and in the pathogenesis of diseases of the nervous system. Researchers also aim to propose and develop novel therapeutic strategies for brain diseases.

The nine research groups that integrate this research line contribute at different levels in the areas of molecular, cellular, circuits and behavioral neuroscience, to understand the brain, from molecules to synapses, to different cell types in the brain, brain circuits and behavior, also with focus on pathogenic mechanisms of disease.

Strong collaboration with the Coimbra University Hospital (CHUC), in particular with the Neurology, Psychiatry and Ophthalmology Units, supports translational research efforts, in which researchers explore potential therapeutic targets (synaptic neuromodulation, mitochondrial dysfunction, neurovascular coupling, neuroinflammation) and investigate biomarkers for brain and vision disorders.

MAIN ACHIEVEMENTS

Recent studies in this research line have identified convergent adenosine and GABA signaling for synapse stabilization during development (Gomez-Castro et al., Science, 2021), and found that ligand-independent activity of the ghrelin receptor modulates AMPA receptor trafficking in the hippocampus and supports memory formation (Ribeiro et al., Science Signaling, 2021). GRASP1 ubiquitination was also found to regulate AMPA receptor surface expression and synaptic activity (Mele et al., FASEB J, 2021). Research on neuromodulation by purines continues to be a strong focus of groups in the Neuroscience and Disease research area, with recent contributions highlighting the role of A2A adenosine receptors during neurodevelopment, by contributing to the radial migration of cortical projection neurons (Alçada-Morais et al., Cerebral Cortex, 2021), their role in ATP release in astrocytes (Madeira et al., Mol Neurobiol, 2021), and in convulsion-associated neuronal damage and hippocampal dysfunction (Augusto et al., Neurobiol Dis, 2021).

In a model of chronic anxiety, sex-specific differences in peripheral metabolism (Ferreira et al., Eur J Clin Invest., 2021) and in resilience and microglia and neuronal morphology remodeling (Gaspar et al., Neurobiol Stress, 2021) were found. Moreover, Ferreira-Marques et al. discovered that caloric restriction or caloric restriction mimetics stimulate autophagy by activating the PI3K/AKT/MTOR and ERK1/MAPK pathways in cortical neurons (Ferreira-Marques et al. Aging, 2021).

Studies on neurodegenerative diseases have focused on Huntington's and Alzheimer's disease. Some very relevant publications show that mitochondrial SIRT3 confers neuroprotection in Huntington's disease by regulation of oxidative challenges and mitochondrial dynamics (Naia et al., Free Radic Biol Med, 2021), and that pridopidine, a selective Sigma-1 receptor (S1R) agonist in clinical development for Huntington's disease and amyotrophic lateral sclerosis, rescues multiple mitochondrial functions in human and mouse Huntington's disease models (Naia et al., Neurotherapeutics, 2021). In addition, studies on Alzheimer's disease pathogenic mechanisms have emerged: One found that a high fat/cholesterol diet recapitulates some Alzheimer's disease-like features in mice, particularly in what regards hippocampal mitochondrial dysfunction (Mancini et al., J Alzheimer's Disease, 2021), another one determined that boldine attenuates synaptic failure and mitochondrial deregulation in cellular models of Alzheimer's disease (Toledo

et al., Front Neurosci,, 2021), and a third one showed that the retina and the brain display early and differential molecular and cellular changes in the 3xTg-AD mouse model of Alzheimer's Disease (Rodrigues-Neves et al., Mol Neurobiol 2021).
Clinical studies are very strong in the Neurology, Psychiatry and Ophtalmology fields. Some examples are i) one report showing that long-term continuous positive airway pressure treatment ameliorates biological clock disruptions in obstructive sleep apnea (Gaspar et al., Ebiomedicine, 2021); ii) one study identifying the SQSTM1 gene as a potential genetic modifier of CADASIL phenotype (Almeida et al., J Neurol, 2021); iii) a publication reporting serum neurofilament light chain as a surrogate of cognitive decline in sporadic and familial frontotemporal dementia (Silva-Spínola et al., Eur J Neurol, 2021); iv) a one year follow-up study analyzing cognitive trajectories following acute infection in older patients with and without cognitive impairment (Silva et al., Front Psych, 2021); v) a 5 year longitudinal study on ocular and systemic risk markers for development of macular edema and proliferative retinopathy in type 2 diabetes (Martinho et al., Diabetes Care, 2021); and vi) the EYE-RISK Consortium study on genetic risk, lifestyle, and age-related macular degeneration in Europe (EYE-RISK Consortium, Ophthalmology, 2021).
Researchers in this area organized in Coimbra the 17th meeting of the Portuguese Society for Neuroscience, and the V Symposium of the Portuguese Glial Network.
These are but a few of the main achievements in the Neuroscience and Disease research line in 2021. Please refer to the individual group reports for other important studies during 2021.

Synapse Biology

Ana Luisa Carvalho (PhD, Group Leader)
Ângela Inácio (PhD)
Dominique Fernandes (PhD)
Gladys Caldeira (PhD)
Joana Ferreira, (PhD)
Luís F Ribeiro, (PhD)
Mário Carvalho (PhD)
Paulo Pinheiro (PhD)
Sandra Santos (MD, PhD)
Raquel Rodrigues, (PhD)
Ricardo Leitão, (PhD)
Beatriz Rodrigues (PhD Student)
Débora Serrenho (PhD Student)
Marina Rodrigues (PhD Student)
Jeannette Schmidt, (PhD Student)
Nuno Beltrão (PhD Student)
Orsolya Antal (PhD Student)
Ana Vasconcelos (MSc Student)
Lia Carvalhais (Msc Student)
Sara Ribau (MSc Student)
Alejandra Núñez Torres, MSc, technical assistant

Neuromodulation

Rodrigo Cunha (PhD, Group Leader)
Ana Patrícia Simões (PhD)
Ângelo Tomé (PhD)
Attila Köfalvi (PhD)
Francisco Queiroz (PhD)
Henrique Silva (PhD)
Joana Marques (PhD)
João Pedro Lopes (PhD)
Nélio Gonçalves (PhD)
Paula Agostinho (PhD)
Paula Canas (PhD)
Ricardo Rodrigues (PhD)
Samira Ferreira (PhD)
Anna Pliássova (PhD Student)
Cátia Lopes (PhD Student)
Daniela Madeira (PhD Student)
Liliana Dias (PhD Student)
Ana Sofia Figueira (MSc Student)
Andreia Oliveira (MSc Student)
Catarina Carreira (MSc Student)
Ingrid Gaspar (MSc Student)
Joana Domingues (MSc Student)
Joana Silva (MSc Student)
João Rocha (MSc Student)
Matilde Jesus (MSc Student)
Rafael Dias (MSc Student)
Joana Silva (Grant Technician)

Redox Biology and Brain Sensing

João Laranjinha (PhD, Group Leader)
Ana Ledo (PhD)
Barbara Rocha (PhD)
Cátia Marques (PhD)
Carla Nunes (PhD)
Diana Jurado Serra (PhD)
Leonor Almeida (PhD)
Rui Barbosa (PhD)
Teresa Dinis (PhD)
Cândida Dias (PhD Student)
João Gonçalves (PhD Student)
Joana Henriques (MSc Student)
Eliana Fernandes (Grant Technician)

Neuroendocrinology and Aging

Claudia Cavadas (PhD, Group Leader)
Alexandrina F. Mendes (PhD)
Ana S. Carvalho (PhD)
Ana Maria F. Capitão (PhD)
Ana Rita C. S. Álvaro (PhD)
Célia Aveleira (PhD)
Fernando Judas (MD, PhD)
Mª Manuel Cruz Silva (PhD)
Sara Carmo Silva (PhD)
Ana Catarina Franco (PhD student)
Bárbara V. Santos (PhD Student)
Catarina C. Almeida (PhD Student)
Cátia Sousa (PhD Student)
Helena Leal (PhD Student)
Laetitia da Silva Gaspar (PhD Student)
Marisa F. Marques (PhD Student)
Rodrigo Ribeiro (PhD Student)
Joaquim Moita (MD)
João Paulo Oliveira (MD)
Eliana Rita Barbosa (MSc Student)
Gabriela S. Moço (MSc Student)
Iara Pratas (MSc Student)
Daniela Costa (Grant Technician)
Vasco A. Lucas (Grant Technician)

Neurotrophin Signaling and Synaptic (Dys)function

Carlos B Duarte (PhD, Group Leader)
Emilia Duarte (PhD)
Filipe Valente Duarte (PhD)
Ivan Lalanda Salazar (PhD)

Miranda Mele (PhD)
Monica Santos (PhD)
Rui O Costa (PhD)
Elena Rodriguez (PhD Student)
Gianluca Masella (PhD Student)
Pasqualino De Luca (PhD Student)
Elisa Corti (Grant Technician)
Emanuel Tahiri (MSc Student)
Francisca Silva (MSc Student)
Giorgioo Belperio (MSc Student)

Neuronal Circuits and Behavior

João Miguel Peça Lima Novo Silvestre (PhD, Group Leader)
Ana Luisa Colaco Cardoso (PhD)
Catarina Morais Seabra (PhD)
Joana Ribeiro Guedes (PhD)
Emanuel Ferreira Fernandes (PhD)
Diana Bela da Luz Sequeira (PhD Student)
Marcos António dos Santos Rodrigues Gomes (PhD Student)
Ana Rafaela Gomes Soares Oliveira (PhD Student)
Marta Isabel Ferreira Leite Pereira (PhD Student)
Mariana Barradas Serrano Laranjo (PhD Student)
Jéssica Margarida Mendes Costa (PhD Student)
Pedro António Cruz Ferreira (PhD Student)
Giuseppe Cammarata (PhD Student)
Solange Martins Nogueira (MSc Student)
Ana Maria Sequeira Cardoso (PhD)
Maria Joana Guimarães Pinto (PhD)
Mariana Martins (PhD Student)

Mitochondria and Neurodegenerative Disorders

Ana C. Rego (PhD, Group Leader)
Ildete Luisa Ferreira (PhD)
Sandra Mota (PhD)
Carla Nunes Lopes (PhD)
Ricardo Lorenzoni (PhD)
Rita Vilaça (PhD)
Lígia Fão (PhD Student)
Daniela Lopes (Grant Technician)
Margarida Beatriz (Grant Technician)
Patrícia Coelho (Grant Technician)
Mariana Pires (MSc Student)
Bernardo Figueiredo (MSc Student)
Bárbara Castanheira (MSc Student)
Beatriz Mendes (MSc Student)
Rodrigo Taveira (MSc Student)

Vision Diseases

Francisco Ambrósio (PhD, Group Leader)
Catarina Gomes (PhD)
Elisa Campos (PhD)
Filipa Baptista (PhD)
Henrique Alves (PhD)
Maria Madeira (PhD)
Paulo Santos (PhD)
Raquel Santiago (PhD)
Rosa Fernandes (PhD)
Ana Bela Campos (PhD Student)
António Campos (MD, PhD Student)
Catarina Neves (PhD Student)
Inês Aires (PhD Student)
Raquel Boia (PhD Student)
Rita Gaspar (PhD Student)
Joana Martins (MSc)
Lia Costa (MSc)
Ana Sofia Ferreira (MSc Student)
Inês Ventura (MSc Student)
Joana Silva (MSc Student)
Sofia Galvão (MSc Student)

Aging and Brain diseases: advanced diagnosis and biomarkers Group

Isabel Santana (MD, PhD, Group Leader)
Ana Paula S. Martins (PhD)
Ana Rita S. Silva (PhD)
Bruno Manadas (PhD)
Carlos A. F. Ribeiro (MD, PhD)
Catarina R. Oliveira (MD, PhD)
Catarina Reis Gomes (PhD)
Edna Filipa P. Soares (PhD)
Filipa C. Baptista (PhD)
Frederico G. Pereira (PhD)
Inês Baldeiras (PhD)
João Freitas (MD, PhD)
Joaquim Cerejeira (MD, PhD)
Marcos Barbosa (MD, PhD)
Mª Rosário Almeida (PhD)
Sónia Batista (MD, PhD)
Ricardo Leitão (PhD)
Alexandre Marques (MD)
Anabela Matos (MD)
Filipe Palavra (MD)
Gustavo Santo (MD)
Inês Correia (MD)
João Durães (MD)
Luis Negrão (MD)
Luisa Santos (MD)
Mª Carmo Macário (MD)

Miguel Pereira (MD)
Patrícia Regueira (MD)
Ricardo Morais (MD)
Sara Pedroso (MD)
Tânia Silva (MD)
Ana Cristina Santos (Graduate Technician)
Diana Duro (PhD)
Ana Catarina Neves (PhD Student)
Anuschka Spínola (PhD Student)
Eliane Sanches (PhD student)
Marisa Neves (PhD Student)
Mª João Leitão (PhD Student)
Milene Gonçalves (PhD Student)
Julie Héléne Reis (Grant Technician)
Alexandra F Cruz (Student)

SYNAPSE BIOLOGY

Head: Ana Luisa Carvalho

Objectives

The Synapse Biology group is focused in understanding the molecular mechanisms underlying neuronal excitability and the function of brain synapses under physiological conditions, and how synaptic dysfunction contributes to neuropsychiatric disorders. We use a wide range of experimental approaches to address the role of molecular players that regulate neuronal polarization, excitability and synaptic function at the presynaptic and postsynaptic levels. Furthermore, we investigate disease-related alterations in synaptic function, either genetic, stress-related, or triggered by antibodies produced by autoimmune synaptic encephalitis patients, to understand how synaptic dysfunction underlies disease pathogenesis. The group has been pursuing the following specific objectives:

Intracellular trafficking and axonal polarization (Luís Ribeiro)
We started the implementation of the project SortAx funded by FCT and the European Commission. The main goal of this project is to characterize the molecular machinery of intracellular trafficking and endosomal sorting responsible for axonal polarization.

The membrane fusion machinery in brain physiology and disease (Paulo Pinheiro)
We are interested in the roles that alternative isoforms of proteins typically involved in neurotransmitter release - SNAP-29 and SNAP-47 - play in neuronal physiology. The work is focused on understanding how they participate in neurogenesis, neuronal development, synaptic function and plasticity, and how they may be linked to synaptic dysfunction in neuropsychiatric disorders, particularly in the context of 22q11.2 deletion syndrome and schizophrenia. We are evaluating the behavioral and neuronal/synaptic phenotypes of genetically modified mice with reduced or absent expression of these proteins.

Transsynaptic interactions in brain function and in neurological disorders (Joana Ferreira)
We have recently found that the pre-synaptic cell-adhesion molecule Neurexin2 interacts directly with post-synaptic NMDA receptors (NMDAR). Given that multiple Neurexins mutations have been found to be associated with schizophrenia and that more and more evidence is sustaining the model of NMDAR hypofunction in this disease, we seek to explore the role of this newly identified interaction.

Mechanisms of chronic stress-induced microRNA-186-5p in cognitive dysfunction (Paulo Pinheiro and Ana Luisa Carvalho)
We have identified post-transcriptional regulation of AMPA receptors by miR-186-5p, which directly targets and modulates the expression of GluA2 AMPA receptor subunit (Silva et al., *PNAS* 2019). We are now interested in understanding how chronic stress-upregulated miR-186-5p affects AMPA receptor composition and synaptic transmission and if manipulation of miR-186-5p levels can both mimic synaptic and cognitive dysfunction associated to chronic stress and constitute a therapeutic target to mitigate its adverse effects.

Synaptic dysfunction and alterations in neuronal excitability in disease-associated human mutations in the *CACNG2* gene encoding stargazin (Ana Luisa Carvalho and Ângela Inácio)
We are interested in understanding how disease-associated human mutations in the *CACNG2* gene encoding for stargazin impact synaptic and cognitive function. We have generated knock-in mice harbouring intellectual disability and schizophrenia-associated human mutations in *CACNG2*, and

we are evaluating neuronal excitability, synaptic transmission, plasticity and behaviour in these mice, towards understanding synaptopathogenic mechanisms.

Mechanisms of CASPR2 antibodies in autoimmune synaptic encephalitis (Ana Luisa Carvalho)
Caspr2, a cell adhesion molecule of the neurexin family, regulates AMPA receptor function, and anti-CASPR2 antibodies from autoimmune synaptic encephalitis patients block synaptic transmission in vitro and in the visual cortex (Fernandes et al., *Cerebral Cortex* 2019). We are now interested in understanding how anti-CASPR2 antibodies impact neuronal excitability, and the underlying pathogenic mechanisms.

The main technical and scientific achievements in 2021 are the following:

Intracellular trafficking and axonal polarization
In order to characterize the proteome of diverse subcellular compartments in neurons without the disadvantages of biochemical fractionation (e.g. cross-contamination of biochemical fractions), we implemented the proximity labeling methodology. We will use this methodology to characterize which axonal cargoes are trafficked to the axon via dendritic endosomes.
Moreover, we have started in the lab the optimization of CRISPR-Cas9-mediated endogenous tagging and CRISPR-Cas9-mediated downregulation of genes of interest. This methodology will have a huge impact in the lab, namely because it will allow us to study the localization and function of our genes of interest by looking at their endogenous expression, thus circumventing overexpression artifacts.

The membrane fusion machinery in brain physiology and disease
We found that mice heterozygous for SNAP29 express about 50% of the protein, causing haploinsufficiency. Electrophysiological analysis reveals altered short-term synaptic plasticity and recovery from synaptic depression. Neuronal cultures from SNAP29 KO mice show subtle deficits in neuronal development, altered spontaneous excitatory synaptic transmission and morphological abnormalities at glutamatergic – but not GABAergic – synapses. RNAseq in the brains of these mice showed altered expression of genes linked to neuronal function, including glutamate receptors, calcium channels and calcium-binding proteins, synaptogenesis an intracellular trafficking.

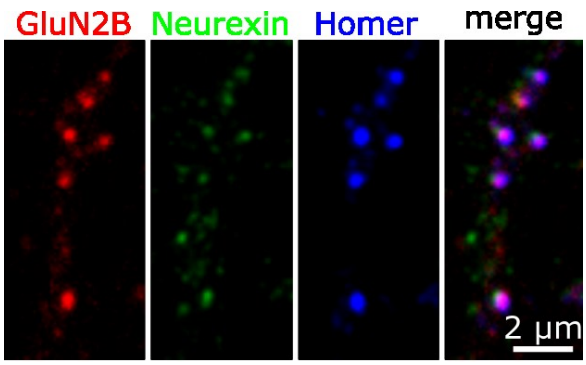
Synaptic and memory modulation by the ghrelin receptor
In addition to its role in stimulating appetite, the hormone ghrelin and its receptor GHS-R1a are implicated in cognition. We found a role for ghrelin-independent GHS-R1a signaling in learning in mice. The use of inverse agonists and mutants revealed that ligand-independent activity of GHS-R1a maintained the synaptic abundance of AMPA-type glutamate receptors through a phosphorylation-dependent trafficking mechanism in both cultured hippocampal neurons and brain slices, thereby ensuring tonic control of synaptic plasticity. Treating mice with a GHS-R1a inverse agonist impaired spatial and contextual memory formation. Thus, the use of ghrelin receptor–blocking therapies—which have been proposed for treating metabolic disorders, acromegaly, cancer, and alcoholism—may also have cognitive side effects (Ribeiro*, Catarino*, Carvalho* et al., *Science Signaling* 2021).

Aberrant hippocampal transmission and behavior in mice with a stargazin mutation linked to intellectual disability
Mutations linked to neurodevelopmental disorders, such as intellectual disability (ID) and schizophrenia (SCZ), are frequently found in genes that encode for proteins of the excitatory synapse. Transmembrane AMPA receptor regulatory proteins (TARPs) are AMPA receptor auxiliary proteins that regulate crucial aspects of receptor function. We have investigated mutant forms of the TARP family member stargazin, described in ID and SCZ patients. Our aim is to

identify alterations in synaptic transmission and plasticity in relevant brain circuits, which may account for the behavior alterations associated with these diseases. Molecular dynamics analyses predicted that the ID-associated stargazin variant, V143L, weakens the overall interface of the AMPAR:stargazin complex and impairs the stability of the complex. Knock-in mice harboring the V143L stargazin mutation (StgID mice) manifest cognitive and social deficits and hippocampal synaptic transmission defects, resembling phenotypes displayed by ID patients. In the hippocampus of stargazin V143L mice, CA1 neurons show impaired spine maturation, abnormal synaptic transmission and long-term potentiation specifically in basal dendrites, and synaptic ultrastructural alterations. These data suggest a causal role for mutated stargazin in the pathogenesis of ID and unveil a new role for stargazin in the development and function of hippocampal synapses (Caldeira, G.L.*; Inácio, A.*; et al. *Molecular Psychiatry* 2022).

Innovative Training Network Syn2Psy

We have coordinated the Innovative Training Network Syn2Psy, an international consortium that aims for training a group of 14 Early Stage Researchers in the topic of Synaptic Dysfunction in Neuropsychiatric Disorders. See the Syn2Psy website for the activities developed.



Transsynaptic interactions – NMDA receptors bind to neurexins. Image shows coincident fluorescent signal for the GluN2B-NMDAR, Neurexin and Homer in hippocampal neurons (Joana Ferreira).

REDOX BIOLOGY AND BRAIN SENSING

Head: João Laranjinha

Objectives

The group´s research programs address:

(a) The molecular and cell biological processes involving free radicals, oxidants and antioxidants inherent in neurovascular and neuroenergetic coupling in brain during aging and age-related disorders. We focus on nitric oxide (NO) as a cell messenger that control the communication between active neurons and local blood microvessels in hippocampus (neurovascular coupling). We aimed at understanding how changes of redox environment affects signaling pathways and neurometabolism supporting a functional brain microcirculation and cognitive performance during aging and age-related disorders. The study of the neurovascular-neurometabolic coupling axis, encompasses mechanistic as well nutritional approaches along the nitrate:nitrite:NO pathway and the microbiota gut-brain axis with potential to restore the functionality of neurovascular coupling and enhance cognition.

(b) Technological innovation in terms of the project, design and implementation of microarray technology consisting of micro(bio)sensors for the real-time monitoring of neuromodulators, neurotransmitters and metabolic intermediates in the brain of anesthetized and freely moving animals. These technological developments enable us to implement multimodal approaches, encompassing metabolic, electric and hemodynamic measurements in rat brain on basis of microelectrode arrays-based design directly implanted in the brain tissue that provided simultaneous neurometabolic and electrophysiological information.

Main Achievements

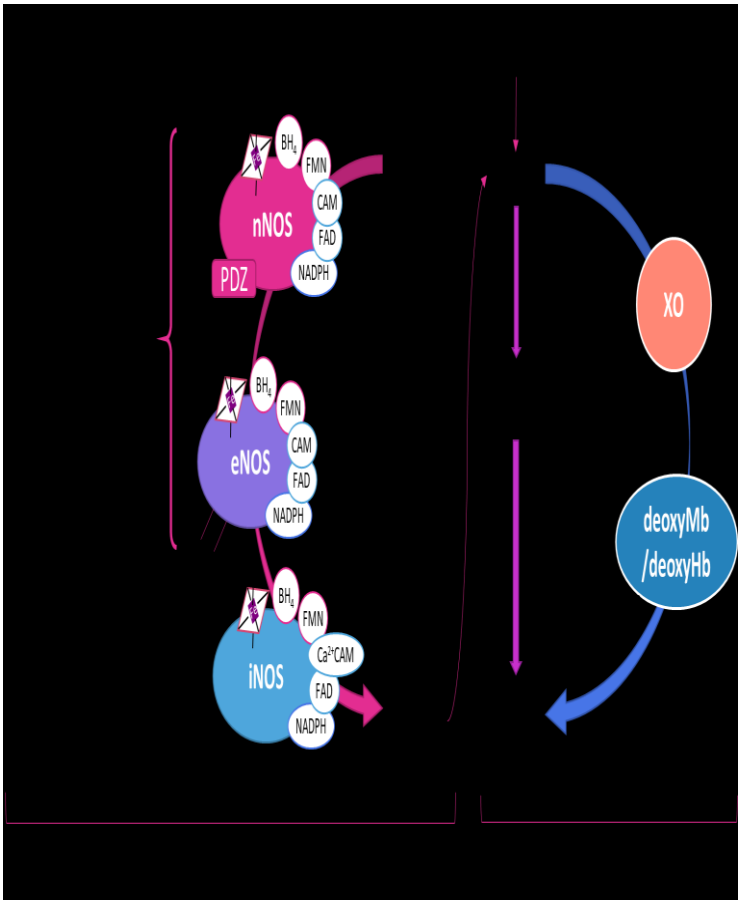
The main achievements encompass technological and scientific components.

We have established a conceptual framework for the understanding of the bioactivity of nitric oxide (NO) as a critical regulator of brain bioenergetics and neurovascular coupling and a stressor in aging and neurodegeneration. The concepts include oxygen-dependent and independent pathways for NO production, mitochondrial dysfunction, dopamine redox metabolism as well as the local redox environment at blood microcirculation sites.

We have formulated an hypothesis for the functional coupling of glutamate-dependent neuronal activity and local blood flow increases under conditions of hypoxia and aberrant brain aging, leading to cognitive enhancement. The hypothesis, involving the redox couple of ascorbate and nitrite, required the design and development of a microelectrode sensor for real-time measurements of nitrite in the living brain, in the presence of ascorbate.
In line with current research programs in the lab on the redox biology of NO along the nitrate:nitrite:NO pathway, we have reviewed pre-clinical and clinical evidences supporting the notion that diets rich in nitrate may prevent, reverse or mitigate the physiological decay observed during aging or age-related disorders.

We supported that learning and memory processes, particularly those that rely on hippocampus, are susceptible to disruption by diets containing high levels of fat and cholesterol. Animals under chronic high fat and cholesterol diet develop an Alzheimer´s-like phenotype. This was supported by a multimodal approach encompassing metabolic, electrophysiologic, dietary and behavioral studies in an animal model (3xTg mouse) of Alzheimer´s disease.

Funding sources:
POCI-01-FEDER-029099 (PI: João Laranjinha) 239,153 €
Cognitive enhancement in aged brain and vascular dementia in humans through improving neurovascular coupling: a mechanism-based approach driven by nitrite and ascorbic acid from diet. 2018-2022.
PTDC-01-0145-FEDER-028261 (PI: Rui Barbosa) 239.897,53 €
Brain Metabolic Probe. 2018-2022
PTDC/SAU-NUT/29089/2017 (PI: Leonor Almeida) 238.694,83 €
"Role of anthocyanins from Portuguese blueberries on gut-to-brain connection in autism spectrum disorder by using *in vitro* and *in vivo* models" (2018 – 2022)



NEUROENDOCRINOLOGY AND AGING

Head: Cláudia Cavadas

The Mission of Neuroendocrinology and Aging Group is to contribute to develop new knowledge in the aging field, namely to demonstrate that neuroendocrine system and related mechanisms can be targeted in experimental models to delay, stop, and in some examples, reverse manifestations of aging and age-related disorders.
The knowledge generated by our group has been contributing to the hypothesis that aging and age-related disorders could be controlled by using neuroendocrine strategies. These strategies are based on targeting the main brain area involved in the neuroendocrine system - the hypothalamus -, its main functions (circadian rhythm, sleep, food intake, metabolism), and also the hypothalamus-periphery axis.

Objectives:

To investigate the neuroendocrine axis contribution to ageing and age-related disorders
To investigate new strategies to delay aging and age-related disorders by targeting the hypothalamus or by targeting hypothalamic related mechanisms;
To use caloric restriction mimetic approaches, as neuropeptides, new sirtuins-1 activators, circadian rhythm reestablishment to prevent aging and age-related diseases or disabilities (osteoarthrite (OA), sleep dysfunctions, neurodegenerative diseases);
To understand if and how obstructive sleep apnea (OSA) or insomnia induce or accelerate molecular mechanisms of ageing;

Main Achievements

We investigated the role of peptides (NPY, ghrelin and leptin) in rescuing the aging phenotype in experimental models of ageing, using Hutchinson-Gilford Progeria Syndrome (HSPS) experimental models. The results obtained show that NPY, ghrelin and also leptin decrease cellular hallmarks of premature aging of progeria fibroblasts, such as enhanced progerin clearance, autophagy stimulation, rescued nuclear abnormalities, increased cell proliferative capacity and delayed cellular senescence of HGPS cells. In in vivo experiments, we observed that ghrelin was able to ameliorate the aging phenotype of HGPS mouse model. These results support that these peptides can be considered a promising strategy to delay or block the premature aging of HGPS.

We investigated the signalling pathways involved in autophagy stimulation by caloric restriction or caloric restriction mimetics in rat cortical neurons, and the results showed that PI3K/AKT and ERK1/2-MAP are key mechanisms.

We showed that Obstructive Sleep Apnea (OSA) alters biological clock-related characteristics that differentially respond to short- and long-term treatment. Long-term treatment is more efficient in counteracting OSA impact on the clock, but the obtained results suggest that it is not fully effective. A better understanding of the impact of OSA and OSA treatment on the clock may open new avenues to OSA diagnosis, monitoring and treatment.

We showed that a new SIRT1 activator - (S)-(+)-carvone - has the potential to counteract the chronic low-grade inflammation characteristic of age-related diseases.

The preliminary data show that peripheral cells (PBMCs) from obstructive sleep apnea (OSA) patients present some hallmarks of aging, namelly mitochondrial dysfunction.

NEUROTROPHIN SIGNALINGAND SYNAPTIC (DYS)FUNCTION

Head: Carlos B. Duarte

Objectives

Research in this group aims at understanding the molecular pathways controlling synaptic activity at the postsynaptic level under normal physiological conditions and how dysregulation of synapses contributes to different disorders of the nervous system. In particular, the work in this research unit is focused on the mechanisms of regulation of the synaptic function by neurotrophins, which account for their role in long-term synaptic plasticity and in learning and memory formation, and how dysregulation of these processes contributes to neuropsychiatric diseases. The other research line addresses the mechanisms underlying the alterations in inhibitory synaptic transmission in epilepsy.

Regulation of glutamatergic synapses by BDNF (PI: Carlos B. Duarte)
The neurotrophin brain-derived neurotrophic factor (BDNF) plays an important role in the functional and structural changes at synapses required for both early- and late phases of LTP in the hippocampus. These effects of BDNF are partly mediated by regulation of the synaptic proteome through regulation of transport of mRNAs along dendrites and their translation at the synapse. The goal of this project is to understand the BDNF-induced alterations in the synaptic proteome with impact on synaptic activity and plasticity mechanisms

NT3/TrkC signaling in the regulation of glutamatergic synaptic plasticity and fear extinction (PI: Mónica Santos)
Anxiety disorders are marked by excessive fear that is resistant to extinction processes. Recent evidence, by us and others, indicates that neurotrophins modulate the neurobiological processes involved in fear conditioning and extinction, making them putative targets for the development of therapies to impart resilience against a wide spectrum of anxiety disorders. In particular, I previously identified a role for neurotrophin 3 (NT3) and its receptor TrkC in the regulation of conditioned fear in a pathological setting. Currently, we aim at investigate the contribution of NT3-TrkC system in the regulation of fear extinction, in physiologic conditions.

MeCP2 in neurodevelopmental and neuropsychiatric disorders (PI: Mónica Santos)
Mutations in the methyl-CpG binding protein 2 gene (MECP2) are the primary cause of Rett syndrome (RTT) and, to a lesser extent, are also responsible by other major neurodevelopmental disorders such as X-linked mental retardation, autism or schizophrenia. More recently, a putative involvement of MeCP2 in stress-related pathologies, such as anxiety and depression has been considered. MeCP2 is a multifaceted protein facilitating several biological processes. In particular, MeCP2 has been shown to contribute to the early-life stress-dependent epigenetic programming of genes that enhance the hypothalamus-pituitary-adrenal axis activity. In this project, we aim to investigate how MeCP2 and MeCP2-environment interactions contribute to the modulation of anxiety and stress behaviors and the underlying neuronal circuits.

Targeting the K^+-Cl^- cotransporter (KCC2) to maintain GABAergic neurotransmission: a novel therapeutic strategy for epilepsy (PI: Miranda Mele)
Chloride homeostasis in neurons is essential for the proper excitatory/inhibitory (E/I) balance in the brain, determining the postsynaptic response to γ-Aminobutyric acid (GABA), which is the major inhibitory neurotransmitter in the CNS. Downregulation of the expression/activity of KCC2, which extrudes Cl^- from neurons, promotes excessive intracellular chloride accumulation and may lead to neuronal hyperexcitability. The objective of this project is to elucidate whether that activation of KCC2 may constitute a potential strategy to restore chloride homeostasis in epileptic conditions, modulating GABAergic neurotransmission and E/I balance.

Main Achievements

Regulation of glutamatergic synapses by BDNF (PI: Carlos B. Duarte)
In immunocytochemistry experiments performed in cultured hippocampal neurons we found that BDNF induces the synaptic accumulation of GluN2A and GluN2B-containing NMDA receptors (NMDAR) with distinct kinetics. The synaptic accumulation of NMDAR was correlated with an upregulation in NMDAR-mediated miniature excitatory postsynaptic currents (mEPSC) and with a reduction in the mobility of the receptors at the synapse, as determined by single receptor tracking with quantum dots. Downregulation of the tyrosine kinase Pyk2 abrogated the effects of BDNF on the synaptic accumulation of GluN2A- and GluN2B-containing NMDAR and Western blot experiments showed that protein kinase C mediates the effects of BDNF-TrkB signaling in the activation of Pyk2. Importantly, inhibition of GluN2B-containing NMDAR abrogated the effects of BDNF in the facilitation of LTP in hippocampal CA1 synapses.

NT3/TrkC signaling in the regulation of glutamatergic synaptic plasticity and fear extinction (PI: Mónica Santos)
Currently we focus on the role of NT3-TrkC signaling in the regulation of fear extinction memories, in a physiological context. If proved, this system will represent a new and promising entry point for therapeutic interventions in the clinic.
In the lab, using the contextual fear conditioning paradigm as a behavioural model, we found that some C57Bl/6J mice undergoing a contextual fear extinction paradigm can extinguish a fear memory (EXT-success), while others fail to do so (EXT-failure). To this contributes, at least partially, the activation state of TrkC (as measured by its phosphorylation levels) in the amygdala and hippocampus brain regions. Over the last year, we have been investigating the role of TrkC specifically at the synapse, using synaptoneurosome preparations from EXT-success and EXT-failure animals, as compared to control animals. We observed an increase in the percentage of TrkC-positive synaptoneurosomes in the amygdala of mice trained in fear extinction, when compared to CTRL-no EXT animals, indicating a higher synaptic recruitment of TrkC. In the hippocampus, the percentage of TrkC-positive synaptoneurosomes was unchanged across conditions, but the intensity of TrkC puncta colocalizing with synaptoneurosomes was higher in EXT-success animals when compared to other groups, suggesting that successful fear extinction results in higher recruitment of TrkC to synapses.
Our previous in vitro experiments showed that NT3 stimulation resulted in the accumulation of synaptic AMPA and NMDA receptors. Here we tested whether the accumulation of synaptic AMPA and NMDA receptors may account for the observed effects of TrkC on fear extinction. The results obtained so far with glutamate receptors in amygdalar synaptoneurosomes showed an upregulation of the GluN2A subunit of NMDA receptors in EXT-failure animals, as compared with CTRL-noEXT and EXT-success groups. Moreover, preliminary data for GluA1 and GluA2 subunits of AMPA receptors in the amygdala, shows a downregulation of both subunits in in EXT-success group as compared with CTRL-noEXT and EXT-failure animals.

MeCP2 in neurodevelopmental and neuropsychiatric disorders (PI: Mónica Santos)
In our last study, we addressed the effects of the interaction MeCP2-early life stress in anxiety sensitivity later in life. We found that in wild-type animals, early-life stress results in a reduction in the anxiety response when animals face an anxiogenic situation later in life. Importantly, deficiency of MeCP2, as that seen in the $Mecp2^{+/-}$ females, is sufficient to mimic the early-life stress effects. Further we could map these behavioral alterations to a reduction in the activation of corticotropin-releasing hormone neurons of the paraventricular nucleus of the hypothalamus (Abellán-Álvaro et al., 2021). Our data suggests that the reported effects of MeCP2 on the reprogramming of the HPA axis, could underlie vulnerability to anxiety disorders later in life.

Targeting the K^+-Cl^- cotransporter (KCC2) to maintain GABAergic neurotransmission: a novel therapeutic strategy for epilepsy (PI: Miranda Mele)

The results obtained so far showed that transient incubation of cultured hippocampal neurons in a medium lacking Mg^{2+}, an *in vitro* model of SE, induces alterations of GABAergic synapses, impairing $GABA_AR$-mediated inhibition. Using this model, we have shown different processes that cooperate to cause the unbalance between excitatory and inhibitory currents in epileptic conditions. Briefly, we demonstrated that SE decreases KCC2 surface expression and this response is coupled to an increase of the $[Cl^-]_i$. This impairment in the Cl^- homeostasis was prevented by the KCC2 activator CLP257, suggesting KCC2 as a potential target to prevent seizures. Overall, these results contribute to elucidate the mechanisms underlying the alteration of chloride homeostasis in epilepsy which is correlated with $GABA_AR$ downmodulation, indicating the transporter KCC2 as a new therapeutic target for epilepsy.

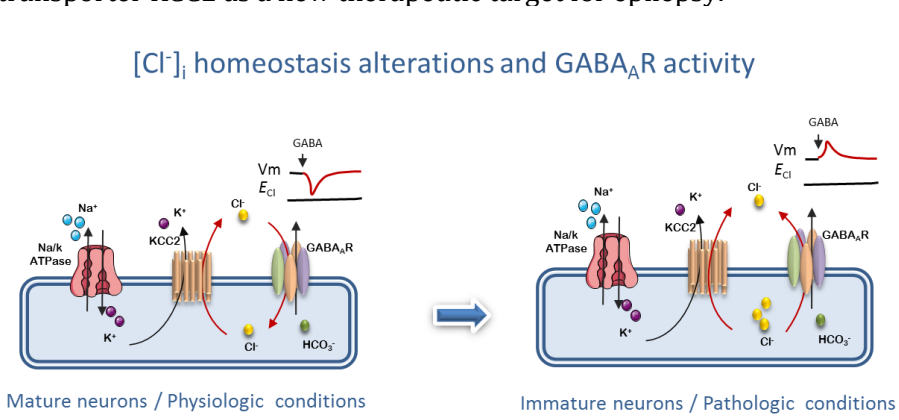


Figure 1. Model for the contribution of KCC2 to neuronal hyperexcitability in epilepsy. Neurological disorders, including epilepsy, have been associated with altered neuronal intracellular chloride homeostasis. Chloride anion plays a key role in neuronal excitability. In fact, the major Cl^- permeable channels are $GABA_AR$, which regulate membrane potential and excitability. One of the regulators of intracellular Cl^- homeostasis in neurons is the K^+-Cl^- cotransporter KCC2 that extrudes chloride. KCC2 down-regulation may contribute to the accumulation of Cl^- within neurons thereby affecting the inhibitory signalling mediated by GABA. In mature neurons, the KCC2 activity results in a $GABA_AR$-mediated Cl^- influx associated with the hyperpolarization of the plasma membrane (left). During development or in pathological conditions, altered KCC2 membrane expression or activity contributes to the accumulation of Cl^- in neuronal cytoplasm (right). Under these conditions GABAergic activity results in the efflux of Cl^- associated with plasma membrane depolarization.

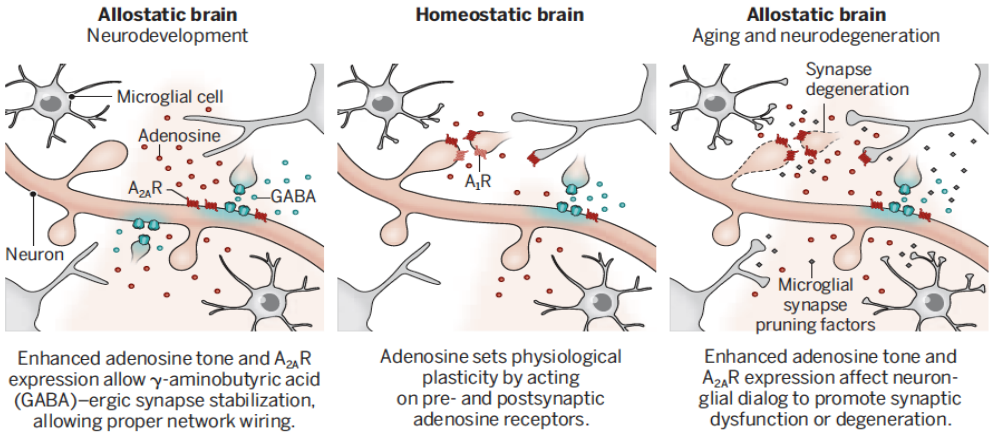
NEUROMODULATION

Head: Rodrigo Cunha
Objectives

The general objective of the group is to identify modulation systems that can be targeted to interfere with the evolution of neurodegenerative diseases, with a central focus on purines (adenosine and ATP). We concentrate on the initial stages of neurodegenerative disorders, under the working hypothesis that one of the key early features transversal to different such diseases is the dysfunction of synapses. This involves both neuronal and glial (astrocytes and microglia) maladaptive changes, with alterations of receptors, metabolic support and neuroinflammatory status, leading to abnormal synaptic plasticity and synaptic pruning that recapitulates features of neurodevelopment. The following organization was implemented:
I-Group Purines@CNC (overall coordination by RA Cunha)
-Astrocyte-neuron communication (P Agostinho, D Madeira)
-A2AR & fear extinction (AP Simões, PM Canas)
-A2AR, stress & depression (PM Canas, AP Simões, L Dias)
-A2AR & reference memory (JP Lopes, A Tomé)
-A2AR & ageing (RA Cunha, C Lopes)
-A2AR in PFC & decision-making (S Ferreira, M Rodrigues)
-A2AR polymorphisms as biomarkers of brain diseases (RA Cunha, P Valadas)
II-Group Cannabinoids and Brain Metabolism (A. Kofalvi, M Rodrigues)
-A2AR & brain glucoregulation
-Endocannabinoid receptor GPR55 & astrocytic glycolysis
III-Group Brain Development (RJ Rodrigues, J Marques, N Gonçalves)
- A2AR in synaptic remodelling in adult brain
- A2AR in cortical principal neurons migration
- P2Y1R & neurodegeneration

Main Achievements

1-Adenosine A_{2A} receptor ($A_{2A}R$) control synapse stability during development
2-ATP-derived adenosine formation through CD73 is critical for the overactivation of $A_{2A}R$ governing neurodegeneration
3-$A_{2A}R$ upregulation may be a novel biomarker of susceptibility to brain diseases
4-$A_{2A}R$ control the migration of cortical principal neurons



Enhanced adenosine tone and $A_{2A}R$ expression allow γ-aminobutyric acid (GABA)–ergic synapse stabilization, allowing proper network wiring.

Adenosine sets physiological plasticity by acting on pre- and postsynaptic adenosine receptors.

Enhanced adenosine tone and $A_{2A}R$ expression affect neuron-glial dialog to promote synaptic dysfunction or degeneration.

NEURONAL CIRCUITS AND BEHAVIOR

Head: João Peça-Silvestre

Objectives

Our long-term goal is to better understand the molecular, cellular and circuit level mechanisms that govern neuronal circuit function in health and disease, particularly in the context of social behaviors. To achieve this goal our laboratory uses a combination of molecular genetics, behavioral studies, electrophysiology, and advanced imaging tools.

Synaptic and circuit function in health and disease:
We are particularly interested in dissecting how mammals' control and regulate social behaviors, and how specific genetic mutations give rise to autism spectrum disorder (ASD). ASD is a neurodevelopmental disorder characterized by persistent deficits in social behaviors, communication, and the presence of restricted interests and stereotypies. Recently, we studied the role played by metabotropic glutamate receptors (mGluRs), which are critical modulators of neuronal plasticity. However, present knowledge of the cellular elements that directly interact, regulate and promote the recycling of these receptors is very limited.
One of our aims is to better understand the cellular biology regulating mGluRs and gain information on the precise cell types that are more vulnerable to discrete ASD risk gene mutations. We also want to assess the possibility of designing tools that regulate mGluRs in a cell-specific manner. Towards this, we recently investigated the role of the family of G-protein coupled receptor-associated sorting proteins (GPRASPs). This large family of genes is known to regulate G-protein coupled receptors (GPCRs) such as mGluRs, by targeting internalized receptors towards lysosomal degradation.
In this line of research, we incorporate advanced models, including novel genetic engineered mice, whole-cell patch clamp and brain organoids derived from patient cells.

Environmental challenges and brain wiring:
Environmental factors have been proposed to underlie vulnerability to mental illness, particularly during sensitive periods of development. There is now strong epidemiological evidence correlating exposure to early life adversity (ELA) - in the form of neglect or abuse - with aberrant brain maturation and a higher risk for psychiatric disorders and other cognitive deficits. Our recent results have shown that a critical alteration following ELA is a phenotype of social subordinance and impulsivity and alterations in the inhibitory system in the prefrontal cortex.
We have also recently established a new line of research dedicated to understanding how environmental triggers, such as early exposure to allergens, may impact the function of microglia during the maturation of neuronal circuits. We hypothesise that alterations in physiological microglial phenotypes in critical periods of circuit maturation may impair neuronal function in adulthood and underlie behavioural deficits reminiscent of neurodevelopmental disorders, including Attention Deficit and Hyperactivity Disorder (ADHD). We are particularly interested in clarifying the contribution of microglia activity to the wiring of the cerebellum and prefrontal cortex circuitry, since these two brain regions suffer important postnatal maturation and are implicated in various neuropsychiatric disorders.
Since we are a small laboratory with research strands that largely intersect, there are currently no subdivisions in the group. The entire lab meets once a week for journal club presentations and PhD holders meet regularly to evaluate student progress and define strategies for the lab.

Main Achievements

In 2014, João Peça started implementing new methodologies and research lines at the Center for Neuroscience and Cell Biology, in 2018 the Neuronal Circuits and Behavior Group became an

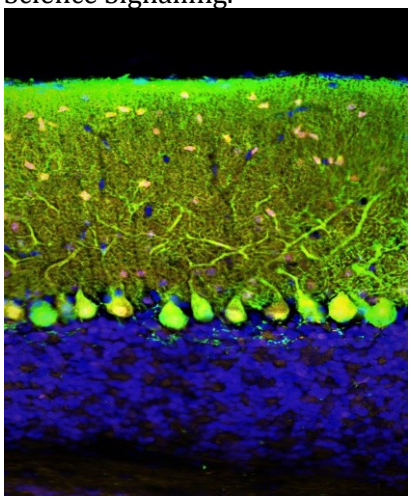
independent research group. Some of the innovative methodologies that were previously not present at CIBB include, advanced mouse molecular genetics, implementation of a mouse behavioural testing facility, implementation of brain slice electrophysiology and the training of several students and postdocs in these techniques. We have also implemented optogenetic manipulation and optogenetic behavioural assays for other groups at CIBB as part of on-going collaboration.

Our group has steadily implemented an independent research plan which is now coming to fruition with publication in top tier journals including papers in Nature communications (2019); Current Opinion in Neurobiology (2019); Molecular Therapy Nucleic Acids (2020); Neuropsychopharmacology (2020); and a recent paper in Nature (2020).

In the last five years we have also published several works on the subject of aging biomarkers. Several lab members were part of the COST Action MouseAGE and responsible for a high impact review on this topic. In this context, we have also investigated the role played by neuroinflammation in Alzheimer's disease (AD) and other neurodegenerative conditions and have identified a set of miRNAs whose levels are upregulated in monocytes from AD patients. More recently, we have published original work on the potential use of miR-31 as a therapeutic tool for this disease.

We have also established partnership with the Coimbra University Hospital Center (CHUC) and have created the first biobank for patient-derived dental stem cells. In parallel, we have established a fibroblast biobank for other neurological disorders, including Frontotemporal Dementia. Using all these samples, we are generating and characterising brain organoids to assess the impact of ASD-linked and FTD-linked mutations in disease pathology.

Despite being one the youngest groups at CIBB, with the youngest group leader, our work has attracted substantial funding and media attention in recent years. Additionally, the group leader is Principal investigator/Scientist-in-charge in 7 projects, co-PI in 3 and member of the team in 2 additional projects. João Peça has been able to attract two Marie Curie Grants (1 Installation grant for the PI and 1 Fellowship Grant), a NARSAD Young Investigator Award, and a prize from the Gulbenkian Foundation. In 2019 our work was acknowledged with the "2019 Pfizer Prize'' in Basic Research, the oldest and one of the most prestigious prizes given in Portugal in the area of Biomedical Sciences. A total of 4 PhD students have completed their training in our group (excluding collaboration and other co-supervisions). In 2021 we were able to attract funding from several sources, including FCT and the coordination of an ERA-NET Neuron Project (SHANKAstro), as well as contract research from YouthBio Therapeutics. Additionally, we continued to publish in high impact papers, including in Nature, Neuropsychopharmacology and Science Signalling.



MITOCHONDRIA AND NEURODEGENERATIVE DISORDERS

Head: Ana Cristina Carvalho Rego
Objectives

"Mitochondria and Neurodegenerative Disorders" group investigates cell and molecular mechanisms of brain neurodegenerative disorders, particularly focusing on early stages of Huntington's (HD) and Alzheimer's (AD) diseases and mitochondria-linked etiopathological processes. These are chronic, debilitating, and age-related brain disorders, characterized by aggregation of misfolded proteins, early and selective neuronal dysfunction, progressively leading to massive brain neurodegeneration. Misfolded proteins, due to posttranslational or oxidation modifications (among other processes) or pre-identified mutations, later form insoluble/fibrillary aggregates. Although there are several mechanisms by which neurons degenerate, the initial pathways of neuronal dysfunction, occurring before the main disease-related symptoms, are not completely understood. In this perspective, by using cellular (e.g. cell lines, neuronal cultures, induced pluripotent stem cells, neural stem cells), *ex-vivo* and *in vivo* animal and human models, we investigate early disease-related modifications affecting mitochondrial function and signaling processes linked to redox deregulation, glutamate postsynaptic dysfunction and/or transcriptional deregulation in different neurodegenerative disorders. Furthermore, we have established a close interaction with neurologists at the local hospital towards the identification of early disease mechanisms and uncover of relevant molecular targets for therapeutic intervention(s). Therefore, the group aligns basic and potential translational research with a main interest in early disease stages, as well as investigation on neuroprotective strategies using pharmacological compounds, modulation of protein expression and/or gene correction strategies.

In 2021 the research group produced fundamental research in HD, a motor neurodegenerative disorder caused by an abnormal expansion of polyglutamines in the huntingtin protein (HTT), and AD, the most common age-related neurodegenerative disorder, by thoroughly investigating:

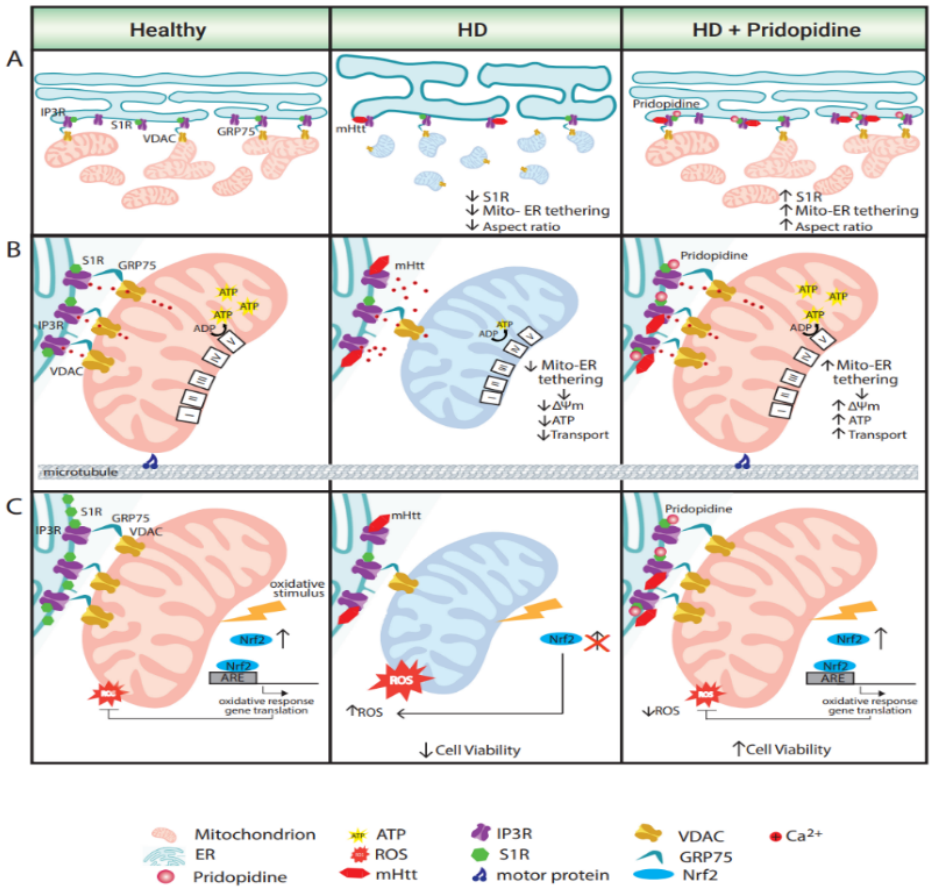
1. The effects of directly targeting SIRT3 in HD. We provided evidence that human caudate obtained from HD patients as well as neuronal and peripheral HD models display a stress-related increase in SIRT3. We demonstrated that SIRT3 is required to regulate mitochondrial radical production and mitochondrial membrane potential, eventually leading to decreased neurodegeneration *in vitro* and in a fruit fly model of HD. Additionally, we provide evidence that SIRT3 fine-tunes the mitochondrial network structure and distribution in HD models rather than increasing mitochondrial mass, thereby supporting overall bioenergetics in neuronal cells.

2. The influence of pridopidine in ameliorating HD mitochondrial dysfunction, representing a mechanism by which pridopidine exerts its neuroprotective effects. In HD models, pridopidine treatment increased tethering between mitochondria and ER, improving mitochondrial elongation, movement, and respiration. We observed that pridopidine, via activation of the Sigma 1 receptors (S1R), rescues mitochondrial dysfunction induced by oxidative damage in both in vitro and ex vivo HD models, namely, in YAC128 transgenic mice, human HD lymphoblasts, and human HD neural stem cells (NSCs). Additionally, we showed that early pridopidine treatment is effective in delaying the onset of HD-related motor symptoms in the YAC128 HD mice.

3. The impact of different type of carnitines, namely L-carnitine (LC), acetyl-L-carnitine and propionyl-L-carnitine (PLC) on the mitochondrial toxicity induced by beta-amyloid peptide oligomers (AβO) in mature rat hippocampal neurons. We showed, for the first time, that carnitines prevent mitochondrial dysfunction and altered dynamics that are associated with cell death following exposure to AβO. Our data also suggest probable mechanistic differences in mitochondrial regulation exerted by distinct forms of carnitines.

Main Achievements

In the context of Huntington's disease (HD), we showed that SIRT3, a major regulator of mitochondrial acetylome, is neuroprotective in HD. Protein and enzymatic analysis revealed that increased SIRT3 is a signature in several HD models, including human HD brain, which is regulated by oxidative species. While loss of SIRT3 further aggravated the oxidative phenotype, antioxidant treatment regularized SIRT3 levels. SIRT3 overexpression promoted the antioxidant effect in cells expressing mutant HTT, leading to enhanced mitochondrial function and balanced dynamics. Decreased Fis1 and Drp1 accumulation in mitochondria induced by SIRT3 expression favoured mitochondrial elongation, while the SIRT3 activator ε-viniferin improved anterograde mitochondrial neurite transport, sustaining cell survival. Notably, SIRT3 fly-ortholog dSirt2 overexpression in HD flies ameliorated neurodegeneration and extended lifespan. These findings provide a link between oxidative stress and mitochondrial dysfunction hypotheses in HD and offer an opportunity for therapeutic development (Naia et al., *Free Radic. Biol. Med*., 2021).
Furthermore, we investigated the protective effects of pridopidine, a selective Sigma-1 receptor (S1R) agonist, on various mitochondrial functions in human and mouse HD models. S1R is a chaperone protein localized in mitochondria-associated endoplasmic reticulum (ER) membranes, a signaling platform that regulates Ca2+ signaling, reactive oxygen species (ROS) and mitochondrial fission. Pridopidine effects on mitochondrial dynamics were assessed in primary neurons from YAC128 HD mice. We observed that pridopidine prevents the disruption of mitochondria-ER contact sites and improves the co-localization of inositol 1,4,5-trisphosphate receptor (IP3R) and its chaperone S1R with mitochondria in YAC128 neurons, leading to increased mitochondrial activity, elongation, and motility. Increased mitochondrial respiration was also observed in YAC128 neurons and in pridopidine-treated HD human neural stem cells (hNSCs). ROS levels were assessed after oxidative insult or S1R knockdown in pridopidine-treated YAC128 neurons, HD hNSCs, and human HD lymphoblasts. All HD models showed increased ROS levels and deficient antioxidant response, which were efficiently rescued with pridopidine. Importantly, pridopidine treatment before H2O2-induced mitochondrial dysfunction and S1R presence were required for HD cytoprotection. YAC128 mice treated at early/pre-symptomatic age with pridopidine showed significant improvement in motor coordination, indicating a delay in symptom onset. Additionally, in vivo pridopidine treatment reduced mitochondrial ROS levels by normalizing mitochondrial complex activity. In conclusion, S1R-mediated enhancement of mitochondrial function contributed to the neuroprotective effects of pridopidine, providing insight into its mechanism of action and therapeutic potential (Naia et al., *Neurotherapeutics*, 2021).
In the context of Alzheimer's disease (AD), we investigated the impact of different forms of carnitines, namely L-carnitine (LC), acetyl-L-carnitine (ALC) and propionyl-L-carnitine (PLC) on mitochondrial toxicity induced by amyloid-beta peptide 1-42 oligomers (AβO; 1 μM) in mature rat hippocampal neurons. Our results indicate that 5 mM LC, ALC and PLC totally rescued the mitochondrial membrane potential and alleviated both the decrease in oxygen consumption rates and the increase in mitochondrial fragmentation induced by AβO. These compounds could also contribute to the prevention of neuronal death by apoptosis. Moreover, only ALC ameliorated AβO-evoked changes in mitochondrial movement by reducing the number of stationary mitochondria and promoting reversal mitochondrial movement. Data suggest that carnitines (LC, ALC and PLC) may act differentially to counteract changes in mitochondrial function and movement in neurons subjected to AβO, counteracting AD-related pathological phenotypes (Mota et al., *Arch Toxicol.*, 2021)



S1R agonist pridopidine restores multiple mitochondrial processes disrupted in HD cells (*see* Naia et al., Neurotherapeutics, 2021; doi: 10.1007/s13311-021-01022-9).

VISION DISEASES

Head: António Francisco Ambrósio
Objectives

Retinal degenerative diseases, namely diabetic retinopathy, glaucoma, age-related macular degeneration (AMD) and retinitis pigmentosa are our main research focus. The general goals are:
- to elucidate the molecular and cellular mechanisms underlying the pathophysiology of retinal degenerative diseases;
- to identify new potential drug targets and develop more efficient therapeutic strategies for the treatment of retinal diseases;
- to identify novel biomarkers of disease, disease progression and response to therapy.
- to identify innovative diagnosis methods.

We are particularly interested in clarifying how (micro)glia-mediated neuroinflammation, as well as the crosstalk between different retinal cell types, dissecting the role of extracellular vesicles and exosomes, contribute to retinal neural, vascular and epithelial dysfunction and degeneration and also neovascularization. The identification of molecular players, such as TRAP1, Ndr kinases, adenosine receptors, etc., with relevant roles in the pathophysiology of these diseases is a major goal.

We have also been exploring neuroprotective strategies based on the modulation of adenosine receptors with the aim of protecting retinal neural cells, and particularly retinal ganglion cells (RGCS). In a translational perspective, we aim to evaluate the efficacy of novel photosensitizers for photodynamic therapy in age-related macular degeneration. We have been also developing biodegradable intraocular implants and light sensitive nanoparticles for drug delivery systems. Moreover, we aim to identify tear fluid biomarkers for early detection and progression of diabetic retinopathy and also biomarkers based on texture analysis of optical coherence tomography (OCT) retinal image data for the diagnosis of diabetic retinopathy and Alzheimer's disease.

In AMD, in human studies, we aim to give insight into: 1) Retinal structure and function; 2) Genomics and metabolomics; 3) Lifestyle and genetics interplay in AMD onset and progression; 4) Drug safety and effectiveness; 5) Development of innovative approaches based on artificial intelligence to facilitate AMD diagnosis.

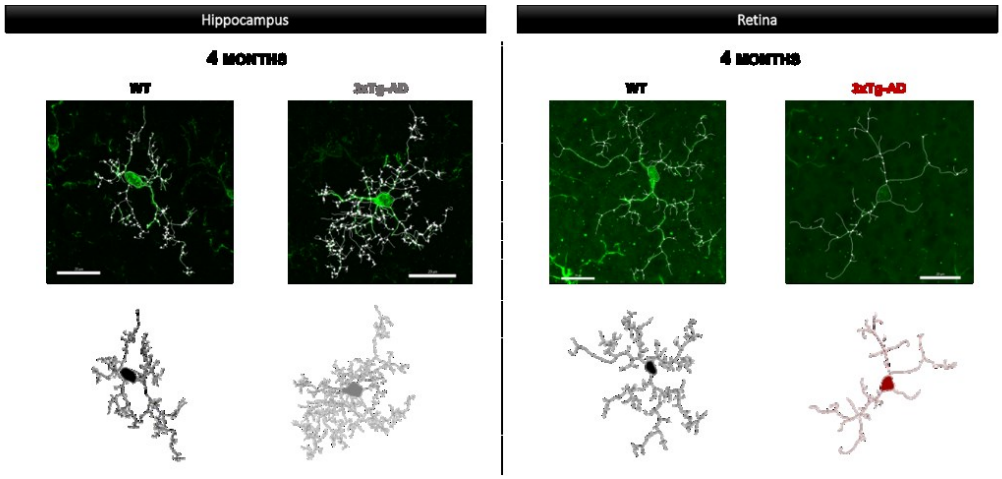


Figure 1 – Early morphological changes in microglial cells in the hippocampus and retina of an animal model of Alzheimer's disease (3xTg-AD).

BIOMARKERS IN NEUROPSYCHIATRIC DISORDERS: FROM MOLECULES TO DIAGNOSIS AND INTERVENTION

Head: Maria Isabel Santana

At the pre-clinical level, our main objective during this year were:

- To investigate the effect of psychostimulants on the Central Nervous System: Focus on Neuroinflammation and Blood-brain barrier (BBB) (dys)function
- Study brain and vision alterations in Attention Deficit/Hyperactivity Disorder (ADHD)
- Understand neurovascular and neuroinflammatory changes after traumatic brain injury and the protective effect of neuropeptide Y (NPY)
- To pinpoint the role of lifestyle including physical exercise on brain health
- To study the role of peripheral immunity in Parkinson disease
- To investigate if microglia, neuronal and vascular changes occur in parallel with increased vulnerability to stress-induced depressive behavior in both sexes.
- To evaluate the impact of prenatal stress on glucose homeostasis and peripheral metabolism of male and female offspring (chronic anxiety animal model).

Regarding clinical studies, during this year we have been particularly focused on:

- Developing non-invasive markers for neurological diseases, particularly blood biomarkers using Single Molecule Array (SiMoA) technology and ocular biomarkers using optic coherence tomography (OCT) and Eye-tracking
- Investigating longitudinal cognitive and multimodal biomarker trajectories in people with presymptomatic and symptomatic genetic Frontotemporal Dementia (FTD)
- Studying the role of cognitive and brain reserve in Social and Classic Cognition in Multiple Sclerosis (MS) patients.
- Evaluating cognitive changes over time in individuals with different patterns of cognitive function (dementia, delirium, delirium superimposed on dementia) who had been hospitalized due to systemic infections
- Investigating predictors of prognosis in acute ischemic stroke, including the influence of severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) infection.

Main Achievements

Results from the pre-clinical studies have shown that methamphetamine (METH) induces a neuroinflammatory response characterized by astrocytic morphological changes and increased TNF-α, iNOS and ICAM-1 protein levels. Additionally, brain edema and blood-brain barrier (BBB) disruption were identified as well as a significant decrease in vessel coverage by astrocytes after METH exposure. Regarding *in vitro* studies with astrocyte cultures, we further identified TNF-α as a key player in METH-induced cell swelling. Importantly, parthenolide (PTL, present in feverfew plant) prevented both animal and in vitro effects induced by METH. In conclusion, we provided important insights on brain dysfunction induced by METH, and we also suggest a new approach to counteract such negative effects.

We put forward that sex-specific differences in microglia plasticity induced by long-term stress exposure may anticipate differences in drug efficacy in the context of stress-induced anxiety or depression-related behaviors. We have also showed that chronic stress significantly alters the behavior and the morphology of microglia and neurons in a brain region- and sex-specific manner. In line with our previous works, we also showed that prenatal stress programs offspring peripheral metabolism in a sex-specific manner. This works highlights that each sex presents different vulnerabilities to psychiatric disorders and to metabolic disorders and may provide clues for the design of preventive strategies and early therapeutic intervention.

Regarding clinical studies in blood-biomarkers for neurodegenerative disease, we have highlighted the potential of serum neurofilament light chain (NFL) as a surrogate of cognitive decline in sporadic and familial FTD. In a data-driven model of a multicenter population of genetic FTD patients, NFL and neuronal pentraxin 2 (NPTX2) were identified as the earliest markers to

change with potential as candidate selection tools for pharmaceutical. Neuroimaging studies on genetic FTD have shown subcortical atrophy in mutation carriers prior to phenoconversion, with C9orf72 expansion carriers showing the earliest and most widespread changes. In a study of the spatial chronnectome in presymptomatic progranullin mutation carriers, a complex dynamic reorganization, including changes in both spatial and temporal aspects of brain network connectivity was found. Interestingly, coupling between functional connectivity and cognition was stronger in presymptomatic FTD mutation carriers than in non-carriers, and increased with proximity to the expected onset of disease, suggesting that the maintenance of functional network connectivity enables carriers to maintain cognitive performance despite progressive brain atrophy.

We have investigated static and dynamic ocular motor abnormalities in genetically confirmed Spinocerebellar Ataxia Type 3 (SCA3) and showed changes both in dynamic ocular motor and static parameters. In a OCT study aiming at assessing the relation between peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell layer (mGCL) atrophy and cognitive performance in early MS, no association with reduced pRNFL or mGCL thickness was found. Our studies on cognitive and brain reserve in MS have shown that higher education (a proxy to cognitive reserve) moderated the impact of subcortical grey matter (GM) atrophy on 'classic' cognitive status. Conversely, greater intracranial volume (a proxy to brain reserve) attenuated the impact of cortical GM atrophy on social cognition. We have also shown that patients with pediatric-onset MS (POMS) were more prone to develop impairment on classic cognitive domains than on social cognition, when compared with adult-onset MS patients. The interference of POMS with critical neurodevelopmental periods, specific for each cognitive domain, may explain different outcomes at adulthood on social and classic cognition.

We have conducted a transcranial color-coded sonography study in patients with large artery occlusion stroke of carotid circulation, who were submitted to endovascular therapy to identify predictors of intracranial hemorrhage (ICH). We identified the ratio between mean flow velocities (MFV) of the symptomatic middle cerebral artery (MCA) and MFV of the asymptomatic MCA (MCA-Ra) as an independent predictor of postinterventional ICH. We also investigated the impact of the apolipoprotein E (ApoE) alleles in the development of symptomatic ICH (sICH), but found no association between ApoE genotypes and sICH. In a multinational observational study on features of consecutive acute ischemic stroke, intracranial hemorrhage, and cerebral venous or sinus thrombosis among SARS-CoV-2–infected patients a considerably higher rate of large vessel occlusions, a much lower rate of small vessel occlusion and lacunar infarction, and a considerable number of young stroke when compared with the population studies before the pandemic was observed.

METABOLISM AGING AND DISEASE

COORDINATOR: PAULO OLIVEIRA

GENERAL OBJECTIVES

The MAD research line involves a multi-/inter-disciplinary study of metabolic and chronic diseases, with emphasis on those that are environment or aging-related, in an integrative approach from in vitro to animal models, human samples and patients. MAD combines strong synergies of expertise in cell metabolism and cardiovascular, hepatic, developmental, oncologic and brain diseases, with integrated and complementary biomarker and drug discovery, translational research, clinical practice, health economics, technology transfer, and public outreach. MAD integrates fundamental and translational scientists, clinicians and economists working together for a more holistic understanding of cause-effect relationships between lifestyles, (epi)genetic variability, organelle (dys)function, and metabolic flux alterations in aging and disease, with translational and value transfer potential. An impending perfect storm of aging, lifestyle, and genetic risk factors will generate a surge in metabolic and degenerative diseases, whose pathophysiologies involve complex intra- and inter-cellular mechanisms impacting multiple tissues and organs. The MAD research is currently to understand those same mechanisms.

MAIN ACHIEVEMENTS

The MAD area obtained important findings during 2021. For example, a lead mitochondria-targeted hydroxycinnamic acid derivative (AntiOXCIN4) prevented oxidative stress in several cell lines and reverted the metabolic phenotype found in skin fibroblasts from sporadic Parkinson Disease (PD) patients. We identified a possible mechanism of AntiOxCIN4 action contributing to a deeper understanding of how mitochondria-targeted antioxidants based on a polyphenol scaffold can be used as potential drug candidates for delaying PD progression. Also, the team identified that the altered secretory function of the adipocyte very early in life may be relevant in identifying early metabolic markers of disease that may inform on the increased risk for specific future comorbidities in this prepubertal children. Some of these alterations were concomitant with alterations in the DNA methylation patterns in the obese group, independent of the impaired insulin levels, which suggests altered epigenetic regulation which can be involved in the later development of metabolic diseases. We demonstrated that chronic exposure to dietary β-N-methylamino-L-alanine (BMAA) can trigger a chain of events that recapitulate the evolution of the PD pathology from the gut to the brain, which is consistent with 'gut-first' PD. In vivo BMAA administration depleted ileum levels of a group of bacteria that regulate gut mucosal immune homeostasis in mice leading to an increase in gut cardiomyocytes through an improvement in calcium handling. When researching oocyte aging, we demonstrate that there is a significant decrease in oocyte cytoplasmic volume after in vitro and in vivo aging. Additionally, the levels of H_2O_2 increased significantly after in vitro and in vivo aging and mitochondrial aggregation patterns were significantly altered. In contrast, no alterations were found regarding mitochondrial mass, distribution and activity. Regarding cancer biology, we detected an impairment of CD4+ Treg follicular-like cells in the regulation of antibody production by myeloma cells and in the immunosuppressive state in patients with multiple-myeloma and the presence of tumor-infiltrating lymphocytes in osteosarcoma microenvironment which allow to stratify patients and monitor therapy response. We published new epidemiological and trial evidence in palliative care in collaboration with colleagues from the Cicely Saunders Institute at King's College London, a worldwide leading research centre in the field, WHO Collaborating Centre for Palliative care, Policy and Rehabilitation. We reported the first worldwide projections of palliative care need, and RCT results showing a community-based short-term integrated palliative care intervention reduced symptom distress for older people with chronic noncancer conditions compared with usual care. We published the first output from an emerging work stream dedicated to promoting the implementation of palliative care in a primary care setting, with publication of results from focus groups with family doctors in Portugal about their role in palliative care. The

group has successfully launched an online survey to evaluate the impact of lockdown due to Covid-19 on the feeling of loneliness and deterioration of health status in the population (with a focus on elderly people). Finally, the group developed health economics research under four main research areas: health systems, value in heath, people in health, and health trajectories, contributing to analyse outcomes resulting from links between fundamental research in metabolic, environmental, genetic and aging-related diseases, good practices and technologies supporting living and active aging, and adoption of healthy lifestyles.

FUTURE PLANS

The covid-19 epidemic brought novel challenges in terms of lifestyle and aging-related diseases. The incidence of obesity, and associated chronic metabolic diseases is expected to increase in the next few years, associated to the presence of a still largely unknown long-covid syndrome and the potential to novel pandemics. The MAD area will continue to use its know-how, technologies and unique clinical translational potential to develop novel therapies for many of those diseases, as well as discovery new biomarkers that can quickly access disease staging, preferably in a lowly invasive manner. The MAD area also plans to increase its internationalization by multiple activities, including participating in EU-funding research networks.

Mitochondria, Metabolism and Disease

Paulo Oliveira (PhD, Group Leader)
Ana Isabel Duarte (PhD)
Anabela Rolo (PhD)
Carla Lopes (PhD)
Carlos Palmeira (PhD)
Elisabete Ferreiro (PhD)
José Teixeira (PhD)
Mª Carmen Alpoim (PhD)
Mª Teresa Oliveira (PhD)
Manuela Grazina (PhD)
Sandra Mota (PhD)
Susana P. Pereira (PhD)
Adriana Carvalho (PhD Student)
Ana Pedrosa (PhD Student)
Caroline Veloso (PhD Student)
Célia Gomes (PhD Student)
Cláudia Deus (PhD Student)
Gabriela Oliveira (PhD Student)
Gonçalo Afonso (PhD Student)
Luís Grilo (PhD Student)
Margarida Sobral (PhD Student)
Maria João Santos (PhD Student)
Pedro Afonso Valente (PhD student)
Ricardo Amorim (PhD Student)
Sónia Pinho (PhD Student)
Carolina Santos (MSc Student)
Henrique Tavares (MSc student)
Ivo Machado (MSc Student)
Juliana Esgueirão (MSc student)
Luiz F. Piochi (MSc student)
Rafael Silveira (MSc student)
Carina Magalhães (Grant Tech.)
Catarina Melim (Grant Tech.)
Debora Mena (Grant Tech.)
Daniel Silva (Grant Tech.)
Mariana Diniz (Grant Tech.)
Márcia Teixeira (Grant Tech.)
Sara Pego (Grant Tech.)
Vanessa Costa (Grant Tech.)
Marta Simões (Technician)
Lucile Bonneau (Volunteer)
Sara Martins (Volunteer)

Metabolic Control Group

John Jones (PhD, Group Leader)
Cristina Barosa (PhD)
Armindo Salvador (PhD)
Eugenia Carvalho (PhD)
Ermelindo Leal (PhD)

Ludgero Tavares (PhD)
Mª Cristina Oliveira (PhD)
Paula Laranjeira (PhD)
Aryane Pinho (PhD Student)
Diana Santos (PhD Student)
Jessica Silva (PhD Student)
Lilica Sanca (PhD Student)
Marija Petkovic (PhD Student)
Pedro Barbosa (PhD Student)
Alejandra Torres (Grant Technician)
Joao Gabriel Silva (Masters Student)
Luis Silva (Masters Student)
Ana Costa (Masters Student)
Fernando Cabral (Masters Student)
Joao Patricio (Masters Student)

Cell Signaling and Metabolism in Disease

Mª Teresa Cruz (PhD, Group Leader)
Ana Cristina Silva (PhD)
Ana Patrícia Marques (PhD)
Ana Raquel Esteves (PhD)
Armanda Santos (PhD)
Cláudia Pereira (PhD)
Cristina Carvalho (PhD)
Diana Silva (PhD)
Mário Pinto (PhD)
Mylene Carrascal (PhD)
Paula Moreira (PhD)
Rosa Resende (PhD)
Sandra M. Cardoso (PhD)
Sónia Correia (PhD)
Susana Cardoso (PhD)
Ana C. Pereira (PhD Student)
Ana Raquel Santos (PhD Student)
Daniel Santos (PhD Student)
Emanuel Candeias (PhD Student)
Gonçalo Brites (PhD Student)
Isabel Ferreira (PhD Student)
João Magalhães (PhD Student)
Patrícia Moreira (PhD Student)
Tânia Fernandes (PhD Student)
Adriana Tavares (MSc Student)
Ana Isabel Sebastião (PhD Student)
Daniela Mateus (PhD Student)
Daniel Ferreira (MSc)
Rita Lavrador (MSc Student)
Ana Isabel Jesus (PhD Student)
Ana Duarte (MSc Student)

Insulin Resistance and Diabetic Angiopathy

Flávio Reis (PhD, Goup Leader)
Raquel Seiça (MD,PhD)
Cristina Sena (PhD)
Paulo Matafome (PhD)
Hans Christian Eickhoff (MD,PhD)
Rui Alves (MD, PhD)
António Pires (MD,PhD)
Sónia Santos (PhD)
Patrícia Borges (PhD)
Sofia Viana (PhD)
Célia Cabral (PhD)
Adriana Roque (MD, PhD Student)
Liliana Letra (MD, PhD Student)
Fernanda Carrilho (MD, PhD Student)
Paula Martins (MD, PhD Student)
Gabriela Tavares (PhD Student)
Sara Nunes (PhD Student)
Tiago Rodrigues (PhD Student)
André Alves (Msc)
Carlota Nóbrega (Msc)
Inês Preguiça (Msc)
Adelaide Barbosa (Msc Student)
Cristina Uriarte (MD)
Miguel Albano (MD)
Pedro Gomes (MD)

Biology of Reproduction & Stem Cell

João Ramalho-Santos (PhD, Group Leader)
Ana Filipa Branco (PhD)
Ana Paula Sousa (PhD)
Ana Teresa A. Santos (MD, PhD)
Anabela Marisa Azul (PhD)
Paula Mota (PhD)
Renata Tavares (PhD)
Sandra Amaral (PhD)
Adriana Fontes (PhD Student)
Andreia Silva (PhD Student)
Bibiana Silva (PhD Student)
Maria Inês Alfaiate (PhD Student)
Maria Inês Sousa (PhD)
Maria Moreira Soares (PhD Student)
Rita Santos (PhD Student)
Rui Tavares (PhD Student)
Sandra Reis (PhD Student)
Sara Rebelo (PhD Student)
Alexandra Carvalho (Phd Student)
Alexandre Pires (PhD student)
Ana Ferreira (PhD student)

Ana Sofia Pais (PhD student)
Mª Inês Cristo (PhD student)
Ines Moniz (collaborator)
Rita Pacheco (collaborator)
Artur MArtins (Msc Student)
Ana Rita Oliveira (Msc Student)
Jennifer Duarte (Msc Student)
Juliana Simões (collaborator)

Molecular Mechanisms of Cardiovascular Diseases

Henrique Girão (PhD, Group Leader)
Carla Marques (PhD)
Elisabete Jorge (MD, PhD)
Gonçalo Coutinho (PhD)
Lino Gonçalves (PhD)
Mª Margarida Gonçalo(PhD)
Mónica Zuzarte (PhD)
Natália António (PhD)
Nuno Coutinho (PhD)
Pedro Antunes (PhD)
Rogério Teixeira (PhD)
Rui Baptista (PhD)
Steve Catarino (PhD)
Tânia Marques (PhD)
Cátia Ferreira (MD)
Joana Silva (MD)
Daniela Almeida (PhD Student)
Jorge Silva (PhD Student)
Teresa Rodrigues (PhD Student)
Maria V.-Cardoso (PhD Student)
Luís Leite (collaborator)
Beatriz Cristóvao (collaborator)

Microbiomes, Metabolism and Omics

Conceição Egas (PhD, Group Leader)
Daniel Martins (PhD Student)
Nadine dos Santos (PhD Student)
Raquel Varandas (PhD Student)
Cristina Barroso (M.Sc., Sup. Technic)
Luciana Pinto (Ph.D, Sup. Technic)
Diogo Pinho (PhD Student)

Human Genome Variation and Environment in Health and Disease

Isabel Marques Carreira, PhD (Group Leader)

Carolino Monteiro (PhD)
Eunice Matoso (PhD)
Fernando Regateiro (MD PhD)
Francisco Corte-Real (MD PhD)
Henriqueta Breda (MD PhD)
Ilda Ribeiro (PhD)
Isabel Poiares Batista (MD PhD)
Joana Barbosa de Melo (PhD)
Jorge M Saraiva (MD PhD)
Maria José Julião (MD)
Mário Laço (MD, PhD)
Sofia Maia (MD, PhD)
André Lázaro (MD, PhD Students)
Daniela Santos Silva (MD, PhD Students)
Celeste Alcobia (MD, PhD Students)
Elisabete Resende (MD, PhD Students)
Francisco Marques (MD, PhD Students)
Inês Santos (MSc, PhD Students)
José Carlo Cardoso (MD, PhD Students)
Joana Ribeiro (MD, PhD Students)
Leonor Barroso (MD, PhD Students)
Tony Rolo (MD, PhD Students)

Healthy Living and Active Ageing

João Malva (PhD, Group Leader)
Ana Todo Bom (PhD)
Anabela Mota Pinto (PhD)
Bárbara Silva (PhD)
Carlos R. Cordeiro (PhD)
Frederico Regateiro (PhD)
Manuel Veríssimo (PhD)
Ramon Raposo (PhD)
Ricardo Leão (PhD)
Manuel Santos (MD)
Hélder Esperto (PhD Student)

Health, Management and Economics

Pedro Ferreira (PhD, Group Leader)
Aida Isabel Tavares (PhD)
Alexandre Rodrigues (PhD)
Alexandre Gomes da Silva (PhD)
Ana Patrícia Antunes (PhD)
Antonio Cruz Ferreira (PhD)
Augusta Silveira (PhD)
Bárbara Antunes (PhD)
Carlota Quintal (PhD)
Elsa Melo (PhD)
Fernanda Daniel (PhD)

Ilda Massano Cardoso (PhD)
Isabel Lopes Silva (PhD)
Lara Ferreira (PhD)
Luís Cavalheiro (PhD)
Luis Pereira (PhD)
Luiz Miguel Santiago (PhD)
Mª Carminda Morais (PhD)
Mª Teresa Sequeira (PhD)
Marília Dourado (PhD)
Ricardo Rodrigues (PhD)
Rui Pimenta (PhD)
Rui Gonçalves (PhD)
Rui Cruz (PhD)
Sandra Oliveira (PhD)
Sonia Guadalupe (PhD)
Teresa Carla Oliveira (PhD)
Vânia Gonçalves (PhD)
Vitor Raposo (PhD)

MITOCHONDRIA, METABOLISM AND DISEASE

Head: Paulo Oliveira

Objectives

Mitochondria play a critical role in energy production, regulation of cell death, redox and calcium homeostasis, and intermediate metabolism. Our group's overarching objective is to identify alterations in mitochondrial metabolism, redox signaling, and stress responses associated with chemical toxicology and the pathophysiology of aging, lifestyle, and genetic diseases. The development of mitochondria-directed therapeutic agents are among the group objectives. Specifically, the group focuses on various research lines:

1. **Mitochondrial role in aging and lifestyle-related diseases**: In this context, we identify mitochondrial dysfunction in different conditions that are related to aging or incorrect lifestyles, including nonalcoholic fatty liver disease, diabetes, cardiovascular disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and cancer. We investigate how mitochondrial protective signaling pathways, metabolic remodeling, and oxidative stress are part of the pathophysiology of different pathologies. We also research non- or lowly invasive cell models and respective optimized culture conditions, which can serve as cellular proxies of the body's metabolic status or represent a platform to test new pharmacological interventions. We investigate mechanisms of drug-induced mitochondrial dysfunction caused by different xenobiotics, including drug-induced injury (e.g., anthracyclines), environmental contaminants, and nanoparticles, and the development of high-throughput methods to investigate mitochondrial function in the context of drug development and toxicology.

2. **Mitochondrial bigenomics and theranostics**: We use biomolecular genetics to support functional genomics (e.g. exome, mitochondrial DNA (mtDNA) pathogenic variations/rearrangements by NGS). Hence, functional studies for pathogenicity study of novel mutations of mitochondrial relevance in nuclear and mtDNA are being developed. We aim to identify genetic alterations and copy number variations defining metabolic profiles or targeting depending on genetics in the scope of theranostics. Genomic and functional research is complemented by wellness biomarkers research, namely the effects on wellbeing state upon social interfaces in the clinical context, supporting efforts in precision medicine.

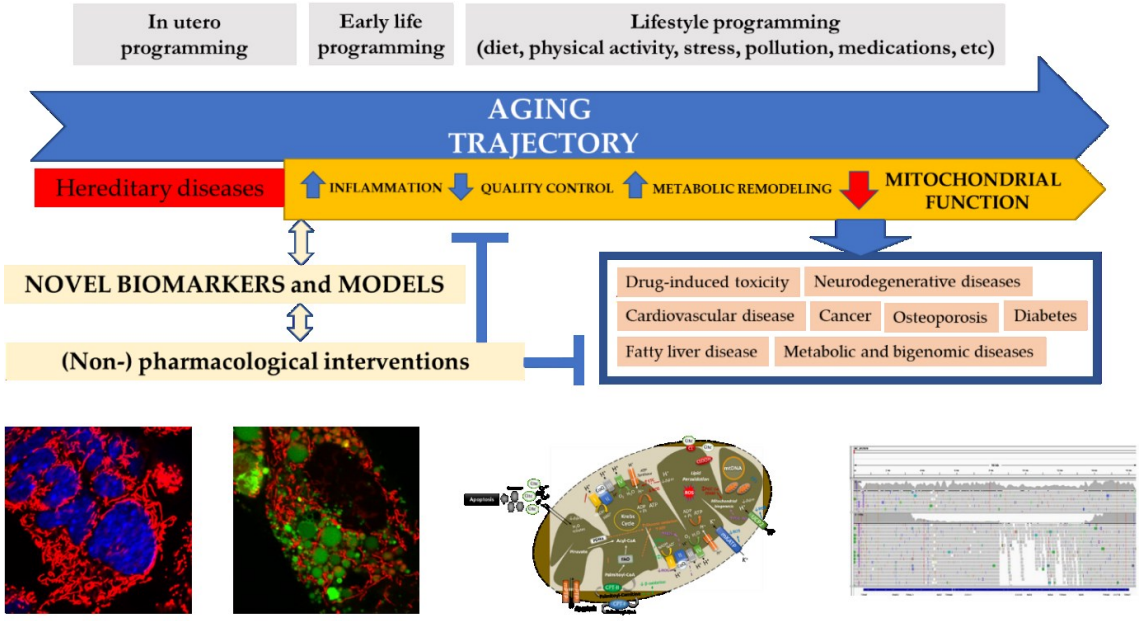
3. **Mitochondria-targeted therapeutics:** As a follow-up to fundamental discoveries in the mechanisms and consequences of mitochondrial dysfunction, we investigate intrinsic, pharmacological, or non-pharmacological (exercise or diet) regulation of mitochondrial biogenesis/metabolism and quality control as a strategy to reduce organ injury during disease or chemical toxicity. We validate novel mitochondrial-directed antioxidants based on dietary components in models for human diseases (cardiovascular/hepatic), phytoestrogens, and new pharmacological conditioning strategies, resulting in the reduction of morbidity and mortality of liver resection surgery. Another objective is to develop specific therapies for cancer stem cells based on their specific metabolic and mitochondrial phenotype.

4. **In utero and early life programming of metabolic and immune fitness**: Our main objective is to understand how in utero or early life cues program metabolic and immune fitness during life. We investigate how metabolic diseases in adult life are already primed in utero by external cues, including maternal under- and over-nutrition. Another objective is to explore how immune cells sense dietary cues and how such signals are integrated with their development and metabolism in the context of cancer and immune defense. One of our aims is to elucidate how micronutrients

control innate-like T cell development and metabolism by exploring novel dietary-immune cell signaling axes relevant to the intestinal immune defense in early life.

Main Achievements

- A lead mitochondria-targeted hydroxycinnamic acid derivative (AntiOXCIN4) prevented oxidative stress in several cell lines and reverted the metabolic phenotype found in skin fibroblasts from sporadic Parkinson Disease (PD) patients. We identified a possible mechanism of AntiOxCIN4 action contributing to a deeper understanding of how mitochondria-targeted antioxidants based on a polyphenol scaffold can be used as potential drug candidates for delaying PD progression.
- We used an exploratory data analysis to investigate time-dependent cellular and mitochondrial effects of different supra-physiological fatty acids (FA) overload strategies, in the presence or absence of fructose (F), on human hepatoma-derived HepG2 cells. Unsupervised learning algorithms created homogeneous and cohesive clusters, with a clear separation between PA and FFA groups to identify a minimal subset of critical mitochondrial markers to attain a feasible model for high throughput screening of possible therapeutic agents.
- The role of mitochondria during fetal development on later-life cardiac dysfunction caused by maternal nutrient reduction (MNR) remains unexplored. We identified that MNR disruption of fetal cardiac mitochondrial fitness likely contributes to the documented developmental programming of adult cardiac dysfunction, indicating a programmed mitochondrial inability to deliver sufficient energy to cardiac tissues as a chronic mechanism for later-life heart failure.
-We optimized and characterized a short (3-day) retinoic acid-based protocol to differentiate the SH-SY5Y cell line into a neuronal-like phenotype. This treatment was associated with p21-linked cell cycle arrest and an increase in cell mass and area, possibly associated with the development of neurite-like extensions. Even though differentiated cells did not have a fully mature/differentiated neuronal phenotype, this rapid protocol can be used to study neurotoxicity processes, mitochondrial dynamics, and bioenergetic impairment.
- We developed a novel quantitative analysis of mitochondria trajectories based on innovative movement descriptors, including straightness, efficiency, anisotropy, and kurtosis using biological data from differentiated SH-SY5Y cells treated with the mitochondrial toxicants 6-hydroxydopamine and rotenone. This innovative analysis provides insights into mitochondrial movement characteristics and can be a consistent and sensitive method to detect alterations in mitochondrial trafficking occurring in the earliest time points of neurodegeneration.
- We showed that retinoic acid (RA) signals regulate natural TCRαβ IEL development and RA-regulated intestinal natural intraepithelial lymphocytes (IELs) are critical for gut protection against pathogen invasion. Natural TCRαβ IEL precursors (IELp) display elevated RA receptors and are responsive to those RA signals. Genetically thymocyte-targeted disruption of RA signalling impaired thymic IELp development, resulted in the lack of natural TCRαβ IEL in the intestine and led to pathogen infection susceptibility at early life. Diet-derived retinoids control natural TCRαβ IELs development and RA-regulated natural TCRαβ IELs are critical to control bacterial invasion after birth.
- We performed a study that included an innovative pharmacogenetic approach featuring zonisamide, metabolized by CYP2C19, to verify if refractory epileptic patients exhibit distinct zonisamide plasma concentrations due to their genetic-dependent predicted metabolic phenotype. A significant association was observed between zonisamide dose and the predicted metabolic profile of extensive metabolizers. This supports the impact of both genetic and environmental factors in plasma concentration and prescribed dose of zonisamide and, consequently, its effectiveness/safety.


In utero programming
Early life programming
Lifestyle programming (diet, physical activity, stress, pollution, medications, etc)
AGING TRAJECTORY
Hereditary diseases
INFLAMMATION
QUALITY CONTROL
METABOLIC REMODELING
MITOCHONDRIAL FUNCTION
NOVEL BIOMARKERS and MODELS
(Non-) pharmacological interventions
Drug-induced toxicity
Neurodegenerative diseases
Cardiovascular disease
Cancer
Osteoporosis
Diabetes
Fatty liver disease
Metabolic and bigenomic diseases

METABOLIC CONTROL

Head: John Grifith Jones

Objectives

Developing integrated analysis of *de novo* lipogenesis and pentose phosphate pathway activity in cells and tissues. In hepatocytes, the pentose phosphate pathway (PPP) is an important generator of NADPH for *de novo* lipogenesis (DNL) and for the maintenance of reduced glutathione in antioxidant defense. The development of non-alcoholic fatty liver disease (NAFLD) secondary to high sugar and/or high fat intake is characterized by elevated DNL rates and increased oxidative stress. It is not known to what extent PPP fluxes are modified in these settings and to what degree they are coupled to DNL activity. We are developing stable-isotope tracer methods that provide information on both DNL and PPP fluxes in various settings including cell cultures and *in situ* liver.

With the goal of enhancing early diagnosis of subjects at risk for diabetes, we have wanted to examine systemic and local factors that are altered in obesity and diabetes and identify dysfunctional pathways, including insulin signaling, oxidative stress, and mitochondrial function in cells and tissues, early in life. Within this context, I am interested in how mitochondrial function and reactive oxygen species (ROS) may contribute to metabolic dysfunction locally in tissues and cells, starting early in life. Building on this work, I have begun to investigate whether thiols and ROS could be used to identify metabolic dysregulation locally in tissues or even in circulation, and whether local tissue dysregulation can be picked up by measuring circulating markers.

Developing an improved assay for drug passive permeation. Predicting the permeability of drugs across membranes *in vivo* is crucial for drug development. Permeability coefficients obtained by following solute equilibration between two membrane-separated compartments *in vitro* are valuable for this goal. While most of these methods rely on molecular properties rarely found in drugs, the pH variation assay can be applied to ionic or ionizable substances, which most drugs are. However, current implementations of this assay require expensive equipment and often yield questionable results. We seek to address these shortcomings to develop a reliable and affordable medium-throughput permeation assay.

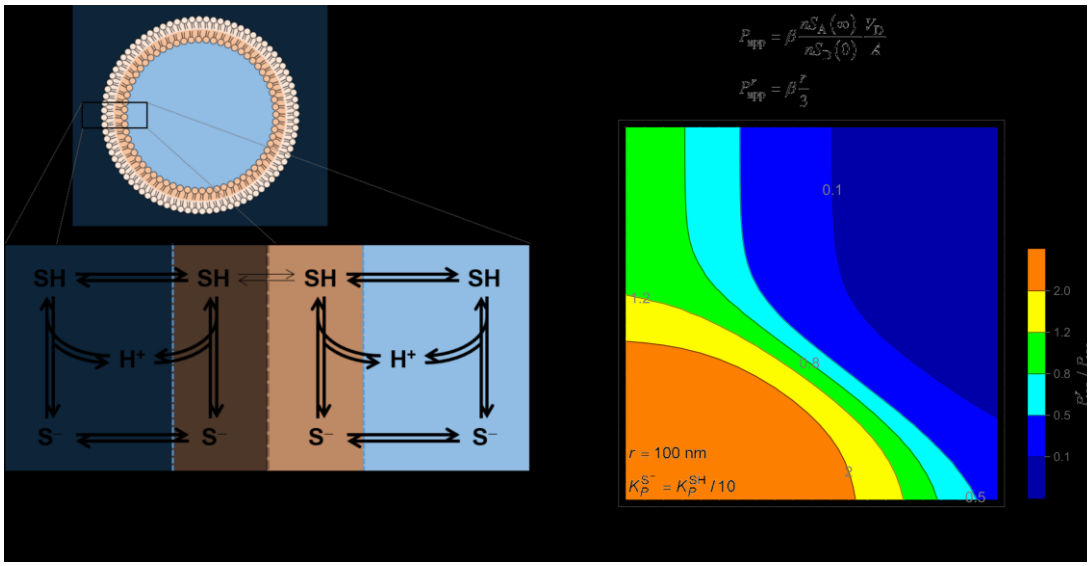
Main Achievements

With regard to Objective a), we developed a new ^{13}C NMR isotopomer method for quantifying overall *de novo* lipogenesis (DNL) fluxes, and for determining the fractional contribution of exogenous glucose carbons to the DNL precursor pool in cells cultured with [U-^{13}C] glucose (doi: 10.1002/nbm.4648). With this advance, we will be able to integrate DNL measurements with our recently developed method for measuring pentose phosphate pathway (PPP) fluxes from the same [U-^{13}C] glucose precursor. We are in the process of applying this approach to study DNL and PPP fluxes in cell culture models of hepatocellular carcinoma. In whole animal models of diet-induced NAFLD, we applied a similar approach to quantify and compare DNL and PPP fluxes in mice fed high sugar and high sugar plus high fat diets. While DNL activities were similar, PPP fluxes were significantly higher in mice fed the more obesogenic high fat + high sugar diet. This may reflect a higher NADPH demand for dealing with a higher degree of oxidative stress following high fat + high sugar feeding.

For objective b), peripheral blood was collected from prepubertal children, and the plasma metabolites were quantified by HPLC. The cohort was stratified by BMI z-scores and HOMA-IR indices into healthy lean (HL), healthy obese (HO), and unhealthy obese (UHO). Fasting insulin

levels were higher in the HO group compared to the HL, while the UHO had the highest. All groups presented normal fasting glycemia. High-density lipoprotein (HDL) was lower while triglycerides and lactate levels were higher in the UHO compared to HO subjects. S- adenosylhomocysteine (SAH) and total homocysteine levels were increased in the HO group compared to HL. Additionally, glutathione metabolism was also altered. Free cystine and oxidized glutathione (GSSG) were increased in the HO as compared to HL subjects. Importantly, the adipocyte secretory function was already compromised at this young age. Elevated circulating leptin and decreased adiponectin levels were observed in the UHO as compared to the HO subjects. Some of these alterations were concomitant with alterations in the DNA methylation patterns in the obese group, independent of the impaired insulin levels. In conclusion, our study informs on novel and important metabolic alterations in the early stages of obesity. Moreover, the altered secretory function of the adipocyte very early in life may be relevant in identifying early metabolic markers of disease that may inform on the increased risk for specific future comorbidities in this population.

With regard to Objective c), we addressed the reasons why current versions of the pH variation assay sometimes yield inaccurate results we developed a kinetic model for solute permeation through lipid membrane barriers that includes the two membrane leaflets as compartments in a four-compartment model. Analysis of this model showed that the often-used expression $P_{app} = \beta \times r/3$ (with β the characteristic constant for solute permeation and r the liposome radius) is inapplicable to very large or very small vesicles, to moderately or highly lipophilic solutes, or when the development of a significant pH gradient opposes the solute's flux. We established useful relationships that overcome these limitations and allow predicting permeability in compartmentalised in vitro or in vivo systems with specific properties. Finally, from the parameters for the interaction of the solute with the membrane barrier, we defined an intrinsic permeability coefficient that facilitates quantitative comparisons between solutes. (doi: 10.3390/MEMBRANES12030254)



CELL SIGNALING AND METABOLISM IN DISEASES

Head: Teresa Cruz

Objectives

Our Group aims:
1) to investigate the disturbance of the endoplasmic reticulum (ER) stress response and of ER-mitochondria contacts in neurodegenerative disorders such as Alzheimer disease (AD) and in psychiatric illnesses, namely bipolar disorder and schizophrenia;
2) the therapeutic potential of compounds obtained from natural resources is another goal of our research group;
3) to develop disease-modifying treatments targeting the amyloid pathology observed in AD and to identify non-canonical markers of AD in peripheral tissues;
4) to investigate the mitochondrial-mediated signaling in brain diseases, particularly in AD and diabetes-associated neurodegeneration;
5) to elucidate the preventive and therapeutic potential of pharmacological and non-pharmacological strategies targeting mitochondria;
6) to understand how mitochondrial damage-associated molecular patterns (DAMPs) trigger sterile pro-inflammatory responses that could drive schizophrenia and Parkinson disease (PD);
7) to investigate the role of environmental bacterial infection on gut-first PD etiology;
8) to study the contribution of immune system cells signaling on the gut-brain axis in PD;
9) to study the immunobiology of innate immune cells, aiming to: i) develop immunotherapy strategies based on dendritic cells for oncology; ii) to evaluate the effect of new Nrf2 activating molecules with anti-inflammatory properties in AD; iii) to develop new strategies for inflammatory skin diseases iv) to develop non-animal approaches for immunotoxicity risk assessment.

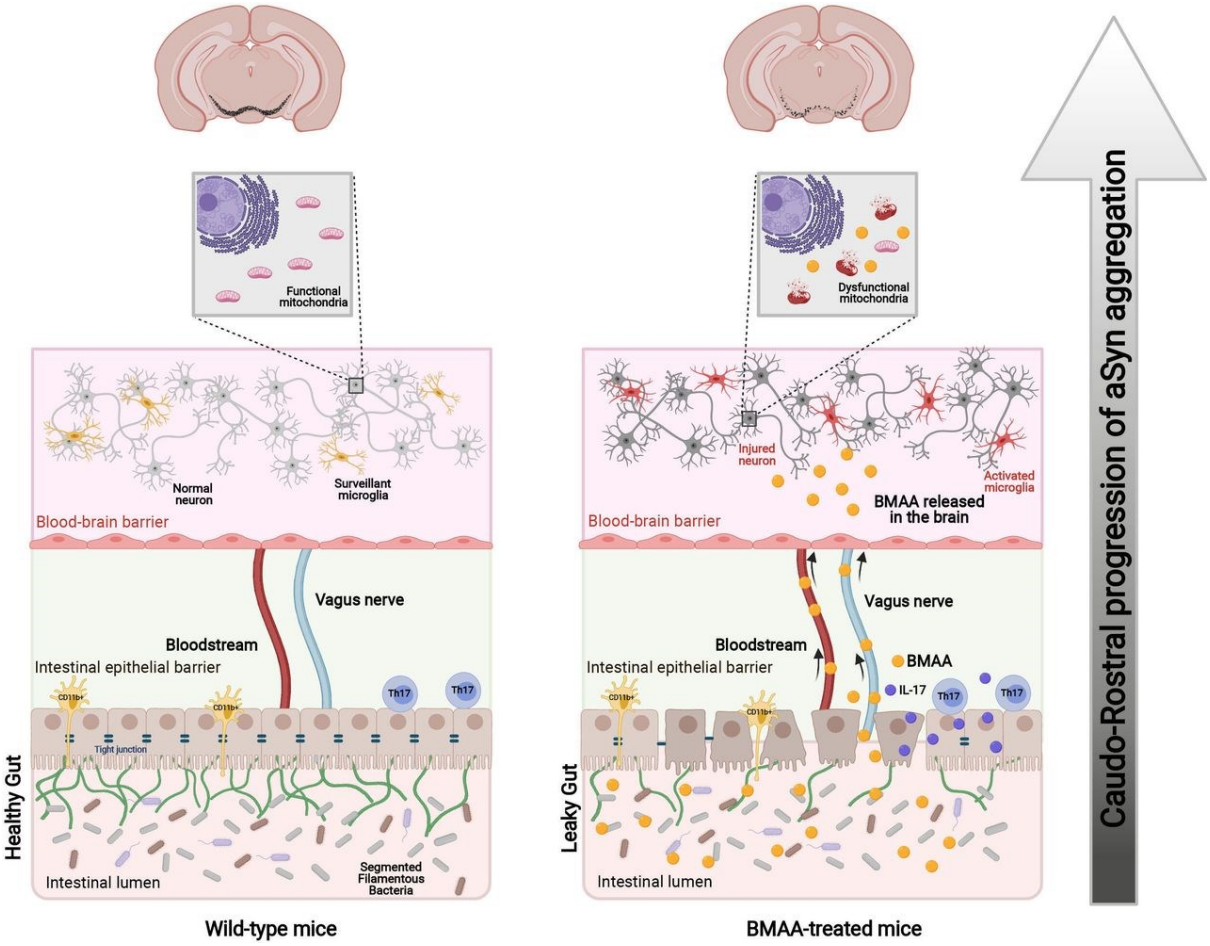
Main Achievements
1) We demonstrated that chronic exposure to dietary BMAA can trigger a chain of events that recapitulate the evolution of the PD pathology from the gut to the brain, which is consistent with 'gut-first' PD. In vivo BMAA administration depleted ileum levels of a group of bacteria that regulate gut mucosal immune homeostasis in mice leading to an increase in gut inflammation, disruption of gut barrier integrity and gut alpha-synuclein (aSyn) aggregation. BMAA specifically targeted mesencephalic mitochondria inducing their fragmentation and cardiolipin exposure, which in turn activated innate immune responses such as NOD-like receptor 3 activation and aSyn aggregation. Gut inflammation potentiated blood-brain barrier permeability and neuroinflammation, which culminated in nigrostriatal neuronal damage and PD-like motor dysfunction.
2) We identified new molecules targeting the Nrf2 signaling pathway with beneficial effects in in vitro and in vivo models of AD. Specifically, isoeugenol was able to activate the transcription factor Nrf2 and decreased the levels of Aβ peptides in N2a-APPswe cells, concomitantly evoking an anti-inflammatory programme in microglial cells. Intranasal administration of isoeugenol also decreased the levels of cerebral Aβ and increased the expression of HMOX1 in the brain of APP/PS1 transgenic mice.
3) We observed that intermittent hypoxic conditioning rescues cognition and mitochondrial bioenergetic profile in a familial mouse model of AD (3xTg-AD). Using the icvSTZ rat model of sporadic AD, we observed that hypoxic preconditioning (HP) prevented memory and learning deficits and tau pathology and attenuated reactive astrogliosis induced by icvSTZ. More, HP abrogated the icvSTZ-related impaired energy metabolism and oxidative damage. Preconditioned hippocampal mitochondria displayed an enhanced mitochondrial respiration, which resulted from a coordinated interaction between mitochondrial biogenesis and fusion-fission events.

Overall, these observations demonstrate the potential preventive and therapeutic potential of hypoxic (pre)conditioning against AD.
4) We showed that Mitochondria-Associated Membranes (MAMs) are affected in an in vitro model of AD, with significant alterations in MAMs components as well as in activity, namely in ER-mitochondria Ca2+ transfer. Furthermore, alterations in these ER-mitochondria contacts were correlated with mitochondrial dysfunction and activation of stress response mechanisms.
5) We obtained evidence demonstrating that ER-mitochondria communication is involved in ER stress-induced NLRP3 inflammasome activation in human innate immune cells, and found a correlation between perturbations in the ER stress response and sterile inflammation in monocytes from patients with bipolar disorder (BD). Furthermore, ER-mitochondria contacts were found affected in fibroblasts obtained from BD patients and to be associated with mitochondrial alterations, namely with impairment of the electron transport chain.
6) We observed that recurrent hypoglycemia up-regulates the activity of mitochondrial hexokinase and Krebs cycle enzymes and the protein levels of TFAM. Both chronic hyperglycemia and recurrent hypoglycemia increased NRF2 protein content and induced divergent effects in mitochondrial dynamics. These findings provide experimental evidence that recurrent hypoglycemia, in the context of chronic hyperglycemia, has the capacity to evoke coordinated adaptive responses in the brain cortex that will ultimately contribute to sustaining brain cell health.
7) We optimized the cell culture conditions to be used in the production of dendritic cells (DCs) for clinical application in cancer immunotherapy and developed proprietary DCs differentiation and maturation protocols (which are ongoing intellectual property protection) that allow the obtention of DCs with superior immunostimulatory properties in comparison to current DCs-based products commonly used in clinical trials.
8) Our findings provide scientific support to the forest bioeconomy demonstrating that the forest biomass is a valuable source of bioactive extracts.

Main sources of funding
O Eixo microbioma-miRNAs na Doença de Parkinson: implicações da resposta inflamatória mediada pela mitocôndria. (2022-2023) EXPL/MED-NEU/1515/2021. (€50.000,00) (PI: Ana Raquel Esteves)
Zfra 1-31: an early intervention in T2D-associated neurodegeneration (2022). Project EXPL/MED-FSL/0033/2021, FCT (€50.000,00) (PI: Cristina Carvalho; CoPI: Susana Cardoso)
Zfra 1-31 peptide as a new candidate to fight type 2 diabetes-associated brain damage: a pilot study (2022) European Association for Clinical Research (€10.000,00) (PI: Cristina Carvalho; Mentor Paula Moreira)
O Eixo Intestino-Sistema Imune-Cérebro na Doença de Parkinson (2021-2023) Project PTDC/MED-NEU/3644/2020, FCT (€248.992,50) (PI: Sandra Morais Cardoso)
The ups and downs of cellular stress: the "MAM hypothesis" for Bipolar disorder pathophysiology (2018-2022) Project POCI-01-0145-FEDER-028214, FCT (€235.872,00) (PI: Cláudia Pereira, CoPI: Nuno Madeira)
The role of quality control mechanisms in the loss of proteostasis in age-dependent neurodegenerative disorders. (2018-2021) Projeto POCI-01-0145-FEDER-030712, FCT. (226,089 Euros) (PI: Ana Raquel Esteves; CoPI: Sandra Morais Cardoso)
InPaCTus – Innovative Products and Technologies. "Added-value extracts from forestry biomass" sub-project, Nacional Agency of Innovation (ANI) (€65.000,00 + PhD student grant during 4 years) (PI at UC: Cláudia Pereira)
Skin allergens: molecules with an improbable therapeutic application for Alzheimer's disease (2018-2022) Project POCI-01-0145-FEDER-029369, FCT (€235.872,00) (PI: Maria Teresa Cruz, CoPI: Cláudia Pereira)
TecniCOV: Development of rapid tests for monitoring Sars-Cov2 antibodies in serum and saliva (2020-2021) Project POCI-01-02B7-FEDER-069745 (€345.230,50) (PI: Goreti Sales)
Development of a Defined Approach for Respiratory Sensitization Hazard Assessment (2021-2022) by Colgate-Palmolive Grants for Alternative Research (€50.000,00) (PI: Isabel Ferreira)

PulManCar: Microparticles design for active compounds pulmonary delivery using insulin as model. Project POCI-01-0145-FEDER-029560 (2018-2022) (€20.125,00) (PI: Cáudia Passos UA, Maria Teresa Cruz PI at CNC)
Giardia lamblia extracellular vesicles in host cell immunomodulation: potential therapeutic application of Giardia EVs in intestinal inflammation (2018-2021) Project PTDC/SAU-PAR/31506/2017 (2018-2022) (€238.721,61) (PI: Maria Céu Sousa, CoPI: Maria Teresa Cruz)

3. Image that illustrates the research of the group (Tiff; Jpg format)



Schematic diagram of 'Gut-first' PD. Environmental microbial toxins lead to the erosion of segmented filamentous bacteria (SFB, green) in the ileum, which potentiates a Th17 proinflammatory response and the loss of intestinal barrier integrity. These events in the gut allow the progression of the disease into the brain either through the blood or the vagus nerve. Microbial toxins target mesencephalic mitochondria and activate neuronal innate immunity followed by aSyn expression, microglial activation and ultimately PD. aSyn, alpha-synuclein; BMAA, β-N-methylamino-L-alanine; IL, interleukin; PD, Parkinson's disease; Th17, T helper 17 (Esteves et al., 2021). (This image was created at BioRender.com)

INSULIN RESISTANCE AND DIABETIC ANGIOPATHY

Head: Flávio Reis

During the reporting period the objectives of the group were those defined for this strategic planning 2020-2023. The group aims to understand the mechanisms underlying the metabolic dysregulation associated with obesity, prediabetes, diabetes and its major vascular complications, in a translational approach from the molecular level to human application. The team is composed by researchers and clinicians, in a truly inter-disciplinary approach to investigate mechanisms, biomarkers and therapeutics and nutraceutical interventions for cardiometabolic and cardiorenal diseases.
Specifically, our main objectives were:
- To understand the role played by perivascular adipose tissue in vascular disorders associated with obesity, insulin resistance and diabetes;
- To dissect the mechanisms of adipose tissue dysfunction and hepatic insulin resistance in obesity, and particularly the role of AGEs and loss of nutrient-sensing, in the adult life and during critical phases of development. To identify new molecular and imaging biomarkers of early diabetic complications and to characterize new neuroendocrine mechanisms which could be therapeutic targets. To study new dietary strategies able to modulate gut nutrient-sensing mechanisms and reduce glycation;
- To evaluate the autonomic gastrointestinal dysfunction in models of metabolic diseases and complications;
- To assess the role of gut microbiota dysbiosis in cardiometabolic disorders, namely during the progression from prediabetes to diabetes and to vascular complications. To dissect the crosstalk between microbiota dysbiosis, insulin resistance, inflammation and immune system deregulation;
- To evaluate the impact of therapeutic and nutraceutical strategies (including prebiotic and probiotic approaches) for the prevention, amelioration or treatment of metabolic and vascular impairment associated with obesity, metabolic syndrome, prediabetes, diabetes and vascular complications;
- To identify phytochemicals with bioactive properties and to develop plant-based health solutions.

Main Achievements:

- Dopamine directly regulates glucose uptake and lipid catabolism in WAT, liver and skeletal muscle, with the distinct involvement of its receptors (Front Pharmacol. 2021; doi: 10.3389/fphar.2021.713418).
- D1 dopamine receptor was downregulated in patients with obesity and insulin resistance and this was correlated with the lower expression of genes involved in metabolism and redox defences. Bromocriptine, an FDA approved drug for the treatment of type 2 diabetes, remodels peripheral dopaminergic signalling type 2 diabetic obese rats, including increased D1R and TH levels, and restores insulin sensitivity and catabolic activity in WAT. (Mol Metab. 2021; doi: 10.1016/j.molmet.2021.101241).
- Omentin-1 ameliorates endothelial dysfunction in T2D and presents therapeutic potential for the treatment of vascular complications associated with T2DM (Free Radic Biol Med. 2021; doi: 10.1016/j.freeradbiomed.2020.10.021).
- Multiparticulate systems of ezetimibe micellar system and atorvastatin solid dispersion reduce high lipid levels and hepatic steatosis in diabetic rats fed a high-fat diet (Pharmaceutics. 2021; doi: 10.3390/pharmaceutics13030421).

- Luteolin improves perivascular adipose tissue profile and vascular dysfunction in goto-kakizaki rats (Int J Mol Sci. 2021; doi: 10.3390/ijms222413671).
- Sugars naturally present in fruit juices and added sugars have distinct effects in energy balance regulation, impairing oxidative stress, glycation and glucose metabolism in an animal model of type 2 diabetes. (Nutrients. 2021; doi: 10.3390/nu13092956).
- Blueberry counteracts prediabetes in a hypercaloric diet-induced rat model and recues hepatic mitochondrial bioenergetics (Nutrients. 2021; doi: 10.3390/nu13124192).
- Acrocomia Acculeata has a therapeutic role in protecting from vascular complications of diabetes due to its glucose-lowering and anti-oxidant effects. (Nutrients. 2021; doi: 10.3390/nu13082856).

Funding:

- *LOLit – Low Literacy at Play. European Union - ERASMUS + Programme (2021-1-NL01-KA220-ADU-000033664). 240k€. 2022-2023. PI at UC: Flávio Reis.*
- Integrating multimodal imaging with metabolomics and oxidative stress outcomes in diabetes. 2019-2021. Funding source: European Foundation for the Study of Diabetes (EFSD)/Sanofi. Group Researcher Participant: Paulo Matafome. Amount: 100 K€.
- MED4Youth – Mediterranean enriched diet for tackling youth obesity. 2019-2021. Funding source: PRIMA programme (Horizon 2020). Total amount: 1,443 K€ (117 K€ to Group Researcher Participant: Paulo Matafome).
- FRUITIFY - Use of blueberry juice as a nutraceutical strategy targeting gut dysbiosis to prevent the progression from prediabetes to diabetes. 2018-2022. Funding source: FCT | COMPETE | FEDER | Portugal 2020. Ref: PTDC/SAU-NUT/31712/2017 | POCI-01-0145-FEDER-031712. Group Researcher PI: Flávio Reis. Amount: 239 K€.
- Modelação de Angiogénese na Diabetes Mellitus tipo 2-integrando abordagens experimentais e teóricas. Funding Source: FCT, Angio_Dia, POCI-01-0145-FEDER-031743. Total amount: 239,824€. Group Researcher Participant: Paulo Matafome.
- CAPEOSBAC - Tailored microenCAPsulation technology for Extreme Oxygen-Sensitive BACteria with beneficial effects on gut microbiota: production, stability and functionality enhancements in various carriers. 2018-2022. Funding source: FCT | COMPETE | FEDER | Portugal 2021. Ref: PTDC/BAA-AGR/31400/2017. Total amount: 239 K€ (Group Researcher Participant: Flávio Reis).
- PHENOLIVA - Contribution of olive and olive oil polyphenolic compounds to the prevention of cardiovascular diseases. 2018-2022. Funding source: FCT | COMPETE | FEDER | Portugal 2021. Ref: PTDC/OCE-ETA/32492/2017. Total amount: 240 K€ (Group Researcher Participant: Flávio Reis).
- CoaMedPlants - Preservation of natural and cultural heritage and scientific validation of practices with medicinal plants from Coa Valley. 2020-2023. Funding source: COA/BRB/0019/2019. Group Researcher PI: Célia Cabral. Amount: 299 K€.

BIOLOGY OF REPRODUCTION & STEM CELL

Head: João Ramalho-Santos

Objectives

A) <u>Male infertility studies (PIs Sandra Amaral & Renata S Tavares)</u>

A1) Searching for novel biomarkers in unknown origin (UOMI) male infertility
Obtain insights on the mechanism beyond infertility of unknown origin (idiopathic-ID/unexplained male infertility-UMI), focusing on new functional aspects, through non-conventional methodologies (as Seahorse Metabolic Flux Analyzer; proteomics) and suggest a biomarker that could be used to diagnose this infertility type, distinguish ID and UMI, and select better gametes. The influence of lifestyle factors and psychological status will also be evaluated.
A2) The impact of anti-sperm antibodies (ASA) on sperm functionality
Understand how ASA impact sperm function and men (in)fertility, through an integrated approach comprising the evaluation of conventional sperm parameters but also crucial functional parameters not routinely evaluated. The analysis will be in 3 fronts: functional, molecular and fertility outcomes evaluation.
A3) Analysing endocrine-disrupting chemicals (EDCs) impact on male fertility
Determine male reproductive status in a heavy metal exposed Portuguese city, unveiling mechanisms of action in sperm responsible for the potential male sub/infertility, in what comprises the 1st study in Portugal monitoring fertility and reproductive health.

B) <u>Female infertility and fertility preservation (PIs Teresa Almeida-Santos & Ana Paula Sousa)</u>

B1) Preservation of Reproductive Potential in Oncological Patients: Angiogenesis Stimulation of Cryopreserved Ovarian Tissue Graft
Promote early angiogenesis in the ovarian tissue graft after cryopreservation, reducing follicles loss and optimizing graft function and duration, using both animal models and human ovarian tissue.

B2) Metabolism of oocyte aging: biomedical evaluation and development of rejuvenating strategies
Explore metabolic modifications that occur during oocyte aging, use strategies/therapeutic treatments to revert oocyte aging. Use the knowledge on the role of age in fertility decline to develop strategies to prevent the age-related fertility decline.

B3) *Analysing endocrine-disrupting chemicals (EDCs) impact on female infertility*
Determine if female reproductive potential is affected in women from a heavy metal contaminated city in Portugal, unveiling mechanisms of action using both an animal model and an in vitro approach. This is the 1st study in Portugal monitoring female fertility.

C) <u>Stem cell Biology (PI João Ramalho-Santos)</u>

C1) *Developing new strategies to induce a novel pluripotent-paused state in mESC culture*
Develop a new, non-pharmacological, strategy to induce paused-pluripotency in mESC culture, by metabolic modulation. Specifically, we aim to induce paused-pluripotency by culturing mESCs in a medium deprived of specific amino acids (Leucine & Arginine) that affect mTOR function.

C2) *Inducing quiescent UC-MSCs through hypoxia*
We hypothesize that umbilical cord-mesenchymal stem cells (UC-MSCs) exposed to specific oxygen levels can achieve cellular quiescence that, by lowering cell activity and energetic demand,

improves survival, stemness and therapeutic function. UC-MSCs are cultured under different oxygen concentrations and treated with five concentrations of the hypoxia mimicking agent Cobalt Chloride (CoCl2). The mTOR dual inhibitor INK-128 was used as a positive control for mTOR-dependent paused state. We also intend to establish a CoCl2 model for hypoxia in UC-MSCs, by performing a comparative analysis between hypoxic oxygen levels and different CoCl2 concentrations.

D) <u>Interdisciplinary studies on metabolism (PIs Anabela Marisa Azul & João Ramalho-Santos)</u>

D1) Interdisciplinary studies on metabolism communication and health promotion
Explore how far comics/visual narratives can go in terms of communication and health promotion, joining biomedical and life/environmental sciences, social sciences, and humanities, and using both qualitative and qualitative approaches.

D2) Functional attributes of fungi for human health
Imbalances in transition metals are known to directly link to human disease ranging from metabolic to neurodegenerative disorders. We intend to investigate the capacity of a zinc-enriched mushroom diet to decrease the absorption of deleterious transition metals in the gastrointestinal tract.

D3) Human–nature interactions for health and well-being
Better understanding the human–nature interactions and their potential (1) as drivers of health and well-being and (2) to the shift needed toward healthy and sustainable diets; joining biomedical and life/environmental sciences, social sciences, and humanities, and using both qualitative and qualitative approaches.

A) <u>Male infertility studies (PIs Sandra Amaral & Renata S Tavares)</u>
A1) Searching for novel biomarkers in unknown origin (UOMI) male infertility
The ID group presented the worst functional results (viability, motility, morphology,acrosome integrity, capacitation, mitochondrial function), thus revealing a compromised function at several levels. Superoxide levels, fertility outcomes and psychological symptoms of anxiety/depression, showed no differences among the groups. The proteomic analysis revealed 145 differentially expressed proteins (DEP), of which 7 were DEP between the 3 groups, thus being the most plausible candidates to distinguish them. These proteins were up-regulated in IDvsCTRL and UMI, and down-regulated in UMIvsCTRL. The analysis of fertility outcomes is ongoing.
A2) The impact of anti-sperm antibodies (ASA) on sperm functionality
The obtained results provide relevant/new information on the effects of ASA on sperm function, identifying new compromised aspects in these patients, as capacitation, acrosome integrity and mitochondrial function. The identification of sperm putative ASA target proteins and DNA genotyping is ongoing. In the end, fertility outcomes of ART patients will be evaluated. A collaborative retrospective work on ASA patients (Centre for Reproductive Medicine & Andrology -CeRA; Germany) is ongoing.

A3) Analysing endocrine-disrupting chemicals (EDCs) impact on male fertility
Although no differences in As and Hg seminal levels were observed among control and populations, physiological As and Hg doses, when combined, reduced sperm viability, motility, mitochondrial function, capacitation, acrosome and chromatin integrity in vitro, possibly via ROS production. These pinpoint the need to monitor places worldwide where both compounds are present.

- **Funding:**

A1) SR&TD Project -PTDC/MEC-AND/28599/2017 (POCI-01-0145-FEDER-028599) (236.679,81€, 3 Yrs, FCT): "Searching for novel biomarkers in unknown origin (UOMI) male infertility"- *extended until July 2021*
A3) Project - OHM-E/2019/Proj.3 (10000€, 2 yrs; LabEx DRIIHM)
-CENTRO-01-0145-FEDER-000012-HealthyAging2020.

B) <u>Female infertility and fertility preservation (PIs Teresa Almeida-Santos & Ana Paula Sousa)</u>

B1) Preservation of Reproductive Potential in Oncological Patients: Angiogenesis Stimulation of Cryopreserved Ovarian Tissue Graft
The results showed an increase of microvessel density with *in vitro* angiogenesis stimulation of human ovarian tissue using several strategies, with no differences in tissue viability.

B2) Metabolism of oocyte aging: biomedical evaluation and development of rejuvenating strategies
So far we demonstrate that there is a significant decrease in oocyte cytoplasmic volume after *in vitro* and *in vivo* aging. Additionally, the levels of H_2O_2 increased significantly after *in vitro* and *in vivo* aging and mitochondrial aggregation patterns were significantly altered. In contrast, no alterations were found regarding mitochondrial mass, distribution and activity.

B3) So far, follicular fluid from control and study populations was collected and As and Hg measurements are underway. Yet, the sample size is still small.

- **Funding:**

B1) Project - CSD006003#IV0337 (140000€, 3 yrs, Merck SA) "Preservation of Reproductive Potential in Oncological Patients: Angiogenesis Stimulation of Cryopreserved Ovarian Tissue Graft".
B3) Project - OHM-E/2020/Proj.5 (8000€, 2 yrs; LabEx DRIIHM)
-CENTRO-01-0145-FEDER-000012-HealthyAging2020.

C) <u>Stem cell Biology (PI João Ramalho-Santos)</u>

C1) *Developing new strategies to induce a novel pluripotent-paused state in mESC culture*.
The results obtained so far show that Leucine and Arginine withdrawal from mESC culture medium induces some of the features observed in paused-pluripotency, namely reduced cell proliferation, cell cycle arrest, reduction in overall glucose metabolism, and decreased protein translation; without affecting the pluripotency status of the culture nor their differentiation potential.

C2) *Inducing quiescent UC-MSCs through hypoxia*
UC-MSCs cultured under 5% O2 and with the lower concentration of CoCl2 displayed higher population doubling than cells cultured in 21% O2. Cells cultured under 5% O2 showed a decrease in cell death. Culture under <1% or with the highest concentration of CoCl2 led to a significant decrease in proliferation. The phosphorylation status of the mTOR effectors 4EBP1 and S6K1 was downregulated in cells exposed to severe hypoxia suggesting a decrease in protein biogenesis, while the phosphorylation of the mTOR target Akt was upregulated in MSCs cultured under severe hypoxia, suggesting an increase in cell survival mechanisms.

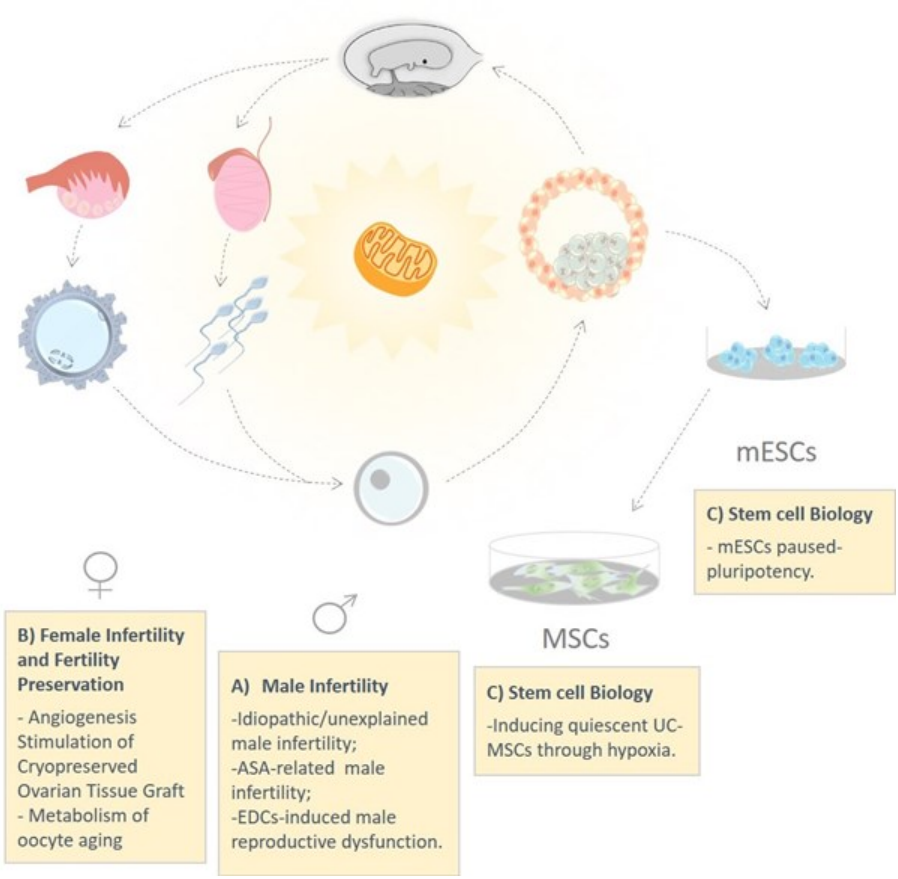
- **Funding (ongoing):**

-Project Stem@Rest: "The Paused State: a novel way for bioengineering Stem Cell fate" - CENTRO-01-0145-FEDER-028871 (239.226,73€; 3 yrs)
-CENTRO-01-0145-FEDER-000012-HealthyAging2020

D) <u>Interdisciplinary studies on metabolism (PIs Anabela Marisa Azul & João Ramalho-Santos)</u>

- **Funding:**

- FOIE GRAS project (H2020-MSCA-ITN-2016), funding from the European Union's Horizon 2020, Research and Innovation programme under the Marie Skłodowska-Curie Grant Agreement No. 722619
- SFRH/BD/136900/2018 (PhD Fellowship; FCT)
- CENTRO-01-0145-FEDER-000012-HealthyAging2020



MOLECULAR MECHANISMS OF CARDIOVASCULAR DISEASES

Head: Henrique Girão

Objectives

Cardiovascular diseases are a leading cause of morbidity and mortality worldwide and represent a major burden for health care systems. A comprehensive and transversal strategy is required to efficiently tackle this group of complex and multifactorial diseases, in their multitude dimensions. To boost the existing capacities and competencies, crossing canonical and static boundaries between disciplines we have implemented a coherent and inclusive approach that brings together basic researchers and clinicians, allowing a strategy "from bench to bedside and back again". In terms of basic research, the group has been investigating the strategies whereby cardiac cells communicate and the mechanisms involved in the maintenance of a healthy proteome. More specifically, we aim to elucidate how the disturbance of protein degradation and intercellular communication systems can contribute to cardiovascular diseases, with a particular focus on autophagy and communication, either direct, between neighbour cells, through gap junctions and tunnelling nanotubes, or at long distances via extracellular vesicles. In terms of clinical competencies, the group has two highly differentiated areas, i) heart failure (HF) and ii) transplantation and interventional cardiology. The team integrates competencies and resources on i) advanced heart failure & transplantation, ii) coronary care, iii) percutaneous structural cardiac intervention, iv) advanced electrophysiology, v) pulmonary hypertension, vi) congenital heart diseases, vii) advanced imaging capabilities (including 3D echocardiography, cardiac resonance imaging,
CT and nuclear cardiology including SPECT and cardiac PET), viii) syncope and ix) telemedicine & telemonitorization. We are National Reference Centers for cardiovascular structural intervention, pulmonary hypertension, congenital heart diseases, and heart transplantation, which give us privileged access to human samples. We have developed fruitful collaborations with other research groups, namely in the field of regenerative medicine, computer modelling for drug dispersion after DES stents implantation, telemonitoring, and psychological aspects of cardiovascular diseases.
Main Achievements
. Microvascular endothelial cell dysfunction has been considered a central player in the development of heart failure with preserved ejection fraction (HFpEF). By increasing vascular inflammation, cellular senescence has been suggested to underlie microvascular endothelial dysfunction. Besides the senescence-associated secretory phenotype (SASP), that includes extracellular vesicles (EVs), senescent cells rely on gap junctions (GJ) to transmit a variety of signaling factors including pro-inflammatory cytokines that are responsible to maintain or induce senescence in an auto and/or paracrine manner. We demonstrated that Cx43 levels and GJ-mediated intercellular communication are increased in senescent endothelial cells and that endothelial-derived EV differentially modulate autophagy activity in target cardiomyocytes, which is dependent on the subpopulation of secreted EVs, either large microvesicles (MVs) or small EVs (exosomes). Moreover, we unveiled that MVs released from senescent endothelial cells affect the function of cardiomyocytes through an increase in Ca2+ handling.
. It is known that HFpEF pathogenesisis dependent on a systemic and proinflammatory state, induced by associated comorbidities, such as hypertension, diabetes, and obesity. One of most important proinflammatory cytokines increased in HFpEF is TNF-α which leads to disruption of EC-cardiomyocyte intercellular communication. Our results showed TNF-α induces an increase of lysosome size and number, with an accumulation of membrane damage markers due to an impairment of membrane repair mechanisms, which triggers the clearance of damaged lysosomes, by autophagy and exocytosis. We found that Cx43 is recruited to LAMP1 positive endolysosomal membranes as well as to galectin-3 positive damaged vesicles ascribing to Cx43 a new role in modulating lysosomal exocytosis induced by TNF-α in ECs.

. Invasive Candidiasis (IC) can be caused by several *Candida* spp., being *Candida albicans* the most prevalent specie worldwide. Macrophages are part of the first line of defense against infections as they can engulf and eliminate *C. albicans* through phagocytosis. In order to survive, macrophages require an efficient cellular response to rapidly counteract the hypha-induced cellular damage. Our results showed an activation of the repair machinery, through the recruitment of Alix and Tsg101, to *C. albicans* containing-phagosomes. In addition, we observed a recruitment of Trim16, a lysophagy component, to the *C. albicans*-containing phagosome. Lastly, we found that Cx43 is recruited to phagosomes containing *C. albicans* and potentiate the folding capacity of macrophages.
. Cardiomyopathies are the leading indication for heart transplantation worldwide, with Dilated Cardiomyopathy (DCM) representing the most common form and entailing for high rates of morbidity and mortality. Approximately 25% of the patients develop DCM due to genetic causes. Among the myriad of genes identified in the subset of DCM, mutations in the Lamin A/C gene (LMNA) are the second most common and are responsible for a higher risk of sudden death when compared to other DCM forms. Our data revealed that LMNA mutations impact on the levels of nuclear Cx43 through a mechanism the relies on microtubules and the ERK1/2 signaling pathway.
. Fluorine-18 sodium fluoride (Na[^{18}F]F) atherosclerotic plaque uptake in positron emission tomography with computed tomography (PET-CT) identifies active microcalcification. We showed that in a high cardiovascular (CV) risk group, the global cardiac microcalcification burden is related to CV risk factors, metabolic syndrome variables and cardiac fat.
. Cardiac sarcoidosis (CS) is clinically diagnosed in 5% of patients with sarcoidosis but imaging studies suggest higher prevalence. We showed that among patients with biopsy-proven sarcoidosis, cardiac involvement detected by [^{18}F]FDG-PET or cardiac magnetic resonance is associated with a higher risk of CV events, irrespective of symptoms.

Portugal 2020 Aprovados
17/SI/2019 - Sistema de incentivos à investigação e desenvolvimento tecnológico). HLABEL – Radio-marcação de vesículas extracelulares para aplicações em diagnóstico e terapêuticas. 678 755,89 euros
COMPETE 2020 Aprovados
AAC nº 31/SI/2017 - BioImage2CTO: Novos biomarcadores de imagem na avaliação das oclusões coronárias crónicas totais. 848 375,83 euros.
FCT: EXPL/MED-OUT/0590/2021
Title: ConCOEUR: um novo papel para a Conexina43 na modulação da expressão génica e suas implicações na evolução da estenose aórtica ehipertrofia ventricular esquerda. 50 000 euros

Cardiovascular diseases are a leading cause of morbidity and mortality worldwide and represent a major burden for health care systems. A comprehensive and transversal strategy is required to efficiently tackle this group of complex and multifactorial diseases, in their multitude dimensions. To boost the existing capacities and competencies, crossing canonical and static boundaries between disciplines we have implemented a coherent and inclusive approach that brings together basic researchers and clinicians, allowing a strategy “from bench to bedside and back again”. In terms of basic research, the group has been investigating the strategies whereby cardiac cells communicate and the mechanisms involved in the maintenance of a healthy proteome. More specifically, we aim to elucidate how the disturbance of protein degradation and intercellular communication systems can contribute to cardiovascular diseases, with a particular focus on autophagy and communication, either direct, between neighbour cells, through gap junctions and tunnelling nanotubes, or at long distances via extracellular vesicles. In terms of clinical competencies, the group has two highly differentiated areas, i) heart failure (HF) and ii) transplantation and interventional cardiology. The team integrates competencies and resources on i) advanced heart failure & transplantation, ii) coronary care, iii) percutaneous structural cardiac intervention, iv) advanced electrophysiology, v) pulmonary hypertension, vi) congenital heart diseases, vii) advanced imaging capabilities (including 3D echocardiography, cardiac

resonance imaging, CT and nuclear cardiology including SPECT and cardiac PET), viii) syncope and ix) telemedicine & telemonitorization. We are National Reference Centers for cardiovascular structural intervention, pulmonary hypertension, congenital heart diseases, and heart transplantation, which give us privileged access to human samples. We have developed fruitful collaborations with other research groups, namely in the field of regenerative medicine, computer modelling for drug dispersion after DES stents implantation, telemonitoring, and psychological aspects of cardiovascular diseases.
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MICROBIOMES, METABOLISM AND OMICS

Head: Conceição Egas

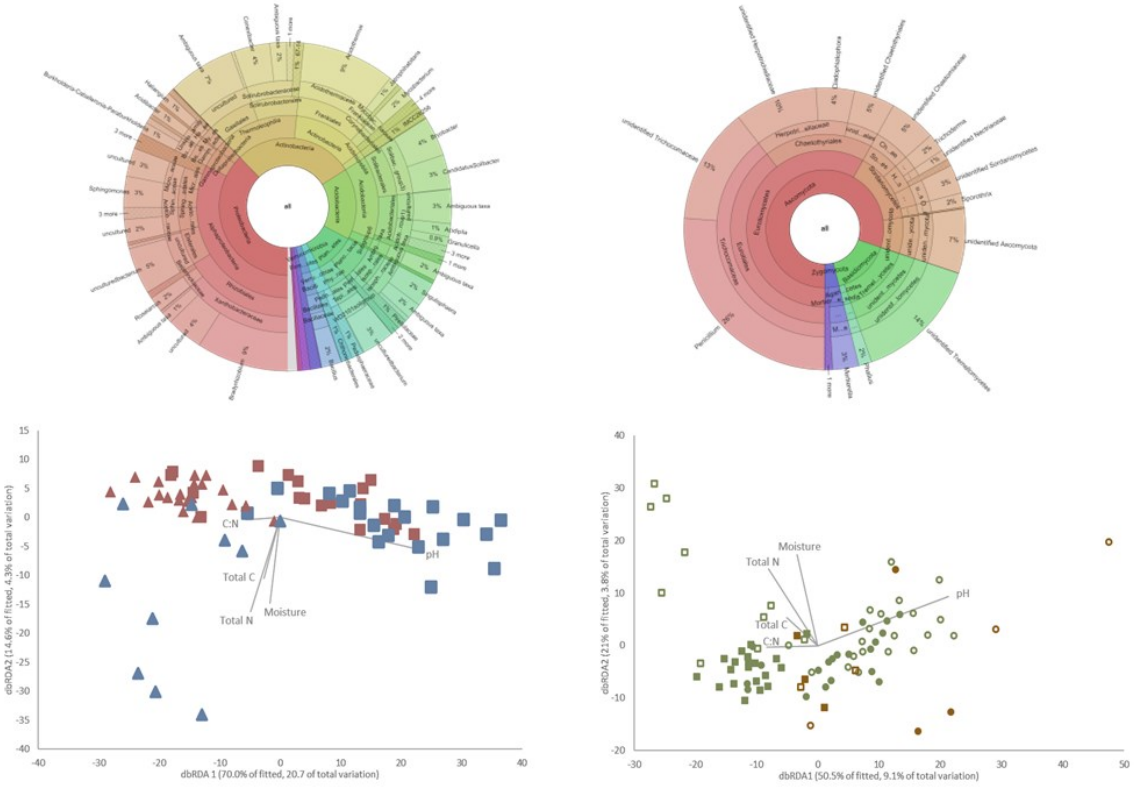
Objectives

The MICROBIOMES, METABOLISM AND OMICS group focuses on the research lines:
a) Microbiomes and hosts: Investigate the role of microbes in host-associated communities through network analysis to derive patterns of co-occurrence, microbial relationships, or high-level functional roles. Identify key organisms and derived biomarkers.
b) Microbes and disease: Characterize adaptation of microbes to environmental niches to understand adaptation to human hosts and disease, in particular the relationship between the gut microbiome and cardiometabolic diseases. Investigate conserved and newly acquired biochemical and metabolic functions through comparative genomics of Bacteria and Archaea from extreme environments to gut to identify key metabolic functions in disease.
c) Biotechnology applications: Identify novel protein families with biotechnological potential from extremophile communities using protein interaction network approaches, focusing on glycosyl hydrolases, lipases, and proteases.
Collaboration with other research groups at the Metabolism, Aging and Disease research line allows to correlate genotype with phenotype, including investigating the regulation of host metabolism by bacterial metabolites.

Main Achievements

a) We have found that in chronic oak decline (COD), the rhizosphere physicochemical properties and microbiome composition correlated with the location of *Quercus suber* sites and stands, but no signification association to tree health was observed. The rhizosphere soils were more acidic, richer in nutrients (C and N) and higher C:N ratio in sites with better forest health. Rhizosphere pH and moisture were the main drivers of microbial composition. Our previous results in Acute oak decline, a condition that leads to rapid oak death, had shown an association of the rhizosphere microbiome composition with tree health. The results obtained suggest that in COD, the prolonged nature of the decline may lead to a time-balanced microbiome, where soil properties have a major role in the disease (Diogo Pinho, Ph.D. Student).
b) We identified a new archaeal species of the *Halorubrum* genera. The new isolate was recovered from an inland saltpan in Portugal, with a 26% NaCl content. Using a culture approach, we recovered 31 bacterial isolates and 131 archaeal isolates from the saltern. The microbial community was dominated by the Halorubrum genus (77% of the isolates). The 16S ribosomal and genome sequencing indicated one of the isolates as a new species. Phenotypic and chemotaxonomic studies are underway to characterize this isolate. The metagenome of the saltern eDNA was sequenced and is under analysis to identify genes/pathways associated to the salt resistance mechanisms.
c) We collaborated with Olga Nunes, Faculty of Engineering of the University of Porto, in the sequencing and analysis of the metagenomes of treated urban wastewater. The study "Rethinking water treatment targets: Bacteria regrowth under unprovable conditions" doi: 10.1016/j.watres.2021.117374, published in Water Research (ranked at the Top 2% of Environmental Sciences and Water Resources) concluded that ozonation of wastewater leads to regrowth of bacteria able to cope with nutrient poor environments, and also presenting ARGs conferring resistance to antibiotics, thus suggesting the need for new wastewater treatments.
d) A new Ph.D. student joined MMO group to develop the project "A computational framework towards the study of metabolic interactions of the gut microbiome and the human host in Type 2 Diabetes".

e) The group has 6 active projects. 1) H2020 project, INNOCORE - Core Technologies for Education and Innovation in Life Sciences, no. KA203-589E724D; 2) three FCT projects, PTDC/BTM-SAL/30550/2017 - Immunotargeting efflux systems for therapeutic modulation of multidrug resistant bacteria, PTDC/ASP-SIL/31999/2017 - POINTERS - Host tree-pinewood nematode interactions: searching for sustainable approaches for pine wilt disease management and CIRCNA/BRB/0156/2019 - Cutting-edge DNA-based approaches for improved monitoring and management of fisheries resources along Magellan-Elcano´s Atlantic route; 3) one Fundo Azul project - Symbioreactor - Sustainable Production of Bioactive Metabolites from Microbial Symbionts of Marine Sponges and Corals, no. FA_05_2017_032; 4) RNIE infrastructure: GenomePT, no. 01/SAICT/2016.



HUMAN GENOME VARIATION AND ENVIRONMENT IN HEALTH AND DISEASE

Head: Isabel Marques Carreira

- Understand genetic predisposition and lifestyle modifications in disease development and knowledge the impact of genetic/epigenetic factors and environmental/microenvironment exposures on health and on the susceptibility, development and progression of developmental disorders/cancer.

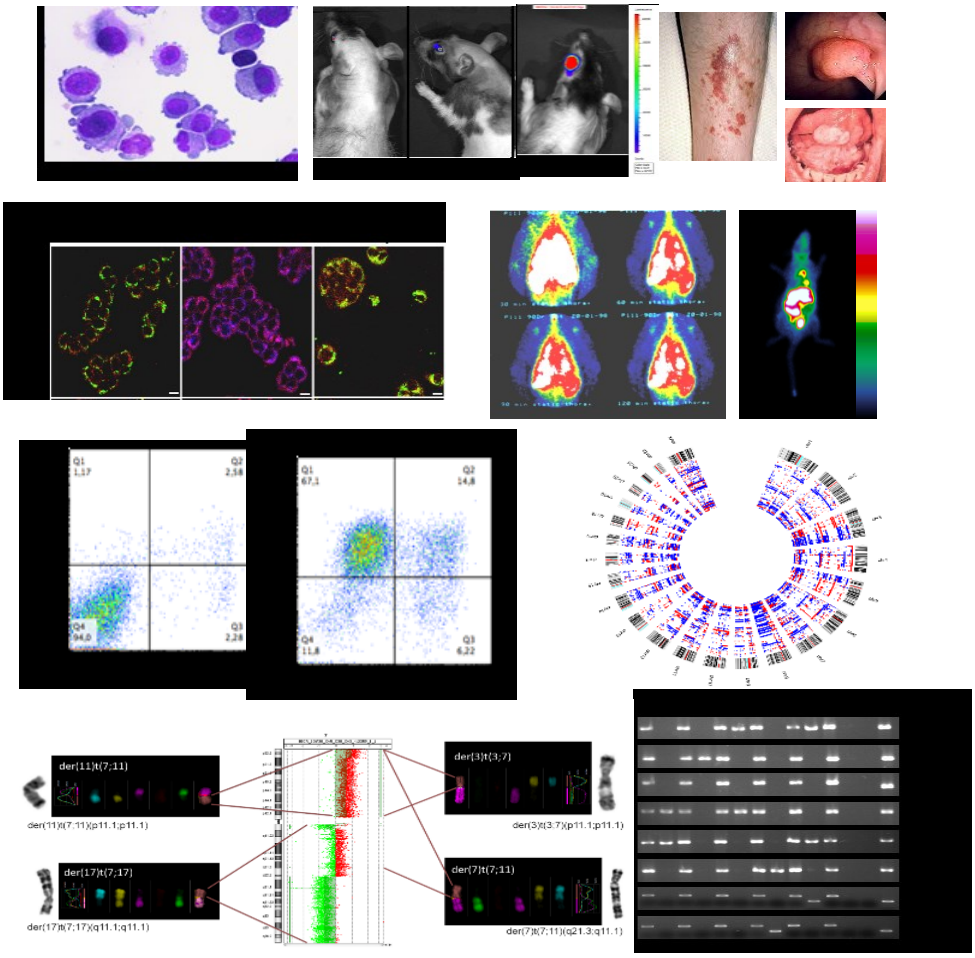
- Study the cellular and molecular mechanisms and human genome variability in order to identify new diagnostic/prognostic biomarkers, essential for disease risk and outcome prediction and, to identify new therapeutic targets and drug response biomarkers, which translated into clinical research could contribute to an effective precision/personalized medicine.

-Development of disease models and integrate complex information from multiple data sources generating a usable output to support prevention, diagnostic, prognostic, and treatment, including ionizing radiation, photodynamic and new targeted therapies.

Main Achievements

- Identification of diagnostic/prognostic and drug response biomarkers are group contributions: oxidative stress and DNA methylation are complementary prognostic biomarkers in myelodysplastic syndromes (MDS) patients (Gonçalves AC et al); plasmatic peroxides levels are good predictive biomarkers of response to erythropoiesis-stimulating agents in lower-risk MDS (Gonçalves AC, et al, Front Cell Dev Biol). Blood-based specimens may be potential source of non-invasive DNA methylation cancer biomarkers in MDS (Jorge J et al) and liquid biopsies offer opportunities to improve the surveillance of cancer patients during treatment (Martins I et al).
- The hydropathy index of the HCDR3 sequences of chronic lymphocytic leukemia (CLL) cells allows the identification of a subgroup of CLL patients with intermediate prognostic features (Rodríguez-Caballero A, et al). In multiple myeloma (MM) patients, several detected genomic alterations can ameliorate MM patient's risk stratification (Couto Oliveira A et al).
- Detection of an impairment of CD4+ Treg follicular-like cells in the regulation of antibody production by myeloma cells and in the immunosuppressive state in patients with MM (Silva A et al) and the presence of tumor-infiltrating lymphocytes in osteosarcoma microenvironment stratify patients and monitor therapy response (Casanova JM, et al).
- In the context of international networking, three reviews in high-impact journals were published focused on therapy resistance, the impact of cancer metabolism (Gonçalves AC et al, Drug Resist Updat), the role of hypoxia (Kopecka J et al) and the molecular mechanisms of tyrosine kinase inhibitors resistance in chronic myeloid leukemia (Alves R et al).
- Array-CGH characterization developed a genomic model comprised of four chromosomal regions that enable the distinction between intrahepatic and extrahepatic cholangiocarcinoma, with an accuracy of 71.43% (Tavares I et al), identified a seven gene signature in 62 samples of oral squamous cell carcinoma, that allow to differentiate the patients that developed metastases or relapses after primary tumor treatment, with an overall accuracy of 79% (Ribeiro IP et al) and revealed a complex genomic profile of cancer-related genes and genomic regions in basal cell carcinomas (Cardoso JC et al).
- The development of new therapeutic approaches are other team contributions, particularly with regard to innovative therapies, such as new anti-cancer molecules (Gomes AR et al, Pires AS et al), atmospheric cold plasma (Silva-Teixeira R et al, Tavares-da-Silva E et al, Almeida-Ferreira C et al), photodynamic therapy (Pereira N et al) and natural compounds (Monteiro-Alfredo T et al.). In collaboration with other CIBB research line, a hybrid nanosystem to deliver a combination of sorafenib and selumetinib to treat hepatocellular carcinoma (HCC) was developed (Farinha D et al).

- In addition to therapy, the team also endeavored to contribute to the prevention of human diseases (Boqué N et al), to understand the underlying mechanisms of the disease (Oliveira RC et al, Silva-Vaz P et al, Madama D et al, Caetano Oliveira R et al, Spinola LP et al), as well as the preservation of fertility after cancer treatments (Pais AS et al).
- Other privileged areas are urology, dentistry and dermatology. In the field of urology, kidney transplantation (Lourenço M, et al, Mira FS, et al), and prostate (Lima JP et al, Marques IA et al) and bladder (Mendes F et al, Tavares-da-Silva E et al) were especially important. For dentistry, the team was particularly interested in the development and characterization of new materials for oral use (Carneiro ER, et al) as well as the repercussions of materials on oral structures (Cardoso M et al, Coelho A et al, Martinho JM et al, Paula AB et al). In dermatology, several guidelines (Gonçalo M et al, Balato A et al, Thyssen JP et al, Wilkinson SM et al, Zuberbier T et al) and a new contrast imaging technique were published (Brinca C et al).



HEALTHY LIVING AND ACTIVE AGEING

Head: João Malva

Objectives

The main objectives for the Healthy Living and Active Ageing for the reporting period 2021 have been set according to two different dimensions:
1- Fundamental research
2- Network building and translational research with societal impact

The objectives defined for dimension 1 on "Fundamental research" include:
a. Evaluation of the mechanism of cell death (toxicity) due to exposure of BV2 microglial cells to methylmercury

Concerning the objectives defined for dimension 2 on "Network building and translational research with societal impact":
2.1. Evaluate the impact of Covid-19 pandemic on loneliness and health status of the population in the center region of Portugal
2.2. Organize the Annual Meeting of Ageing@Coimbra, European Innovation Partnership on Active and Healthy Ageing
2.3. Implement the second year of EIT Health funded, EIT Health Ageing PhD School
2.4. Successfully complete and report the H2020 ERA Chair project "ERA@UC"
2.5 Collaborate with strong international partners in the field of palliative care and build foundational work on its implementation in primary care and bereavement care

Main achievement for the reported period includes:
1.1. Characterization of the cell death pattern of BV2 following acute exposure to low micromolar concentrations of methylmercury. The group has shown that low micromolar concentrations of methylmercury induce a necrotic-like cell death partner of microglial cells.
2.1. The group has successfully launched an online survey to evaluate the impact of lockdown due to Covid-19 on the feeling of loneliness and deterioration of health status in the population (with a focus on elderly people). This project has been implemented following a successful application to ERASMUS+ "Healthyloneliness" project.

2.2. In spite of the emergence of the OMICRON variant pandemic wave the Ageing@Coimbra consortium could organize a successful onsite meeting (December 2021) at Con cento São Francisco (Coimbra) and award the selected best practices supporting Active and Healthy Ageing in the Center Region of Portugal (a partnership with the Regional Authority CCDRC).

2.3. Our group coordinates the pan-European PhD School funded by EIT Health "EIT Health Ageing PhD School". In this PhD School network that supports advanced training on ageing research, but also international and cross sector mobility of PhD students to deliver innovation and entrepreneurship training for new PhD's, we successfully recruited 32 students across Europe. The PhD School has been funded by EIT Health for a 4-year cycle.

2.4. We successfully closed and reported to EU the implementation of the H2020 2.5 M€ funded ERA Chair project ERA@UC (April 2021).

2.5. We published new epidemiological and trial evidence in palliative care in collaboration with colleagues from the Cicely Saunders Institute at King's College London, a worldwide leading

research centre in the field, WHO Collaborating Centre for Palliative care, Policy and Rehabilitation. The two articles (published in *Int J Nurs Stud* and *Palliat Med)* report the first worldwide projections of palliative care need, and RCT results showing a community-based short-term integrated palliative care intervention reduced symptom distress for older people with chronic noncancer conditions compared with usual care.

2.6. We published the first output from an emerging work stream dedicated to promoting the implementation of palliative care in a primary care setting, with publication of results from focus groups with family doctors in Portugal about their role in palliative care (*Int J Env Res Public Health)*

2.7. We contributed with two chapters to the book "*Luto: Manual de Intervenção Psicológica*", as part of FCT funded research we are undertaking on bereavement.

Funding active in 2021:
>FCT -POCI-01-0145-FEDER; Neurotoxicity of methylmercury in the neurogenic niches of the adult brain; **239.476€** *(João Malva, Co-PI)*
>ERASMUS+; Development of a training program for improving QoL of seniors living in loneliness through educational activities; **80,562€** *(João Malva, Coordinator UC Team)*
>EIT Health Campus, Students; EIT Health Ageing PhD School BP2021; ~**485,000€** *(João Malva, Project Coordinator)*
>H2020 Widespread-2014-2 ERA Chairs; 669088 ERA@UC; ERA@UC – Enhancing Ageing Research at the University of Coimbra; **2.486.165€** *(João Malva, Project Coordinator)*
>Cons©elhos Repórteres 55+ BPI "la Caixa" Rural; 48.406,00€ (Anabela Mota Pinto, Coordinator Team FMUC)
>FCT SFRH/BD/136331/2018; Variations in the access and outcomes of bereavement support for family carers of cancer patients; **63,538.28** *(Maja de Brito PhD Student, Bárbara Gomes, João Malva and Lucy Selman PhD Supervisors)*

The image represents the concept developed in 2021 for the new call (deadline March 2022) of the Horizon Europe call on Excellence Hubs.

HEALTH, MANAGEMENT AND ECONOMICS

Head: Pedro Ferreira

The Health, Management and Economics group is formed by researchers originally from the Centre for Health Studies and Research of the University of Coimbra (CEISUC), developing a transdisciplinary research approach in health systems and services, focusing in particular on the Portuguese system. The group's objective is to develop research on health systems/services and its main objectives are to contribute to the development of the health economics research of under four main research lines: health systems, value in health, people in health, and health trajectories, contributing to analyse outcomes resulting from links between fundamental research in metabolic, environmental, genetic and aging-related diseases, good practices and technologies supporting living and active aging, and adoption of healthy lifestyles.
The first research line – health systems – approaches governance and the global strategies of the system, including the analysis of the definition of evidence-based health policies and the dynamics of health systems.
In the second research line – health value – CEISUC proposes to contribute to the determination of the value that individuals attribute to various health states, through utility measures preference-based and measures of effectiveness and health status or quality of life, maintaining the Repository of Instruments for Measuring and Assessments of Health (RIMAS).
The third research line – people in health – addresses the human component of care delivery, such as communities, users, informal carers and professional caregivers, including topics such as literacy, the knowledge that patients of various pathologies have about their disease, empowerment and monitoring of the satisfaction of healthcare professionals and users, and the so-called people-cantered medicine.
The fourth research line – health trajectories – health in the process of the lives of people, families and communities, also dependent on the physical, social and economic environments to which they are exposed. Including determining health gains and monitoring the impact on quality of life of patients' journeys in treatment and the socio-economic impacts of ageing.
The research group is involved in a large range of scientific activities including post-graduate programs, participation in scientific national and international networks and dissemination of scientific activities. It includes skills from economics, management, statistics, health administration, medicine, nursing, physical therapy, and psychology.

Objectives

The main objectives are to contribute to the development of the field of health economics research under four main research areas: health systems, value in heath, people in health, and health trajectories, contributing to analyse outcomes resulting from links between fundamental research in metabolic, environmental, genetic and aging-related diseases, good practices and technologies supporting living and active aging, and adoption of healthy lifestyles.

Main Achievements

During 2021, we were envolved in several research projects such as:

- Health systems

– CuidIn - Support and Care for informal caregiver, Operational Program Social Inclusion and Employment (POISE) and the European Social Fund;
– Development and application of an impact assessment model of the CuiDando project;
– Örenäs Research Group, WONCA – EUROPE;
– Portuguese Health Systems Observatory;
– Portuguese Palliative Care Observatory.

- Value in health
  - RIMAS – Repository of Health Measurement and Assessment Instruments.
- People in health
  - Health literacy in the higher education community of the University of Coimbra;
  - Training Project of the Center Region for Genomic Medicine, Program CENTRO2020.
- Trajetorias em saúde
  - Evaluation of User Satisfaction of UCSP and USF Functional Units of the Central Region, Central Regional Health Authrity;
  - Health and well-being of the Portuguese citizens: impacts of the COVID-19", La Caixa BPI Foundation;
  - Monitor the satisfaction of users and professionals, Hospital and University Center of Coimbra;
  - Programme for a Long Society - Operational PSL programme, European Regional Development Fund;
  - Research Innovation and Sustainable Pan-European Network in Peripartum Depression Disorder - Riseup-PPD (CA18138).

INNOVATIVE THERAPIES

COORDINATOR: LINO FERREIRA

General Objectives

The Innovative Therapies thematic line brings together researchers with the purpose of performing interdisciplinary research for the development of innovative tools and approaches for prevention and treatment of a selected group of disorders that are exacerbated in the aged population, such as neurodegenerative, ischemic, infectious and cancer diseases. This thematic line is strategic because it will create translational and economical value for the Center Region of Portugal in the area of biotechnology/ health sciences. The strand is formed by 10 research groups integrating a matrix of complementary expertise aiming at investigating ways to create innovative therapies that can be moved from the bench top to the bedside. These groups have contributed with novel approaches for the treatment of ischemic diseases, in the development of viral and non-viral therapies for neurodegenerative and cancer diseases, the identification of new therapeutic targets to treat brain diseases such as Machado Joseph disease, in the identification of cell reprogramming factors to reprogram fibroblast cells into hematopoietic stem cells and in the identification of new targets as well as therapeutic approaches to treat and prevent infection and infection-associated damage.

Main Achievements

Members of the Innovative Therapies thematic strand line contributed scientifically in different areas including infection [(i) understanding the role of macrophages in rickettsial pathogenesis, (ii) demonstrating the mechanism of rickettsial retropepsin, (iii) studying the catalytic mechanism of cocaine hydrolysis by the human carboxylesterase, (iii) characterizing the tolC-like channel-tunnels of different Gram-negative bacteria, using bioinformatics tools, (iv) demonstrating the antifungal of plant extracts, (v) investigating the role of transcription factor E2F1 in the regulation of microRNAs upon infection, (vi) demonstrating the impact of host cell cycle on Salmonella infection, (vii) identification of molecular mechanisms related with the gut-brain axis], neurosciences [(i) demonstration of SCA3 mechanism using in vitro and in vivo models of spinocerebellar ataxia type 3, (ii) development of targeted miRNA-based therapy for glioblastoma and (iii) development of nanoparticles targeted for vaccination], regenerative medicine [(i) development of personalized *in vitro* platforms based on human pluripotent stem cell-derived endothelial cells and smooth muscle cells to evaluate the interaction of nanomaterials with the vascular system, (ii) development of strategies to enrich the content of miRNAs in extracellular vesicles to use them as drugs delivery systems, (iii) development of a database that summarizes the evolutionary and physicochemical properties of dimeric proteins, (iv) demonstration that the cooperative transcription factor binding mediates hemogenic induction and pioneered cell fate reprogramming approaches in immunology and induced dendritic cells, (v) identifying the role of miRNA in cardiac fibrosis] and cancer [(i) development of different formulations for both individual and combined gene and drug delivery into hepatocellular carcinoma cells and (ii) *in vivo* demonstration of nucleolin as a marker for the therapeutic targeting of nanomedicine-based formulations against solid tumors (orphan drug designation for the treatment of malignant mesothelioma)].

Future Plans

In the next 5 years, the thematic strand of Innovative Therapies aims to enhance the outputs in 5% regarding the capacity to: (i) publish peer-reviewed publications in high impact factor journals, (ii) to attract international funds, (iii) to train a new generation of scientists in the area of therapies and diagnostic and (iv) to file new intellectual property.

Advanced Therapies

Lino Silva Ferreira (PhD, Group Leader)
Akhilesh Rai (PhD)
Arnab Banerjee (PhD)
Artur Rodrigues (PhD)
Catarina Rebelo (PhD)
Cristiana Paulo (PhD)
Henrique Almeida (PhD
Hugo Fernandes (PhD)
Luís Estronca (PhD)
Miguel Lino (PhD)
Patricia Martins (PhD)
Patrícia Pitrez (PhD)
Ricardo Neves (PhD)
Sérgio Sousa (MD, PhD)
Sónia Pinho (PhD)
Susana Rosa (PhD)
Susana Simões (PhD)
Vítor Francisco (PhD)
Andreia Marques (PhD Student)
Andreia Vilaça (PhD Student)
Deolinda Santinha (PhD Student)
Helena Aires (PhD Student)
Inês Ribeiro (PhD Student)
João Novo (PhD Student)
Luís Monteiro (PhD Student)
Ricardo Abreu (PhD Student)
Rita Sá Ferreira (PhD Student)
Sandra Pinhanços (PhD Student)
Tiago Reis (PhD Student)
Ana Carolina Caetano (Grant Technician)
Ângela Sandoval (Grant Technician)
Carlos Jesus (Grant Technician)
Francesca Tomatis (Grant Technician)
Inês Albino (Grant Technician)
Marta Barão (Grant Technician)
Rafaela Ferrão (Grant Technician)
Tiago Rondão (Grant Technician)
Ricardo Santos (Student)
Simão Santos (Student)
João Novo (PhD Student)
Diogo Cruz (MSc Student)
Francisco Tejo (MSc Student)
Joana Padrão (MSc Student)
Rita Pereira (MSC Student)

Vectors, Gene and Cell Therapy

Luis Fernando Morgado Pereira Almeida (PhD, Group Leader)
Rui Jorge Gonçalves Pereira Nobre (PhD)
Liliana Simões Mendonça (PhD)
Catarina Sofia Oliveira Miranda (PhD)

Rita Catarina Gonçalves Perfeito (PhD)
Sónia Patrícia Dias Duarte (PhD)
Magda Matos Santana (PhD)
Sérgio Abílio Teixeira Bernardo de Sousa (MD, PhD)
Maria da Conceição Monteiro Pedroso de Lima (Agr)
Maria Amália da Silva Jurado (PhD)
Dina Maria da Silva Rodrigues Pereira (PhD)
Pedro Ricardo Lucas Perdigão (PhD)
Sara Isabel Monteiro Lopes (PhD)
Diana Isabel da Silva Santos (PhD)
Ana Cristina Lopes Vasconcelos Ferreira (PhD)
António David Rufino-Ramos (PhD Student)
Maria Inês Morgado Oliveira Martins (PhD Student)
Patrícia Alexandra Rosado Albuquerque (PhD Student)
Miguel Monteiro Lopes (PhD Student)
Kevin Costa Leandro (PhD Student)
Maria Inês Veiga de Almeida Barros (PhD Student)
Patrick Joel da Silva (PhD Student)
Carina Santos Henriques (PhD Student)
Daniel Alexandre Sousa Henriques (PhD Student)
Diana Filipa Duarte Lobo (PhD Student)
Ana Carolina Pinheiro Silva (PhD Student)
Ana Rita Moura Fernandes (PhD Student)
Rodrigo Ribeiro (PhD Student)
Frederico Pena (PhD Student)
Valentin Fernandez (PhD Student)
Ricardo Moreira (PhD Student)
Catarina Mendes Morais (PhD Student)
Maria Manuel Martins Pinto (PhD Student)
Daniela Oliveira (PhD Student)
Beatriz Machado Serra (PhD Student)
Rafael Baganha (PhD Student)
Maria Inês Santos (PhD Student)
Diana Adão (PhD Student)
Maria do Rosário Ferreira da Costa Faro (Grant Technician)
Jisette González Núñez (PhD Student)
António Silva (Msc Student)
Mariana Machado (Msc Student)
Olga Maria Fernandes Borges Ribeiro (PhD)
Sandra Cristina Campos de Jesus (PhD)
Alexandra Melo (Msc Student)
Armando Remondes (Msc Student)
Lucas (Msc Student)
Micaela Figueiredo (Msc Student)
Paulo Felix (Msc Student)
João Braz (Grant Technician)
Ana Catarina Vinhas (Grant Technician)

Tumor Microenvironment and Targeted Therapies

João N. Moreira (PhD, Group Leader)
Anália Carmo (PhD)
Henrique Faneca (PhD)

Luís Bimbo (PhD)
Rosemary Cordeiro (PhD)
Sérgio Simões (PhD)
Teresa Martins (PhD)
Marta Pereira (MD)
Ana Rita Ribeiro (PhD student)
Daniela Santo (PhD Student)
Dina Farinha (PhD Student)
Mariana Biscaia (PhD student)
Filipa Cruz (Grant Technician)
Teresa Abreu (PhD student)
Albina Bushmalyova (Student)
Daniel Oliveira (Student)
Inês Pinto (Student)

Cell Reprogramming and Developmental Hematopoiesis

Carlos Filipe Pereira (PhD, Group Leader)
Cristiana Pires (PhD)
Lavínia Romera (PhD)
Alexandra Ferreira (PhD Student)
Inês Caiado (PhD Student)
Rita Alves (PhD Student)
Luís Oliveira (PhD student)
Susana Pedreiro (Grant Technician)

Medicinal Chemistry & Drug Discovery

Jorge Salvador (PhD, Group Leader)
Alcino Leitão (PhD)
Clarissa Faria (PhD)
Gabriela Silva (PhD)
Maria do Céu Sousa (PhD)
Sara Domingues (PhD)
Sofia Anastácio (PhD)
Vânia Moreira (PhD)
Judite Coimbra (PhD Student)
Pedro Fernandes (PhD Student)
Sara Moura (PhD Student)
Tiago Lima (PhD Student)
Rita Oliveira (PhD Student)
Ágata Lourenço (Grant Technician)
Daniela Alho (Collaborator)
Pedro Sobral (Collaborator)

Molecular Biotechnology and Protein Engineering

Isaura Simões (PhD, Group Leader)
Alexandra Carvalho (PhD)
Carlos Faro (PhD)
Paula Veríssimo (PhD)

Pedro Curto (PhD)
Ricardo Vieira-Pires (PhD)
Pedro Figueiredo (PhD Student)
Beatriz Almeida (PhD Student)
Ricardo Cunha (PhD Student)
Tiago Ôchoa-Pires (PhD Student)
André Simões (MSc Student)
Rafaela Seabra (MSc Student)

Functional Genomics and RNA-Based Therapeutics

Miguel Mano (PhD, Group Leader)
Ricardo Silva (PhD Student)
Flávia Rodrigues (PhD Student)
Inês Lopes (PhD Student)
Jane Dias (PhD Student)
Susana Costa (PhD Student)

RNA & Infection

Ana Eulalio (PhD, Group Leader)
Caio Franco (PhD)
Laura Alcântara (PhD)
Inês Lopes (PhD Student)
Jane Dias (PhD Student)
Susana Costa (PhD Student)

Molecular Microbiology and Microbiome

Nuno Empadinhas (PhD, Group Leader)
Ana Maranha (PhD)
John D. Marugg (PhD)
Susana Alarico (PhD)
Daniela Nunes-Costa (PhD Student)
Inês Roxo (PhD Student)
Ana Rita Fonseca (Volunteer)
Sara Gonçalves (Volunteer)

Medical Microbiology

Teresa Gonçalves (PhD, group leader)
António Carlos Miguéis (MD, PhD)
Chantal Fernandes (PhD)
Lisa Rodrigues (PhD)
Célia Nogueira (PhD)
Patrícia Diogo (MD, PhD)
Rui Soares (MD, PhD Student)
Gil Correia (MD, PhD Student)
Edmilson Correia (PhD Student)

Mariana Afonso (PhD Student)
Joana Oliveira (MSc)
Daniela Calheiros (MSc)
Rita Domingues (MSc)
Jorge Varandas Lindo (MD Student)
Ana Filipa Silva (MSc Student)

ADVANCED THERAPIES

Head: Lino Ferreira

Objectives

The main scientific objectives of the group are: (i) to use stem cell-based therapies for the treatment of ischemic diseases, (ii) to develop innovative strategies for cell reprograming, (iii) to implement stem cell-based assays and in silico approaches for drug screening and (iv) to deliver novel therapeutic compounds identified in the previous high-throughput approaches using nanotechnology-based non-viral vectors.
1- Stem cell-based therapies for the treatment of ischemic diseases. To evaluate the therapeutic effect of stem cells in the treatment of ischemic diseases (e.g. stroke, myocardial infarction and chronic wounds).
2- To implement stem cell-based assays and in silico approaches for drug screening. Develop several tissue models from stem cells as platforms for drug discovery programs related to ischemic diseases. Develop biomaterials and bioengineering platforms for the efficient maturation/specification of stem cells and their progenies and the high-throughput identification of non-coding RNAs to modulate (stem) cell activity, by the design of new biomaterials with relevant biological information, molecular and cell biology, microfluidic systems, high content analysis, and animal experimentation.
3- Development of novel therapeutic compounds identified from high-throughput approaches using nanotechnology-based non-viral vectors.
The complex mechanisms of cancer multidimensional signalling, and complex formation was largely unknown, thereby hindering efforts to create new effective drugs. In the last year we have focused on:
- understand and map the universal principles underlying key soluble and membrane protein targets families using pharmacogenomic and pharmacoproteomic data.
- attain comprehensive databases.
- assemble genomic and biophysical data and create predictive methodologies with those.
- create various public easy-access platforms available at www.moreiralab.com and https://github.com/MoreiraLAB.

This could only be achieved by integrating and analyzing large-scale data, the sheer amount, diversity, and source(s) of which prompted the usage of the most advanced computational/programming techniques, in particular Artificial Intelligence (AI) algorithms. Our methodological innovations were achieved in different areas (omics, structural biophysics, and computer science) and its applications span very different subfields of Drug-Target Development.

The main training/outreach activities objectives of the group were: (i) to participate in post-graduate programs, specifically in the PhD program of CNC "Biomedicine and Experimental Biology" and the PhD program of MIT-Portugal in "Bioengineering" and (ii) to participate in outreach activities organized by CIBB or associated institutions (IEC)

Main Achievements

In 2021 the group continued to achieve progresses to address the scientific questions that drives the research of the group: (i) can we use stem cells to generate *in vitro* models of ageing and for drug screening? (ii) can we modulate stem cell niche by nanomaterials? (iii) what are the miRNAs involved in (stem) cell survival after transplantation to ischemic sites?

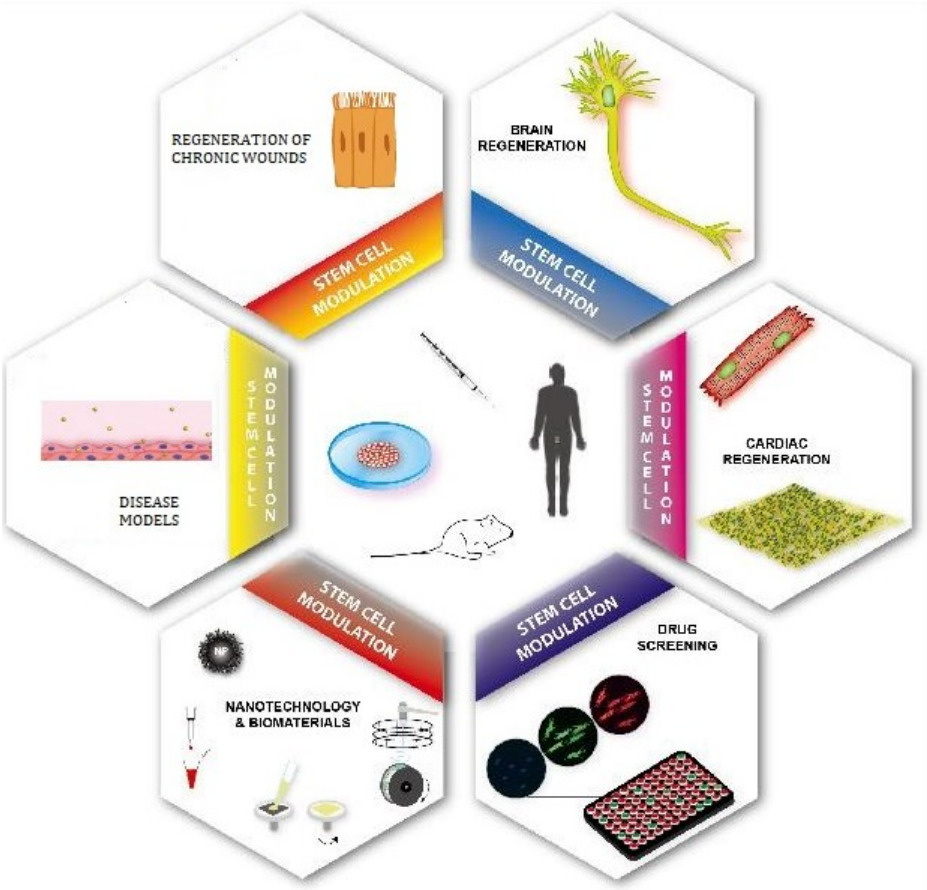
We developed personalized human in vitro platforms composed of human-induced pluripotent stem cell (hiPSC)-derived endothelial cells (ECs) and hiPSC-derived smooth muscle cells (SMCs)

with “young” and “aged” phenotypes which we used to evaluate the interaction of nanomaterials with the vascular system and the results were validated in a reporter zebrafish model of vasculogenesis. These results highlight the relevance of using hiPSC-derived vascular systems to screen vascular nanomaterial interactions (Estronca et al, Nanoscale Horizons 2021

We successfully used a fluorescently-labelled miRNA to quantify the efficiency of different methods to modulate the cargo of sEVs. The modulated sEVs were able to delivery miR-155-5p into a reporter cell line, confirming the successful delivery and functionality of the miRNA to the target cell (Abreu et al., Journal of Extracellular Vesicles, 2021)

We developed the MEmbrane protein dimer Novel Structure Analyser database (MENSAdb). This interactive web application summarizes the evolutionary and physicochemical properties of dimeric MPs to expand the available knowledge on the fundamental principles underlying their formation (Matos-Filipe et al., Database, 2021)

In order to centralized the different resources establishing Disease-Disease Associations (DDAs), we have proposed SicknessMiner, a biomedical Text-Mining (TM) approach towards the centralization of DDAs. Our methodology encompasses Named Entity Recognition (NER) and Named Entity Normalization (NEN) steps, and the DDAs retrieved were compared to the DisGeNET resource for qualitative and quantitative comparison. We believe is a valuable tool to extract disease-disease relationship from RAW input corpus. (Rosario-Ferreira et. al., BMC Bioinformatics, 2021)



VECTORS, GENE AND CELL THERAPY

Head: Luis Pereira de Almeida

Objectives

The research in the Group Vectors, Gene and Cell Therapy is devoted to the creation of new effective therapies for brain diseases that can be moved from the bench to the bedside. For this, the group designs and uses technological platforms based on viral and non-viral gene transfer vectors, and induced pluripotent stem cells for the:

1. Establishment of models of brain disease;
2. Study of disease mechanisms;
3. Development of new molecular and stem cell, therapeutic and prophylactic approaches for brain disorders, particularly neurodegenerative diseases, notably Machado-Joseph's disease (MJD)/ spinocerebellar ataxia type 3, as well as brain tumours.
4. Development of polymeric nanoparticles as vaccine adjuvants for prophylactic and/or therapeutic vaccines

The group results from a restructuration of the former "Vectors and Gene Therapy" group, and has a strong expertise in gene transfer (viral and non-viral) and stem cells for brain disease-modeling and therapy and for genetic vaccines. Our technological platforms include:

- Lentiviral and adeno-associated AAV viral vectors;
- Exosomes and nanoparticles targeted to the brain repair and vaccination;
- Gene editing with CRISPR-Cas9;
- Induced pluripotent stem cells for disease modelling;
- Neural Stem Cell and mesenchymal stromal cells transplantation for brain repair;
- Biomarker discovery from patient fluids.

Our studies on non-viral vectors have been mainly focused on the evaluation of the potential of novel lipid-based nanosystems and polymeric nanoparticles in gene therapy strategies for the treatment of both cancer and neurodegenerative disorders, and for the development of vaccines. Non-viral vectors, such as cationic liposomes, cationic polymers, stable nucleic acid lipid particles and cell-penetrating peptides have been explored as carrier systems to deliver nucleic acids, including plasmid DNA encoding therapeutic proteins and miRNA mimics, as well as antisense oligonucleotides, siRNAs and anti-miRNA locked nucleic acids, aiming at promoting silencing of known oncogene proteins and cancer-related miRNAs. The group is interested in investigating the anti-tumoral effect of gene therapy strategies, either *per se* or in combination with chemotherapeutic agents, both *in vitro* and in animal models for different types of cancer. A lipidomic approach to cancer has been developed using RNA interference to unravel the role of membrane lipids in cancer cell signaling and chemoresistance.

Fundamental research work addressing the development and physicochemical characterization of new nucleic acid delivery systems has also deserved the attention of our group. Research efforts have been developed to define, through a biophysical approach, the architecture parameters that endow vectors with the ability to transpose membranes and efficiently deliver their cargo into the cell.

Our group is also dedicated to the design and preparation of polymeric nanoparticles with immunomodulator or immunopotentiator effect to vectorize antigens and stimulate antigen presenting cells (APC's) in order to develop new vaccines. Particularly, the development of a therapeutic vaccine for the hepatitis B, based on glucan and chitosan particles is the objective of the main project of the group running in 2021.

The research developed relies on collaborative efforts of a dynamic team including fundamental, pre-clinical, and clinical, junior and senior researchers.

Main Achievements

The group has been particularly successful in disclosing SCA3 underlying mechanisms related to autophagy and calpain-ataxin-3 interactions in *in vitro* and *in vivo* models of the disease. Furthermore, we have also been developing progressive research in the field of gene therapy, by knocking-down ataxin-3 mediated by miRNA, which proved to alleviate the molecular disease hallmarks in a transgenic mouse model of SCA3. We have also contributed to the identification of possible biomarkers of Machado-Joseph disease, in collaboration with international researchers.
Following our *in vitro* and *in vivo* studies on the development and application of a targeted miRNA-based therapy for glioblastoma (GB), we found that the generated chlorotoxin-coupled stable nucleic acid lipid particles (SNALPs) are efficiently internalized by human glioblastoma stem cells (GSCs). These findings reveal that such tumor-targeted nanoparticles constitute a promising nanosystem for *in vivo* targeted delivery of therapeutic nucleic acids to tumors established from human GSCs orthotopically implanted in nude mice, a new animal tumor model that is currently being developed under a joint collaboration with the University of Madrid, Spain.
The therapeutic relevance of increasing the expression of miRNA-302a, which was not detected in human GB samples, was shown to emerge from two lines of evidence. Firstly, miRNA-302a mimics promoted differentiation of human GSCs, impairing tumor cell progression and chemoresistance. Secondly, silencing of the lncRNA-MVIH, which was demonstrated to act as a miRNA-302a sponge, resulted in inhibition of human GB cell survival, proliferation, migration/invasion, autophagy and energy metabolism, due to the release of miRNA-302a, rendering this miRNA available to inhibit the translation of its target mRNAs.
On the other hand, we provided evidence that disturbances in human GB cell energy metabolism (induced by upregulation of the miRNA-200) as well as in lipid metabolism (resulting from downregulation of the enzyme SCD1) lead to a significant increase in the susceptibility of GB cells to the chemotherapeutics temozolomide and sunitinib, respectively. Importantly, in this latter case, the combined therapy resulted in a synergistic effect on GB cell viability, as determined using the Bliss independence criterion.
As already mentioned, the group is also interested in the development of nanoparticles targeted for vaccination. The chitosan and glucan were the selected polymers for the preparation of nanoparticles with adjuvant function. During this year mechanistic studies with human monocytes and dendritic cells were performed to study the immunomodulatory properties of β-glucans nanoparticles. The activation of the immune system and the induction of cellular responses by β-glucans is a result of their specific interaction with several pattern recognition receptors (PRRs), such as Dectin-1. However, we found that the size of the glucan particles has a direct effect on this interaction. For instance, the results showed a transient and concentration-dependent ROS production at 45 min for Curdlan and GPs samples, and a time and concentration-dependent ROS production for Glu 355 NPs and Glu 130 NPs. However, ROS production induced by Glu 130 NPs appears to be related to a decreased cell viability, even though the concentrations tested were lower than for the rest of the samples. In contrast, Glu 355 NPs were able to induce an impressive increase in ROS production, not diminishing cellular viability of the cells.

TUMOR MICROENVIRONMENT AND TARGETED THERAPIES

Head: João Nuno Moreira

Objectives

Main objectives have focused on the design and characterization of targeted entities, namely inorganic-, lipid- or polymeric-based nanosystems for small drugs and nucleic acid delivery, either as single or combined regimens, addressing the underlying mechanism of interaction with the tumor microenvironment and cancer cells, both at the cellular and molecular level, at the *in vitro* and *in vivo* level. With this, novel antitumor targeted strategies are expected to be generated against tumors associated with clear unmet medical needs, with higher therapeutic efficacy and improved safety profile relative to the corresponding standard treatments.

Additional goal point towards the identification and validation of target proteins overexpressed in tumors, combined with the demonstration of their importance for the tumorigenic process. We believe that this strategy will enable to establish the mechanism of action of the targeted strategies the members of the group have been working on, either with single or drug combinations. It will ultimately overcome the challenges posed by drug resistance and metastasis, thus leading to decrease of overall tumor burden and relapse as well, clearly benefiting cancer patients.

Main Achievements

Different formulations have been designed and developed in order to generate efficient delivery nanosystems, both for individual and combined gene and drug delivery into hepatocellular carcinoma (HCC) cells. A library of galactose containing cationic glycopolymers, based on poly(2-aminoethyl methacrylate hydrochloride) (PAMA) and poly(2-lactobionamidoethyl methacrylate) (PLAMA), with different molecular weights, carbohydrate/cationic ratios, and different compositions (block or statistical) were synthesized by ARGET ATRP. Among the different glycopolymers prepared, the nanocarriers generated with the statistical $PAMA_{114}$-*co*-$PLAMA_{20}$glycopolymer exhibited higher transfection activity than that obtained with the nanocarriers used as reference. This best formulation, presented small mean diameter, positive surface charge, high DNA protection and an improved biological activity/biocompatibility relationship compared to the glycoplexes prepared with the corresponding block glycopolymer. $PAMA_{114}$-*co*-$PLAMA_{20}$-based polyplexes specifically bind to the ASGP receptor, being internalized by clathrin-mediated endocytosis.
We have also developed different polymer-coated mesoporous silica nanoparticles to simultaneously deliver chemotherapeutic agents and genetic material into HCC cells. They exhibited small mean diameters, positive surface charge, high DNA protection and a significant drug loading capacity. The developed hybrid nanosystem based on silica and PEG-*b*-PAMA block copolymer revealed good performance in simultaneously transporting and delivering the anticancer drug epirubicin and plasmid DNA containing the HSV-TK gene in 2D and 3D cancer cell culture models. A single dose of the combinatorial therapeutic strategy showed higher efficiency than the individual chemotherapeutic strategy, highlighting the importance of this combined strategy.

As an additional main achievement was the in vivo demonstration of nucleolin as a marker for therapeutic (and safe) targeting of (intravenous administered) nanomedicines-based strategies to nucleolin-overexpressing solid tumors (Fonseca et al., 2021, IF: 20.722). This strategy has

resulted in improved intracellular tumor bioavailability of encapsulated drug, at low systemic exposure, associated with a safe toxicological profile (in mice, rats and dogs). Levels of cell surface nucleolin dictated the antitumor activity of the developed targeted nanoparticle against nucleolin-overexpressing solid tumors of diverse histological origin, evidencing a significant growth inhibition of malignant mesothelioma over the standard of care. Those observations were paralleled by an impairment of the nucleolin-positive vasculature and downregulation of typically overexpressed genes. Patient stratification based on nucleolin mRNA expression correlated with prognosis and enabled identification of breast and mesothelioma tumors that may potentially benefit from the developed strategy. Overall, a novel principle of drug delivery was generated with potential therapeutic impact across nucleolin-overexpressing human cancers, upon adequate patient-stratification.
This work, along with the research activity of TREAT U, SA, a spin-off from CNC and UC, on a targeted Lipid Nanoparticle targeted to nucleolin was the basis for the Orphan Drug Designation for the treatment of malignant mesothelioma, awarded by EMA (url: t.ly/ZfIi) and FDA (url: t.ly/Pkus).

FUNDING
"Tackling CANcer STEM CELls: a challenge and an opportunity to advance in anti-cancer therapy". COMPETE2020 (ERDF)/FCT; Ref.: POCI-01-0145-FEDER-016390/€45.808,50.

Development of an innovative targeted-nanoparticle formulation for combined gene therapy and chemotherapy application in hepatocellular carcinoma. IF/01007/2015; FCT; 2017-2021 (50 000.00€).

Development of an innovative nanosystem to mediate a combined and multi-target therapeutic strategy to hepatocellular carcinoma. POCI-01-0145-FEDER-30916; FCT; 2018-2021 (239 884.55€).

CELL REPROGRAMMING AND DEVELOPMENTAL HEMATOPOIESIS

Head: Carlos Filipe Pereira

Objectives

The focus of our research is to understand the molecular determinants underlying cellular reprogramming and hematopoietic specification. Cellular reprogramming can be achieved experimentally in different ways, including nuclear transfer, cell fusion or expression of transcription factors. The emergent ability to reprogram any human cell into desired hematopoietic cell-types is opening avenues to the discovery of new therapies for immune and blood diseases. The goals of my laboratory are a) to understand at the molecular level how hematopoietic cellular identities are specified employing cellular reprogramming and b) to use this knowledge to manipulate genes and pathways that ultimately may allow the generation of patient-specific hematopoietic cells for regenerative medicine and immunotherapy.

Main Achievements

My research group has shown that cooperative transcription factor binding mediates hemogenic induction and pioneered cell fate reprogramming approaches in immunology with induced dendritic cells. This conceptual shift opens exciting opportunities to merge cellular reprogramming and cancer immunotherapy. We have published 8 papers in 2021 and had 1 PhD thesis completed from Fábio Rosa on dendritic cellular reprogramming

MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Head: Jorge Salvador

MOLECULAR BIOTECHNOLOGY AND PROTEIN ENGINEERING

Head: Isaura Simões

Objectives

The general objectives of our group are to contribute to a better understanding of mechanisms of disease and pathogenicity in the context of infection by *Rickettsia*, contribute for the identification of bacterial virulence proteins susceptible of antibody-based targeting strategies for the development of new biological drugs, and the rational design of enzymes with increased activities, new specificities and improved selectivities using our own developed protocols based on state-of-the-art computational biochemistry methods. In a parallel strand we also aim to continue exploring the functional and biotechnological aspects of plant proteases, namely their role and potential targetability in allergic disorders.

Our research programs combine diverse methodologies from cell biology, structural and molecular biology, recombinant DNA technology and heterologous protein production, biochemical and biophysical protein characterization, protein chemistry, computational methods like Quantum Mechanics/Molecular Mechanics (QM/MM) method, Molecular docking and molecular dynamics, complemented with various system-wide quantitative approaches.

Main Achievements

We pursued with studies to understand in detail the role of macrophages in rickettsial pathogenesis. We evaluated proteome signatures by SWATH-MS (at 24 hpi) of THP-1 macrophages infected with different *rickettsial species responsible for mild rickettsioses*. We demonstrate that the mildly pathogenic *Rickettsia parkeri*, *Rickettsia africae*, and *Rickettsia massiliae*, all successfully proliferating in macrophages, trigger different proteome signatures in these cells and differentially impact critical components of innate immune responses by inducing different levels of beta interferon (IFN-β) and interleukin 1β (IL-1β) and different timing of pyroptotic events during infection. Our work reveals novel nuances in rickettsia-macrophage interactions, offering new clues to understand *Rickettsia* pathogenicity. **DOI:**https://doi.org/10.1128/spectrum.00814-21

We demonstrated that APRc (rickettsial retropepsin) targets host serum components, combining nonimmune immunoglobulin (Ig)-binding activity with resistance to complement-mediated killing. We confirmed nonimmune human IgG binding in extracts of different rickettsial species and intact bacteria. Our results revealed that the soluble domain of APRc is capable of binding to human (h), mouse, and rabbit IgG and different classes of human Ig (IgG, IgM, and IgA) in a concentration-dependent manner. APRc-hIgG interaction was confirmed with total hIgG and normal human serum. We provided evidence of interaction preferentially through the Fab region and confirmed that binding is independent of catalytic activity. We demonstrated that expression of the full-length protease in E. coli is sufficient to promote resistance to complement-mediated killing and that interaction with IgG contributes to serum resistance. Our findings position APRc as a novel Ig-binding protein and a novel moonlighting immune evasion factor of Rickettsia, contributing to the arsenal of virulence factors utilized by these intracellular pathogens to aid in host colonization. **DOI:**https://doi.org/10.1128/mBio.03059-21

In the last year we have studied the catalytic mechanism of cocaine hydrolysis by the human carboxylesterase 2 (CES-2). This was a benchmark study for the hydrolysis of xenobiotic compounds by CES-2. We have also designed conjugates of synthetic derivatives of nucleic acids with peptides, characterized an aspartic protease and kept working on the development of tools

for biosynthetic pathways, including bacterial allosteric transcription factors (aTFs), such as UxuR.

We published the first edited Volume on the IgY-Technology field; the work addresses the historical and dynamic development of IgY-applications, covering the biological basis and theoretical context, methodological guidance, and applications of IgY-Technology. A particular focus was done on the use of IgY-antibodies for prophylactic/therapeutic purposes in human and veterinary medicine. The book is a valuable resource and guide for Scientists, Clinicians and Health Product Developers in both human and veterinary medicine (DOI: 10.1007/978-3-030-72688-1).
We further explored and characterized outer-membrane TolC-like channel-tunnels of different Gram-negative bacteria, using bioinformatic tools, with particular focus on the extracellular region of the channel. We revealed in particular unique sequence composition features of the extracellular loop regions, elucidating individual signatures across different Gram negatives (A.Simões, Msc Thesis).
In addition, we developed recombinant vaccines against *Vibrio spp* extracellular loops and launched subsequent immunization protocols using avian hosts. Finally, we also designed and successfully produced recombinant E.coli-Vibrio TolC chimeras for subsequent in vivo functional efflux assay studies (R.Seabra and A.Simões, Msc Thesis).

FUNCTIONAL GENOMICS AND RNA-BASED THERAPEUTICS

Head: Miguel Mano

Objectives

The research of the Functional Genomics and RNA-based Therapeutics laboratory is focused on three main areas: i) the identification and molecular characterization of novel cellular factors relevant to cardiac regeneration and repair, and the translation of this knowledge into effective RNA-based therapeutic strategies, ii) the development of improved strategies for precise genome correction based on CRISPR; and iii) the development and application of high-throughput and high-content screening technologies using genome-wide siRNA, microRNA and CRISPR libraries.

Cardiovascular diseases, including myocardial infarction, are the leading cause of death globally. In this context, the main topics of our research are the identification and characterization of novel cellular factors that control regeneration and repair of cardiac tissue following injury, focusing on the processes leading to cardiac fibrosis.
The group has also an interest in the development of strategies to increase the efficiency of precise genome editing based on CRISPR, specifically through the understanding of the molecular correlates controlling homology-directed repair.
An additional area of research is the development of high-throughput and high-content screening technologies and their application to different areas of biomedical research. (e.g. regenerative medicine, infection biology, intracellular signaling, and cancer). The laboratory has an extensive network of collaborations in different areas to fully explore the potential of this technology.

Main Achievements

Heart repair following injury occurs typically through the formation of a fibrotic, poorly contractile scar tissue. Cardiac fibroblasts are essential to cardiac function, but the persistence of activated fibroblasts after injury and excessive deposition of extracellular matrix proteins, particularly collagen, leads to stiffening of the heart wall and deterioration of heart function. Given the pervasive role of miRNAs in the control of gene expression through the concomitant regulation of multiple targets, miRNA modulation stands as a very attractive strategy to modulate complex biological processes. The study of miRNA function in the context of cardiac fibrosis has been limited to analysis of miRNA expression in model animals or to functional studies with a small subset of miRNAs.
To systematically address this important biological and clinical problem, we performed a series of image-based high-throughput functional screenings using genome-wide libraries of miRNAs (2,588 mature sequences) for the identification of miRNAs controlling phenotypes critical to cardiac fibrosis: cardiac fibroblast proliferation, fibroblast differentiation into myofibroblasts, and collagen deposition. Using this multipronged screening approach, we identified multiple miRNAs exhibiting very striking and interesting anti-fibrotic phenotypes.
To better characterize the effect of the miRNAs showing marked effects on the different fibrosis-related phenotypes analyzed, we next applied a high-throughput PCR approach, which allowed the evaluation of the effect of the modulation of a panel of 90 selected miRNAs on a set of 90 genes related to fibrosis and ECM remodeling. This extensive gene profiling allowed the identification of miRNAs eliciting similar molecular signatures, which contributed to the final selection of the miRNAs for the in-depth characterization of mechanisms of action and in vivo studies, currently in progress.

Although CRISPR/Cas9 can be targeted to virtually any desired genome locus and efficiently induce double-stranded DNA breaks, the outcome of genome editing relies on the repair of the DNA breaks by the endogenous DNA repair machinery. Given the prevalence of non-homologous

end joining (NHEJ), repair frequently results in gene disruption/knockout caused by insertions or deletions at the target site, rendering the precise outcome of the repair process unpredictable in most biological scenarios.
By performing a genome-wide CRISPR screening, we tested the effect of the knockout of all human protein-coding genes on the process of HDR, using a functional readout. We have identified gene perturbations that lead to a significant increase in HDR, which are currently being characterized in detail. We aim at harnessing this knowledge to increase the efficiency of precise genome editing, using as paradigm the correction of a pathogenic mutation in the MYBPC3 gene responsible for hypertrophic cardiomyopathy.

Funding
FCT Research & Development Grant - PTDC/BIA-MIC/029894/2017
FCT-CAPES Portugal-Brazil Transnational Cooperation Programme

RNA & INFECTION

Head: Ana Eulálio

Objectives

The work in the RNA & Infection research group is mainly focused on the study of the intracellular lifestyles of bacterial pathogens, with a particular interest on the role of microRNAs in infection by the bacterial pathogens. We have been applying systems biology approaches, in particular high-throughput functional screening to identify microRNAs that regulate infection, and RNA-sequencing to identify microRNAs that are regulated upon infection. This is typically followed by a detailed investigation of the targets of the microRNAs of interest, to gain insights into the underlying mechanisms of action. Overall, our work is unravelling novel mechanisms whereby invasion, survival and/or replication of bacterial pathogens is modulated by host microRNAs. The identification and characterization of downstream microRNA targets is also leading to the discovery of novel molecular players and pathways relevant for the host-pathogen interplay, with potential clinical implications.

Main Achievements

Analysis of reprogramming of microRNA expression upon *Salmonella* infection

MicroRNAs are a well-studied class of genome-encoded small non-coding RNAs that play a pervasive role in the post-transcriptional control of eukaryotic gene expression, by repressing target transcripts containing partially complementary binding sites. Despite their relatively low number (ca. 2,500 annotated human mature microRNAs), microRNA-mRNA regulatory networks are highly intricate and it is estimated that ca. two thirds of the human transcriptome is regulated by microRNAs. Although microRNAs were initially shown to be part of the host immune response to fight infection, emerging evidence demonstrates that the host microRNA pathway can also be subverted by bacterial pathogens for their own benefit.

Advances in RNA-sequencing have contributed to revealing that infections by various bacterial pathogens induce extensive changes of the host miRNome. Notwithstanding, the molecular mechanisms underlying most of the described microRNA regulations remain poorly understood. Furthermore, the comparative analysis of microRNA profiles in cells with internalized bacterial and neighboring non-infected bystander cells, as well as the evaluation of their potential relevance for infection, have yet to be investigated.

We analyzed the role of the transcription factor E2F1 in the regulation of microRNAs upon infection with the bacterial pathogen *Salmonella enterica* serovar Typhimurium (hereafter, *Salmonella*). E2F1 is a central player in numerous processes, binding to hundreds of promoter regions of genes involved in numerous cellular pathways, including microRNA genes. We have previously shown that E2F1 expression is decreased upon *Salmonella* infection. We have now determined that E2F1 is a pivotal player in the regulation of the miRNome during *Salmonella* infection, both in infected and bystander cells. Mechanistically, we show that the secretome of *Salmonella*-infected cells is sufficient to induce E2F1 and microRNA regulation in naïve cells, through the activation of the endoplasmic reticulum stress response pathway, involving intercellular signaling mediated by secreted HMGB1 and its interaction with the transmembrane receptor RAGE. Collectively, this work reveals that the downregulation of E2F1 and consequently of microRNAs promotes infection, by promoting on one hand the bacterial replication within infected cells, as well as by priming bystander cells for efficient *Salmonella* infection.

Impact of host cell cycle on *Salmonella* infection

Modulation of the host cell cycle has emerged as a recurrent feature in bacterial pathogenesis. Several molecular strategies are exploited by bacterial pathogens to control the host cell cycle, including the secretion of bacterial effectors and toxins (generally called cyclomodulins) into the host cytosol, or via the modulation of host microRNAs that regulate the cell cycle machinery. Although the most frequent outcome of host cell cycle regulation during bacterial infections is to favor host cell colonization, in most cases the exact benefit to the infection process remains unclear.
Similar to other bacterial pathogens, *Salmonella* has been shown to manipulate the host cell cycle. Indeed, we have previously shown that *Salmonella* actively induces G2/M arrest of host cells (in part via the regulation of microRNA expression), and that infection is severely inhibited in cells arrested in G1.
We have now demonstrated that *Salmonella* vacuolar replication is inhibited in host cells blocked in G1, while the cytosolic replication of the closely related pathogen *Shigella* is not affected. Mechanistically, we show that cells arrested in G1, but not cells arrested in the G2, present dysregulated endolysosomal trafficking, displaying an abnormal accumulation of vesicles positive for late endosomal and lysosomal markers. In addition, the autophagic flux and degradative lysosomal function are strongly impaired. This endolysosomal trafficking dysregulation results in sustained activation of the SPI-1 type III secretion system and lack of vacuole repair by the autophagy pathway, ultimately compromising the maturation and integrity of the *Salmonella*-containing vacuole. As such, *Salmonella* is released in the host cytosol. Collectively, our findings demonstrate that the modulation of the host cell cycle occurring during *Salmonella* infection is related to a disparity in the permissivity of cells arrested in G1 and G2/M, due to their intrinsic characteristics.

Funding
FCT Investigator Programme - IF/01105/2015/CP1280/CT0006
FCT Research & Development Grant - PTDC/BIA-MIC/29999/2017
EMBO Young Investigator Grant

MOLECULAR MICROBIOLOGY AND MICROBIOME

Head: Nuno Empadinhas

Objectives

The threat posed by nontuberculous mycobacteria (NTM), which cause an increasing number of lung infections, has been largely and negligently underestimated in countries of the European Union and in other developed countries. NTM more often infect people with fragile immune systems or underlying chronic conditions namely cystic fibrosis, chronic obstructive pulmonary disease, and naturally the elderly. COVID-19 survivors are also likely at higher risk because of damaged lung tissue and other organs. Our goal is to decipher novel pathways unique to mycobacteria, and that could grant new targets for rational drug design. We are currently also engaged in sampling municipal waters to catalogue NTM prevalence and diversity, as well as to unveil their highly successful but enigmatic adaptive strategies. We aim at uncovering epidemiological links between the exposure to water NTM and the incidence of lung infections and other chronic diseases. Our goal is to influence public health policies in modernizing the water screening protocols in place, to improve microbiological safety of drinking water and to ameliorate the NTM health burden often leading to premature deaths and to irreparable social costs. In a parallel line of research we also aim to unveil the biosynthesis and role of neurotoxins of microbial origin in the context of Parkinson's Disease. Public health authorities neglect the levels of certain toxins in water and foodstuffs of aquatic origin, although their chronic consumption may elicit gut dysbiosis, gut mucosal barrier impairment and chronic inflammation, which collectively may foster neurodegeneration, as we have recently demonstrated in Esteves et al, Gut (2021).

Funding (2021-2025):

NTMENACE-Nontuberculous mycobacteria from drinking water: beyond the lung disease epidemic. PTDC/BIA-MIC/0122/2021, FCT-Fundação para a Ciência e a Tecnologia, Portugal (PI: Nuno Empadinhas). 249.975€ (2022-2025)

Microbiome-miRNAs axis in Parkinson's disease: involvement of mitochondrial mediated inflammatory response. EXPL/MED-NEU/1515/2021, FCT/FEDER (PI: A.R. Esteves, CNC). 49.981€ (2022-2023).

STOPD-The Gut-Immune-Brain Axis in Parkinson disease. PTDC/MED-NEU/3644/2020, FCT/FEDER, Portugal (PI: S.M. Cardoso; Co-PI: N. Empadinhas). 248.922€ (2021-2024).

STERILAEROGEL-Green method to prepare sterilized biopolymers-based aerogels. POCI-01-0145-FEDER-032625, FCT/FEDER (PI: M. Braga, DEQUC; N. Empadinhas @CNC). 29.000€ (2018-2022).

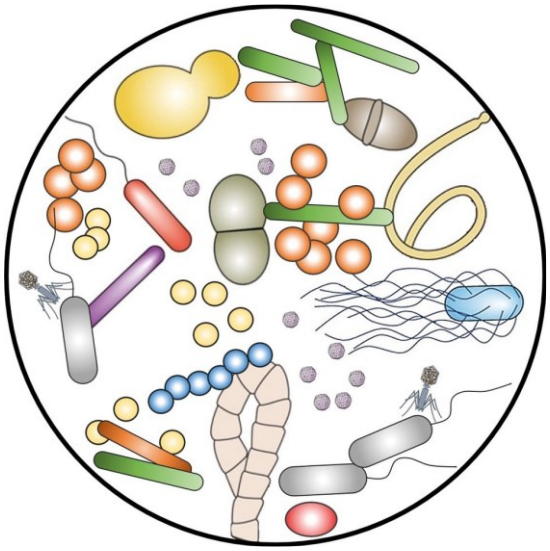
POLYREP-An intriguing mycobacterial polysaccharide: recycling, replication and beyond. POCI-01-0145-FEDER-029221, FCT/FEDER (PI: N. Empadinhas). 236.321€ (2018-2021).

HealthyAging2020 – WP9. Deciphering microbiome signatures in chronic diseases for early diagnosis and modulation therapies. CENTRO-01-0145-FEDER-000012-N2323. HR 50.700€ (2017-2021).

Research achievements in brief:

Gut microbiome & brain disease – We identified molecular mechanisms through which chronic exposure to a dietary neurotoxin of microbial origin and often detected in seafood, elicit a selective erosion of members of the gut microbiota that regulate Th17 immunity, activating chronic mucosal inflammation and neurodegenerative processes across the gut-brain axis including mitochondrial damage and motor impairment compatible with Parkinson's Disease. Our study confirmed that, although without major gut microbiota variations, the ablation of specific and minor gut bacterial groups had a pronounced impact locally, across the gut-brain axis and in the central nervous system. For further details read Gonçalves et al, Antioxid Redox Signal (2021); Munoz-Pinto et al, Ageing Res Rev (2021); Esteves et al, Gut (2021).

Mycobacteria Research - Building on our previous achievements (Ripoll-Rozada et al, 2019, PNAS), a novel mechanism for recycling and semi-conservative replication of mycobacterial polysaccharides of methylmannose (MMP) was identified and described, novel enzymes were characterized, and a role for MMP in adaptation to cold unveiled (Maranha et al, submitted). Water and biofilms sampled from mycobacteria-infected patients' homes and showerhead biofilms confirmed the ubiquity of these opportunists and myriad other microbes, which recommends urgent surveillance by public health authorities. Numerous opportunistic NTM species were isolated from 90% households from both the Center and North regions, five of them were novel species of which we know very little in terms of ecology and pathogenicity.



MEDICAL MICROBIOLOGY

Head: Teresa Gonçalves

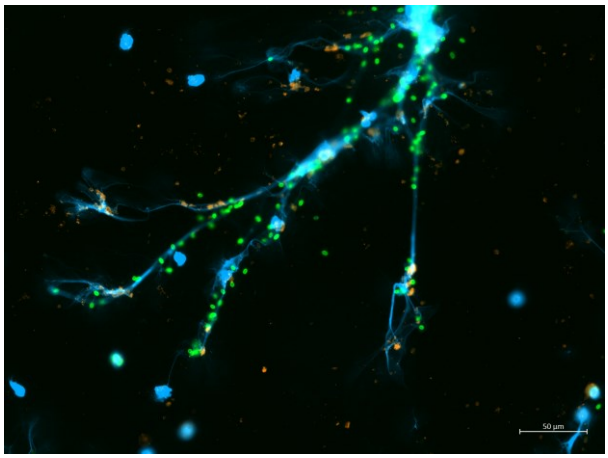
Objectives

The main interests of the Medical Microbiology Group are centered in microbial agents of human disease, its biological traits relevant to infection and seeking for innovative therapies. Immunosenescence, rendering the elderly more susceptible to infection, is one of our major focus (e.g. gut inflammation and respiratory diseases). To accomplish this the group uses both *in vivo* and *in vitro* infection models, human samples, analytical tools. We assembled Standard Operation Procedures (SOPs) for antimicrobials screenings (antiviral, antibacterial and antifungal). Together with permanent medical specialists collaborators (e.g. allergology, otorhinolaryngology, clinical pathology) it fosters the translational between basic- and patient-oriented research. We keep fruitful collaborations with research centers of excellence, nationals, such the BioChem at CIMO (Portugal), N Santos at IMM (Portugal), MC Gameiro da Silva and J Costa of ADAI (Portugal) and international, such as the John Hopkins University (USA), and more recently, with Jay E Slater, Division of Bacterial Parasitic and Allergenic Products, Office of Vaccines Research and Review, of the U.S. Food and Drug Administration (FDA) .
Our research efforts are directed to:

- The role of purines and its receptors, in particular adenosine receptors, in the switch commensalism-infection and in microbiota homeostasis, opening novel approaches to alleviate infection-related damage and chronic inflammation, especially in the elderly;
- The biology and proteome of filamentous fungi considered major agents of respiratory allergic and invasive diseases, identification of novel allergens and delivery modes, aiming to improve diagnosis, treatment and prevention severe respiratory diseases;
- Monitorization, quantification and control of airborne agents transmission (viral, bacterial, fungal)
- Seeking for novel antimicrobials extracted from natural resources, an effort aligned with one of the Human Health Priorities, in the quest for effective infection control drugs.

Main Achievements

- Antifungal activity of plant extracts (tea, coffee spent, African plant)
-Pyomelanin synthesis as a pathogenic trait in filamentous fungi during animal host infection
- Implementation of models to monitor, quantify and control airborne agents transmission (viral, bacterial, fungal)
- Microbial ectonucleotidases as key regulators of NETs
- Adenosine receptors role in chronic leishmaniasis



Candida induced-NETs production

Wheat Germ Aglutinin (WGA; red) for sialic acids, DAPI (blue) for nucleic acids and Oregon Green (OG; green) for yeast.

INTERNATIONALIZATION

Internationalization is a concern of the CIBB strategy. To attain this goal the researchers have been encouraged to establish colaborations and joint projects with laboratories abroad, and to colaborate in the organizaton of international scientific meetings.

NEUROSCIENCE, AND DISEASE

Synapse Bology

Graduate training:
Coordination of the Innovative Training Network Syn2Psy-Synaptic Dysfunction in Neuropsychiatric Disorders [H2020-MSCA-ITN-2018 (813986)]
Co-organization of the PDBEB 2020/21 course on Synapse Structure and Function.
Co-organization of the Synapse Biology course, part of the PDBEB Courses 2021/2022.
Co-organization of the Advanced Imaging course with Luísa Cortes (MICC, CNC-UC), José Rino (iMM, UNL) and Pedro Matos Pereira (ITQB, NOVA), part of the PDBEB Courses 2021/2022.

Invited/selected talks at the international level:
Invited lecture at POST-TRANSLATIONAL MODIFICATIONS IN NEURONAL PHYSIOLOGY AND BRAIN DISORDERS, virtual symposium organized by IN-CNR & Humanitas Research Hospital (Matteo Fossati & Alessandra Folci), July 2021 (Ana Luisa Carvalho)
Selected oral communication at POST-TRANSLATIONAL MODIFICATIONS IN NEURONAL PHYSIOLOGY AND BRAIN DISORDERS, virtual symposium organized by IN-CNR & Humanitas Research Hospital (Matteo Fossati & Alessandra Folci), July 2021 (Joana Ferreira)
Invited lecture at the Current Trends in Biomedicine workshop 'Synaptic Dimension of Brain Disorders', Universidad Internacional Andalucia, Baeza, Spain, October 2021 (Ana Luisa Carvalho)
Selected oral communications at the Current Trends in Biomedicine workshop 'Synaptic Dimension of Brain Disorders', Universidad Internacional Andalucia, Baeza, Spain, October 2021 (Dominique Fernandes and Orsolya Antal)
Seminar at mini-symposium at the Interdisciplinary Institute for Neuroscience, University of Bordeaux, France, December 2021 (Ana Luisa Carvalho)

Redox Biology and Brain Sensing

Collaboration with Erich Gnaiger (Oroboros Instruments, Austria) for the optimization of devices developed in our group for the high-resolution respiration measurements in brain slices. This involved a stay of a Cândida Dias (PhD in our group) at Gnaiger labs.

Collaboration with the group of Andreza Fabro de Bem (Dept. Bioquímica, CCB, UFSC, Florianópolis, Brasil), involving the stay of one of her PhD students developing work in our group, resulting the in the following publication:
Mancini G, Dias C, Lourenço CF, Laranjinha J, de Bem A and Ledo, A (2021) A high fat/cholesterol diet recapitulates some Alzheimer's disease-like features in mice: focus on hippocampal mitochondrial dysfunction. Journal of Alzheimer´s Disease 82, 1619-1633. doi: 10.3233/JAD-210122

Ongoing collaboration with Greg Gerhardt (Univ. Kentucky, USA), Jon Lundberg (Karolinska Institute, Sweden) and Enrique Cadenas (University of Southern California) as members of the team and advisors in currently running FCT-funded projects in the group.

The PI is member of the Advanced Courses committee of FEBS, involved in the reviewing, approval and participation as FEBS member-in-charge in Advanced Courses across Europe.

Neuroendocrinology and Aging

Collaborative publications:
Laetitia S. Gaspar, Janina Hesse, Müge Yalçin, Bárbara Santos, Catarina Carvalhas-Almeida, Mafalda Ferreira, Joaquim Moita, **Angela Relógio**, Cláudia Cavadas, Ana Rita Álvaro (2021); Long-term Continuous Positive Airway Pressure Treatment Ameliorates Biological Clock Disruptions in Obstructive Sleep Apnea. EBiomedicine; Volume 65, 103248. doi: https://doi.org/10.1016/j.ebiom.2021.103248

Daniel Klyonsky, …, Célia Aveleira, ...Cláudia Cavadas,…et al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). Autophagy. 2021 Jan;17(1):1-382. doi: 10.1093/gerona/glz280.
Collaborators:
Angela Relógio - Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt - Universität zu Berlin, and Berlin Institute of Health, Institute for Theoretical Biology, Germany (circadian rhythm, co-supervisor).
Carlos Lopez Otin - Facultad de Medicina, Universidad de Oviedo, Oviedo, Spain (Collaborative Research, Graduate training; Premature aging and progeria models; hallmarks of aging; scientific advisor)
Xavier Nissan - I-Stem, Paris, France (Collaborative Research & Co-supervisor of PhD student; host of PhD student Marisa Marques (October 2019-February 2020)

David Smith - Sleep Center, Cincinnati Children's Hospital Medical Center, OH, USA
https://www.cincinnatichildrens.org/bio/s/david-smith; PhD student Laetitia Gaspar will be a visiting PhD student at Simth's lab during 2021 (Fulbright Award)

Amita Sehgal - Perelman School of Medicine, University of Pennsylvania, USA
https://www.med.upenn.edu/sehgallab/, Co-supervisor of the PhD student Catarina Almeida.

João Passos, Cell and Molecular Aging Lab, Mayo Clinic in Rochester, Minnesota, USA
https://www.mayo.edu/research/labs/cell-molecular-aging/overview ; Co-supervisor of the PhD student Ana Catarina Franco.

Neurotrophin Signaling and Synaptic

The experimental work for the master thesis: "Alteration of neuronal networks in epilepsy: the role of the K+-Cl− co-transporter KCC2." was performed by Claudia Corso during an international graduate training supported by the Erasmus+ program of the Università degli Studi del Sannio, Italy. This thesis will be presented at the University of Sannio in April 2022

Emanuel Tahiri. Master thesis. Early autophagy dysfunction in Alzheimer's disease: the role of WIPI2. Master in Cellular and Molecular Biology, University of Coimbra, CNC (Coimbra) and Master in Biology, University of Sannio (Italy) (Supervisor: Rui O. Costa). Emanuel Tahiri was a

student of the Double Master Degree program between the University of Coimbra (Portugal) and University of Sannio (Italy).

Neuromodulation

-Networks:

International Alliance for Healthy Ageing (with Univ. Newcastle, Groningen Medical School, Univ. Copenhagen, Mayo Clinics, Univ. Minnesota)

Association for Science and Information on Coffee

Neuronal Circuits and Behaviour

Participation in the Syn2Psy European Training Network Grant agreement ID: 813986.

Coordinator of the SHANKAstro ERA-NET Neuron Project

Mitochondria and Neurodegenerative Disorders

Graduate Training:

- "Neuroscience and Mental Health", *The Doctoral Programme in Health Sciences (PhDHS)*, organized by the Faculty of Medicine, University of Coimbra

Coordinators: Ana Cristina Rego and Isabel Santana

Date: January 18-22, 2021

International collaborative publications:

Geva M., Gershoni-Emek N., Naia L., Ly P., Mota S., Rego A. C., Hayden M. R., Levin L. A. (2021) Neuroprotection of retinal ganglion cells by the sigma-1 receptor agonist pridopidine in models of experimental glaucoma. *Sci. Rep.* 11, 21975. doi: 10.1038/s41598-021-01077-w. PMID: 34753986

Mota S. I., Pita I., Águas R., Tagorti S., Virmani A., Pereira F. C.*, Rego A. C.* (2021) Mechanistic perspectives on differential mitochondrial-based neuroprotective effects of several carnitine forms in Alzheimer's disease *in vitro* model. *Arch Toxicol.* 95, 2769-2784. doi: 10.1007/s00204-021-03104-1. PMID: 34164711. *Co-corresponding authors

Naia L., Ly P., Mota S. I., Lopes C., Maranga C., Coelho P., Gershoni-Emek N., Ankarcrona M., Geva M., Hayden M. R., Rego A. C. (2021) The Sigma-1 receptor mediates pridopidine rescue of mitochondrial function in Huntington disease models. *Neurotherapeutics* 18, 1017-1038. doi: 10.1007/s13311-021-01022-9. PMID: 33797036

Naia L., Pinho C. M., Dentoni G., Liu J., Leal N., Ferreira D. M. S., Schreiner B., Filadi R., Fão L., Connolly N. M. C., Forsell P., Nordvall G., Shimozawa M., Greotti E., Basso E., Theurey P., Gioran A., Joselin A., Arsenian-Henriksson M., Nilsson P., Rego A. C., Ruas J. L., Park D., Bano D., Pizzo P., Prehn J. H. M., Ankarcrona M. (2021) Neuronal cell-based high-throughput screen for enhancers of mitochondrial function reveals luteolin as a modulator of mitochondria-endoplasmic reticulum coupling. *BMC Biology* 19, 57. doi: 10.1186/s12915-021-00979-5. PMID: 33761951

Toledo J. P., Fernández-Pérez E. J., Ferreira I. L., Marinho D., Riffo-Lepe N. O., Pineda-Cuevas B. N., Pinochet-Pino L. F., Burgos C. F., Rego A. C.*, Gerardo Aguayo L.* (2021) Boldine attenuates synaptic failure and mitochondrial deregulation in cellular models of Alzheimer's disease. *Front. Neurosci. (section Neuropharmacology)* 15, 617821. doi: 10.3389/fnins.2021.617821. PMID: 33679301

Naia L., Carmo C., Campesan S., Fão L., Cotton V. E., Valero J., Lopes C., Rosenstock T. R., Giorgini F., Rego A. C. (2021) Mitochondrial SIRT3 confers neuroprotection in Huntington's disease by regulation of oxidative challenges and mitochondrial dynamics. *Free Radic. Biol. Med.* 163, 163-179. doi: 10.1016/j.freeradbiomed.2020.11.031. PMID: 33285261

Speaker(s) in international meetings:

Fão L., Mota S. I., Rego A. C. (2021) Altered autophagy-dependent c-Src/Fyn degradation in Huntington's disease – impact on NMDAR activity. 45th FEBS Congress "Molecules of Life: Towards New Horizons", speed talk SpT-02-02, 3-8 July, 2021 (virtual event organized at Ljubljana, Slovenia).

Beatriz M., Vilaça R., Daley G., Januário C., Schlaeger T., Rego A. C., Lopes C. (2021) Extracellular vesicles from fibroblasts of Huntington's Disease patients are involved in the transfer of mitochondrial components. European Society for Clinical Investigation (ESCI) 2021 Virtual Meeting - Session 2 : Mitochondria in pathophysiology, 9-11 June, 2021 -online.

Research collaboration with the following investigators:
Flaviano Giorgini (PhD), Department of Genetics and Genome Biology, University of Leicester, U.K.
George Daley (MD, PhD), Harvard Medical School and Boston Children's Hospital, Boston, USA
Luis G. Aguayo (PhD), Universidad de Concepción, Barrio Universitario, Concepción,Chile
Maria Ankarcrona (PhD), Karolinska Institutet, Stockholm, Sweden
Michael Hayden (MD, PhD), University of British Columbia, Vancouver, Canada
Michal Geva (PhD), Prilenia Therapeutics LTD, Herzliya, Israel
Thorsten Schlaeger (PhD) Boston Children's Hospital, Boston, MA, USA
Tiago Fleming Outeiro (PhD), University Medizin Goettingen, Goettingen, Germany

Vision Diseases

Collaborative publications
Razawy W, **Alves CH**, Koedam M, Asmawidjaja PS, Mus AMC, Oukka M, Leenen PJM, Visser JA, van der Eerden BCJ, Lubberts E. IL-23 receptor deficiency results in lower bone mass via indirect regulation of bone formation. Sci Rep. 2021 May 13;11(1):10244. doi: 10.1038/s41598-021-89625-2. PubMed PMID: 33986359.
Boon N, **Alves CH**, Mulder AA, Andriessen CA, Buck TM, Quinn PMJ, Vos RM, Koster AJ, Jost CR, Wijnholds J. Defining Phenotype, Tropism, and Retinal Gene Therapy Using Adeno-Associated Viral Vectors (AAVs) in New-Born Brown Norway Rats with a Spontaneous Mutation in Crb1. Int J Mol Sci. 2021 Mar 30;22(7). doi: 10.3390/ijms22073563. PubMed PMID: 33808129**.**
Buck TM, Vos RM, **Alves CH**, Wijnholds J. AAV-CRB2 protects against vision loss in an inducible CRB1 retinitis pigmentosa mouse model. Mol Ther Methods Clin Dev. 2021 Mar 12;20:423-441. doi: 10.1016/j.omtm.2020.12.012. PubMed PMID: 33575434**.**
Optical Coherence Tomography Angiography Metrics Monitor Severity Progression of Diabetic Retinopathy-3-Year Longitudinal Study. Marques IP, Kubach S, Santos T, Mendes L, Madeira MH, de Sisternes L, Tavares D, Santos AR, Lewis W, Lobo C, Durbin MK, Cunha-Vaz J. J Clin Med. 2021 May 25;10(11):2296. doi: 10.3390/jcm10112296. PMID: 34070479
Terheyden JH, Behning C, Lüning A, Wintergerst L, Basile PG, Tavares D, Melício BA, Leal S, Weissgerber G, Luhmann UFO, Crabb DP, Tufail A, Hoyng C, Berger M, Schmid M, **Silva R**, Martinho CV, Cunha-Vaz J, Holz FG, Finger RP; MACUSTAR consortium. Challenges, facilitators and barriers to screening study participants in early disease stages-experience from the MACUSTAR study. BMC Med Res Methodol. 2021 Mar 17;21(1):54. doi: 10.1186/s12874-021-01243-8
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García-Layana A, Recalde S, Hernandez M, Abraldes MJ, Nascimento J, Hernández-Galilea E, Olmedilla-Alonso B, Escobar-Barranco JJ, Zapata MA, **Silva R**, Caballero Arredondo M, Lopez-Sabater MC, Mendez-Martínez S, Pardiñas-Barón N, Calvo P, Fernández-Robredo P. A Randomized Study of Nutritional Supplementation in Patients with Unilateral Wet Age-Related Macular Degeneration. Nutrients. 2021 Apr 10;13(4):1253. doi: 10.3390/nu13041253
Martins TGDS, Miranda Sipahi A, Dos Santos FM, Schor P, Anschütz A, Mendes LGA, **Silva R**. Eye disorders in patients with celiac disease and inflammatory bowel disease: A study using clinical data warehouse. Eur J Ophthalmol. 2021 Apr 25:11206721211012849. doi: 10.1177/11206721211012849.

Kodjikian L, Parravano M, Clemens A, Dolz-Marco R, Holz FG, Munk MR, Nicolò M, Ricci F, **Silva R**, Talks SJ, Verma RK, Zarranz-Ventura J, Zweifel SA. Fluid as a critical biomarker in neovascular age-related macular degeneration management: literature review and consensus recommendations. Eye (Lond). 2021 Aug;35(8):2119-2135. doi: 10.1038/s41433-021-01487-0

Colijn JM, Meester-Smoor M, Verzijden T, de Breuk A, **Silva R**, Merle BMJ, Cougnard-Grégoire A, Hoyng CB, Fauser S, Coolen A, Creuzot-Garcher C, Hense HW, Ueffing M, Delcourt C, den Hollander AI, Klaver CCW; EYE-RISK Consortium. Genetic Risk, Lifestyle, and Age-Related Macular Degeneration in Europe: The EYE-RISK Consortium. Ophthalmology. 2021 Jul;128(7):1039-1049. doi: 10.1016/j.ophtha.2020.11.024

Ruiz-Medrano J, Flores-Moreno I, Ohno-Matsui K, Cheung CMG, **Silva R**, Ruiz-Moreno JM. Correlation Between Atrophy-Traction-Neovascularization Grade For Myopic Maculopathy And Clinical Severity. Retina. 2021 Sep;41(9):1867-1873. doi: 10.1097/IAE.0000000000003129

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García-Layana A, Garhöfer G, Aslam TM, **Silva R**, Delcourt C, Klaver CCW, Seddon JM, Minnella AM. Exploring Consensus on Preventive Measures and Identification of Patients at Risk of Age-Related Macular Degeneration Using the Delphi Process. J Clin Med. 2021 Nov 20;10(22):5432. doi: 10.3390/jcm10225432

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Standardisation of Optical Coherence Tomography Angiography Imaging Biomarkers in Diabetic Retinal Disease. Ophthalmic. Vujosevic S, Cunha-Vaz J, Figueira J, Löwenstein A, Midena E, Parravano M, Scanlon PH, Simó R, Hernández C, Madeira MH, Marques IP, Martinho AC, Santos AR, Simó-Servat O, Salongcay RP, Zur D, Peto T. Res. 2021 Jul 30. doi: 10.1159/000518620. PMID: 34348330

International collaborations (among others):

Peter Quinn, Columbia University, USA

Francis Luca, University of Pennsylvania, USA

Michael May, University of Pennsylvania, USA

Joan Miller, Harvard Medical School, USA

Elena Vecino, University of Basque Country, Spain

Manuel Vidal Sanz and Marta Agudo Barriuso, University of Murcia, Spain

The European *Eye* Epidemiology (*E3*) consortium

Collaborative research stay

Post-Doc: Xandra Pereiro Díez (March 2020 - December 2021), Fellowship from the Basque Country, Spain

PhD student: Maria Josefa González Riquelme (September - December 2021), University of Murcia, Spain

Biomarkers in Neuropsychiatric Disorders: from Molecules to Diagnosis and Intervention

Benussi A, Premi E, Gazzina S, Brattini C, Bonomi E, Alberici A, Jiskoot L et al. Progression of Behavioral Disturbances and Neuropsychiatric Symptoms in Patients With Genetic Frontotemporal Dementia. JAMA (2021) doi:10.1001/jamanetworkopen.2020.30194.

Bergström S, Öijerstedt L, Remnestål J, Olofsson J, Ullgren A, Seelaar H, van Swieten JC et al. A panel of CSF proteins separates genetic frontotemporal dementia from presymptomatic mutation carriers: a GENFI study. Mol Neurodegen 16 1 (2021) doi:10.1186/s13024-021-00499-4.

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Neuray C, Sultan T, Alvi JR, Franca MC, Assmann B, Wagner M, et al. Early-onset phenotype of bi-allelic GRN mutations. Brain. 2021 doi: 10.1093/brain/awaa414

Öijerstedt L, Andersson C, Jelic V, van Swieten JC, Jiskoot LC, Seelaar H, Borroni B et al. Practice effects in genetic frontotemporal dementia and at-risk individuals: a GENFI study. Journal of Neurology, Neurosurgery & Psychiatry (2021) doi:10.1136/jnnp-2021-327005.

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Rojas JC, Wang P, Staffaroni AM, Heller C, Cobigo Y, Wolf A, Goh SYM et al. Plasma Neurofilament Light for Prediction of Disease Progression in Familial Frontotemporal Lobar Degeneration. Neurology 96 18 (2021) doi:10.1212/wnl.0000000000011848.
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Shahjouei S, Tsivgoulis G, Farahmand G, Koza E, Mowla A, Vafaei Sadr A, et al. SARS-CoV-2 and Stroke Characteristics: A Report From the Multinational COVID-19 Stroke Study Group. Stroke. 2021 doi: 10.1161/STROKEAHA.120.032927.
Shoamanesh A, Hart RG, Connolly SJ, Kasner SE, Smith EE, Martí-Fàbregas J, et al. Microbleeds and the Effect of Anticoagulation in Patients With Embolic Stroke of Undetermined Source: An Exploratory Analysis of the NAVIGATE ESUS Randomized Clinical Trial. JAMA Neurol. 2021 doi: 10.1001/jamaneurol.2020.3836.
Tipton PW, Dredla BK, Castillo PR, Mauricio EA, Lemos J, Eggenberger ER. Eyelid Closure Downbeat Nystagmus: A Rare Cause of Insomnia. J Neuroophthalmol. 2021 doi: 10.1097/WNO.0000000000000982
Tsvetanov KA, Gazzina S, Jones PS, van Swieten J, Borroni B, Sanchez-Valle R, et al. Brain functional network integrity sustains cognitive function despite atrophy in presymptomatic genetic frontotemporal dementia. Alzheimers Dement. 2021 doi: 10.1002/alz.12209.
van der Ende EL, Bron EE, Poos JM, Jiskoot LC; Panman JL, Papma JM, Meeter LH et al. A data-driven disease progression model of fluid biomarkers in genetic frontotemporal dementia. Brain (2021) doi:10.1093/brain/awab382.
Wilke C, Reich S, Swieten JC, Borroni B, Sanchez-Valle R, Moreno F, Laforce R et al. Stratifying the Presymptomatic Phase of Genetic Frontotemporal Dementia by Serum NfL and pNfH: A Longitudinal Multicentre Study. Annals of Neurology 91 1 (2021) doi:10.1002/ana.26265.
Young AL, Bocchetta M, Russell, LL, Convery RS, Peakman G, Todd E, Cash DM et al. Characterizing the Clinical Features and Atrophy Patterns of MAPT-Related Frontotemporal Dementia With Disease Progression Modeling. Neurology 97 9 (2021): doi:10.1212/wnl.0000000000012410.

METABOLISM, AGING AND DISEASE

Mitochondria and Metabolism and Disease

a) collaborations:
A Llerena, Extremadura U Hospital, Spain
A Rizvanov, Kazan Federal U, Russia
A Valli, Centro Cardiologico Monzino, Italy
A Sadun, Doheny Eye Institute, USA
A Zhitkovich, Brown U, USA
B Ghesquiere, VIB, Leuven, Belgium
C Steegborn, U Bayreuth, Germany
D Dorta, U São Paulo, Brazil
D Sinclair, Harvard Medical School, USA

E Zambrano, Instituto Nacional de Nutrition, Mexico
E Heinzle, U Saarlandes, Germany
E Gnaiger, Oroboros, Austria
F di Lisa, U Padova, Italy
F Scaglia, Baylor College of Medicine, USA
I Vega-Naredo, U Oviedo, Spain
J Wise, U Louisville, USA
J Kopecky, Academy of Sciences, Czech Republic
J Stuart, Brock U, Canada
J Neuzil, Griffith U, Australia
J Rosselo, CSIC, Spain
J Mogas, Blanquerna U, Spain
J Valero, U Salamanca, Spain
L Bindoff, U i Bergen, Norway
L Dalgaard, Roskilde U, Denmark
L Sobrevia, Pontificia U Católica, Chile
M Almeida, U Arkansas, USA
M Brizzi, U degli Studi di Torino, Italy
M Börkqvist, Lund U, Sweden
M Bolognesi, U Bologna, Italy
M Portillo, U Basque Country, Spain
M Wieckowski, Nenski Institute, Poland
M Zeviani, U degli Studi di Padova, Italy
N Danial, Dana-Farber Cancer Institute, USA
N Kaludercic, U Padova, Italy
J Holy, K Wallace, U Minnesota, USA
P Nathanielsz, U Wyoming, USA
P Portincasa, U Bari, Italy
P Cohen and C Lee, USCA, USA
R Artuch, Hospital Saint Joan de Déu, Spain
R Taylor, U Newcastle upon Type, UK
S Hussain, Wright State U, USA
U Hiden, PlacentalLab, Austria
V Carelli, U Bologna, Italy
W Koopman, Radboud U, The Netherlands
Z Rello, U Valladolid, Spain

Coordination of international networks:
"FOIE GRAS", H2020-MSCA-ITN-2016
"mtFOIE GRAS", MSCA-RISE-2016

Participation in international networks:
MetabERN (Rare Inherited Metabolic Diseases)
Ibero-American Network of Pharmacogenetics and Pharmacogenomics studies
Group study of Coenzyme Q10 deficits
Crowdfightcovid19.org
EIT Health scientific network
European Cooperation in Science and Technology (e-COST)
Prospective Focus Discussion on *Alzheimer's Disease, by* the *Fondation Médéric Alzheimer*

Metabolic Control

Collaborative publication with Mayo Clinic: Laurenti, M.C., Dalla, M.C., Varghese, R.T., Andrews, J.C., Jones, J.G., Barosa, C., Rizza, R.A., Matveyenko, A., De Nicolao, G., Bailey, K.R., Cobelli, C., and Vella, A. 2021. Insulin pulse characteristics and insulin action in non-diabetic humans. J. Clin. Endocrinol & Metab. 106, 1702-1709.
Collaborative funding with University of Florida Advanced Magnetic Resonance Imaging and Spectroscopy Facility: National Science Foundation (P19803) "Developing $H_2{}^{18}O$ as a tracer of carbohydrate metabolism: Positional analysis of liver glycerol and glycogen ^{18}O-enrichment by isotope-shifted ^{13}C and ^{31}P NMR". 15,000 USD.
Elisabet Borsheim and Shannon Rose at the Arkansas Children Research Institute, US
Project Title: Assessment of oxidative capacity in obese children. Funded by NIH.
PhD student Pedro Barbosa is working on analysis of the results on these studies.

Louise Daalgard and Havard Jenssen at Roskilde University, Denmark
Project Title: Combination therapy synergistically accelerates diabetic wound closure. Funded by the European Foundation for the Study of Diabetes.
PhD student Marija Petkovic is working on concluding her PhD studies on this work.

Mirela Delibegovic at the University of Aberdeen, UK
Project Title: Effects of PTP1b modulation on Wound Healing. Funded by Diabetes UK.
Ermelindo Leal and Master student Ana Figueiredo are analyzing the data and preparing manuscripts.

Jan Eriksson and Maria Joao Pereira at Uppsala University, Sweden
Project Title: Antipsychotic drug induced metabolic dysfunction. Funded by ITN Marie Curie.
PhD student Assel Sarsenbayeva is finalizing these studies.

Morten Bjerregaard-Andersen at the University of Southern Denmark, Denmark
Project Title: COVID-19 and Type 1 Diabetes – a multi-center study. Collaboration with Pediatric clinics in Denmark and Portugal.

University of Otago (New Zealand):
Researchers: Christine Winterbourn, Alexander Peskin
Projects:
Characterizing the operation of the Prx2/Trx1/TrxR system in human erythrocytes.
Characterizing the kinetics and molecular mechanisms of human 2-Cys peroxiredoxins.
Understanding the redox responses of erythrocytes of G6PD-deficient children.

University of São Paulo (Brasil)
Researchers: Flávia Meotti, Luiz F. de Souza
Project: Characterizing the kinetics and molecular mechanisms of human 2-Cys peroxiredoxins.

University Sains Islam Malaysia (Malaysia)
Researchers: Fook-Choe Cheah
Project: Understanding the redox responses of erythrocytes of G6PD-deficient children

Cell Signaling and Metabolism in Disease

Erwin van Vliet and Karsten Mewes, Cosmetics Europe, which represents about 40 of the world's largest cosmetics companies, including L'Oreal, Unilever, Procter & Gamble, Henkel, GSK, Beiersdorf, Colgate-Palmolive SA, Shiseido, among others. (https://www.cosmeticseurope.eu).

João Barroso, Scientific Officer at European Commission, DG Joint Research Centre, Chemical Safety and Alternative Methods Unit / European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)
(https://www.linkedin.com/in/jfbarroso/?originalSubdomain=it).

Carmen García-Rodriguez from Institute of Biology and Molecular Genetic. CSIC-University of Valladolid, Spain. (https://www.csic.es/es/investigaci%C3%B3n/investigadoresmaria-carmen-garcia-rodriguez).

Maurício Sforcin, Professor at Department of Microbiology and Immunology, UNESP, 18618-Botucatu, São Paulo, Brasil. (https://unesp.br/portaldocentes/docentes/67796?lang=pt_BR).
Martin Bachmann, Professor of Immunology at the University of Bern and at the University of Oxford. (https://www.bachmannlab.ch/team/prof-dr-martin-bachmann).

Biology of Reproduction & Stem Cell Group

Male infertility studies (PI Sandra Amaral, PI Renata S Tavares)
Collaboration with the Centre of Reproductive Medicine and Andrology (CeRA;University of Münster, Germany), a Center of Excellence for research and clinical service in andrology and reproduction. This collaboration entails not only the development of projects with common aspects, or that can be complemented by one of the partners, but also the joint applications for grants.

Review Editor on the Editorial Board of Molecular and Cellular Reproduction**,** specialty section of Frontiers in Cell and Developmental Biology (2296-634X), Frontiers Media S.A.

Female infertility and fertility preservation (PI Teresa Almeida-Santos, PI Ana Paula Sousa)

Part of the oncofertility consortium: Woodruff TK, Ataman-Millhouse L, Acharya KS, Almeida-Santos T, *et al.,* A View from the past into our collective future: the oncofertility consortium vision statement. J Assist Reprod Genet. 2021 Jan;38(1):3-15. doi: 10.1007/s10815-020-01983-4.

Insulin Resistence and Diabetic Angiopathy

Collaborations:
Abhay K. Pandey, Univ. Allahabad, India
Anindita Das, Virginia Commonwealth Univ., USA
Catalina Picó, Univ. Balearic Islands, Spain
Cláudia Carbone, Univ. Catania, Italy
Eduardo Ortega, Univ. Extremadura, Badojoz, spain
Isabel M. Pires, University of Hull, UK
Javad Sharifi-Rad, Semnan Univ. Medical Sciences, Iran
Kely de Picoli, Federal Univ. Grande Dourados, Brazil
Maria Rosaria Lauro, Dep. Pharmacy, Univ. Salerno, Italy
Mohammad Sanad Abu-Darwish, Al-Balqa Applied Univ., Jordan
Pamela Mayer, Salk Inst. Biological Studies, USA
Paulo Mathias, State Univ. Maringá, Brazil
Rodrigo Mello-Gomes, Federal Univ. Goiás, Brazil
Thomas Efferth, Johannes Gutenberg Univ., Mainz, Germany

Collaborative publications:

doi: 10.1093/nutrit/nuaa074
doi: 10.3390/biology10020155
doi: 10.1111/eci.13625.
doi: 10.1016/j.phrs.2021.105638.
doi: 10.1111/iej.13572.
doi: 10.3390/nu13082856.
doi: 10.1155/2021/8858165.
doi: 10.3389/fphar.2021.802750.
doi: 10.1016/j.jsbmb.2021.105950.
doi: 10.1016/j.celrep.2021.108982
doi: 10.3389/fcell.2021.659032.
doi: 10.1002/ptr.6884.
doi: 10.3390/pharmaceutics13030421.

Special issues edited:
Nutrients – Polyphenols for Diabetes.
https://www.mdpi.com/journal/nutrients/special_issues/Polyphenols_Diabetes
International Journal of Molecular Sciences – mTOR Signaling: new insights into cancer, cardiovascular diseases, diabetes and aging.
https://www.mdpi.com/journal/ijms/special_issues/mTOR_Diseases

Students' co-supervision:
Marcos Júnior. Long-term effects of methylglyoxal administration in lactating rats and overnutrition during the lactation phase in their offspring. Graduate Program in Biological Sciences at the Federal University of Goiás. Co-supervisor: P. Matafome.
Tamaeh Alfredo. Evaluation of the Pharmacological Potential of Acrocomia aculeata (Jacq.) Lodd ex. Doctorate in Health Sciences. Federal University of Grande Dourado and UC. Co-supervisor: P. Matafome

Microbiomes, Metabolism and Omics

Training Networks:
The group leader, Conceição Egas, participated in the INNOCORE - Core Technologies for Education and Innovation in Life Sciences, an EU graduate Training Network project. Conceição Egas taught a two-hour lesson on "Metagenomics – capturing the diversity and function of environmental microbes" for B.Sc. students at the University of Trento.
Biotechnological applications:
a) Characterization of new DNA polymerases for isothermal DNA amplification with the group of Modesto Pedrejo-Rodríguez, Universidad Autónoma de Madrid, Spain.
b) Development of flow- based methods for the study of biofilm microbiomes with the groups of Alexander Wentzel – SINTEF, Norway and Aurelio Hidalgo, Universidad Autónoma de Madrid Spain.
Collaborative Research:
a) Genome sequencing and analysis of a new *Bacillus subtilis* isolated from *Vitis vinifera*, with the group of Florence Fontaine, University of Reims Champagne-Ardenne, Reims, France.
b) Taxonogenomics analysis of two new deep-sea actinobacteria isolates representing the new species *Miltoncostaea marina*, the new genus *Miltoncostaea*, the new family *Miltoncostaeaceae* and the new order *Miltoncostaeales* with the group of Xin-Peng Tian, Southern Marine Science and Engineering Guangdong Laboratory, Guangzhou, China.

Human Genome Variation and Environment in Health and Disease

European Board of Medical Genetics in the area of graduate training networks.

European Society of Human Genetics (ESHG)-EuroGentest Quality Sub-Committee.

Red Transfronteriza de Innovación en Diagnóstico Precoz de Leucemia para un envejecimiento saludable – IDIAL-NET Portugal e Espanha - Interreg-POCTEP, 2019/2021).

New diagnostic and therapeutic tools against multidrug resistant tumors - STRATAGEM (COST action CA17104), 2018/2022.

International Network for Translating Research on Perinatal Derivatives into Therapeutic Approaches - SPRINT (COST Action CA17116), 2018-2022.

European interdisciplinary guidelines on skin cancer in the European Dermatology Forum (EDF) consortium, the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC).

Task Forces on Quality of Life and Patient Oriented Outcomes (QoL/PO) on occupational skin diseases (OSDs), Contact Dermatitis statement on coronavirus disease-19 (COVID-19) of the European Academy of Dermatology and Venereology (EADV)

Yánez Benítez C, et al. International cooperation group of emergency surgery during the COVID-19 pandemic. Eur J Trauma Emerg Surg. 2021. 47(3):621-629. doi: 10.1007/s00068-020-01521-y.

Isaksson M, et al. Patch Testing With a New Composition of the Mercapto Mix-A Multicenter Study from the International Contact Dermatitis Research Group. Dermatitis. 2021. 32(3):160-163. doi: 10.1097/DER.0000000000000669.

Isaksson M, et al. Patch Testing with Methylchloroisothiazolinone/Methylisothiazolinone Using a New Diagnostic Mix-A Multicenter Study From the International Contact Dermatitis Research Group. Dermatitis. 2021. 32(4):220-224. doi: 10.1097/DER.0000000000000657.

Healthy Living and Active Ageing

The Healthy Living and Active Ageing group of CIBB holds the coordination of the European Innovation Partnership on Active and Healthy Ageing Reference Site Ageing@Coimbra.
The group is the creator and coordinator of the pan-European PhD School on Ageing, EIT Health Ageing PhD School.

In addition, we highlight the collaborative publications in palliative care with colleagues from King's College London (*Int J Nurs Stud* and *Palliat Med).* These two articles report on the first worldwide projections of palliative care need, and RCT results showing a community-based short-term integrated palliative care intervention reduced symptom distress for older people with chronic noncancer conditions compared with usual care.

Health, Management and Economics

Bárbara Atunes - NIHR ARC Research Associate, Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge
Lara Ferreira - Researcher in the project "Programme for a Long Society - Operational PSL programme", an European project funded by the European Regional Development Fund through the Programme INTERREG V A España Portugal (POCTEP) 2014-2020. (Refª 0551_PSL_6_E). (01.11.2018 – 31.12.2021).

Lara Ferreira and Pedro Lopes Ferreira – Principal investigators and researchers in the project entitled "Health and well-being of the Portuguese citizens: impacts of the COVID-19" funded by the La Caixa BPI Foundation (ref. La Caixa-Health and Well-being), lasting 14 months (01.12.2020 – 31.01.2022).
Pedro Lopes Ferreira – Co-coordinator of the Portuguese Health Systems Observatory.
Pedro Lopes Ferreira – Co-coordinator of the Portuguese Palliative Care Observatory.
Pedro Lopes Ferreira – Member of the Academic Network of Health Literacy and principal reasearcher of the project "Health literacy in the higher education community of the University of Coimbra.
Pedro Lopes Ferreira – Principal investigator of cultural adaptations and validations of health oucomes measures, such as the Scleroderma Health Assessment Questionnaire (SHAQ), the UCLA Systemic sclerosis gastrointestinal tract instrument (UCLA SCTC-GIT 2.0), the Skidex-10 used for pruritic dermatologic disorders, and the Systemic Lupus Erythematosus Quality of Life Questionnaire (SLEQOL)
Pedro Lopes Ferreira – Principal investigator of the project "Evaluation of User Satisfaction of UCSP and USF Functional Units of the Central Region".
Pedro Lopes Ferreira – Principal investigator of the project to monitor the satisfaction of users and professionals of the Hospital and University Center of Coimbra.
Pedro Lopes Ferreira – Researcher in the Training Project of the Center Region for Genomic Medicine, whose princpal investigator is Fernando J Regateiro, PhD (UCGenomics/Institute of Medical Genetics, Faculty of Medicine, University of Coimbra / ICBR), funded by the CENTRO2020 programme and (CENTER-08-5864-ESF-000039).
Pedro Lopes Ferreira, Carminda Morais, Rui Pimenta – Researchers of tje project "Development and application of an impact assessment model of the CuiDando project, Health House of São João de Deus, Barcelos.
Rui Pimenta. Programa de Promoção da Aprendizagem da Língua Portuguesa financiado pelo Norte 2020.

Gonçalves V, Ferreira P, Saleh M, Tamargo C, Quinn G (2021). Attitudes of Young Women With Gynaecologic Cancers on Fertility, Fertility Preservation and Parenthood: a Systematic Review. 21th WPA World Congress of Psychiatry. 18th October 2021. E-poster Presentation.
Luiz Santiago. The "Örenäs Research Group" inside the EGPRN a branch of WONCA – EUROPE.
Oliveira TC, Lira de Carvalho FE, Raposo V. Leadership by Consent or Constraint? Alternatives for Hospital Management in Enhancing Social and Psychological Contracts. 20th European Association of Work and Organizational Psychology (EAWOP) Congress, Glasgow, Sctoland, 11/14-Jan-2022.
Pedro Lopes Ferreira – Principal investigator of the project "CuidIn - Support and Care for informal caregiver" funded by Operational Program Social Inclusion and Employment (POISE) with the financial participation of the European Social Fund
Pedro Lopes Ferreira – Reseracher on the COST Action "Research Innovation and Sustainable Pan-European Network in Peripartum Depression Disorder - Riseup-PPD (CA18138)".
Vânia Gonçalves. Scientific Committee Member. Scientific board member of the Humanities Oncofertility Scientific Committee Oncofertility Consortium. Michigan State University, USA, 2021.

INNOVATIVE THERAPIES

Advanced Therapies

M. Commune, A. Rai, P. Palma, C. TondaTuro, L. Fereira, Antimicrobial and pro-angiogenic properties of soluble and nanoparticle-immobilized LL37 peptides, *Biomaterials Science*, 2921, 9, 8153, DOI: 10.1039/D1BM01034D. Here the collaboration is with Dr. Chiara TondaTuro from

Politecnico di Torino, Turin, Italy. Currently, 1 Master student from Politecnico di Torino, Turin is pursuing her master thesis project.
Matos-Filipe P, Preto AJ, Koukos PI, Mourão J, Bonvin AMJJ, Moreira IS, MENSADB: a through structural analysis of membrane protein dimers, 2021, 2021:baab013. URL: http://doi.org/10.1093/database/baab013
Rosário-Ferreira N, Bonvin AMJJ, Moreira IS, Hot-spots as the key to understanding protein interactions: past and future in the AI era. WIRES Computational Molecular Science. 2022, e1602. https://doi.org/10.1002/wcms.1602

Vectors, Gene and Cell Therapy

Collaborative publications:

Hengel, H., Martus, P., Faber, J., Garcia-Moreno, H., Solanky, N., Giunti, P., Klockgether, T., Reetz, K., van de Warrenburg, B. P., Pereira de Almeida, L., Santana, M. M., Januário, C., Silva, P., Thieme, A., Infante, J., de Vries, J., Lima, M., Ferreira, A. F., Bushara, K., Jacobi, H., … Schöls, L. Epub 2021 Oct 29. *Characterization of Lifestyle in Spinocerebellar Ataxia Type 3 and Association with Disease Severity*. Movement disorders: official journal of the Movement Disorder Society, 37(2), 405–410. https://doi.org/10.1002/mds.28844.
Hübener-Schmid, J., Kuhlbrodt, K., Peladan, J., Faber, J., Santana, M. M., Hengel, H., Jacobi, H., Reetz, K., Garcia-Moreno, H., Raposo, M., van Gaalen, J., Infante, J., Steiner, K. M., de Vries, J., Verbeek, M. M., Giunti, P., Pereira de Almeida, L., Lima, M., van de Warrenburg, B., Schöls, L., … Riess, O. (2021). *Polyglutamine-Expanded Ataxin-3: A Target Engagement Marker for Spinocerebellar Ataxia Type 3 in Peripheral Blood.* Movement disorders: official journal of the Movement Disorder Socie*ty*, *36*(11), 2675–2681. https://doi.org/10.1002/mds.28749.
Klionsky, D. J., Abdel-Aziz, A. K., Abdelfatah, S., Abdellatif, M., Abdoli, A., Abel, S., Abeliovich, H., Abildgaard, M. H., Abudu, Y. P., Acevedo-Arozena, A., Adamopoulos, I. E., Adeli, K., Adolph, T. E., Adornetto, A., Aflaki, E., Agam, G., Agarwal, A., Aggarwal, B. B., Agnello, M., Agostinis, P., … Tong, C. K. (2021). *Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)*. Autophagy, 17(1), 1–382. https://doi.org/10.1080/15548627.2020.1797280.

Shadi Mahjoum, David Rufino-Ramos, Luís Pereira de Almeida, Marike L.D. Broekman, Xandra Owens Breakefield, Thomas S van Solinge. 2021. *Living Proof of Activity of Extracellular Vesicles in the Central Nervous System*. Int. J. Mol. Sci., 22(14), 7294; https://doi.org/10.3390/ijms22147294.

Jonas Walter, Silvia Bolognin, Suresh K Poovathingal, Stefano Magni, Deborah Gérard, Paul M A Antony, Sarah L Nickels, Luis Salamanca, Emanuel Berger, Lisa M Smits, Kamil Grzyb, Rita Perfeito, Fredrik Hoel, Xiaobing Qing, Jochen Ohnmacht, Michele Bertacchi, Javier Jarazo, Tomasz Ignac, Anna S Monzel, Laura Gonzalez-Cano, Rejko Krüger, Thomas Sauter, Michèle Studer, Luis Pereira de Almeida, Karl J Tronstad, Lasse Sinkkonen, Alexander Skupin, Jens C Schwamborn. 2021. *The Parkinson's-disease-associated mutation LRRK2-G2019S alters dopaminergic differentiation dynamics via NR2F1.* Cell Rep. 37(3):109864. doi: 10.1016/j.celrep.2021.109864.
PROJECTS

Fighting Sars-CoV-2 (CENTRO-01-01D2-FEDER-000002) – Dina Pereira
POCI-01-0145-FEDER-030737, sponsor: Portuguese Foundation for Science and Technology, 2018; "The impact of induced pluripotent stem cells-derived neuroepithelial stem cells transplantation in Machado-Joseph disease" – IR: Liliana Mendonça

Role of microRNA deregulation in Machado-Joseph Disease: On the development of a microRNA-based therapeutic strategy - PTDC/MED NEU/32309/2017 FCT – IR: Sónia Duarte

MicroRNA-specific small molecule modifiers as a new and promising therapeutic approach for Machado-Joseph disease/spinocerebellar ataxia type 3 (MJD/SCA3); NAF Young Investigator Award – IR: Sónia Duarte

Repurposing FDA-approved Drugs as microRNA-specific modifiers towards a new and promising therapeutic approach for Machado-Joseph disease/spinocerebellar ataxia type 3 (MJD/SCA3); AFM Trampolin Grant -23755; The French Muscular Dystrophy Association (AFM-Téléthon) – IR: Sónia Duarte

2021-2022 Japan Agency for Medical Research, Multiomics approach for studying mitochondrial dysfunction in aging to harness stem cell therapy; Role: Multi-PI with Catarina Miranda, Tatsuma Shoji (Research Funds).

Title: Genome editing to rescue Machado-Joseph disease by alternative splicing". Reference: EXPL/MED NEU/0936/2021; Fundação para a Ciência e Tecnologia, MCTES, Portugal; IR: Pedro Perdigão.

2018-presente: Bloqueio da neurodegenerescência por dispersão de silenciadores génicos (PTDC/BTM-SAL/29716/2017); Coordinators: Luís Pereira de Almeida (CNC/UC) and Rui Jorge Nobre (CNC/UC e III/UC); Fundação para a Ciência e a Tecnologia.

2021-present: Vacina Intranasal genética contra o COVID: estudos de imunização em murganhos; Gillead Sciences; 40 000 euros; Coordination: Olga Borges (CNC/UC)

POCI-01-0145-FEDER-030331; Production of glucan-based particles towards selective delivery hepatitis B antigens to immune cells to induce antiviral activity; 234 902,55 euros; (2018-2021).

CENTRO-01-0145-FEDER-029369; Skin allergens: molecules with an improbable therapeutic application for Alzheimer's disease; 235 872 euros (2018-2021).

SAU-PAR/31506/2017; Giardia lamblia extracellular vesicles in modulation of host immune cells: potential application of Giardia EVs against intestinal inflammation; 238721,61euros (2018-2021).

POCI-01-0247-FEDER-021874 (sub-projecto 4/Papel UWF:Novos produtos papel com propriedades específicas via funcionalização; financiamento global UC: 2.157.868,65 euros; incentivo total UC: 1.618.401,49 euros; financiamento sub-projecto: 92.039,00 euros; início: 01-03-2018; fim: 28-02-2022.

Tumor Microenvironment and Targeted Therapies

Farinha D, Migawa M, Sarmento-Ribeiro AB, **Faneca H**. A Combined Antitumor Strategy Mediated by a New Targeted Nanosystem to Hepatocellular Carcinoma. *International Journal of Nanomedicine* 2021;16:3385-3405. DOI: 10.2147/IJN.S302288

Jones ECL, Bebiano SS, Ward MR, Bimbo LM, Oswald IDH (2021) Pressure-induced superelastic behaviour of isonicotinamide. *Chem Comm* 57(89): 11827-11830 doi.org/10.1039/D1CC04692F

Brignole C, Bensa V, Fonseca NA, Del Zotto G, Bruno S, Cruz AF, Malaguti F, Carlini B, Morandi F, Calarco E, Perri P, Moura V, Emionite L, Cilli M, De Leonardis F, Tondo A, Amoroso L, Conte M, Garaventa A, Sementa AR, Corrias MV, Ponzoni M, Moreira JN, Pastorino F (2021) Cell surface Nucleolin represents a novel cellular target for neuroblastoma therapy. *J Exp Clin Cancer Res* **40**: 180, doi:10.1186/s13046-021-01993-9.

Fonseca NA, Gregório AC, Mendes VM, Lopes R, Abreu T, Gonçalves N, Manadas B, Lacerda M, Figueiredo P, Pereira M, Gaspar M, Colelli F, Pesce D, Signorino G, Focareta L, Fucci A, Cardile F, Pisano C, Cruz T, Almeida L, Moura V, Simões S, Moreira JN (2021) GMP-grade nanoparticle targeted to nucleolin downregulates tumor molecular signature, blocking growth and invasion, at low systemic exposure. *Nano Today* **37**: 101095, doi:10.1016/j.nantod.2021.101095.
Lopes R, Shi K, Fonseca NA, Gama A, Ramalho JS, Almeida L, Moura V, Simões S, Tidor B, Moreira JN (2021) Modelling the impact of nucleolin expression level on the activity of F3 peptide-targeted pH-sensitive pegylated liposomes containing doxorubicin. *Drug Deliv Transl Res* doi:10.1007/s13346-021-00972-z.

Molecular Biotechnology and Protein Engineering

Collaborative Research
Dr. Pitter Huesgen, Central Institute for Engineering, Electronics and Analytics (ZEA-3), ForschungszentrumJülich, Germany

Prof. Patricia M. Morgan, Emerita Lecturer, School of Natural Sciences, National University of Ireland Galway, Galway, Ireland

Prof. Xiaoying Zhang, College of Biological Science and Engineering, Shaanxi University of Technology, Hanzhong, China

Prof. Rüdiger Schade, Emeritus Professor, Institute of Pharmacology, Charité – Universitätsmedizin Berlin, Germany

Prof. Kristala Prather, MIT, USA

Molecular Microbiology and Microbiome

Mouritzen MV, Petkovic M, Qvist K, Poulsen SS, Alarico S, Leal EC, Dalgaard LT, Empadinhas N, Carvalho E, Jenssen H (2021) Improved diabetic wound healing by bovine lactoferricin is associated with relevant changes in the skin immune response and microbiota. ***Molecular Therapy-Methods & Clinical Development*** 20:726-739. https://doi.org/10.1016/j.omtm.2021.02.008 (IF=6.698)

Medical Microbiology Group

Publications:
Marcos-Tejedor, Felix, Marta Mota, María J. Iglesias-Sánchez, Raquel Mayordomo, and Teresa Gonçalves (2021). "Identification of Fungi Involved in Onychomycosis in Patients of a Spanish Rural Area" Journal of Fungi 7 (8): 623. https://doi.org/10.3390/jof7080623

Fernandes C, Mota M, Barros L, Dias MI, Ferreira IC, Piedade AP, Casadevall A, Teresa Goncalves (2021). • Pyomelanin synthesis in Alternaria alternata inhibits DHN-melanin synthesis and decreases cell wall chitin content and thickness. Frontiers in Microbiology, 12. DOI: 10.3389/fmicb.2021.691433.

Afonso M, Mestre AR, Silva G, Almeida AC, Cunha RA, Meyer-Fernandes JR, Gonçalves T and Rodrigues L (2021). Candida Extracellular Nucleotide Metabolism Promotes Neutrophils

Extracellular Traps Escape. Front. Cell. Infect. Microbiol. 11:678568. doi: 10.3389/fcimb.2021.678568

Figueiredo AB, de Oliveira E Castro RA, Nogueira-Paiva NC, Moreira F, Gonçalves FQ, Soares RP, Castro-Borges W, Silva GG, Cunha RA, Gonçalves T, Afonso LCC (2021). Clustering of adenosine A2B receptors with ectonucleotidases in caveolin-rich lipid rafts underlies immunomodulation by *Leishmania amazonensis*. FASEB J. May;35(5):e21509. doi: 10.1096/fj.202002396RR. PMID: 33813781.
Research:

Arturo Casadevall at John Hopkins University (USA) & Jay E Slater, Division of Bacterial Parasitic and Allergenic Products, Office of Vaccines Research and Review, of the U.S. Food and Drug Administration (FDA): Biology and proteome of filamentous fungi considered major agents of respiratory allergic and invasive diseases, identification of novel allergens and delivery modes, aiming to improve diagnosis, treatment and prevention severe respiratory diseases;

Functional Genomics and RNA-based Therapeutics Group

J.P.S. Nunes, P. Andrieux, P. Brochet, R.R. Almeida, E. Kitano, A.K. Honda, L.K. Iwai, D. Andrade-Silva, D. Goudenège, K.D. Alcântara Silva, R.S. Vieira, D. Levy, S.P. Bydlowski, F. Gallardo, M. Torres, E.A. Bocchi, M. Mano, R.B.H. Santos, F. Bacal, P. Pomerantzeff, F.R.M Laurindo, P.C. Teixeira, H.I. Nakaya, J. Kalil, V. Procaccio, C. Chevillard and E. Cunha-Neto (2021). "Co-Exposure of cardiomyocytes to IFN-γ and TNF-α induces mitochondrial dysfunction and nitro-oxidative stress: Implications for the pathogenesis of Chronic Chagas Disease Cardiomyopathy".
Frontiers in Immunology 12:755862 | doi: 10.3389/fimmu.2021.755862

Publication from collaborative work with Prof. C. Chevillard (Aix Marseille Université, Marseille, France) and Prof. E. Cunha-Neto (Heart Institute, Sao Paulo, Brazil) on Chagas Disease Cardiomyopathy (mitochondrial function).

Active collaborative projects:
Prof. E. Cunha-Neto (Heart Institute, Sao Paulo, Brazil) - drug repurposing to counteract T. cruzi infection
Prof. M. Fanciulli and S. Iezzi (Regina Elena National Cancer Institute, Rome, Italy) – RNAi screening for modulators of Che-1 transcriptional activity
Prof. R. Beijersbergen (Netherlands Cancer Institute, Amsterdam, The Netherlands) - CRISPR screening for regulators of homologous-directed repair

RNA & Infection Group

Reprogramming of microRNA expression via E2F1 downregulation promotes Salmonella infection both in infected and bystander cells.
Aguilar C, Costa S, Maudet C, Vivek-Ananth RP, Zaldívar-López S, Garrido JJ, Samal A, Mano M, Eulalio A.
Nature Communications. 2021;12(1):3392. doi: 10.1038/s41467-021-23593-z.

This publication included the collaboration with the research groups of Professor Juan Jose Garrido (Cordoba University, Spain) and Professor Areejit Samal (IMSc, HBNI, India).

MASS SPECTOMETRY UNIT

The research group integrated the European Proteomics Association (EuPA) into the education committee and was enrolled in the European Early Career Researchers (ECR) day with a talk representing the Portuguese Proteomics Association (ProCura). The research team was also integrated into international collaborations with European researchers, and European companies and established contacts for projects to start in 2022 with a Brazilian partner.

PARTICIPATION IN THE ORGANIZATION OF SCIENTIFIC MEETINGS

2ª Reunião Virtual do Grupo de Estudos da Retina. February 27

Conference 'Emerging Infectious Diseases and Related Environmental, Clinical and Translational Challenges', organized by the Portuguese EU Presidency and EMBL, April 27th, Coimbra, Portugal (Member of the Scientific Committee with C. Sunkel, P. Beltrao, A. Typas, P. Cossart, J.P. Simas) (vide https://www.uc.pt/en/2021PortugalEU/EID/organizing_committee)

2nd Coimbra Simulation Week-FMUC. Martins P, Alexandrino H, Camilo H. 31 may- 6 june

Co-organization of the 55th European Society for Clinical Investigation (ESCI) Virtual Meeting 2021 – The Micro Me's - Exploring Microbiota in Health and Disease. June 9-11 + Organization of Symposium "Mitochondrial Biology and Medicine", part of the 55th European Society for Clinical Investigation (ESCI) Virtual Meeting. June 9-11

Congresso da Cirurgia Implanto-Refrativa de Portugal, Albufeira. June 10-12

Armindo Salvador: Member of the Scientific and Organizing Committees, 7th International Iberian Biophysics Congress, Coimbra (Portugal) June 14- 16th, 2021

Simpósio da Cirurgia Implanto-Refrativa de Portugal. Reunião de Verão da Sociedade Portuguesa de Oftalmologia. Aveiro. July 2-3

35ª Reunião do Grupo de Estudos de Envelhecimento Cerebral e Demência – July 2- 3 (evento On-line)

30th European Academy of Dermatology Venereology Congress, Anniversary Edition. Gonçalo M - Scientific programming committee. Virtual, 29 september-2 october

Membership of the Scientific Committee of the 17th World Congress of the European Association for Palliative Care, online, October 6-8 (Barbara Gomes).

Palestras comemorativas do Dia Mundial da Alimentação. Doutora Eugénia Carvalho (CNC) e o Doutora Raquel Soares (Faculdade de Medicina da Universidade do Porto). October 13-21

Reunião do Grupo Português de Retina e Vítreo. Coimbra. October 15-16

Co-organization "Mitochondria, Apoptosis, and Cancer 2021" meeting, Singapore and online. November 25-28

V Symposium of the Portuguese Glial Network. Coimbra, November 30. + V Meeting of the Portuguese Glial Network, Coimbra, Portugal (team members were co-organizers), November

XVII Meeting of the Portuguese Society for Neuroscience (SPN2021)
Data: December 1-3. Venue: Convento de São Francisco, Coimbra, Portugal

Organization of the Annual Meeting of Ageing@Coimbra, Convento de São Francisco, Coimbra, December 7

64º Congresso Português de Oftalmologia. Vilamoura. December 9-11
Palestra integrada na Comemoração dos 100 anos da descoberta da insulina, organizada pela Sociedade Portuguesa de Diabetologia. Eugénia Carvalho, Paulo Matafome, Lelita Santos, Davi Oliveira, associação de jovens diabéticos de Portugal. Realizado por: Diana Catarino, Diana Santos, Pedro Barbosa, Ermelindo Leal. November and December

SHORT COURSES

Advanced Course for PhD and MSc students, "Introduction to Pharmacogenomics – clinical applications". February 22-26

Facetas da preparação à cimentação. Paula A, Marto CM Coelho AS, Amaro I, Saraiva J, Ferreira MM, Carrilho E. FMUC. April 10-11

Restauração de Dentes Anteriores: Técnica de Estratificação Avançada. Paula A, Marto CM Coelho AS, Amaro I, Saraiva J, Ferreira MM, Carrilho E. XXX Reunião Anual de Medicina Dentária e Estomatologia de Coimbra- April 12

Novas técnicas de Endodontia e restauração de dentes com terapêutica endodôntica. Paula A, Marto CM Coelho AS, Amaro I, Saraiva J, Paulo S, Martinho JP, Carvalho AC, Ferreira MM, Carrilho E. FMUC. May 28-30

VIII Cell Culture and Tissue Training Course "Beyond the Microscope, Culturing Life!" - Biophysics Institute-FMUC, CIMAGO and Coimbra Health School (ESTESC). Pires AS-Organizing committee and practical trainer. Online and onsite. June

Greg Gerhard "Bioanalytical Methods for Neurochemical Research". Advance course offered to PhD programs (including FFUC). Seminar (via Zoom): Translational opportunities for (bio)sensing neurotechnology, 13-15 July

VIII Cell Culture and Tissue Training Course "Beyond the Microscope, Culturing Life!" - Biophysics Institute-FMUC, CIMAGO and Coimbra Health School (ESTESC). Pires AS-Organizing committee and practical trainer. Online and onsite. July

Curso de Introdução à Neurossonologia, Albufeira (organizador: João Sargento). October 27

Dentisteria Minimamente Invasiva. Paula A, Marto CM Coelho AS, Amaro I, Saraiva J, Ferreira MM, Carrilho E. FMUC. October 23 (curso)

Curso de Metodologia Científica em Medicina Dentária. Paula A, Marto CM Coelho AS, Vale F, Ferreira MM, Carrilho E. FMUC. October 25-29

Semana nacional da Ciência & Tecnologia. Grupo Obesidade, Diabetes e Complicações do CNC UC. Diana Santos, Jéssica Silva e Pedro Barbosa, alunos de doutoramento. November 22-27

Como conseguir um sorriso? Da teoria à prática. Paula A, Marto CM Coelho AS, Amaro I, Saraiva J, Ferreira MM, Carrilho E. FMUC. November 13 (curso)

OTHER

Retreat of the Centre for Innovative Biomedicine and Biotechnology (CIBB), Neuroscience and Disease research strand (virtual). Coimbra. May 24-25

Co-Organization of MAD Retreat "Science Out Of the Box". November 17-18

Reunião do Consórcio IDIAL-NET. Sarmento Ribeiro AB-Organização. FMUC. Coimbra, December, 17

Organization of Science Communication Event "A Vida em 4 tempos (the life in 4 times/seasons/beats)" – Part 1 (Spring and Summer). November 17

Organization of Science Communication Event "A Vida em 4 tempos (the life in 4 times/seasons/beats) – Part 2 (Autumn and Winter)". November 24

Organization of a fundraising dinner event "Ciência à la carte (Science à la carte)", at "Restaurante Rei dos Leitões", with Science Communication lecture. July 2

GRADUATE STUDIES PROGRAMME

During 2021 CIBB organized 8 Advanced Courses (inserted at the Doctoral Programme in Experimental Biology and Biomedicine - PDBEB at CNC) and hosted 70 seminars.
Due to the COVID-19 Pandemic several courses had to be cancelled and the students will attend the courses in the following year. The seminars, which cannot be in person, were given through the Zoom platform.
Besides the organization of courses and seminars, CIBB also supported ongoing research work for Ph.D. and M.Sc. theses. Throughout this year 33 Ph.D. and 155 M.Sc. theses were concluded.

CIBB SEMINARS

January

15.01.2021|G protein-coupled receptor heteromers as targets for neuropsychiatric disorders Sergi Ferré, Chief, Integrative Neurobiology Section, National Institute on Drug Abuse | NIH IRP, Baltimore USA
Host: Attila Kofalvi, CNC

15.01.2021| Light affects behavioral despair involving the clock gene Period 1, Urs Albretch (Department of Biology, University of Fribourg), Switzerland
Host: Cláudia Cavadas, CNC

22.01.2021|Implementation Science: Adaptation as Translation of Nutrition and Physical Activity Evidence, Taren Swindle, College of Medicine, University of Arkansas for Medical Sciences
Host: Eugénia Carvalho, CNC

27-28.01.2021| Webinar CIMAGO–Vírus e Cancro
Host: Isabel Carreira, ICBR

February

3.02.2021|Cellular senescence in development, regeneration and cancer, Manuel Collado, University of Santiago de Compostela
Host: Lino Ferreira, CNC

5.02.2021|BioAll Gear Box Accelerator Webinar, Sofia Fernandes, Diretor, Business Development da Building Global Innovators
Host: Catarina Cunha Santos, CNC

25.02.2021| From academia to consulting to sleep entrepreneurship: my journey, Els van der Helm (CEO and co-founder of Shleep), Amsterdam, Netherlands
Host: Cláudia Cavadas, CNC

26.02.2021|Analysing biomolecular networks to explore human diseases, Francisco Pinto, BioISI (Biosystems and Integrative Sciences Institute), Faculty of Sciences, University of Lisbon, Lisbon, Portugal
Host: Irina Moreira and Armindo Salvador, CNC

March

5.03.2021|Effectiveness of community-based disease prevention programs among food insecure communities, Christopher Long, University of Arkansas for Medical Sciences
Host: Eugénia carvalho, CNC

9.03.2021| Investigating the molecular basis of mitochondrial genetic disease, Robert Taylor, Newcastle University, UK
Host: Paulo Oliveira, CNC

11.03.2021| Mitochondrial senescence and the consequence to metabolic regulation in the aging individual, Kendall Wallace, University of Minnesota, USA
Host: Paulo Oliveira, CNC

12.03.2021|SUCLG2 is a new tumour suppressor in paraganglioma and pheochromocytoma
Jiri Neuzil, Academy of Sciences of the Czech Republic, Prague
Host: Paulo Oliveira, CNC

12-13.03.2021| Simpósio Mast cell-drive diseases at the Skin Allergy Meeting (EAACI) Digital event
Host: Gonçalo M, iCBR

17.03.2021|Identification and characterization of Chlamydia trachomatis virulence proteins
Jaime Mota
Faculdade de Ciências e Tecnologia, Universidade NOVA de Lisboa (FCT NOVA)
Host: Isaura Simões, CNC

18.03.2021| Sleep and aging: of men and mice, Tom de Boer (Department of Cell and Chemical Biology of the Leiden University Medical Center) The Netherlands
Host: Isaura Simões, CNC

19.03.2021 |Fighting infection at body borders: Micronutrient immune sensing and early-life intestinal defence
Manuela Ferreira, CNC, UC-Biotech, Biocant Park & Champalimaud Foundation, Champalimaud Centre for the Unknown
Host: Nuno Empadinhas, CNC

24.03.2021|Presynaptic plasticity in hippocampal circuits
Christophe Mulle, Institut Interdisciplinaire des Neurosciences, Bordeaux University, France
Host: Paulo Pinheiro, CNC

26.03.2021|Global remodeling of the proteome during extreme terminal differentiation
Daniel Finley, Department of Cell Biology, Harvard Medical School
Host: Ivan Lalanda, CNC

April

09.04.2021|Improving synaptic transmisson in failing brain
Ira Milosevic, University of Oxford
Host: João Peça, CNC

16.04.2021|Biomimetic NanoZymes as promising sensors, photo-activatable antimicrobial agents and pro-drug therapies
Vipul Bansal, Sir Ian Potter NanoBioSensing Facility, School of Science, RMIT University, Melbourne, Australia
Host: Eugenia Carvalho, CNC

22.04.2021| Chrononutrition and Metabolic Health
Olga Ramich (Molecular Nutritional Medicine research group, German Institute of Human Nutrition) Postdam-Rehbruecke, Germany
Host: Cláudia Cavadas

23.04.2021|Overcoming barriers for brain gene therapy
Beverly L. Davidson, Perelman School of Medicine, University of Pennsylvania, USA
Host: Luis Pereira de Almeida, CNC

23.04.2021|Chemistry and Biotech Inventions - rules, tips and tricks
Anabela Carvalho, Patentree
Host: Ana Catarina Cunha Santos, CNC

30.04.2021|Role of protein tyrosine phosphatase 1B (PTP1B) in diabetes and heart disease
Mirela Delibegovic, University of Aberdeen, UK
Host: Eugenia Carvalho, CNC

May

05.05.2021|Microscale Degradomics: Hunting N-termini in Small Specimen
Pitter Huesgen, Forschungszentrum Juelich, Germany
Hosts: Isaura Simões, CNC

07.05.2021| Proteomics approaches to study SARS-CoV-2 biology and to identify antiviral drugs
Pedro Beltrão, EMBL-EBI, Cambridgeshire, UK
Hosts: Ivan Lalanda, CNC

13.05.2021| New methods in Radiotherapy: Physical Basis and Potential Clinical Applications of FLASH Radiation Therapy, Emil Schuler, MD Anderson Cancer Center (MDACC), University of Texas, USA
Hosts: Isabel Carreira, ICBR

14.05.2021|Jornalistas e Investigadores: Como Comunicar
Teresa Firmino, Jornal Público
Hosts: Sara Amaral, CNC

21.05.2021|New non-viral options for therapeutic delivery
Koen Breyne, Department of Neurology, Massachusetts General Hospital, Harvard Medical School
Hosts: Luís P. Almeida, CNC

24.05.2021|Vigilância Tecnológica
Daniela Rosa, Technology Transfer Officer UC Business
Host: Ana Catarina Cunha Santos, CNC

27.05.2021| Chronoleadership - The new time battle is about working in sync with your biological clock
Camilla Kring (PhD, founder of Super Navigators & B-Society), Copenhagen
Host: Cláudia Cavadas, CNC

June

04.06.2021|Communicating the intangible: wonder and human endeavour
Ana Godinho, Head of Education, Communication and Outreach, CERN
Hosts: Sara Varela Amaral, CNC

17.06.2021| Sleep is more than line down and closing your eyes
Till Roenneberg (Ludwig-Maximilians-University) Munich, Germany
Hosts: Cláudia Cavadas, CNC

18.06.2021|ARMS/Kidins220 regulates BDNF secretion: implications in Huntington Disease and nociception
Juan Carlos Arévalo, Department of Cell Biology and Pathology, Institute for Neurosciences Castilla and Leon, University of Salamanca, Spain
Host: Ramiro Almeida, CNC and iBiMED

July

02.07.2021|Narrative Medicine: Challenges and Opportunities in Healthcare Restauração de Dentes Anteriores: Técnica de Estratificação AvançadaEducation/Practice and in Scientific Research
Susana Magalhães, Instituto de Investigação e Inovação em Saúde da Universidade do Porto (i3S)
Host: Anabela Marisa Azul, CNC

09.07.2021|Diabetic Foot Ulceration: Transcriptomic landscape
Aristidis Veves, Professor of Surgery at Harvard Medical School
Host: Eugénia Carvalho, CNC

15.07.2021| Light, Circadian Rhythms & Sleep: Signalling Pathways to New Therapeutics Russel Foster (Nuffield Department of Clinical Neurosciences, University of Oxford), UK
Host: Cláudia Cavadas, CNC

16.07.2021|A microglial view of neuronal homeostasis
João B. Relvas, I3S

Host: Carlos B. Duarte, CNC

23.07.2021|Perspectives on the History of Psychiatry: Where the Past meet the Future
Erick Messias, Professor of Psychiatry, COM, Professor of Epidemiology, COPH, University of Arkansas for Medical Sciences, Editor-in-Chief, Medicine and Meaning
Host: Eugénia Carvalho, CNC

September

15.09.2021|Factors influencing the accuracy of glycated hemoglobin measurement in diabetes mellitus. Interference caused by the presence of hemoglobin variants
Enikő Nemes-Nagy, University of Medicine, Pharmacy, Science and Technology, "GE Palade", Tîrgu Mureş, Romania
Host: Manuela Grazina and Rodrigo Cunha, CNC

17.09.2021|Glucose transport in Alzheimer's disease: Mechanisms distinct from diabetes
Steven Barger, University of Arkansas for Medical Sciences
Host: Eugénia Carvalho, CNC

17.09.2021|Investigation of microvasculopathy in hypertensive patients
Enikő Nemes-Nagy, University of Medicine, Pharmacy, Science and Technology, "GE Palade", Tîrgu Mureş, Romania
Host: Manuela Grazina and Rodrigo Cunha, CNC

24.09.2021|The effect of air pollution on metabolism - evidence from pregnancy to adulthood
Patricia Prada, School of Applied Sciences (FCA) at UNICAMP, Campinas, Brazil
Host: Eugénia Carvalho, CNC

October

08.10.2021|Design & Development of a Novel Synthetic Wound Matrix in a Start-Up Environment
Ana Tellechea - Translational Scientist & Product Development Manager, Gel4Med Inc., Lowell, MA, USA
Host: Ermelindo Leal, CNC

13.10.201| Laboratory meat
Ruth Wonfor & Neil Stephens
Host: Eugénia Carvalho, CNC

14.10.2021| Protein enriched bread
Viktoria Zettel
Host: Eugénia Carvalho, CNC

15.10.2021| Nutritional value of algae
Ana Marta Gonçalves
Host: Eugénia Carvalho, CNC

15.10.2021|Marine macroalgae applications and therapeutic potential

Ana Marta Gonçalves, MARE – Marine and Environmental Sciences Centre, Department of Life Sciences, University of Coimbra
Host: Eugénia Carvalho, CNC

18.10.2021|The impact of water intake on health and metabolismo
Joseph Takahashi (Howard Hughes Medical Institute, Department of Neuroscience, University of Texas Southwestern Medical Center) Dallas, USA
Host: Cláudia Cavadas, CNC

18.10.2021| The importance of water
Stavros Kavouras
Host: Eugénia Carvalho, CNC

19.10.2021| Circular economy
Lene Lange
Host: Eugénia Carvalho, CNC

20.10.2021| Polyphenolds and nutrition
Iva Fernandes & Joana Oliveira
Host: Eugénia Carvalho, CNC

21.10.2021| Insects the novel food
Guilherme Pereira
Host: Eugénia Carvalho, CNC

27.10.2021| The value of plant-based diets
Manuela Meireles
Host: Ermelindo, CNC

27.10.2021| Circadian Clocks and their role in Metabolism and Longevity
Stavros Kavouras, Arizona State University, AZ, USA
Host: Eugénia Carvalho, CNC

27.10.2021|Graphene and the generation of materials driven by its use
Bruno Figueiredo, Graphenest SA
Host: Artur Filipe Rodrigues, CNC

28.10.2021|Challenges for Epidemiology and Credible Scientific Literature during the Covid19 Pandemic
Prof. John Ioannidis, Department: Medicine - Med/Stanford Prevention Research Center, CA
Host: Francisco Ambrósio, ICBR and FMUC

29.10.2021|Bioelectricity in cell populations
Paulo Rocha, Bioelectronics & Bioenergy Research Lab, Centre for Functional Ecology, Department of Life Sciences, University of Coimbra.
Host: Ana Luísa Carvalho, CNC

29.10.2021|Reproducibility in Scientific Research
Prof. John Ioannidis, Department: Medicine - Med/Stanford Prevention Research Center, CA
Host: Paulo Oliveira, CNC

November

05.11.2021| How super-resolution microscopy changes our vision of glutamatergic synaptic transmission!
Eric Hosy, Dynamique de l'organisation et des fonctions synaptiques", IINS - UMR 5297 - CNRS - Université de Bordeaux
Host: Paulo Pinheiro, CNC

12.11.2021|Flagship initiatives to prevent/treat diabetes - a burden of western societies
Peter Goulden, Division of Endocrinology and Metabolism, Mount Sinai Health System, NYC, USA
Host: Eugénia Carvalho, CNC

19.11.2021|Amyloid beta oligomers in neurodegeneration and neurodevelopment
William Klein, Department of Neurobiology, Weinberg College o Arts & Sciences, Northwestern University, USA
Host: Rui Costa, CNC

25.11.2021| Local and global aspects of sleep regulation
Vlad Vyazovskiy (Department of Anatomy, Physiology and Genetics of the University of Oxford, Sleep and Circadian Neuroscience Institute)
Host: Cláudia Cavadas, CNC

26.11.2021|Neuronal regulation of immune fitness
Henrique Veiga-Fernandes, Champalimaud Research, Champalimaud Centre for the Unknown, Lisbon, Portugal
Host: João Peça, CNC

December

03.12.2021|Models and strategies to identify targets and restore cellular homeostasis in ALS
Dora Brites, iMed.ULisboa, Lisboa, Portugal
Host: Elisabete Ferreiro, CNC

10.12.2021|Modulation of TDP-43 with protein kinase inhibitors, a new avenue for ALS pharmcotherapy
Ana Martinez, CSIC · Biological Research Centre-CIB, Madrid, Spain
Host: Elisabete Ferreiro, CNC

16.12.2021| How sleep is linked to the immune system: studies in the Drosophila model Julie A. Williams (Department of Neuroscience, Perelman School of Medicine, University of Pennsylvania)
Host: Cláudia Cavadas

17.12.2021|Building advanced human neuromuscular organoids to study development and disease
Mina Gouti, Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany
Host: Elisabete Ferreiro, CNC

17.12.2021|New Disease Mechanisms and Therapeutic Targets for ALS Discovered Using Patient Stem Cells
Justin Ichida, University of Southern California, Los Angeles, USA
Host: Elisabete Ferreiro, CNC

17.12.2021| Building advanced human neuromuscular organoids to study development and disease
Mina Gouti (Max Delbrück Center for Molecular Medicine in the Helmholtz Association), Germany
Host: Paulo Oliveira, CNC

PHD THESIS CONCLUDED IN 2021

Ana Rita Gonçalves Gaspar. "Microglia morphology and susceptibility to depression – impact of sex differences". Programa Interuniversitário de Doutoramento em Envelhecimento e Doenças Crónicas. Supervisor: Isabel Santana

Anna V. Pliassova, "Pathophysiological role of adenosinergic modulation within the basolateral complex of the amygdala" – March 26th, 2021 – Faculdade de Medicina da Universidade de Coimbra - Programa Interuniversitário de Doutoramento em Envelhecimento e Doenças Crónicas. Supervisor: Rodrigo Cunha

Bernardete Sofia de Freitas Melo. "Targeting the carotid bodies to treat obesity. PhD in Mechanisms of disease and regenerative medicine". Faculty of Medical Sciences, Universidade Nova de Lisboa and University of Algarve. 2021. Supervisor: Flávio Reis

Catarina de Barros Pinto Salvador Domingues. "Mechanomodulation of the mesenchymal stem cell proteome elucidation of mechanisms and evaluation as a therapeutic opportunity". PhD in Experimental Biology and Biomedicine, Biotecnhology and Health, University of Coimbra. Supervisor: Mário Grãos, Bruno Manadas, João Lopes de Carvalho

Cátia Moreira de Sousa, "Elucidation of the structure-activity relationship of p-menthane derivatives: from a screening assay of anti-inflammatory properties to a lead compound and its mechanism of action". University of Coimbra, Faculty of Pharmacy, 4th June 2021. Supervisor: Cláudia Cavadas

Chrysoula Dioli. "Chronic stress and glucocorticoid actions in brain plasticity and Tau pathology". 'Doutoramento em Envelhecimento e Doenças Crónicas', University of Minho, Braga. *Main supervisor:* Ioannis Sotiropoulos (ICVS, University of Minho); 2nd co-Supervisor: Sheela Vyas (Inst. Biology Paris-Seine, University of Sorbonne, Paris). September 7th. Co-supervisor: Ana Cristina Rego

Cláudia Deus. "An Innovative Metabolic and Epigenetic Engineering Approach to Reverse the Parkinson Disease Cell State", Biomedicine and Experimental Biology Doctoral Program, University of Coimbra (http://hdl.handle.net/10316/95433). Supervisor: Paulo Oliveira

Diana Filipa Dias Duro. "Clock Drawing test in the detection of cognitive impairment: validation studies for the Portuguese population". Programa Doutoral Interuniversitário em Envelhecimento e Doenças Crónicas. Supervisor: Isabel Santana

Diana Sequeira. "Isolation, characterization and differentiation of stem cells from the apical papilla: potential uses in regenerative medicine". PhBEB, IIIs, UC. Supervisor: João Peça Silvestre

Emanuel Monteiro Candeias. "The amazing anti-type 2 diabetic drugs in neurodegeneration: the impact of exendin-4, liraglutide and linagliptin in type 2 diabetes, Alzheimer disease and Parkinson disease (2021). FCT SFRH/BD/90036/2012, PhD in Biomedicine and Experimental Biology, University of Coimbra. Supervisor: Ana Duarte e Paula Moreira

Fábio Fiuza Rosa. "Generating Dendritic Cells by Direct Cell Reprogramming". June 2021
Supervisor: Filipe Pereira, William Agace and João Ramalho-Santos

Gabriela Pires Tavares. "Unraveling the role of peripheral dopaminergic signaling in metabolism. Interuniversity Doctoral Program in Aging and Chronic Diseases". Faculty of Medicine from the

University of Coimbra and Faculty of Medical Sciences of the Nova University of Lisbon. 2021. Supervisor: Flávio Reis

Getachew Debas Belew. "Fructose metabolism and lipogenesis fluxes in mice models of diet-induced non-alcoholic fatty liver disease." Ph.D. in Experimental Biology and Biomedicine with specialization in Health and Biotechnology - University of Coimbra. Supervisor: Eugénia Carvalho

Giada Di Nunzio: "Tracing Hepatic Glycogen and Lipid Metabolism with Stable Isotope Tracers: Insights From Murine Studies". Ph.D. in Experimental Biology and Biomedicine with specialization in Health and Biotechnology - University of Coimbra. Supervisor: Eugénia Carvalho

Inês Pereira Dias Marques. "Progress – Identificação de sinais e *surrogate outcomes* de progressão de Retinopatia Diabética" PhD in Health Sciences, University of Coimbra. September 2021. Supervisor: Francisco Ambrósio

Isabel Ferreira. "Development of an in-vitro/in chemico platform for the identification of respiratory allergens" (2021). FCT SFRH/BD/110717/2015, PhD in Pharmacology, University of Coimbra. Supervisor: Teresa Cruz

Jeannette Schmidt, "Characterization of the novel Rho-GTPase activating protein, ARHGAP8, in the Central Nervous System". Doctoral Program in Experimental Biology and Biomedicine, University of Coimbra. Supervisor: Ana Luísa Carvalho

João Calmeiro. Development of platforms based on dendritic cells for toxicological and pharmacological screening (2021). FCT PD/BDE/135076/2017, PhD in Pharmacology, University of Coimbra. Supervisor: Teresa Cruz

José Luis Monteiro Alves. "Neuropeptide response in traumatic brain injury". Programa de Doutoramento em Ciências da Saúde, ramo de Medicina. Supervisor: Isabel Santana
José Luís Monteiro Alves. "Resposta Neuropeptídica no Traumatismo Crânio-Encefálico (Neuropeptidic response in Traumatic Brain Injury)". Dezembro 2021. Supervisor: Anabela Mota Pinto

Josephine Blersch. "Biocompatible nanoparticles to modulate cell activity". PhD in Experimental Biology and Biomedicine, Biotecnhology and Health, University of Coimbra, Supervisor: Lino Ferreira e Akhilesh Rai

Luciana Albuquerque. "Classification and Identification of Thermophilic Organisms from São Pedro do Sul Hot Spring and Revision of the Classification of Genus *Meiothermus*: Integration of Genomics Into Prokaryotic Taxonomy.." University of Coimbra, 2021. Supervisor: Conceição Egas

Marija Petkovic "Regulatory roles of microRNAs and host defence peptides in diabetic wound healing". Eugénia Carvalho

Mário Carvalho. "Peptides that signal hunger – a new role in memory and social behaviors" MIT Portugal. Supervisor: João Peça Silvestre

Mireia Alemany i Pagès "A Healthy Liver Will Always Deliver – Development of a comic to raise awareness about Non-Alcoholic Fatty Liver Disease (NAFLD) and other metabolic disorders" from the Doctoral Program in Biomedicine and Experimental Biology (PDBEB) of the Institute for Interdisciplinary Research of the university of Coimbra (IIIUC) (October 8th 2021). Supervisor: João Ramalho Santos

Pedro Renato Sousa da Silva Vaz. “Pancreatite aguda: novas fronteiras no prognóstico”. Doutoramento em medicina da Universidade da Beira Interior. 27 maio 2021. Supervisor: José Guilherme Tralhão e Ana Margarida Coelho Abrantes.

Raquel Sofia Freitas Boia. “Activation of A3 adenosine receptor using intraocular biodegradable implants as a strategy for the treatment of glaucoma” Interuniversity PhD Program in Ageing and Chronic Diseases. University of Coimbra. September 2021. Supervisor: Francisco Ambrósio

Remy Cardoso. “Role of TOMM40’523-ApoE aplotypes in Alzheimer’s Disease etiology – from clinics to mitochondria”. Programa Doutoral Interuniversitário em Envelhecimento e Doenças Crónicas. Supervisor: Isabel Santana

Rui Caetano Oliveira. “Carcinoma colorretal e metástases hepáticas. O efeito do microambiente”. Tralhão. Doutoramento em Medicina da Universidade do Porto. 7 junho 2021. Supervisor: Maria Filomena Botelho e José Guilherme Tralhão

Rui Simões “Neuronal mitochondrial metabolism and dynamic profiling under physiological and pathological conditions using biological-based machine learning approaches”, Biomedicine and Experimental Biology Doctoral Program, University of Coimbra (http://hdl.handle.net/10316/96436). July 20, 2021. Supervisor: Paulo Oliveira

Sara Isabel Monteiro Lopes. “Gene editing technologies to Machado-Joseph disease”. October 2021; University of Coimbra. Supervisor: Luís Pereira de Almeida

Tamaeh Monteiro Alfredo. Avaliação do potencial farmacológico do extrato aquoso das folhas de Acrocomia aculeata (Jacq.) Lodd ex. Mart. PhD in Health Sciences under the Cotutela regime between the University of Coimbra and the Federal University of Grande Dourados, Brasil. 2021. Supervisor: Flávio Reis

Thiago Gonçalves dos Santos Martins. “Modelo e metodologia para ensino de oftalmoscopia direta e sua aplicação no desenvolvimento de algoritmos para interpretação de imagens oftalmológicas”, PhD in Health Sciences. University of Coimbra. June 2021. Supervisor: Francisco Ambrósio

MSC THESIS CONCLUDED IN 2021

Adriana Filipa Fonseca Bernardino. “Avaliação das necessidades e das discrepâncias de respostas sociais nos Cuidados Paliativos a nível nacional: A formação e o papel do Assistente Social nas Equipas de Cuidados Paliativos”. Mestrado em Cuidados Continuados e Paliativos da Faculdade de Medicina da Universidade de Coimbra. Dezembro de 2021. Supervisors: Marília Dourado and Manuel Luis Capelas.

Afonso Manuel Freitas de Aguiar. “Sistema Imunitário, Inflamação e Cancro do Pâncreas [Immune System, Inflammation and Pancreatic Cancer]”. 2021. Supervisor: Anabela Mota-Pinto.

Aida Genabú Rodrigues de Sów Valdez. “INFLUÊNCIA DOS FATORES AMBIENTAIS NA EXPRESSÃO DO QUERATOCONE”. Integrated Master in Medicine, Faculty of Medicine, University of Coimbra. September 2021. Supervisor: Francisco Ambrósio

Alda Veloso. “Consulta não presencial do enfermeiro de família: impacte no isolamento social e qualidade de vida da pessoa idosa na comunidade”. Mestrado em Enfermagem de Saúde Familiar, Universidade de Aveiro. 2021. Supervisor: Elsa Melo.

Ana Carolina Marques Ferreira. “Preclinical evaluation of the therapeutic potential of Vaccinium corymbosum L. (blueberry) leaf biomass in experimental Multiple Sclerosis”. Master in Biomedical Research, Faculty of Medicine from the University of Coimbra. 2021. Supervisor: Flávio Reis

Ana Carolina Martins Real. “O sistema endócrino como alvo terapêutico para a progeria ou sindrome de Hutchinson-Gilford”. Mestrado em Investigação Biomédica, da Faculdade de Medicina da Universidade de Coimbra. Supervisor: Joana Barbosa de Melo.

Ana Carolina Pereira Barge. “Metastização óssea no cancro da próstata [Bone metastases in prostate cancer]”.2021. Supervisor: Anabela Mota-Pinto.

Ana Carolina Real. “Targeting the endocrine system to slow down aging in Hutchinson-Gilford Progeria Syndrome”. Master in Biomedical Research, Faculty of Medicine, University of Coimbra. December 2021. Supervisor: Cláudia Cavadas.

Ana Catarina Coelho Paulo. “O que sabemos sobre a síndrome de transfusão feto-fetal? [What do we know about feto-fetal transfusion syndrome?]”. 2021. Supervisor: Anabela Mota-Pinto.

Ana Catarina Vales de Almeida. “Candida albicans 5’-3’-ectonucleotidase in the regulation of NETs”. Mestrado em Investigação Biomédica da Faculdade de Medicina da Universidade de Coimbra.

Ana Filipa Pereira Alves Dinis. “A Psicologia Positiva na procura da felicidade: Promoção do flourishing na população portuguesa e proposta de intervenção com base na Acceptance and Commitment Therapy”. 2º Ciclo em Psicologia Clínica e da Saúde, Universidade Fernando Pessoa. 2021. Supervisor: Isabel Silva.

Ana Fonseca. “Identification of NTM proteins involved in cellular aggregation and biofilm formation”. Masters in Biochemistry. 2021. Supervisor: Susana Alarico.

Ana Maria Rocha. “Acompanhamento do Doente em Consulta na Unidade de uma Equipa Intra Hospitalar de Suporte em Cuidados Paliativos - Monitorização da Sua Evolução e Visão da Família”. Mestrado em Cuidados Continuados e Paliativos da Faculdade de Medicina da Universidade de Coimbra. 2021. Supervisor: Marília Dourado.

Ana Martinho. “Identification of Schizophrenia Biomarkers Using a Proteomics Approach on PBMCs”. Supervisor: Bruno Manadas.

Ana Raquel Silva Dias. “Caracterização molecular de doentes sensibilizados em aeroalergénios com rinite e asma [Molecular characterization of patients sensitized to aeroallergens with rhinitis and asthma]”. 2021. Supervisor: Anabela Mota-Pinto.

Ana Rita Amaral. “Desprescrição em cuidados continuados e paliativos: uma scoping review. Mestrado em Cuidados Continuados e Paliativos da Faculdade de Medicina da Universidade de Coimbra”. Setembro de 2021. Supervisors: Marília Dourado and Manuel Luis Capelas.

Ana Rita Azevedo Henriques da Cunha. “Perturbation of ER-mitochondria crosstalk in bipolar disorder: effect of Sigma-1 receptor modulation”. Master in Cellular and Molecular Biology, Faculty of Sciences and Technology, University of Coimbra. 2021. Supervisor: Teresa Cruz.

Ana Rita Coutinho. “Pharmacogenetic approach to epilepsy treatment with zonisamide – a pilotstudy”. Master’s Degree in Applied Pharmacology, University of Coimbra. December 2021. Supervisor: Paulo Oliveira.

Ana Rita Silva Ribeiro. “Fatores de prognóstico na leucemia linfoblástica aguda pediátrica”. Mestrado Integrado em Medicina, Faculdade de Medicina da Universidade de Coimbra. Março 2021Supervisors: Emília Cortesão and Joana Azevedo.

Ana Sofia Cardoso dos Santos. “Adjuvant vs neoadjuvant chemotherapy in women with breast cancer: Psychosocial correlates”. 2º Ciclo em Psicologia Clínica e da Saúde, Universidade Fernando Pessoa. 2021. Supervisor: Isabel Silva.

Ana Sofia Carvalho Costa. “Psychotic disorders and the use of cannabis in adolescents and young adults”. Mestrado Integrado em Ciências Farmacêuticas. Supervisor: Isabel Santana.

André Faria Pita Simões. “Characterizing the diversity of the extracellular region of Gram-negative bacteria outer-membrane channel-tunnels.” Master in Biochemistry. Faculty of Sciences and Technology, University of Coimbra, Coimbra, Portugal.

André Figueiredo Silva. “Comparar a sensibilidade de contraste e cromática entre doentes implantados com a nova lente Alcon Vivity (EDOF não difrativa) vs Alcon PanOptix (multifocal difrativa) vs Alcon Clareon (monofocal simples)”. Integrated Master in Medicine, Faculty of Medicine, University of Coimbra. May 2021. Supervisor: Francisco Ambrósio.

Andreia Margarida Silva Barro. “Characterization of APRc as an immune evasion factor of Rickettsia.” Master in Biotechnology Universidade Nova de Lisboa Faculdade de Ciências e Tecnologia, Portugal.

Andreia Raquel Cardoso da Silva. “A Satisfação no Trabalho, as Estratégias de Coping e o Suporte Organizacional Percebido nas Unidades de Cuidados Intensivos, durante a pandemia COVID-19, na área metropolitana de Londres”. Mestrado em Gestão e Economia da Saúde. Dezembro 2021. Supervisors: Vítor Raposo and Aida Isabel Tavares.

Andreia Raquel Cardoso Silva. “Satisfação no Trabalho, Estratégias de Coping e Suporte Organizacional nas Unidades de Cuidados Intensivos”. Mestrado em Gestão e Economia da Saúde, Faculdade de Economia da Universidade de Coimbra. 2021. Supervisor: Vitor Raposo.

António Francisco de André Girão Neto Parra. “Drug encapsulation in extracellular vesicles for age-related macular degeneration treatment”. Master in Biomedical Engineering, Faculty of Sciences and Technology, University of Coimbra. December 2021. Supervisor: Francisco Ambrósio.

António Pereira da Costa. “Impacto dos instrumentos de sopro na cavidade oral: Caracterização da autopercepção dos músicos”. Provas de Mestrado Integrado em Medicina Dentária. Faculdade de Ciências da Saúde da Universidade Fernando Pessoa. Novembro 2021. Supervisor: Isabel Silva.

Beatriz Maria Lemos Ormonde. “Propriedades antiaterogénicas de polifenóis de oliveira e do azeite - Estudo experimental em modelo animal”. Master in Biochemistry, Faculty of Science and Technology, University of Coimbra. 2021. Supervisor: Flávio Reis.

Beatriz Mota Coelho Marques Catita. “Leucemia Mielóide Crónica na Era dos Inibidores de Tirosina Cinase: Incidência de Neoplasias Secundárias”. Mestrado Integrado em Medicina, Faculdade de Medicina da Universidade de Coimbra. Junho 2021. Supervisors: Ana Bela Sarmento Ribeiro. And Raquel Guilherme.

Bruno Alexandre de Almeida Henriques. “A importância do Project Management Office em projetos de grande dimensão - utilização de ferramentas colaborativas”. Mestrado em Gestão. Setembro 2021. Supervisor: Vítor Raposo.

Bruno Miguel Faustino Sequeira. “Alterações vasculares na doença de Alzheimer”. Integrated Master in Pharmaceutical Sciences, Faculty of Pharmacy, University of Coimbra. 2021. Supervisor: Teresa Cruz.

Carina Magalhães. “The role of Sestrin 2 in cellular adaptation to hypoxic stress”. Cellular and Molecular Biology Master, University of Coimbra. November 2021. Supervisor: Paulo Oliveira.

Carina Oliveira Soares. “Literacia relacionada com medicamento: tradução, validação e aplicação do questionário RALPH”. Mestrado em Gestão e Economia da Saúde da FEUC. Dezembro 2021 Supervisor: Prof. Doutor Rui Cruz (ESTeSC).

Carina Sofia da Silva Martins. “Satisfação profissional dos enfermeiros da Santa Casa da Misericórdia de Lisboa e seus determinantes”. Mestrado em Gestão da Saúde da ENSP-UNL. Abril 2021. Supervisor: Prof. Doutor Paulo Boto da ENSP-UNL.

Carla Santos. “Literacia em saúde alimentar de pais com filhos em idade pré-escolar: contributo do enfermeiro de família”. Mestrado em Enfermagem de Saúde Familiar, Universidade de Aveiro. 2021 . Supervisor: Elsa Melo.

Carlos Bernardo Albuquerque Fernandes Braz Saraiva. “Evaluating Biometric Outcomes in Cataract Surgery Using Subjective Refraction and Aberrometric Refraction”. Integrated Master in Medicine, Faculty of Medicine, University of Coimbra. March 2021. Supervisor: Francisco Ambrósio.

Carolina Marques dos Santos. “Can the extracellular vesicles released by Müller glial cells provide neuroprotection to retinal ganglion cells?”. Master in Biomedical Research, Faculty of Medicine of the University of Coimbra. December 2021. Supervisor: Francisco Ambrósio.

Carolina Santos. “A mother's heart: impacts of gestation habits on maternal cardiac mitochondria metabolism”. Cellular and Molecular Biology Master, University of Coimbra. (November 2021). Supervisor: Paulo Oliveira.

Catarina Bernardino Carreira. “Optogenetic activation of intracellular adenosine A2A receptor signaling in the amygdala as a model of stress in rodents”. Mestrado em Biologia Celular e

Molecular, Departamento de Ciências da Vida, Faculdade de Ciências e Tecnologia, Universidade de Coimbra. Dezembro 2021. Supervisors: Paula Canas & Ângelo Tomé

Catarina Corte-Real Gonçalves. "Epiretinal membrane: evaluating the prognostic impact of recent optic coherence tomography-based classification". Integrated Master in Medicine, Faculty of Medicine, University of Coimbra. May 2021. Supervisor: Francisco Ambrósio

Catarina Filipa Carvalho Pinto. "Cuidados Paliativos: Conhecimentos e crenças nos estudantes e profissionais da área da saúde e na população portuguesa em geral". 2º Ciclo em Psicologia Clínica e da Saúde, Universidade Fernando Pessoa. 2021. Supervisor: Isabel Silva.

Catarina Massano. "Outcomes on Social Cognition in adults with Pediatric-onset Multiple Sclerosis". Mestrado Integrado em Medicina da Universidade de Coimbra. Supervisor: Isabel Santana

Catarina Santana Martins de Oliveira. "Doença Inflamatória Intestinal: Novos alvos terapêuticos [Inflammatory Bowel Disease: New therapeutic targets]". 2021. Supervisor: Anabela Mota-Pinto.

Catarina Tristão Sena da Silva. "Caracterização imagiológica do olho contralateral em pacientes com Vasculopatia Polipóide da Coroideia unilateral". Integrated Master in Medicine, Faculty of Medicine, University of Coimbra. Supervisor: Francisco Ambrósio

Cláudia Dias. "Estratégias Comunitárias de manutenção de resultados após reabilitação respiratória: perspetiva dos doentes e cuidadores". Mestrado de Fisioterapia da Universidade de Aveiro. 2021. Supervisor: Elsa Melo.

Cláudia Sofia Cortesão Carvalho. "O impacto na qualidade de vida na síndrome de apneia obstrutiva do sono". Mestrado em Gestão e Economia da Saúde da FEUC. nov-2021.

Daniel Alexandre Dias Ribeiro. "Impacto do Exercício Físico Aeróbio nos Teores Circulantes do Fator Neurotrófico Derivado do Cérebro (BDNF) e da Neurotrofina 4/5 (NT 4/5)". Mestrado em Biocinética, Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra. Supervisor: Isabel Santana

Daniel João Silva e Sousa Oliveira Henriques. "Prevalência e abordagem de massas testiculares incidentais. Uma revisão sistemática [Incidental testicular masses. Prevalence and management. A systematic review]". 2021. Supervisor: Anabela Mota-Pinto.

Daniel José Vasconcelos Silvério. "Decoding Partner Specificity in Opioid Receptor Family". 2021. Master's Degree in Biochemistry, Faculty of Sciences and Technology, University of Coimbra. Supervisor: Irina Moreira.

Daniela Filipa Borges Silva. "A infeção por microorganismos como hipótese etiológica da DA". Integrated Master in Pharmaceutical Sciences, Faculty of Pharmacy, University of Coimbra. Doença de Alzheimer em Indivíduos com o Síndrome de Down. Integrated Master in Pharmaceutical Sciences, Faculty of Pharmacy, University of Coimbra. 2021. Supervisor: Teresa Cruz

Daniela Filipa da Conceição Henriques. "Vacina BCG na imuno-profilaxia durante a Pandemia do COVID-19 [BCG Vaccine for Immune-prophylaxis during the Pandemic of COVID-19: a systematic review]". 2021. Supervisor: Anabela Mota-Pinto.

Daniela Jacinto Gonzaga. "Evaluating the potential of mesenchymal stromal cells for promoting alleviation of blood- brain barrier impairments in Machado-Joseph disease". Master's degree in Pharmaceutical Biotechnology; Faculty of Pharmacy; University of Coimbra.

Daniela Marques Calheiros. "Antifungal activity of plant extracts: spent coffee grounds". Mestrado em Bioquímica pelo Departamento de Ciências da Vida da Universidade de Coimbra.

Daria Vartanova. "Impacts of the second-home tourism on the Algarve region". Mestrado em Gestão na FE-UAlg. Dezembro 2021. Supervisor: Luis Pereira.

Diana Carina Oliveira Soares. "Literacia Relacionada com Medicamento: Tradução, Validação e Aplicação do Questionário RALPH". Mestrado em Gestão e Economia da Saúde, Faculdade de Economia, Universidade de Coimbra.

Diana Farinha. "Avaliação de propriedades antitumorais de plantas do Vale do Côa: Rumex induratus Boiss. & Reut". Master in Biodiversity and Plant Biotechnology, Faculty of Science and Technology, University of Coimbra. 2021. Supervisor: Flávio Reis.

Eliana Barbosa. "Skin aging-delaying potential of PXA4 and comparison with other Sirtuin-1 activators". Master in Applied Pharmacology, University of Coimbra, December 2021. Supervisor: Cláudia Cavadas.

Emanuel Tahiri. "Early autophagy dysfunction in Alzheimer's disease: the role of WIPI2". Master in Cellular and Molecular Biology, University of Coimbra, CNC (Coimbra) and Master in Biology, University of Sannio (Italy). Supervisor: Rui O. Costa.

Erika Muñoz. "Development of LC-MS/MS method for the determination of glutamine and GABA in CSF - case study on Alzheimer's disease patients". 2021. Supervisor: Bruno Manadas.

Eva Sofia Quinteiro dos Santos. "Literacia em saúde na população do ensino superior da Universidade de Coimbra". Mestrado em Gestão e Economia da Saúde da FEUC. Dezembro 2021 Supervisor: Prof. Doutor Vítor Raposo (FEUC).

Eva Sofia Quinteiro dos Santos. "Literacia em saúde na população do ensino superior da Universidade de Coimbra". Mestrado em Gestão e Economia da Saúde. Dezembro 2021. Supervisors: Vítor Raposo and Pedro Lopes Ferreira.

Filipe Oliveira Ginja. "Microbioma e desfechos obstétricos adversos [Microbiome and adverse obstetric outcomes]". 2021. Supervisor: Anabela Mota-Pinto.

Flávia Marlene Bento Sousa. "O Perfil Psicológico de Abusadores Sexuais de Menores nas Relações Intrafamiliares e Extrafamiliares". Mestrado em Medicina Legal e Ciências Forenses - Faculdade de Medicina da Universidade de Coimbra. Fevereiro 2021. Supervisor: Bárbara Oliveiros and Diana Silva.

Francisca Silva. "Dissection of NT3/TrkC intracellular signaling in the processing of fear". Master in Cellular and Molecular Biology, University of Coimbra & CNC, Coimbra Portugal. Supervisor: Mónica Santos.

Francisco Mano. "Longevidade parental como fator protetor para Doença de Alzheimer". Mestrado Integrado em Medicina da Universidade de Coimbra. Supervisor: Isabel Santana.

Gabriela Moço. "Synthesis of PXA4 derivatives and pharmacological evaluation of their anti-osteoarthritic properties". Master in Applied Pharmacology, University of Coimbra, December 2021. Supervisor: Claudia Cavadas.

Helena Cristina Nunes da Costa. "Efeito de neurotoxinas bacterianas intestinais na função da microglia na doença de Parkinson". Master in Medicine, Faculty of Medicine, University of Coimbra. 2021. Supervisor: Teresa Cruz .

Henrique José Xavier Duarte. “Inulin particles as a vaccine adjuvant for Hepatitis B”. Master’s degree in Pharmaceutical Biotechnology; Faculty of Pharmacy; University of Coimbra.

Ilda Cristina Pereira Morais. “Reorganização da Unidade de Apoio à Gestão. Mestrado em Gestão das Organizações – ramo de Gestão de Unidades de Saúde”. Escola Superior de Saúde do Politécnico do Porto. Dezembro 2021. Supervisor: Rui Pimenta.

Inês Alexandra Ferreira Rodrigues. “Evaluation of the ability of CIAD7, a natural compound, to induce the pro-resolution phenotype in murine macrophages”. Master in Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Coimbra. 2021. Supervisor: Teresa Cruz.

Inês Alves. “The Twitter Factor: How Does Twitter Impact Stroke Journals and Articles?”. Mestrado Integrado em Medicina da Universidade de Coimbra. Supervisor: Isabel Santana.

Inês Carmona Lameiras e Silva Moniz. “Hypoxia-induced quiescence: A New Approach on MSC Preservation”. Master Thesis submitted in October 2021 to the Faculty of Medicine of the University of Coimbra. 2021. Supervisor: João Ramalho Santos.

Inês Carolina Fernandes Gomes. “Estratificação do Risco na Resposta à Radiação Ionizante na Síndrome Hereditária para Cancro da Mama e Ovário associada aos genes BRCA1 e BRCA2”. Mestrado Integrado em Engenharia Biomédica com especialização em Imagem e Radiação - Faculdade de Ciências e Tecnologias da Universidade de Coimbra. Novembro 2021. Supervisors: Ana Margarida Coelho Abrantes and Maria Filomena Rabaça Roque Botelho.

Inês Rodrigues Fernandes. “Crenças, Conhecimentos e Práticas sobre os Medicamentos Genéricos na população portuguesa: estudo de coorte”. Mestrado em Farmácia, Especialização Farmacoterapia Aplicada, Escola Superior de Tecnologia da Saúde de Coimbra, IPC.

Inês Rodrigues. “Pharmacological characterization of PXA4 as a potential drug for the treatment of Alzheimer’s disease”. Master in Pharmaceutical Biotechnology, University of Coimbra, December 2021. Supervisor: Cláudia Cavadas.

Inês Sofia de Moura. “Deficiências nutricionais pré-natais e Perturbação de Hiperatividade e Défice de Atenção na descendência: o que sabemos até agora? [Prenatal nutritional deficiencies and Attention-Deficit/Hyperactivity Disorder in the offspring: what do we know so far?]”. 2021. Supervisor: Anabela Mota-Pinto .

Inês Sofia Russo Correia Ribeiro. “Avaliação económica de PPD”. Mestrado em Gestão e Economia da Saúde da FEUC. Defesa Dezembro 2021.

Inês Vieira Peres Ventura. “Characterisation of glycoproteins involved in sea urchin adhesion”. Master in Biomedical research, Faculty of Medicine, University of Coimbra.2021. Supervisor: Teresa Cruz.

Iolanda Daniela Teixeira Vaz. “A literacia em saúde dos cuidadores formais e informais. Dissertação do Mestrado em Gestão das Organizações – ramo de Gestão de Unidades de Saúde”. Escola Superior de Saúde do Politécnico do Porto. Janeiro 2021. Supervisor: Rui Pimenta.

Isa Morais Penas. “The role of immune system in polyglutamine diseases: immunogenicity prediction of ataxin-3 and its cleavage fragments”. Master’s degree in Pharmaceutical Biotechnology; Faculty of Pharmacy; University of Coimbra.

Isadora Pombeiro. “Stress-reducing treatments as adjuvant therapies for diabetic chronic wounds – a randomized controlled trial – a blind randomized pilot study”. University of Coimbra, Portugal. Supervisor: John Jones.

Jéssica Ferreira. “Skin allergens: molecules with a possible therapeutic role in Alzheimer´s disease”. Faculty of Pharmacy, Master in Applied Pharmacology, Faculty of Pharmacy, University of Coimbra. 2021. Supervisor: Teresa Cruz.

Jisette González Núñez. “Non-pathogenic viral vectors of SARS-CoV-2 to study drug repurposing and immunization strategies”. Master’s degree in Pharmaceutical Biotechnology; Faculty of Pharmacy; University of Coimbra.

Joana Alexandra Lima Gonçalves. “The Impact of Protein Tyrosine Phosphatases on the activation of Intraepithelial Lymphocytes”. Master in Biomedical research, Faculty of Medicine, University of Coimbra. 2021. Supervisor: Teresa Cruz.

Joana Filipa Figueiredo Simão. “Smart delivering and drug targeting to treat age-related macular degeneration”. Master in Medicinal Chemistry, Faculty of Sciences and Technology, University of Coimbra. June 2021. Supervisor: Francisco Ambrósio.

Joana Margarida Rodrigues e Sousa. “Melhoria da decisão clínica e dos resultados - avaliação de uma recomendação de monitorização em utentes com diabetes mellitus tipo 2”. Mestrado em Gestão e Economia da Saúde. Dezembro 2021. Supervisors: Vítor Raposo and Joao Rodrigues.

Joana Patrícia Sousa da Silva “Synaptic senescence in Alzheimer’s disease”. Mestrado em Biologia Celular e Molecular, Faculdade de Ciências da Universidade do Porto. Novembro 2021. Supervisor: Rodrigo Cunha.

Joao Gabriel Branco Silva. “The effects of high fat feeding on the metabolomics of heart, kidney and skeletal muscle in C57BL6J mice as analysed by 1H NMR”. M.Sc. in Cellular and Molecular Biology - University of Coimbra. Supervisor: John Jones.

Joao Miguel Vicente Ventura. “Mechanistic studies on the enzymatic conjugation of polyesters with bioactive compounds”. Master in Biochemistry, Universidade de Coimbra.

Laura Alexandrina Sequeira Neves. “Linking mitochondrial Src and hippocampal dendritic changes in Alzheimer’s disease”. Integrated Master in Biomedical Engineering, Faculty of Science and Technology, University of Coimbra, Portugal. February, 2021 – online (zoom). Supervisor: Ana Cristina Rego.

Leonor Serrano Lopes. “Astrocytes´morphological alterations with fear extinction- Impact of adenosine A2A receptors blockade”. Mestrado integrado em Medicina, Faculdade de Medicina da Universidade de Coimbra. Junho 2021. Supervisors: Paula Agostinho & Paula Canas.

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Mafalda Sofia da Silva Ferreira. “Desenvolvimento de resiliência individual na gestão de incidente crítico. Dissertação do Mestrado em Gestão das Organizações – ramo de Gestão de Unidades de Saúde”. dezembro 2021. Escola Superior de Saúde do Politécnico do Porto. Supervisor: Rui Pimenta.

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Mariana Diniz. “Made in the Womb: maternal programming of offspring cardiovascular function”. Biochemistry Master, University of Coimbra. November 2021. Supervisor: Paulo Oliveira.

Mariana Jacinto Araújo. “Mediadores no filme lacrimal em doentes com queratocone”. Integrated Master in Medicine, Faculty of Medicine, University of Coimbra. May 2021. Supervisor: Francisco Ambrósio.

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Mariana Sousa Silva. "The Influence of Personality on Quality of Vision after Multifocal Intraocular Lens Implantation". Integrated Master in Medicine, Faculty of Medicine, University of Coimbra. May 2021. Supervisor: Francisco Ambrósio.

Marina Albino Costa. "Machado-Joseph Disease Comorbidities and Symptomatic Treatments: a large cohort analysis". Master's degree in Pharmaceutical Biotechnology; Faculty of Pharmacy; University of Coimbra.

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Marta Oliveira da Silva. "Caracterização e análise de custos da Disfagia Orofaríngea numa Unidade de Cuidados Continuados de Média Duração e Reabilitação". Dissertação do Mestrado em Gestão das Organizações – ramo de Gestão de Unidades de Saúde, Escola Superior de Saúde do Politécnico do Porto. Janeiro de 2021. Supervisor: Rui Pimenta.

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Nádia Pereira. "SARS-CoV-2 characterization – an in-silico approach". 2021. Master's Degree in Biochemistry, Faculty of Sciences and Technology, University of Coimbra. Supervisor: Irina Moreira.

Nelson Lopes Cardoso. "Gamapatias Monoclonais: Diagnóstico Diferencial e Diagnóstico da Amiloidose AL". Mestrado Integrado em Medicina, Faculdade de Medicina da Universidade de Coimbra. Junho 2021. Supervisor: Catarina Geraldes and Ana Bela Sarmento Ribeiro.

Nuno Guilherme Linhares Chiote. "Neuromodulação bioelétrica para distúrbios gastrointestinais: eficácia e mecanismos [Bioelectric neuromodulation for gastrointestinal disorders: effectiveness and mechanisms]". 2021. Supervisors: Anabel Mota-Pinto and Nuno Guilherme Linhares Chiote.

Patrícia Gomes Santos. "Adenocarcinoma do Pâncreas - Estratégias Terapêuticas Atuais e Perspectivas Futuras [Pancreatic Adenocarcinoma - Current Therapeutical Strategies and Future Perspectives]". 2021. Supervisor: Anabela Mota-Pinto.

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Rita Carolina Ivo Pacheco. "Proteomic approach to the characterization of unknown origin male infertility" for the Master in Biomedical Research from the Faculty of Medical Sciences of the Nova University, Lisbon. (September 2020-March 2022). Supervisor: Sandra Amaral and Renata Tavares.

Rita Sofia de Jesus Pita Domingues. “Optimization of the recovery of extracellular vesicles from filamentous fungi”. Mestrado em Bioquímica pelo Departamento de Ciências da Vida da Universidade de Coimbra.2021.

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Sara Alexandra Palos Alves Costa. “Impacto da Covid-19 sobre os diagnósticos da urgência de Oftalmologia”. Integrated Master in Medicine, Faculty of Medicine, University of Coimbra. March 2021. Supervisor: Francisco Ambrósio.

Sara Gonçalves. “Biosynthesis of serotonin in bacteria: an exploratory study”. Masters in Pharmaceutical Biotechnology. 2021. Supervisor: Nuno Empadinhas.

Sara Margarida Vaz Rodrigues Amaral Pinto. “Os custos da não adesão ao tratamento da hipertensão arterial: uma revisão sistemática da literatura”. Mestrado em Gestão e Economia da Saúde, Faculdade de Economia da Universidade de Coimbra, outubro de 2021.

Simão Santos. “Novel molecular targets and therapeutic strategies for Hutchinson-Gilford Progeria Syndrome's cardiovascular system”. 2021. Master’s Degree in Molecular and Cell Biology, University of Coimbra. Supervisors: Lino Ferreira and Ana Luísa de Carvalho.

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Sofia Gomes Salgueira. “Perceção sobre o cancro do testículo na população universitária Portuguesa [Perceptions of testicular cancer among Portuguese university students]”. 2021. Supervisor: Anabela Mota-Pinto.

Tânia Alves. “Cannabis: Um potencial candidato na terapêutica da doença de Alzheimer”. Mestrado Integrado em Ciências Farmacêuticas. Supervisor: Isabel Santana.

Tatiana da Cruz Almeida. “Characterization of Copy Number Variation in Autism Spectrum Disorder: Identification of driver genes”. Mestrado em Biomedicina Molecular, departamento de Ciências Médicas, Universidade de Aveiro. Julho 2021. Supervisor: Ilda P Ribeiro. Instituição de acolhimento – Laboratório de Citogenética e Genómica – FMUC.

Tatiana Lúcia Donai Lopes. “Sleep quality of drivers: a study based on self -perceived and sleep companions feedback”. Dissertação do Mestrado em Bioestatística e Bioinformática Aplicadas à Saúde, Escola Superior de Saúde do Politécnico do Porto. Dezembro 2021. Supervisor: Rui Pimenta.

Telma Ferreira Rodrigues. “Obstáculos e adesão ao tratamento em adultos com diabetes tipo 1”. 2º Ciclo em Psicologia Clínica e da Saúde, Universidade Fernando Pessoa. 2021. Supervisor: Isabel Silva.

Tiago Filipe Marques Gonçalves. “Esclerose múltipla: mecanismos fisiopatológicos e fármacos modificadores de doença”. Mestrado Integrado em Ciências Farmacêuticas. Supervisor: Isabel Santana.

Tiago José Brasil Roquito.” The impact of curcumin-encapsulated glucan nanoparticles on hepatic cells and immune cells: oxidative stress and immunomodulatory properties”. Master’s degree in Pharmaceutical Biotechnology; Faculty of Pharmacy; University of Coimbra.

Vanessa Alexandra Duarte Costa. “Influência do alelo Ɛ4 da Apolipoproteína E na avaliação cognitiva breve no espetro da Doença de Alzheimer”. Mestrado Integrado em Medicina da Universidade de Coimbra. Supervisor: Isabel Santana.

Verónica José P Santos Cavadas. “Automedicação, evidencia do INS 2019. Mestrado em Gestão e Economia da Saúde”. Faculdade de Economia da Universidade de Coimbra. 2021. Supervisor: Pedro Lopes Ferreira da FEUC).

Verónica José Pessoa Barros Alves dos Santos Cavadas. "INS2019 - Caracterização da prevenção – Automedicação". Mestrado em Gestão e Economia da Saúde da FEUC (coorientação da Prof. Doutora Aida Isabel Tavares do ISEG). Defesa em 29-nov-2021.

Whandra Braga Pinheiro dos Reis Alburquerque. Emoções negativas e adesão terapêutica: um programa de intervenção em pacientes com diabetes Mellitus II. Mestrado em Educação para a Saúde, Escola Superior de Tecnologia da Saúde de Coimbra, IPC.

TECHNOLOGY TRANSFER

Head: Ana Catarina Cunha Santos

CIBB fosters innovation and socio-economic growth by translating the scientific and technological knowledge developed in our laboratories into solutions to major societal challenges in healthcare. The biomedical nature of our research brings additional responsibility to society. Our institute has been committed to transferring the novel technologies herein developed to local industries and organizations towards regional development through technology transfer.

Technology Transfer (TT) transforms scientific and technological knowledge into innovations. In the context of CIBB, the main goal of technology transfer is to valorise the intellectual assets of our institute through a transaction that is beneficial to all parties involved. As long-term goals, technology transfer assures the practical use of the scientific and technological advances by the general public and research community, creates qualified jobs, promotes the recognition and reputation of our institute, generates revenue for further research funding, and stimulates the local and regional socio-economic development.

In 2021, CIBB continue to consolidate the recently (in 2019) created Technology Transfer Office (TechTransfer) mainly through the implementation and assessment of procedures for protection and valorisation of technological knowledge towards commercialization.

Of note regarding Intellectual Property achievements, CIBB had two granted US patents, one granted national patent, and one granted utility model during the 2021 year. CIBB also made a contract for services provision with a broker, expert in biomedicine and biotech, to help valorise three technologies in these areas.

CIBB TechTransfer participated in a consortium of seven institutions distributed among five European Countries (Innocore) with total funding of ~500 000€ and was a team member in three projects/project applications: one Exploratory FCT project approved (to start on January 2022); one "La Caixa Research Health 2022" (under revision) and one EIC Pathfinder Open (under revision). The CIBB was able to raise 25.000€ in patent consulting and licensing negotiation (five services) from the European Programme IP Booster and assisted Coimbra University in one more service approval. One R&D Centre of CIBB consortium (Center for Neuroscience and Cell Biology) was awarded the designation "Center for Technology Transfer and Valorisation" by the National Innovation Agency (ANI).

Regarding scientific research projects, CIBB TT Office assisted researchers in delineating the Intellectual Property protection and commercialization for project applications in international (e.g. CaixaImpulse Validate) and national (e.g. 2021 FCT Call for Projects in all Scientific Domains) calls.

Regarding academy-industry collaborations, CIBB TechTransfer engaged with valorisation platforms such as Innospin and In-Part to contact industrial partners and opportunities for further development and exploitation of the technologies developed at our institute. In 2021, we raised a total of ~452 711€ in collaborative and research agreements with national and international companies.

The TechTransfer of CIBB is committed to the training and awareness of researchers and students to tech transfer-related topics. In 2021, our office supervised two MSc students in Pharmaceutical Biotech from Coimbra University focused on TT in academic settings, organized three CIBB seminars in entrepreneurship and Intellectual Property topics, and lectured the annual one-day training on the Course "Connecting Researchers with the Society" from the CIBB PhD Programme in Experimental Biology and Biomedicine and a few classes. CIBB also founded the first social media group on LinkedIn devoted to the Portuguese TT network, named "Rede TechTransfer PT" (https://www.linkedin.com/groups/9010987/).

CIBB constructed a database containing an exhaustive list of healthcare research players in the Portuguese innovation ecosystem named "HealthPT Database" and protected it by *sui generis*

rights—Intellectual Property type that protects the content of a database against non-authorized use. This database will be soon commercialized as a product, the first of this kind in Portugal.
The main achievements of the CIBB TechTransfer Office in 2021 were the following:

- 5 Invention Disclosure Forms;
- 4 provisional patent applications;
- 2 international patent applications through the PCT system;
- 1 granted utility model;
- 2 granted US patents;
- 1 granted national patent;
- 2 patents entered the national phases (in 9 countries/regions);
- 2 MSc students supervised (one of them concluded in December 2021);
- 15 non-disclosure agreements;
- 3 results sharing agreements;
- 3 CIBB seminars in patent writing, Venture Capital, and technological vigilance topics;
- 7 CIBB-industry contracts or agreements in a total of ~452 711€ attracted for CIBB;
- 1 project under review as leader of a consortium of three entities (awarded in 2022);
- 5 services (equivalent to 25.000€) attracted through the European Programme IP Booster;
- 1 *sui generis* rights – a database containing an exhaustive list of healthcare research players in the Portuguese innovation ecosystem named "CNC HealthPT Database"
- 1 participation in research projects;
- 1 participation in an awarded project by FCT (to start on January 2022);
- 2 participation in projects under revision.

Through technology transfer, CIBB leverages the investment in science and releases its transformative power into real value for society.

SCIENCE COMMUNICATION

Head: Sara Varela Amaral, PhD.
Team: Carla Veríssimo, Carolina Caetano, João Cardoso, Lia Lopes, Marta Quatorze, and Sara Varela Amaral

One of the major challenges of the contemporary research is to develop new and innovative ways to engage society in science. Recognizing the importance of science communication, CIBB have been deeply involved in public engagement activities in order to foster dialogue between scientists and groups of society, to provide public accountability, to spread our findings through media and foster scientific culture. Reach and engage different groups of the society will be one of the most important hallmarks of the research center strategy. Our highly multidisciplinary team brings together people with a broad and well-built expertise, essential for the development of an outstanding science communication strategy. All the CIBB community are actively engaged in our outreach efforts. These valuable in-house conditions can guarantee *per se* the scientific accuracy of the disseminated information and its suitableness to non-specialized target audiences.
Our partnerships - Ciência Viva, Science Museum of the University of Coimbra, University of Coimbra, Maratona da Saúde, Instituto de Educação e Cidadania, Jornal Público, Dana Foundation, between others – are crucial to strategically target different publics. Our activities have been supported by several associations and scientific societies as Biochemical Society, Federation of European Neuroscience Societies, Sociedade Portuguesa de Neurociências, Sociedade Portuguesa de Imunologia, Associação Portuguesa do Sono, Alzheimer Portugal, Associação Portuguesa de Doentes de Huntington, Associação Portuguesa de Diabéticos de Portugal, Associação Portuguesa de Ataxias Hereditárias and Sociedade Portuguesa de Biologia da Reprodução.

CIBB at the Media

The Science Communication Office is in charge of the public relations process, communicating science with news-values in the context of different agenda-settings, preserving the accuracy of scientific knowledge, and successfully liaising researchers with journalists. This process is done always in collaboration with the University of Coimbra.

In 2021 CIBB was in the news **1000 times** with an advertising value of **2.973.375 euros**, reaching a total number of **42.793.302 audiences**.

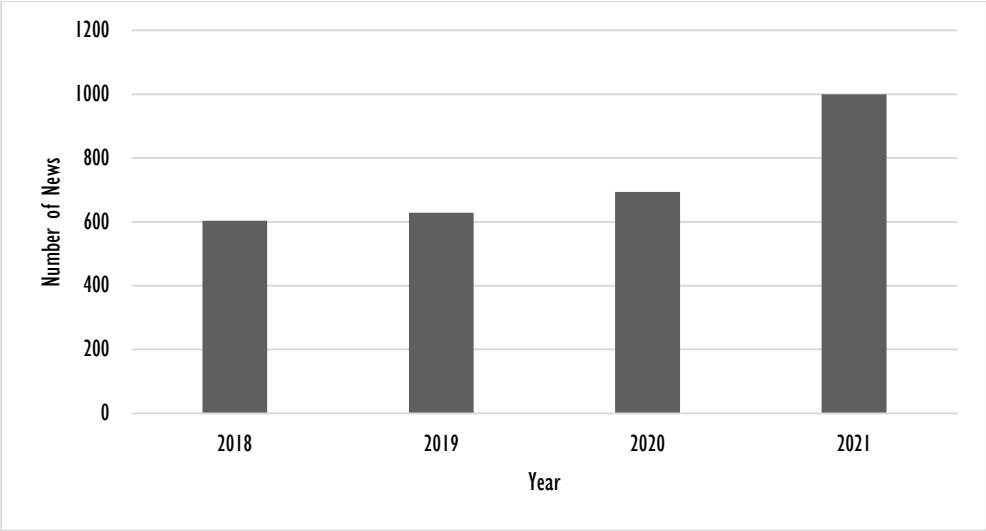


Figure 1 – CIBB news in 2018, 2019, 2020 and 2021.

Figure 2 – CIBB news, audiences and advertising value in 2021.

To reach a wider population we improve our presence in social networks. At the end of 2021 we have more than **18.000 followers** at different social networks: Facebook, Twitter, Linkedin, Instagram and Youtube.

Public Engagement in Science at CIBB

CIBB is strongly involved in Public Engagement in Science projects that engage society. We participated in several national and international initiatives that involves different stakeholders / audiences all over the year.

Figure 3 – CIBB numbers for public engagement projects in 2021.

Rare Disease Day
February 2021

During Rare Disease Day we organized an online event "Energias Raras: Ver mais Além" that was streaming at our CNC media channel. The event had about 150 visualizations and involved 5 researchers.

Brain Awareness Week (BAW)
March 2021

Brain Awareness Week (BAW) is an initiative that aims to increase public awareness of the progress and benefits of brain research. BAW is celebrated every March and it is coordinated by the Dana Foundation, with the support of the Federation of European Neuroscience Societies(FENS). In Portugal, the campaign is coordinated by the Portuguese Society for Neuroscience(SPN) in collaboration with Ciência Viva.
CIBB celebrates BAW every year, providing activities for school audience and the general public. Researchers visit schools and carry out games, "hands-on" activities and lectures on brain-related subjects. Open Labs allow the public to get to know the research carried out at CNC and iCBR. Several events such as exhibitions, concerts, Science cafes, lectures and debates are also organized during BAW.

Figure 4 – 2021 BAW programme.

In 2021 we organized the following activities:

- <u>"Brain Gain" online sessions series</u>

On March 10, 17, 24 and 31, this online sessions series approached neurosciences from 4 different points of view: Neurosciences and Technology, Brain Pathologies and Therapies, Models to Study the Brain and Bioethics and Brain Professions. The main goals were to reinforce Neurosciences as a strong research area in Portugal and to inspire undergraduate and graduate students to follow neuroscience-related careers. This initiative was supported by the Portuguese Society for Neuroscience (SPN). We received more than 900 registrations and gathered around 300 people each session. In total, we counted with the participation of an audience of around 1070 people and 22 speakers.

- <u>Online sessions with Schools</u>

From March 15 to 26, more than 20 researchers presented their work, engaging around 890 elementary, middle and high school students, as well as graduate students.

- <u>Bipolar Disorder Day</u>

On March 30, we have created a comic about Bipolar Disorder Day to celebrate World Bipolar Day. This comic was published in a national newspaper – Público, and aimed to raise awareness about this disorder and the importance of fighting the social stigma that still surrounds mental diseases. We have worked within a multidisciplinary team of researchers, science communicators, and psychiatrists from the Coimbra University Hospital Centre. The publication had around 7100 interactions (visualizations and shares). The comic is available here.

Figure 5 – Bipolar Disorder Day Comic

- <u>World Sleep Day</u>

To celebrate World Sleep Day, we promoted a digital campaign on social network in collaboration with the Portuguese Sleep Association. This campaign aimed to share facts about sleep and to raise awareness about the importance of healthy sleep habits. We have shared sentences and videos every day during March. We reached around 18.000 people online.

<u>Science at the Lab</u>
July 2021

Science at the Lab program is an initiative promoted by Ciência Viva that aims to give high schools students an opportunity to get in touch with the reality of scientific and technological research, promoting summer internships in laboratories at national research institutions. This program raises students' awareness of career opportunities in Science. Every year, since 1990, CIBB welcomes students who join several research groups and have the opportunity to conduct hands-on research under the mentorship of expert researchers. In 2021 5 high-school students participated at this program at out labs.

Summer with Science
September 2021

During one month CIBB received 30 students for internships at different labs. One studentdeveloped a video about the initiative available here. This programme was funded by FCT.

European Researchers´Night (ERN)
September 2021

European Researchers´ Night is an initiative promoted by the European Union that aims to join education and entertainment creating meeting places between scientists and different public, promoting a real interaction through science communication strategies as hands-on activities, one-on-one conversations, exhibitions and artistic performances. In Coimbra ERN was organized by University of Coimbra and CIBB has been a partner of this event in Coimbra since 2009. In 2021 the activities were organized in different places over the city in a huge event that engaged more than 300 researchers. 80 CIBB Researchers participated and reached more than 1800 people.

Figure 6 – Some images of CIBB activities at ERN 2021.

Stem Cell Day
October 2021

CIBB joined the Portuguese Society of Stem Cells and Cell Therapy to celebrate Stem Cell day for the first time in Portugal. We organized several science communication sessions with schools to disseminate stem cell research and concepts. 300 students participated in the initiative organized by 10 CIBB researchers.

FICA
October 2021
In 2021 CIBB participated at FICA with University of Coimbra team. We took 3 hands-on activities that explored our 3 main areas: neurosciences,
biotechnology and metabolism. More than 200 people went to our activities and more than 10 researchers participated.

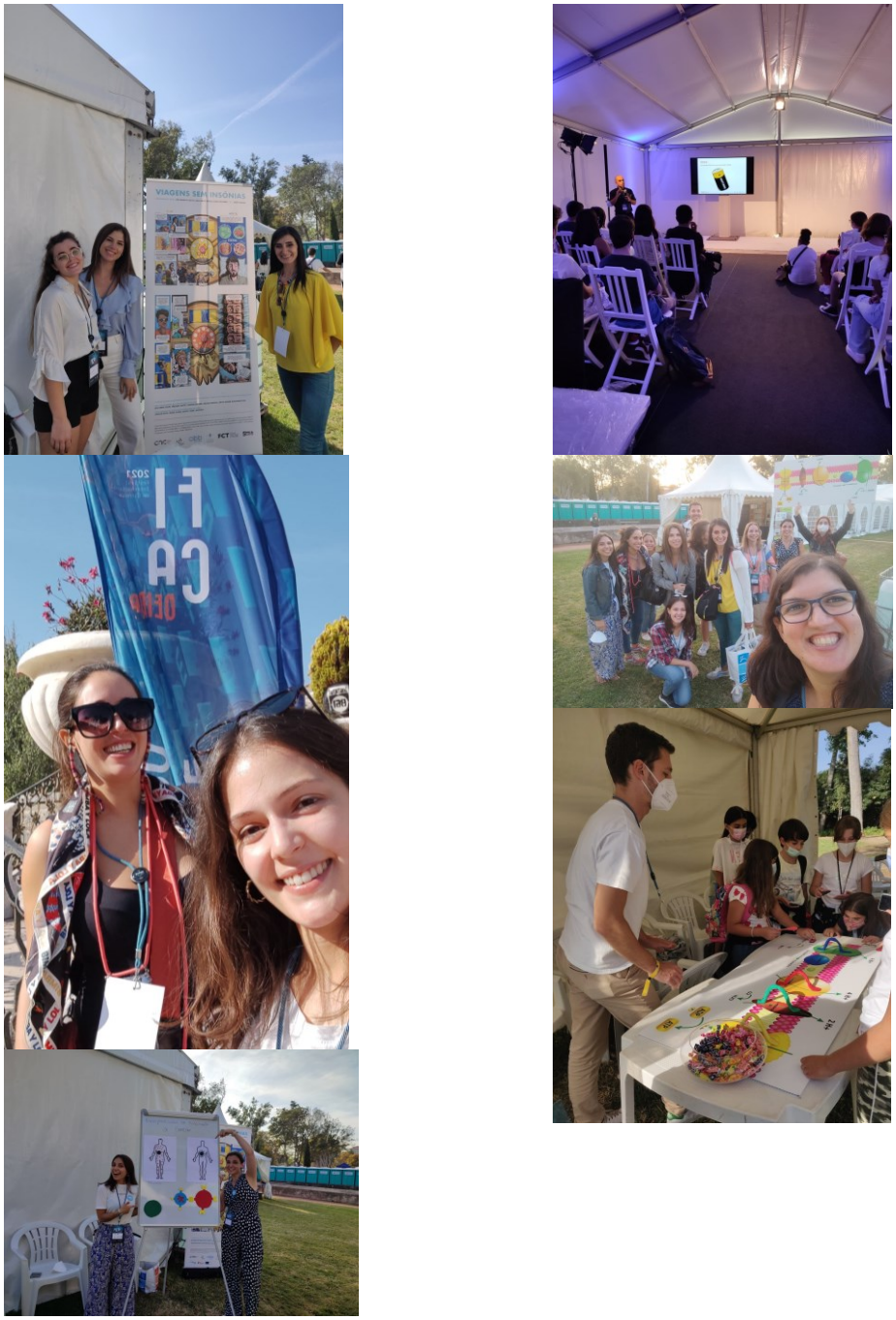


Figure 7 – CIBB researchers at FICA science festival.

Science and Technology Week
November 2021

Science and Technology Week is a national initiative coordinated by Ciência Viva that is celebrated every year in November, in the scope of the National Scientific Culture Day (November 24th).
National Scientific Culture Day was established in 1996 by the former Minister of Science and Technology, José Mariano Gago, to honor Rómulo de Carvalho/António Gedeão – professor, science communicator, and poet. During Science and Technology Week, research institutes, universities, schools, and museums open their doors, allowing the public to perform scientific observations and get in touch with researchers from different fields. CIBB has been celebrating this initiative for over 20 years, organizing open labs, visits to schools, associations, and senior universities, and public events such as lectures and Science cafes. In 2021 more than 700 people participated at our activities.

Educational initiatives with IEC
All the year

Instituto de Educação e Cidadania (IEC) is a science center in Mamarrosa that promotes the science education among the local community. CNC actively collaborate with IEC initiatives in 2021: more than 1000 people participated in the conferences and/or advanced courses promoted by 21 CIBB researchers.

A Saúde no Saber
January - December 2021

Health in Knowledge is a national project that aims to effectively contribute to the development of a scientific culture in Portugal, by creating a health literacy campaign. This project wants to promote public discussion of health-related topics, engaging society in the development of Science Shops – meeting when CNC researchers and citizens discuss and share knowledge and experiences, and in the co-creation of science communication materials. We discussed topics such as Sleep, Cancer, Menopause, Fertility and Pregnancy, Immunity, Neuropsychiatric Diseases, Neurodegenerative Diseases, Neuronal Development, Rare Diseases, Microbiology and Infectious Diseases, Nutrition and Metabolic Diseases and Biotechnology and Advanced Therapies. This project is funded by Ciência Viva in the scope of Comunicar Saúde contest. We engaged more than 35 researchers in this project. This project aims to promote health literacy in Portugal through:

1) Getting society in contact with research carried out in health-related fields Creating health literacy helps society to take advantage of the benefits of Science, allowing more conscious and informed decisions. Getting CNC researchers closer to social stakeholders such as politics, patients, formal and informal care givers and students, allow us to directly answer questions raised by the society.

2) Production of science communication materials The creation of science communication materials will be made involving different social stakeholders and through several formats and media.

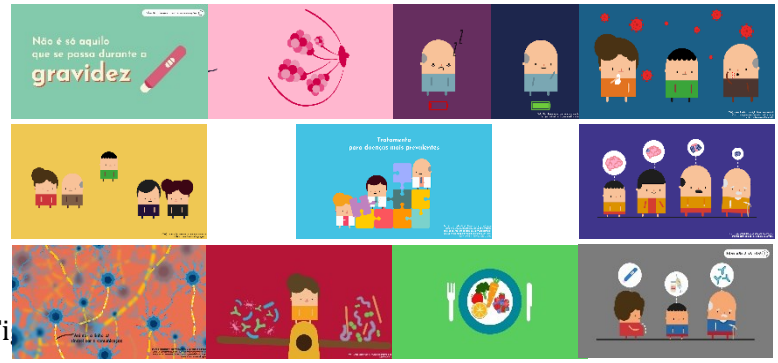
In 2021 we produced and spread several materials under this national campaign – every month explored a different scientific theme:

- Audiovisual animations

11 animations were produced with close collaboration with design and multimedia professionals from Department of Informatic Engineering and researchers from the different fields explored. The animations were disseminated through our social networks and in TOMI screens (one week campaing). The metrics from the TOMI campaign are:

- Lisboa: 267.876 exibitions (1.488 h) | 50 TOMI screens
- Àgueda: 10.735 exibitions (60 h) | 2 TOMI screens
- Algarve: 91.934 exibitions (511 h) | 17 TOMI screens

- Figueira da Foz: 10.735 exibitions (60 h) | 2 TOMI screens

Fi 

- Radio Interviews

With the collaboration of Rádio Universidade de Coimbra (RUC), we produced a set of short radio pieces "A Saúde no Saber: desevendar ciência em menos de 3 minutos" that explored different scientific themes:

- Uma criança nasce com um quadro em branco do ponto de vista biológico?, with João Ramalho-Santos
- O cancro não tem cura?, with João Nuno Moreira
- Dormir é uma perda de tempo?, with Ana Rita Álvaro
- O vírus da gripe transmite-se por sairmos de casa com o cabelo molhado?, with Teresa Cruz
- As vacinas causam autismo?, with João Peça
- O tamanho do nosso cérebro é proporcional à nossa inteligência?, with Ricardo Rodrigues
- Vale a pena financiar a investigação em doenças raras?, with Luís Pereira de Almeida
- A demência é algo que só acontece à população idosa?, with Paula Moreira
- Os microrganismos são nossos inimigos e são os antibióticos a melhor arma para os combater?, with Ana Maranha
- Se passarmos a vida a tomar antioxidantes ficamos livres de doenças?, with Paulo Oliveira
- A biotecnologia traz riscos para a saúde humana?, with Isaura Simões

The interviews were broadcasted at RUC and through our social networks and are available online.

- Illustrated Chronicles

11 chronicles were published at Público online. All the chronicles were illustrated by André Caetano and the illustrations were the result of brain stormings between science communicators, researchers, medical doctors and patients. The following are the themes of the chronicles:

- O futuro é hoje: como preservar a fertilidade;
- Cancro, a fatalidade de sempre?
- Porque razão a luz dos dispositivos electrónicos afeta o sono?
- Sem animais, como é que a cosmética testa agora os seus produtos?
- O que é a perturbação de hiperactividade e défice de atenção? Serão só bichos-carpinteiros?
- Desenvolvimento do cérebro: quando os neurónios têm que viajar.
- Terapia génica: uma chave para o tratamento de doenças raras?
- Doenças neurodegenerativas: um quebra-cabeças com solução à vista?
- Micobactérias da água: uma ameaça silenciosa
- Gravidez: uma janela de oportunidade para um futuro saudável
- A paleta de cores da biotecnologia

Figure 9 – *Health in Knowledge* illustrated chronicles.

- Video interviews

We produced a podcast at our youtube channel with *Health in Knowledge* long interviews – A Saúde no Saber: o podcast. All the podcast videos are available online at CNC media channel.

Training in Science Communication

Give tools and inspire scientists to communicate is crucial and requires knowledge not only of science, but of about ethics, information technologies, journalism, visual communication and public engagement. Science Communication Office organized the advanced course *Connecting Researchers with the Society*, integrated in PhD Programme in Experimental Biology and Biomedicine (PDBEB), in order to help scientists to engage the public in different environments. 13 students, from PDBEB and from other PhD programs, participated in this intensive course (5-days) with the participation of more than 10 speakers from different fields as public engagement in science, visual communication, media, technology transfer, career development and art&science. A video to celebrate the Scientist National Day was produced by the students with the support of UC Communication Office and CNC Science Communication Office – see here.

Figure 10 – Frame from the video produced by PDBEB students

CORE FACILITIES

ANIMAL HOUSE CNC

Head of Unit: Doutora Paula Mota

The Animal House Facilities are a shared resource that provides services in laboratory animal experimentation and husbandry, for all CNC and FMUC scientists, UC science community and companies using animals in their research. CNC is among the institutions that signed the Transparency Agreement on Animal Research in Portugal.
In the year 2021, the Animal Facilities supported directly 48 research projects and indirectly other 15 research projects and, approximately 50% of the papers authored by CNC researchers (Pubmed), report the use of CNC animal facility resources, either by use of animal tissues or performance of animal experimentation procedures.
In collaboration with iCBR, CNC animal Facilities also organized the V edition of the Modular structure training course in Laboratory Animal Science, recognized by the National Authority for Laboratory Animals (DGAV), to improve training of their scientist in this area.
CNC runs two animal facilities, UC-BIOTECH Animal Facility located at UC-BIOTECH building in Cantanhede and FMUC/CNC Animal Facility located at Faculdade de Medicina, Polo I, Coimbra.
In 2021 the FMUC/CNC Animal Facility, a conventional type facility, increased animal production and experimental capacity by opening two new rooms for mice, supporting the expansion of studies in ageing and neurodevelopmental diseases. It sustained the production and use of 21 genetically altered strains and 2 wild type strains.
The CNC_UC-BIOTECH Animal Facility, with the capacity to house 1500 specific pathogen free (SPF) animals and a level 2 biosafety area (ABSL2- for performing animal experiments associated with agents with moderate potential risk to humans and/or the environment, including agents that cause mild diseases in humans and are not transmitted by aerosols) sustained the production and use of 10 genetically altered strains and 1 wild type strains.
The animal facilities provided specialized animal services, namely breeding and housing of transgenic/knockout strains, production of rats/mice embryos and litters and support to animal experimentation procedures. At the UC-Biotech animal facility, the ABSL-2 unit also supported animal procedures associated with agents with moderate potential risk to humans and/or the environment, including agents that cause mild illness in humans and are not transmitted by aerosols.

Staff:
Paula Mota (Designated Veterinarian and Animal Facilities Coordinator)
Carmen Semião (FMUC/CNC Animal Facility coordinator, Animal Welfare responsible and caretaker)
Sandra Freire (FMUC/CNC Animal Welfare responsible and caretaker)

Fátima Moreira (UC-BIOTECH Animal Welfare responsible and caretaker)
Milene Ribeiro (UC-BIOTECH Animal Welfare responsible and caretaker)
Fátima Graça (FMUC/CNC caretaker)
Mónica Serrano (FMUC/CNC caretaker)
Cristina Teixeira (caretaker)
Maria Eugénia Campos (FMUC/CNC assistant technician)
Cláudia Figueiredo (assistant technician)
Cláudia Santos (UC-BIOTECH assistant technician)
Diogo Ferreira (UC-BIOTECH assistant technician)

ANIMAL HOUSE ICBR

Head: Ana Raquel Santiago

Staff:
Ana Raquel Santiago (Coordinator)
Susana Barroso (Designated Veterinarian)
Beatriz Ormonde (caretaker)
Gonçalo Ferreira (caretaker)
Virgílio Andrade (caretaker)
Cláudia Serra (caretaker)
Cláudia Caridade (administrative support)

The Animal Facilities at iCBR are conventional type facilities for the housing of laboratory animals (small rodents, rats and mice). Scientific research involving animals at the Animal Facilities of iCBR has contributed to advances in biomedical research.
iCBR is a signatory of the Transparency Agreement on Animal Research in Portugal. It is a joint initiative of the European Animal Research Association (EARA) and the Portuguese Society of Sciences Laboratory in Animals (SPCAL), which brings together all Portuguese teaching and research institutions using laboratory animals.

The Animal Facilities can house approximately 3000 animals. There are 4 rooms dedicated to animal production (mice and rats) and two experimental areas, one with2 rooms for housing of both species and the second dedicated to surgery of rats. There are adjacent laboratories dedicated to support animal research in areas mostly related to Vision Sciences, Oncology, Cardiology, Neurosciences and Metabolic diseases.

TRAINING and dissemination

Postgraduate Course on Laboratory Animal Sciences
15th to 26th of November
The practical component of this course takes place at the Animal Facilities of iCBR. 40 attendees
Workshop on Communication of Animal Experimentation
6 May 2021
96 participants
Workshop on Pain Severity
21 July 2021
37 participants
#TransparencyThursday
An initiative promoted by EARA, in which researchers answer questions about their animal research on the EARA Instagram pag

FLOW CYTOMETRY UNIT

Platform Scientific Director: Carlos Filipe Pereira, Ph.D.
Platform Coordinator: Isabel Nunes Correia, Ph.D.
Unit Technician: Cândida Mendes, MSc
Unit Technician: Susana Pedreiro, MSc

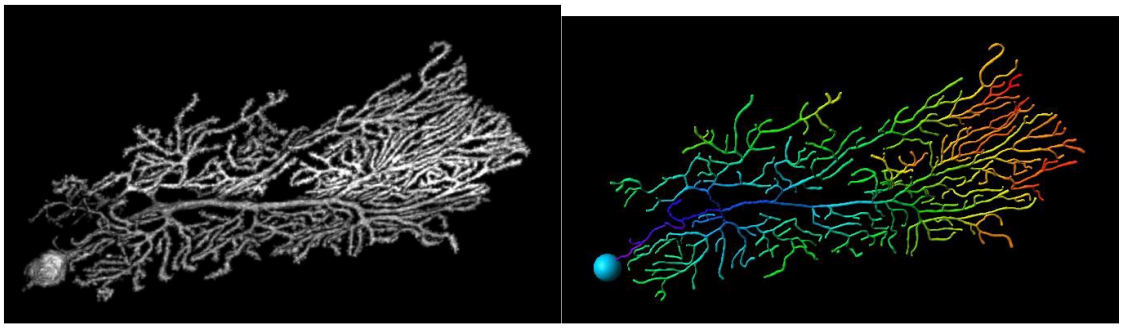
The Flow Cytometry Unit, at the Center for Neuroscience and Cell Biology, provides scientific and technical support to all CNC researchers, external academic units and companies. The Unit is divided between Polo I in Coimbra and in UC-Biotech in Cantanhede, that are currently equipped with a Becton Dickinson FACSCalibur cell analyser (4 colours) and a Partec CyFlow Space cell sorter (7 colours), and with a Becton Dickinson Accuri™ C6 cell analyser (4 colours) with auto-sampler and a Beckton Dickinson FACSAria III cell sorter (12 colours), respectively. Since 2007, when the unit was created, flow cytometry has emerged as an important and central technique for the fulfilment of many CNC research projects, and there has been an important investment in acquiring state of the art technology so that new research areas can be implemented. The unit provides training to inexperienced researchers and organizes annual flow cytometry seminars with the purpose to make this powerful technology known and available to all CNC researchers

MICROSCOPY IMAGING CENTER OF COIMBRA

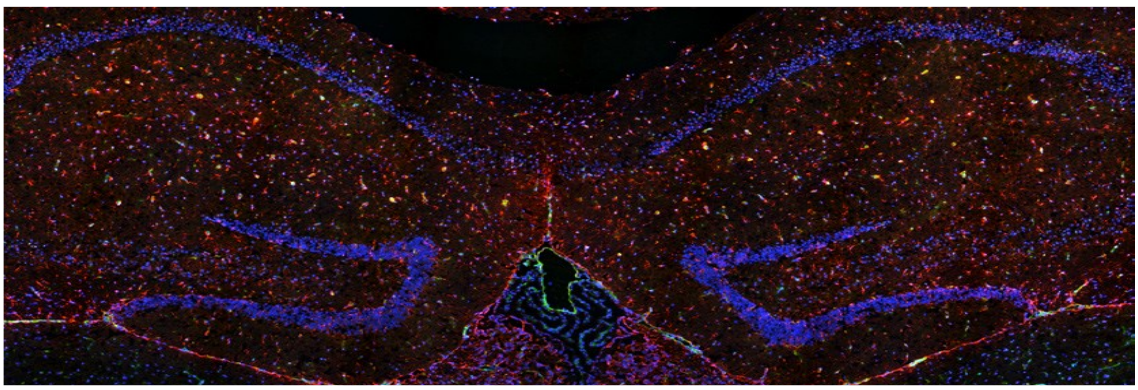
Head: Luisa Cortes, PhD.

Team: Luísa Cortes, PhD
Margarida Vaz Caldeira, PhD
Tatiana Catarino, PhD

The Microscopy Imaging Center of Coimbra, at the Center for Neuroscience and Cell Biology (MICC-CNC), is an open infrastructure for conventional and advanced imaging techniques, based on Light Microscopy.
The MICC-CNC has highly skilled and multidisciplinary scientific staff deeply committed to the training of new users and the planning of microscopy-based experiments, by advising on equipment selection and acquisition protocol, and performing imaging processing and analysis. In 2021, the MICC facility supported around 190 users from 58 research groups, with more than 15000 hours of equipment usage.
MICC-CNC kept on supporting external users from different Portuguese research institutions: University of Coimbra, University of Algarve, University of Minho, University of Beira Interior, CEBAL, and University of Évora. The most requested services are: widefield microscopy, confocal microscopy and laser microdissection.



The facility organizes regular advanced courses to all the scientific community providing the fundamentals, as well as the advanced techniques on fluorescence microscopy, live cell imaging and image analysis. Catarino T., Caldeira M.V. and Cortes L. organized the BEB-PhD course "Core Technologies @ CNC" (CNC, January 18th- 29th). The MICC team organized the remote workshop "Tissue Clearing Workshop" (Online, May 18th-20th), with high international participation. Cortes L co-organized the "Advanced Imaging Methods in Neuroscience" an EIT Health Aging PhD School (May 17th – 28th) and lectured at several post-graduation courses: PDBEB PhD courses, and MCB Master Programme from the University of Coimbra.
Cortes L. was a member of the Organizing Committee of the meetings: CTLS2021 (Online, Sept. 13th-15th); SPAOM2021 (Online, Nov. 23rd-25th) and SPN2021 (Coimbra, Dec 1st-3rd).
MICC-CNC is a Zeiss Labs@location Partner sharing and providing in depth knowledge and dedicated services, with expertise in specific applications of imaging technologies. In accordance with the Lab@location protocol agreement, in 2021, MICC-CNC has performed external services for Carl Zeiss Microscopy.
Moreover, MICC-CNC is a node of the Portuguese Platform for BioImaging (PPBI), a research infrastructure of the RNIE roadmap and a Node of the European RI EuroBioimaging. Cortes L being the Coordinator for the Mondego & Beiras Pole.
Finally, Cortes L. is an active member of the CTLS-Core Technologies for Life Sciences European association, being the co-chair of the CTLS Training Working Group, and a team member of the Innocore Erasmus+ project.



MASS SPECTOMETRY UNIT

Head: Bruno Manadas, PhD.

The main goals of the Life Sciences Mass Spectrometry (LSMS) group are to contribute with high-performance mass spectrometry (MS) approaches to monitor proteins and metabolites to identify new disease biomarkers mainly focused on neurodegenerative and neurological disorders.

The LSMS is led by Bruno Manadas (ORCID 000-0002-2087-4042). He has been leading the mass spectrometry platform since 2006, leading three projects as PI since 2008, multiple projects as co-PI, and leading the LSMS at CNC since 2017. Over the past 20 years, he has made significant contributions in neuroproteomics to understand neuronal proteome changes in different scenarios, from neurotrophin signaling to pain induction and translational biomarkers.

Besides the PI, the group integrates 4 PhDs, 4 clinicians, 6 Ph.D. students, 6 MSc students, and one MSc research technician.

In 2021 the research team was enrolled in 15 funded projects, one as PI, and two as co-PI. For a period of 3 years, this represents a total of 1 million euros. The source of funding was mainly FCT and the European Foundation for the Study of Diabetes and services.

The research team was also enrolled in two funded projects to start in 2022, an exploratory project from FCT and a Santa Casa da Misericórdia project.

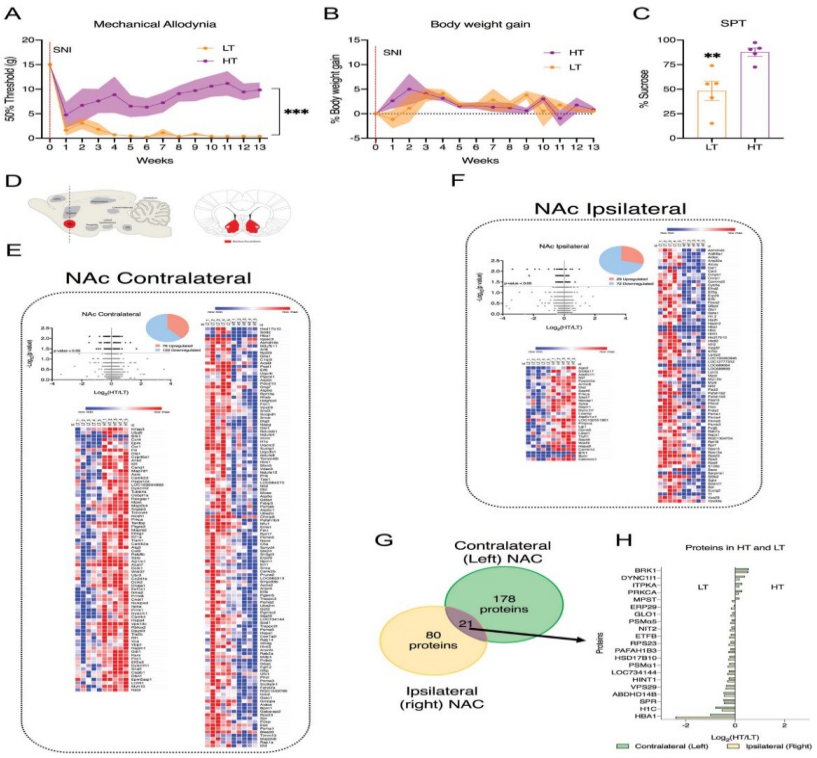
1. Objectives

The main objectives for 2021 were to develop approaches for hypoxic-ischemic encephalopathy (HIE) translational biomarker research, perform screening on PBMCs proteomics profiling on patients with the first episode of psychosis and perform systematic reviews and meta-analysis considering the pandemic scenario. We were able to publish a systematic review on stem cell therapeutic approaches for animal models of HIE, and three other systematic reviews and meta-analyses will be published in 2022. It was also our goal to participate in international events and webinars through online events and increase our knowledge of data analysis tools. This last objective has already resulted in publications using MetaboAnalyst for data analysis and biological integration.

2. Main Achievements

In 2021 the research team published 14 papers, was enrolled in 15 funded projects, and two new projects were approved to start in 2022. We also increased the number of companies either as collaborators or service providers. The research team increased the diseases covered in our lab, from neurodegenerative disorders (mainly AD and PD) to HIE, schizophrenia, bipolar disorder, and diabetes. One major achievement in participating in different disorders is the ability to correlate data from different diseases. One such example was to identify the protein clusterin as being modulated in the plasma of patients with AD, as previously reported, but also with PD. We also found that apolipoproteins, highly studied in AD, are also modulated in PD, schizophrenia and bipolar disorder.

3. Image that illustrates the research of the group


A
Mechanical Allodynia
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**
% Sucrose
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D
E
NAc Contralateral
F
NAc Ipsilateral
G
Contralateral (Left) NAC
178 proteins
21
80 proteins
Ipsilateral (right) NAC
H
Proteins in HT and LT
LT
HT
Proteins
Log2(HT/LT)
Contralateral (Left)
Ipsilateral (Right)

Pain 20

SERVICES

LABORATORY OF MITOCHONDRIAL BIOMEDICINE AND THERANOSTICS

Head of Unit: Manuela Grazina
Staff:
Maria João Santo (MSc); Marta Simões; Márcia Teixeira (MSc);
Sara Martins (MSc)
Certification NP EN ISO 9001:2015

Previous note:
Due to the continuation of COVID-19–related pandemic, the samples' income continued to suffer a drastic decrease and the activity was reduced and adapted, in order to accomplish the Institution's safety rules in alignment with DGS.

The Director of the Laboratory of Mitochondrial BioMedicine and Theranostics (LBioMiT) (Manuela Grazina, MSc, PhD) maintains international collaborations, allowing significant developments in the assays performed, namely with Doctor Fernando Scaglia (Baylor College of Medicine, Houston – Texas, USA), Prof. Massimo Zeviani (Dipartimento di Neuroscienze, Università degli Studi di Padova), Prof. Robert Taylor (Mitochondrial Pathology, University of Newcastle upon Tyne, UK), Prof. Valerio Carelli (Department of Biomedical and Neuromotor Sciences, University of Bologna – Bologna), Prof. Alfredo Sadun (Doheny Eye Centers, Department of Ophthalmology - Los Angeles), Dr. Rafael Artuch (Hospital Saint Joan de Déu, Barcelona, Spain), Prof. Changhan D Lee and Prof. Pinchas Cohen (School of Gerontology, University of Southern California, USA), Prof. Adrián LLerena (CICAB Clinical Research Centre at Extremadura University Hospital and Medical School, Universidad de Extremadura, Badajoz, Spain) and Prof. Zoraida Verde Rello (Universidad Valladolid, Spain). The Director of LBioMiT also integrates two international consortia: CoQ deficiency study group (since 2010) and CEIBA-Consortium of the Ibero-American Network of Pharmacogenetics and Pharmacogenomics (RIBEF), since February 2012.

Cell culture for diagnosis

Skin biopsies are meant to obtain fibroblasts which cultures allow to carry out additional biochemical, genetic and functional genomics' studies fitted in the diagnostic research of patients with suspected mitochondrial disorder followed up in the hospitals. Therefore, the cells were always cryopreserved for future testing in case of necessity (two samples requested) or retests (three samples requested functional studies); they were simply harvested to assays, or used to prepare some enriched mitochondrial fractions, concerning those tests on fibroblasts towards the diagnostic evaluation.

Biochemical analysis

Mitochondrial Respiratory Chain (MRC) and Krebs cycle enzymes
Biochemical assays related to MRC biogenesis, functioning and maintenance are essential for achieving the probable diagnosis of Mitochondrial Diseases. Isolated or multiple deficiency and functional impairment of Krebs cycle of like causes of impaired energy production are screened when there is a suspicion.

A total of 15 patients suspected of mitochondrial cytopathies were studied, corresponding to the analysis of 16 samples, including lymphocytes isolated of peripheral blood (10) and, muscular (4) and skin (2), biopsies. A MRC deficiency was detected in only one patient (7%); Krebs cycle enzymes activities analyzed in one patient (two samples) showed no deficiency. Additionally, ATP levels were evaluated, as appraisal of energetic deficit associated to the biochemical and clinical profiles of the patients. The results showed to be deficient in one out of two samples analysed.

CoQ10 quantification
The samples from patients suspected of a CoQ10 deficiency were studied by HPLC to determine the CoQ10 levels, which was performed in samples from three patients, muscle and plasmas. The results were normal.

Biomarkers of well-being investigation
The analysis of wellness's biomarkers, aiming to establish the determination of alterations on well-being biomarkers levels in disease and/or environmental/stressful conditions, as well subsequently to social or medical interfaces for diverse target populations, was proceeded with the correlation analyzes between analytes and psychological outcomes, in the study performed upon social interfaces with patients in clinical context.

Functional studies

Functional genomics' assays were performed in three patients, highlighting the reverse translational research nature of the work developed at LBioMiT.
During this year, the studied patients were, firstly, two siblings of a patient that had been studied since last year, presenting with a late-onset neurodegenerative condition of cerebral small vessel disease and motor neuron disease with a novel mutation identified in a gene encoding for a mitoribosome protein. Secondly, a girl with polyneuropathy, with a sister presenting the same clinical phenotype, and in whom novel heterozygous sequence variation of undetermined significance in the POLG gene was found with the need of clarifying pathogenicity. The performed analyses included the MRC complexes' assembly by native page electrophoresis, analysis of the important protein steady state levels by western-blotting and the analysis of respiratory rates in fibroblasts from the patients and controls.

Genetic analysis

Genetic screening is the only available tool for attainment of a definitive diagnosis in many diseases. Concerning OXPHOS disorders and given its dual genetic origin, complexity and heterogeneity, the study of nuclear genome, mitochondrial DNA (mtDNA) and bigenomic crosstalk factors, using a genetic integrative approach is mandatory, although very complex. Twenty-five samples (blood – 19, muscle – 4 and skin-derived fibroblasts - 2) were received for DNA extraction. Four DNA samples were also received for genetic analysis.
During 2021, 70 genetic tests were performed at LBioMiT.

***mtDNA genomes studies*:**
Molecular differential analyses of mitochondrial cytopathies have been performed by total mtDNA sequencing analysis using Next Generation Sequencing (NGS), with the adaptation for detection and characterization of mtDNA deletions, covering all mtDNA sequence variations, including confirmed pathogenic mutations associated to MRC diseases. During 2021, 45 samples of 38 patients were analysed using this strategy and findings, included several benign sequence variations, were identified in all samples. A large deletion

(3365pb) was detected in one sample. The pathogenic m.8993T>G point sequence variation was identified in one patient.

The "24h testing of the Top-3 LHON primary mutations" was performed in six samples. The pathogenic m.11778G>A point sequence variation was identified in an asymptomatic female, with positive cases in her maternal lineage.

Copy number (mtDNA) assays are part of the genetic mitochondrial genome screening for diagnostics of Mitochondrial DNA depletion syndromes (MDS), which are caused by defects in intergenomic communication and comprising a heterogeneous group of diseases, namely due to pathogenic alterations in nuclear genes, leading to severe reduction of mtDNA content, associated with energy failure. Concerning mtDNA copy number assays for depletion screening, 8 samples of 8 patients were investigated. Depletion (mtDNA content below 30%) was not confirmed in any sample in two independent analyses (both in triplicates).

Concerning the screening of nuclear genome (nDNA) defects causative of MRC diseases, 9 samples were screened for whole exome sequencing by NGS.
Additionally, *OPA1* gene was also analysed in one sample, allowing the detection of one pathogenic and likely pathogenic sequence variations according to American College of Medical Genetics (ACMG).
Screening of *CDKN1B gene* (1 sample) also revealed sequence variations without pathogenicity.

Bioinformatics' analyses

Regarding the **bioinformatics' analysis** and following the genetic screening of both genomes, including mtDNA content, the application of *in silico* tools is a highly laborious task that allows the identification of sequence variants in the patients, but also the prediction of its pathogenicity, essential for preliminary evaluation prior to start a functional genomics approach.
According to the procedure followed at the LBioMiT, around 1,248 sequence variations were assigned in the mtDNA, including several polymorphisms and reported alterations.
Concerning the **bioinformatics of exome analysis**, the approach is highly complex and laborious. The workflow for the bioinformatics' analysis at the LBioMiT was fulfilled, allowing detection of thousands of genetic variations, which were submitted to several bioinformatics' filtering algorithms for identifying the most probable cause of the disease. Among the samples in study, the full examination and application of the decision diagrams was completed in 10 cases.

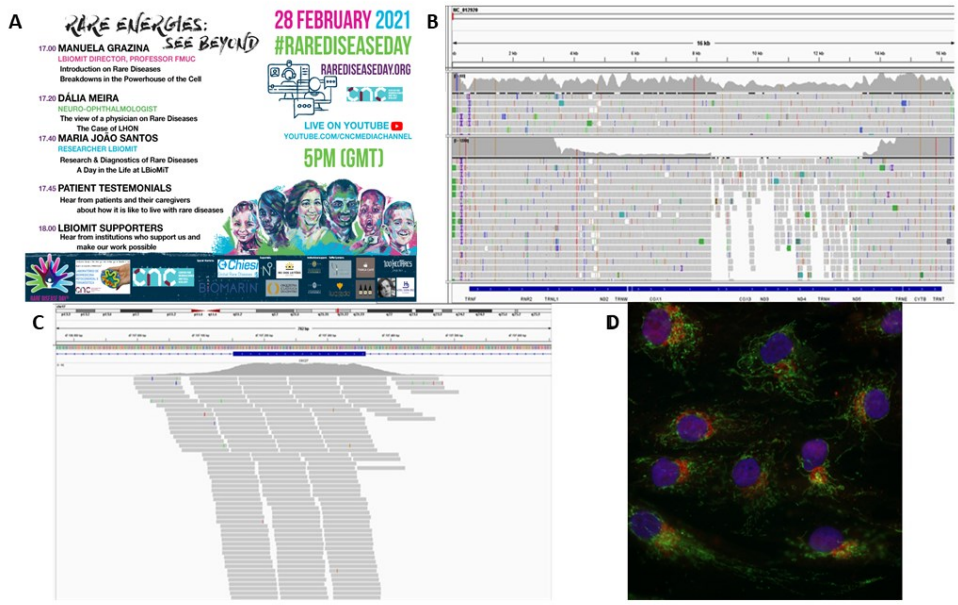


Fig. 1 – **Illustration representative of activities occurring at LBioMiT.**
A: Poster of the rare disease event organized by the LBioMiT team (Coordinated by the Director of LBioMiT), with the collaboration of the Science Communication Office. **B**: Visualization of sequence alignment data from complete mitochondrial DNA sequencing of two samples using the Integrative Genomics Viewer (IGV). **C**: Visualization of sequence alignment data of a nuclear gene exon from whole exome sequencing using IGV. **D**: Immunofluorescence analysis of fixed fibroblasts of a mitochondrial disease patient with a novel mutation in *MRPS16* gene encoding for a mitoribosome protein (red), co-stained for the protein TFAM (transcription factor A, mitochondrial (green)), and with DAPI (nuclei (blue)) (63x).

LABORATORY OF NEUROGENETICS

Head of Unit: Maria Rosário Almeida
Team: Ana Cristina Santos

In 2021 the Neurogenetics Laboratory has continued to provide genetic testing for different Neurological diseases such as: Dementias (Alzheimer disease, Frontotemporal dementia and Fatal familial insomnia), Parkinson disease, Amyotrophic lateral sclerosis, Small vessel diseases, Deficiency of Adenosine Deaminase 2, Cerebral cavernous malformations and Gliomas. Most of the patients were referred from the Neurology Department of *Centro Hospitalar e Universitário de Coimbra* (CHUC) while their asymptomatic relatives were referred from the Genetic Department of the Pediatric Hospital in Coimbra. Last year, this laboratory increased the number of genetic tests available and therefore, expanded the range of Neurological diseases studied. Thus, new NGS panels have been designed to study genetic forms of Epilepsy, Tuberous Sclerosis and Spastic paraparesis to provide an accurate diagnosis, and a better patients prognosis and management. In addition, it has been also implemented different approaches to diagnose patients with repeat expansion disorders affecting the nervous system, such as: Huntington disease, Friedreich ataxia and

Machado-Joseph disease. These additional genetic tests available have had a major impact on the organization of the health care locally and its importance became more visible and better recognized as a key determinant for a better patient care. As in previous years, the Neurogenetics laboratory has been focused in maximizing the diagnostic yield towards the end of a long diagnostic odyssey felt often by different patients who suffer from genetic mediated forms of Neurological diseases. Also, in 2021, this laboratory has been devoted to improving the procedures concerning the interpretation and classification of the genetic variants identified in the lab which constituted a significant challenge for clinical laboratory geneticists. Hence, the integration of different sources of information in a variant interpretation pipeline, according to the American College of Medical Genetics and Genomics (ACMG), along with the Association for Molecular Pathology (AMP) has been applied to categorize the identified variants into one of the five different classes: "Pathogenic"–"Likely pathogenic"–"Benign"–"Likely benign"–"Variant of Uncertain Significance (VUS)".

LABORATORY OF GENOME SEQUENCING

Head of Unit: Conceição Egas
Staff:
Cristina Barroso | Graduate Technician

Activity report

The genome sequencing unit - Genoinseq – is specialized in the field of omics. The Unit grants access to the full potential of the state-of-the-art of next-generation sequencing equipment and bioinformatics data analysis. The Unit has accumulated expertise in sequencing and bioinformatics, delivering personalized solutions, from consultancy in experimental design to data analysis with user-friendly outputs.

Genoinseq provides services to companies and research groups in the field of Life Sciences and collaborates on R&D projects with other companies or institutes.

Services available at Genoinseq (sequencing and bioinformatics):

- Small genome sequencing and annotation
- Exome sequencing and variant annotation
- Whole transcriptome and RNA-Seq
- Biodiversity studies on environmental communities
- Metagenome sequencing and annotation

The Laboratory is part of GenomePT - National Facility for Genome Sequencing and Analysis (RNIE) (ref.01/SAICT/2016) and is certified under NP EN ISO 9001:2015 for next-generation sequencing of nucleic acids and bioinformatics tools for DNA and RNA analysis.

In 2021, Genoinseq expanded biodiversity studies to include metabarcoding for addressing microalgae communities from eDNA. The implemented approach includes sequencing and the bioinformatics pipelines for identifying microalgae taxonomy and abundance.
Genoinseq also supported CNC groups in biodiversity studies of human- and mousse-associated communities, providing sequencing and bioinformatics data analysis. One of

those studies has already been published (doi: 10.1136/gutjnl-2021-326023). Exome sequencing and bioinformatics analysis for variant calling, annotation and prioritization with ExomeLoupe were also provided to CNC groups and services.

In 2021, the work provided by Genoing sequencing and data analysis resulted in the publication of 15 studies in peer-reviewed journals by our clients. Additionally, the lab continues to provide omics services for Biocant Park companies and other national companies. We highlight the Industrial strain genomic stability service aiming to provide information on the absence of major genomic alterations of industrial clonal isolates, and the sequencing and analysis of antibodies repertoires.
Genoinseq participates in the R&D projects:

- Cutting-edge DNA-based approaches for improved monitoring and management of fisheries resources along Magellan-Elcano´s Atlantic route. FCT ref. CIRCNA/BRB/0156/2019. 2020-2023.
- INNOCORE - Core Technologies for Education and Innovation in Life Sciences. H2020. Ref. KA203-589E724D. 2019-2022.
- Symbioreactor –Sustainable Production of Bioactive Metabolites from Microbial Symbionts of Marine Sponges and Corals. Fundo Azul. Ref. FA_05_2017_032. 2020-2022.
- GenomePT. Project for the development and implementation of research infrastructures within RNIE. 01/SAICT/2016. 2017-2021.
- PTDC/BTM-SAL/30550/2017 - Immunotargeting efflux systems for therapeutic modulation of multidrug resistant bacteria. 2018-2021.
- POCI -01 -0145 -FEDER -031999 POINTERS - Interações nemátode da madeira do pinheiro-árvore hospedeira: à descoberta de alternativas sustentáveis para a gestão da doença da murchidão do Pinheiro. 2018-2021.

Outreach
Genoinseq presented the core facility, sequencing applications and research results in 7 external events.

Organization of conferences
GenomePT Annual Symposium (2021/07/07)

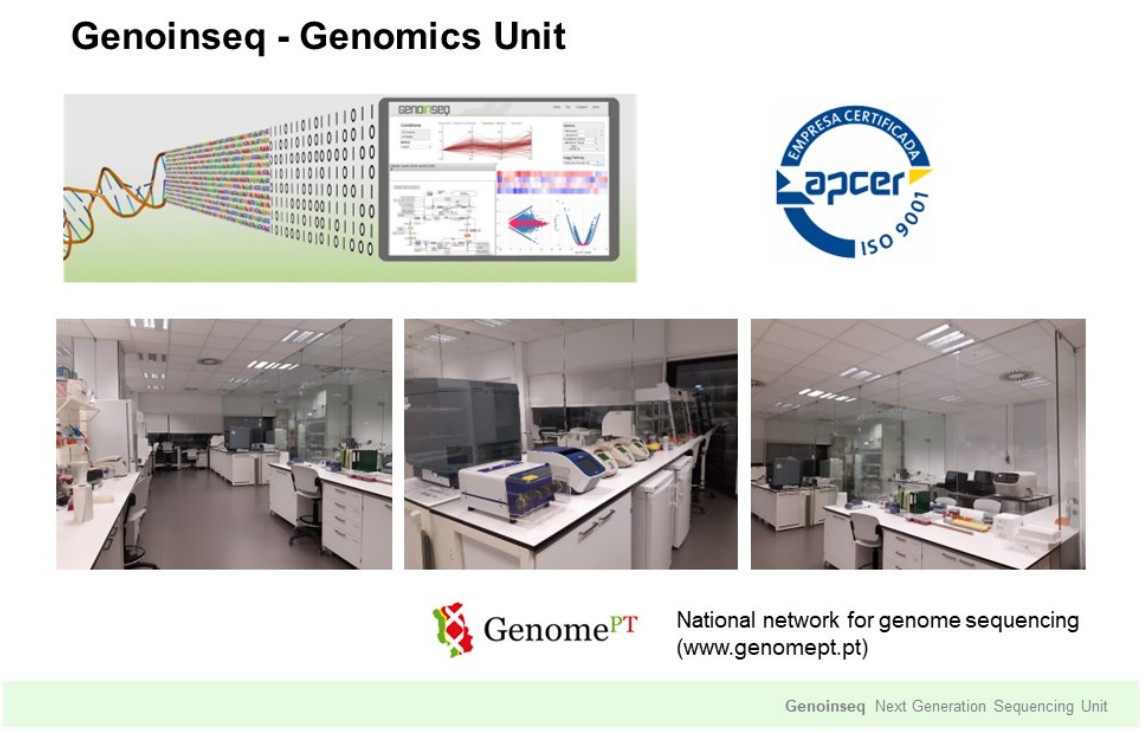
Conceição Egas and the team organized the 2021 GenomePT symposium. This symposium was completely online and had 347 attendants from 73 national and international institutions and 17 companies. The symposium had 26 speakers in 22 presentations, 8 of which were international speakers.
The symposium had three main objectives:

1. "Bringing Knowledge and Technology Together for Advanced Genome Science," where speakers from both the scientific component (members of the different nodes) and the technological component (six companies supplying equipment and reagents) presented their latest studies and technological developments.
2. "Genome, Data Analysis and other Infrastructure Initiatives," which had the presence of two Keynote speakers from the area of Precision Medicine, Dr. Eric Green, Director of the National Human Genome Research Institute, USA, with the presentation on the US strategy for Genomics and Precision Medicine by 2030 "The Forefront of Genomics," and Benilton Carvalho, Researcher at the University of Campinas, Brazil, with the presentation "Developments of the Brazilian Initiative in Precision Medicine." Two other sequencing projects were also presented, ERGA "European Reference Genomes Atlas – generating reference genomes for biodiversity conservation" and the European project "1 Million Genomes Initiative. Speakers from the Microbial Resource Research Infrastructure (MIRRI) and Bio.Data also presented these infrastructures.
3. Attract students for Genomics. For this purpose, junior students/researchers were invited to present their work as a poster or an oral presentation. 41 works were presented

in poster format and there were 3 oral presentations by students or junior researchers, in a total of 44 works.

Research papers:

- Leal, C., Fontaine, F., Aziz, A. et al. Genome sequence analysis of the beneficial Bacillus subtilis PTA-271 isolated from a Vitis vinifera (cv. Chardonnay) rhizospheric soil: assets for sustainable biocontrol. Environmental Microbiome 16, 3 (2021). doi:10.1186/s40793-021-00372-3
- Moreira N.F.F., Ribeirinho-Soares S., Viana A.T., Graça C.A.L., Ribeiro A.R.L., Castelhano N., Egas C., Pereira M.F.R., Silva A.M.T., Nunes O.C. Rethinking water treatment targets: bacteria regrowth under unprovable conditions. Water Res., 117374 (2021), 10.1016/j.watres.2021.117374



MITOXT SERVICES LABORATORY: PREDICTIVE MOLECULAR TOXICOLOGY BASED ON MITOCHONDRIAL FUNCTION

Coordinator: Paulo J. Oliveira

Background: During drug development, the road towards successful market entry also depends on whether toxicity to tissues is properly predicted in pre-clinical stages. At this critical time for the development of novel drugs, it is critical to assess whether a drug candidate presents cellular and mitochondrial liabilities which may cause off-target toxicity. Since mitochondria are the cell powerhouses and responsible for many critical tasks in cell metabolism, chemical entities which cause mitochondrial liabilities lead to a bioenergetic disruption of the cell, followed by organ failure. One example is drug-induced liver injury, which is the mechanism behind several cases of drug withdrawal from the market. Prediction of mitochondrial toxicity in early pre-clinical stages is thus essential to pharma companies for a more successful road to market.

Our mission: The main objective of the MitoXT Service platform is to support companies or academic research groups in predicting the mitochondrial toxicity of single molecules or mixtures with applications in pharmaceutical industry, environmental sciences, nanoparticles and polymer development, food industry, as well as other applications, with the ultimate objective of introducing safer chemicals in the environment and human systems. Our team has know-how in cell and mitochondrial metabolism and toxicology, standard and verified protocols that can be adapted to high-throughput screening as well as in data analyses.

Technology available: Seahorse XF96 Extracellular flux Analyzer; Cytation 3 Multiplate Reader, gTOXXs analyzer, MBIO AquaSpec mid-infrared spectroscopy analyzer, Hansatech Oxygraph, CFX-96 qRT-PCR machines.

R&D: Developing new screening methods and identifying biomarkers of disease and drug-induced mitochondrial toxicity; developing in-silico predictors of mitochondrial toxicity.

CLIENTS: Clients for our service have included Universities in Portugal and abroad (USA, Czech Republic), and private research centers (Spain).

Team: Paulo Oliveira (coordinator), Vilma A. Sardão, Teresa Cunha-Oliveira

FINANCIAL REPORT

FUNDING AT CNC

Introduction

In 2021 funding of "Laboratório Associado – Centro de Neurociências e Biologia Celular" ascended the amount of 8.252,375,15€.

The main financing contribution was made by "Fundação para a Ciência e Tecnologia (FCT)", concerning global institution programs and national projects, namely amount of 6.318.390,29€ distribuited as follows:

Strategical Project:	1.357.997,54€
Science Program:	1.857.506,50€
FCT Projects:	3.102.886,25€

The related items supported the main part of Center for Neuroscience and Cell Biology expenses during 2021.
Besides Center for Neuroscience is financed by other national and international agencies. In 2021 Center for Neuroscience allocated the amount of 1.467.472,95€, wheras other services had expenditure of amount 466.509,91€.
Main Services, not listed, is another important vector of our institution which ascends 729.981,41€ in 2021.
In the following are listed FCT ongoing projects as well as other national and international projects.

Note: Financing values apart from main services are based on expenditure values 2021

Title	Financing Agency	Starting Date	Ending date	Budget	Expenditure
Financiamento Base UIDB/04539/2020 - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para a Ciência e a Tecnologia - REF. UIDB/04539/2020	01/01/2020	31/12/2023	4 145 331,20	913 521,02

Financiamento Programático UIDP/04539/2020- COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. UIDP/04539/2020	01/01/2020	31/12/2023	449 982,45	-947,70
Laboratório Associado LA/P/0058/2020 - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. LA/P/0058/2020	01/01/2021	31/12/2025	5 580 689,14	445 424,22
Sub-Total Strategical Project					**1 357 997,54**
Programa Investigador FCT_4ª edição - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. Programa Investigador FCT_4ª	01/11/2016	31/12/2021	2 065 304,67	371 966,76
Norma transitória-DL 57 - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. Norma transitória-DL 57	04/01/2019	31/12/2025	8 811 340,96	1 156 042,43
Concurso Estímulo ao Emprego Científico Individual 2017 - Contrato - Programa - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. Concurso Estímulo ao Emprego Científico Individual 2017 - Contrato - Programa	15/02/2019	28/02/2025	2 798 759,33	329 497,31
Sub-Total Science Program					**1 857 506,50**

A reação neuroinflamatória em respostas à inflamação sistémica aguda durante delirium e o seu impacto na trajectória cognitiva e progressão para demência: estudo caso-controlo longitudinal com biomarcadores imagiológicos e moleculares - COORDINATOR: Joaquim Manuel Soares Cerejeira	Fundação para Ciência e a Tecnologia - REF. PTDC/MEC-PSQ/32501/2017	26/07/2018	25/07/2022	233 309,26	42 134,57
Exossomas libertados de celulas estaminais pluripotentes induzidas - impacto na (dis)função mitocondrial na Doença de Huntington e potencial sistema p - COORDINATOR: Ildete Luísa Araújo Fereira	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-TOX/32316/2017	06/07/2018	30/06/2022	235 334,58	72 707,21
Exossomas libertados de celulas estaminais pluripotentes induzidas - impacto na (dis)função mitocondrial na Doença de Huntington e potencial sistema para distribuição de terapêutica baseada em microRNA - COORDINATOR: Ana Cristina Carvalho Rego	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-TEC/29621/2017	06/07/2018	04/07/2022	238 749,98	38 814,29

CANCEL STEM - Estaminalidade das células do cancro: um desafio e uma oportunidade para avançar no tratamento em Oncologia - COORDINATOR: João Nuno Sereno de A. Moreira - PROPONENTE: IPATIMUP - PARTICIPANTS: CNBC; INEB; FCG; UC	Fundação para Ciência e a Tecnologia - REF. CANCEL STEM-SAICTPAC/0022/2015	01/01/2017	30/06/2021	774 925,51	120 005,80
Alterações no proteoma sináptico e excitabilidade neuronal num modelo de epilepsia do lobo temporal induzido por administração de pilpcarpina - COORDINATOR: Carlos Jorge A. M. B. Duarte	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/28656/2017	01/07/2018	31/03/2022	238 747,12	72 898,11
Regulação da fissão mitocondrial pelo factor neurotrófico derivado do cérebro (BDNF): importância na plasticidade sináptica e na epileptogénese - COORDINATOR: Carlos Jorge A. M. B. Duarte	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/3736/2020	29/03/2021	28/03/2024	249 916,74	31 845,35
O transportador de K+ - CL- (KCO) como alvo para manter a neurotransmissão GABAergica: uma nova estratégia terapeutica para a epilepsia -	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-FAR/30659/2017	01/06/2018	31/05/2022	237 446,83	50 259,02

COORDINATOR: Miranda Mele					
Caracterização do papel de microRNAs na fibrose cardíaca através de abordagens de genómica funcional. - COORDINATOR: Miguel Luís Cunha Mano	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-TEC/29894/2017	26/07/2018	25/06/2022	234 226,71	49 081,46
Novas abordagens em Encefalopatia hipóxicoisquémica : investigação translacional para diagnosticar e monitorizar resposta a terapia com células estamin - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UBI	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-TEC/29311/2017	01/06/2018	31/12/2021	203 025,04	30 851,80
Distúrbios afetivos: biomarcadores e deteção precoce - COORDINATOR: Bruno José F. O. Manadas	Fundação para Ciência e a Tecnologia - REF. PTDC/MEC-PSQ/30943/2017	26/07/2018	25/07/2022	238 743,45	69 900,27
POINTERS - Interações nemátode da madeira do pinheiro-árvore hospedeira: à descoberta de alternativas sustentáveis para a gestão da doença da murchidão do pinheiro -	Fundação para Ciência e a Tecnologia - REF. PTDC/ASP-SIL/31999/2017	26/07/2018	25/07/2022	53 749,75	8 903,86

COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC					
Impacto da agreação generalizada de proteínas ao longo da vida em mamíferos e implicações para o desenvolvimento de doenças relacionadas com o envelhecimento - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Universidade de Aveiro - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-TEC/29843/2017	01/06/2018	31/05/2022	26 250,00	10 170,28
Além do Beta-Amilóide - As Alterações Patagénicas Precoces na Doença de Alzheimer - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Universidade de Lisboa_Faculdade de Medicina - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/27946/2017	01/09/2018	31/08/2022	106 997,37	12 107,14
Melhoria cognitiva no cérebro idosoe demênsia vascular em humanos através da funcionalização do acoplamento neurovascular: uma estratégia mecanística - COORDINATOR:	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/29099/2017	26/07/2018	25/07/2022	100 955,61	11 076,33

João António Nave Laranjinha - PROPONENTE: Centro de Neurociencias e Biologia Celular - PARTICIPANTS: CHUC, UC					
Influência das antocianinas extraídas de mirtilos cultivados em Portugal na conexão entre o intestino e o cérebro nas pertubações do espetro do autismo: utilização de modelos in vitro e in vivo - COORDINATOR: Leonor Martins de Almeida	Fundação para Ciência e a Tecnologia - REF. PTDC/SAU-NUT/29089/2017	01/06/2018	28/02/2022	238 694,84	75 538,38
Monitorização in vivo de marcadores neurometabólicos com biossensores baseados em microelétrodos - COORDINATOR: Ana Margarida da Cruz Ledo - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/28261/2017	25/07/2018	24/07/2022	106 478,94	23 718,90
Bloqueio da neurodegenerescência por dispersão de silenciadores génicos. - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/29716/2017_Spread Silencing	01/07/2018	30/06/2022	238 749,59	50 990,07
O papel dos grânulos de stress nas doenças de poliglutaminas: da patogénese à terapia molecular	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/29480/2017	13/10/2018	12/10/2021	57 000,00	20 384,94

- COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Universidade do Algarve - PARTICIPANTS: CNBC					
ViraVector4Covid-Viral - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. 587 - ViraVector4Covid	09/07/2020	08/01/2021	45 000,00	-4 659,75
Estudo das propriedades sináticas do envelhecimento em neurónios humanos derivados por conversão direta - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Instituto de Medician Molecular João Lobo Antunes - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/3890/2020	01/03/2021	29/02/2024	30 000,00	0,00
Papel da desregulação dos microRNAS na doença de MAchado - Joseph: Desenvolvimento de uma estratégia terapeutica baseada em microRNAS - COORDINATOR: Sonia Patricia Dias Duarte	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/32309/2017	06/07/2018	30/06/2022	239 947,00	65 650,62
O impacto do transplante de células estaminais neuroepiteliais derivadas de células estaminais pluripotentes induzidas na doença de Machado-Joseph -	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-ORG/30737/2017	15/06/2018	14/06/2022	238 600,73	74 054,90

COORDINATOR: Liliana Mendonça					
O papel do metabolismo extra-hepático da frutose no desenvolvimento de doença hepática gordurosa não alcoólica - COORDINATOR: John Griffith Jones - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UA	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-BQM/28147/2017	01/06/2018	31/03/2022	185 084,57	35 254,58
Recetores A2A da adenosina como desencadeadores de disfunção mnemónica na doença de Alzheimer: Mecanismos e possobilidade terapeutica - COORDINATOR: Rodrigo Pinto S. A. Cunha	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/31274/2017	01/07/2018	30/06/2021	237 247,37	33 353,85
O estado pausado: um método inovador para bioengenharia de Células Estaminais - COORDINATOR: João Ramalho de Sousa Santos	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/28871/2017	01/06/2018	31/05/2022	237 976,10	68 245,26
Pesquisa de novos biomarcadores para a infertilidade masculina de origem desconhecida - COORDINATOR: Sandra Catarina Gomes Amaral	Fundação para Ciência e a Tecnologia - REF. PTDC/MEC-AND/28599/2017	06/07/2018	05/07/2022	236 679,82	49 224,23

Desenvolvimento de novos antioxidantes dirigidos para as mitocondrias na melhoria do fenótipo da Esclerose Lateral Amiotrofica familiar SOD1 - COORDINATOR: Ana Isabel Marques Duarte - PROPONENTE: Centro de Neurociencias e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-FAR/29391/2017	01/05/2018	28/02/2022	148 765,17	43 726,30
Doenças ognitivas como sinaptopatias: Impacto de mutações humanasno gene CACNG2 - COORDINATOR: Ana Luisa Monteiro de Carvalho	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/28541/2017	01/07/2018	31/12/2021	236 245,47	69 239,77
Desenvolvimento de ferramenta moleculares para a doença de Machado-Joseph: moduladores de conformações tóxicas em proteínas com poliglutaminas - COORDINATOR: Ana Luisa Monteiro de Carvalho - PROPONENTE: Instituto Biologia Molecular e Celular - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-BFS/31173/2017	01/07/2018	30/06/2022	38 600,01	4 774,76

Mecanismos patogénicos da encefalite autoimune sináptica associada a anticorpos anti-CASPR2 - COORDINATOR: Sandra Manuela D. Santos	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/29452/2017	15/06/2018	31/12/2021	236 222,74	73 100,00
Os altos e baixos do stress celular:" a hipótese MAM" para a patofisiologia da doença Bipolar - COORDINATOR: Cláudia Maria Fragão Pereira	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/28214/2017	26/07/2018	25/07/2022	237 822,11	72 009,01
Desenvolvimento de micropartículas para transporte de compostos ativos em aplicação pulmonar usando insulina como modelo - COORDINATOR: Maria Teresa T. Cruz Rosete - PROPONENTE: Universidade de Aveiro - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/EQU-EPQ/29560/2017	01/07/2018	30/06/2022	20 125,00	9 124,68
NiNjA - Nova estratégia Neuroendócrina para um envelhecimento saudável - COORDINATOR: Cláudia Margarida G. Cavadas	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-FAR/30167/2017	01/06/2018	31/12/2021	238 646,90	43 144,50
A detecção precoce da Apneia do Sono como uma nova estratégia para atrasar o envelhecimento - COORDINATOR: Ana Rita Álvaro	Fundação para Ciência e a Tecnologia - REF. PTDC/MEC-MCI/29002/2017	06/07/2018	31/12/2021	237 109,13	81 601,93

Cartilfactory - Desenvolvimento e Construção de um Sistema Automatizado de Fabricação em Larga Escala de Engenharia de Cartilagem Combinado Eletrofiação 3D de condrócitos e expansão celular 3D com estímulo mecânico em bioreator - COORDINATOR: Alexandrina M. F. S. P. Mendes - PROPONENTE: Universidade de Aveiro - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/EME-SIS/28424/2017	01/06/2018	31/12/2021	70 234,46	22 515,12
Development of an innovative targeted-nanoparticle formulation for combined gene therapy and chemotherapy application in hepatocellular carcinoma - COORDINATOR: Henrique Manuel S. Faneca	Fundação para Ciência e a Tecnologia - REF. IF/01007/2015	01/07/2017	31/10/2021	50 000,00	21 958,58
SNAPs alternativas na libertação de neurotransmissores: da função molecular à disfunção neurocognitiva - COORDINATOR: Paulo César da Silva Pinheiro	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-CEL/29451/2017	01/10/2018	30/09/2022	234 410,41	47 369,41
Eficácia pré-clinica do sulforafano ou do extrato total de Brássicas: Uma	Fundação para Ciência e a Tecnologia - REF. PTDC/ASP-HOR/29152/2017	01/06/2018	28/02/2022	41 577,40	8 633,55

estratégia para combater a obesidade e valoriza os subprodutos de Brássicas - COORDINATOR: Paulo Jorge G. S. S. Oliveira - PROPONENTE: Universidade de Trás os Montes e Alto Douro - PARTICIPANTS: CNBC					
Uso de fitoquímicos redox-activos para desencadear a hormesis mitocondrial: Desenvolvimento de uma nova geração de ingredientes para a cosmética - COORDINATOR: Paulo Jorge Gouveia Simoes Da Silva Oliveira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-MOL/28607/2017	26/07/2018	25/07/2021	159 006,95	40 860,86
Organelle-targeted Radiocomplexes for Auger Therapy of Cancer - COORDINATOR: Paulo Jorge G. S. S. Oliveira - PROPONENTE: IST - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-QUI/1554/2020	01/01/2021	31/12/2023	41 875,00	2 165,35
Desenvolvimento e validação de métodos inovadores da saúde mitocondrial. -	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/29297/2017	06/07/2018	05/12/2021	166 749,26	63 993,29

COORDINATOR: Maria Teresa M. C. Oliveira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UC					
O Eixo Intestino-Sistema Imune-Cérebro na doença de Parkinson - COORDINATOR: Sandra Morais Cardoso	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/3644/2020	12/01/2021	11/01/2024	248 992,50	78 526,88
O papel dos mecanismos de controlo de qualidade da perda da homeostase proteica nas doenças neurodegenerativas associadas a idade - COORDINATOR: Ana Raquel Fernandes Esteves	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/30712/2017	15/06/2018	14/12/2021	224 839,21	52 673,75
Caracterização dos mecanismos moleculares de sobrevivência de Rickettsia no hospedeiro para desenvolvimento de novas estratégias terapêuticas - COORDINATOR: Isaura I. Gonçalves Simões	Fundação para Ciência e a Tecnologia - REF. PTDC/SAU-INF/29592/2017	26/07/2018	25/07/2022	236 788,94	53 896,13
IF/01182/2015 - COORDINATOR: Vilma A. Sardão	Fundação para Ciência e a Tecnologia - REF. IF/01182/2015	01/07/2017	27/10/2021	50 000,00	60,00
IF/01272/2015 - COORDINATOR: Alexandra Teresa Pires Carvalho	Fundação para Ciência e a Tecnologia - REF. IF/01272/2015	01/07/2017	06/06/2021	50 000,00	25 455,62

IF/01492/2015 - COORDINATOR: Paula Canas	Fundação para Ciência e a Tecnologia - REF. IF/01492/2015	01/07/2017	31/10/2021	49 950,00	15 976,09
IF/00825/2015 - COORDINATOR: Célia Alexandra F.O. Aveleira - PROPONENTE: CNBC	Fundação para Ciência e a Tecnologia - REF. IF/00825/2015	01/07/2017	31/12/2021	50 000,00	6 162,79
Alergénios cutâneos: moléculas com uma aplicação terapêutica improvavel para a doença de Alzheimer - COORDINATOR: Maria Teresa T. Cruz Rosete	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-FAR/29369/2017	26/07/2018	31/05/2022	235 872,07	42 002,21
Contribuição dos Fatores Psicológicos na Cura da Úlcera do Pé Diabético, em Indicadores Fisiológicos de Prognóstico de Cura e Qualidade de Vida: Um Estudo Longitudinal Randomizado de Avaliação de Eficácia - COORDINATOR: Eugénia Maria L. Carvalho - PROPONENTE: Universidade do Minho - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/PSI-GER/28163/2017	26/07/2018	25/07/2022	26 015,63	5 578,31
Um polissacarídeo intrigante de micobactérias: reciclagem, replicação e aplicações. - COORDINATOR: Nuno Miguel Silva Empadinhas -	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-TEC/29221/2017	15/06/2018	31/12/2021	132 118,82	8 358,77

PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: IBMC; UM					
Métodos verdes para preparar aerogel esterilizado à base de biopolímeros - COORDINATOR: Nuno Miguel Silva Empadinhas - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/EQU-EPQ/32625/2017	25/07/2018	24/07/2022	29 849,56	13 993,53
Os receptores A2A para a adenosina controlam a formação de axónios durante o desenvolvimento neuronal: novas estratégias para prevenir a epileptogénes - COORDINATOR: Joana Medeiros Vieira Marques	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/28160/2017	06/07/2018	31/12/2021	238 108,56	75 951,25
Identificação e caracterização funcional de microRNAs que regulam a infecção por estirpes de Stphylococcus aureus clinicamente relevantes. - COORDINATOR: Ana Sofia Bregieiro Eulálio	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-MIC/29999/2017	26/07/2018	25/07/2022	234 226,71	72 133,03
Desenvolvimento de um nanossistema inovador para mediar um estratégia terapêutica combinada e multi-alvo para o	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-MAT/30916/2017	01/07/2018	30/06/2022	239 192,12	32 037,18

carcinoma hepatocelular. - COORDINATOR: Henrique Manuel S. Faneca					
Um modelo vascular de Progeria para identificar mediadores da perda de células do musculo liso. - COORDINATOR: Lino da Silva Ferreira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UC	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/29229/2017	26/07/2018	25/05/2022	213 487,06	36 517,37
Desenvolvimento de novos materiais piezoelétricos baseados em de peptídeos auto-organizado nanoestruturados - COORDINATOR: Lino da Silva Ferreira - PROPONENTE: Universidade de Aveiro - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/CTM-CTM/31679/2017	01/06/2018	31/12/2021	24 375,00	19 820,11
BrainEdition:controlo remoto da edição genética em celulas estaminais neurais. - COORDINATOR: Sónia Luzia Claro de Pinho	Fundação para Ciência e a Tecnologia - REF. PTDC/NAN-MAT/28060/2017	22/06/2018	21/01/2022	239 947,07	88 078,55
Uma biblioteca de nanoparticulas activáveis por acção da luz para a libertação de terapias baseadas em RNA -	Fundação para Ciência e a Tecnologia - REF. PTDC/EQU-EQU/29414/2017	06/07/2018	05/07/2022	238 697,08	58 814,13

COORDINATOR: Vitor Francisco					
Abordagens avançadas baseadas em ADN no apoio à monitorização e gestão de recursos pesqueiros ao longo da rota Atlântica de Magalhães-Elcano - COORDINATOR: Maria da Conceição V. Egas - PROPONENTE: Universidade do Minho - PARTICIPANTS: Instituto Português do Mar e da Atmosfera, I. P. (IPMA); Instituto Português do Mar e da Atmosfera, I. P. (IPMA)	Fundação para Ciência e a Tecnologia - REF. CIRCNA/BRB/0156/2019	24/08/2020	23/08/2023	66 189,34	5 579,08
Modelar a Demência Frontotemporal em organoides cerebraishumanos - COORDINATOR: Maria do Rosário P.M.N.Almeida	Fundação para Ciência e a Tecnologia - REF. PTDC/MEC-NEU/4814/2020	01/01/2021	31/12/2023	249 733,77	64 619,57
Vacina Terapêutica para a Hepatite B crónica: Desenvolvimento de nanopartículas à base de glucano com o objectivo de direccionar os antigénicos para as células imunitárias e induzir actividade antiviral - COORDINATOR: Olga Maria	Fundação para Ciência e a Tecnologia - REF. PTDC/MEC-GAS/30331/2017	15/07/2018	14/07/2022	234 902,55	48 109,06

Fernandes R. Borges					
Caracterização da maquinaria molecular responsável pela polarização neuronal - COORDINATOR: Luís Filipe da Silva Ribeiro	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-CEL/2286/2020	28/03/2021	28/03/2024	250 000,00	13 469,00
Uma estratégica terapêutica para combater o envelhecimento da barreira hemato-encefálica (BBB) - COORDINATOR: Susana Carvalho Rosa - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: Universidade de Coimbra	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/5174/2020	01/03/2021	29/02/2024	186 678,76	30 407,56
EXO-HEART: Protecção e regeneração cardíaca mediada pela administração sistémica e direccionada de exosomas. - COORDINATOR: Hugo Agostinho Machado Fernandes	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/29919/2017	01/07/2018	30/06/2022	237 289,21	33 632,61
Indução de Células Apresentadoras de Antigénio por Reprogramação Celular Direta - COORDINATOR: Carlos Filipe R. L. Pereira	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-CEL/30013/2017	01/06/2018	31/12/2021	238 471,74	70 648,81

Reconstrução do Programa de Células Estaminais do Cancro - COORDINATOR: Carlos Filipe R. L. Pereira - PROPONENTE: Instituto de Patologia e Imunologia Molecular UP - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-DNC/29017/2017	01/07/2018	31/12/2021	56 250,06	-10,06
Translação da reprogramação celular direta em células dendrítcas na imunoterapia do cancro. - COORDINATOR: Carlos Filipe R. L. Pereira	Fundação para Ciência e a Tecnologia - REF. CENTRO-01-0145-FEDER-039473	01/04/2018	31/03/2021	48 925,50	0,00
Elucidar a diversidade de células dendríticas com a reprogramação celular - COORDINATOR: Carlos Filipe R. L. Pereira	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-IMU/4520/2020	01/01/2021	31/12/2023	249 866,28	50 182,63
Reorganização pós-natal do cerebelo via interação neurónio-microglia: o papel da IL-4 como um medidor entre PHDA e alergias - COORDINATOR: Ana Luisa Colaço Cardoso	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/5993/2020	01/02/2021	31/01/2024	244 027,77	91 530,17
Imunoterapias contra sistemas de efluxo para modulação de bactérias multiresistentes - COORDINATOR: Ricardo Simão Vieira Pires - PROPONENTE:	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/30550/2017	15/11/2018	14/11/2022	220 849,74	31 117,77

Centro de Neurociências e Biologia Celular - PARTICIPANTS: UNL					
Propriedades viscoelásticas do cérebro em Esclerose Multipla e implicações em mecanomodulação de oligodendrócitos: uma abordagem celular e clínica - COORDINATOR: Mário Grãos - PROPONENTE: CNBC - PARTICIPANTS: UNIVERSIDEDE DE COIMBRA	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/29516/2017	26/07/2018	25/07/2022	192 615,35	36 263,23
Aplicação de Deep Learning ao processo de investigação de novas drogas anticancerígenas - COORDINATOR: Irina Moreira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: INESC-Instituto de Engenharia de Sistemas e Computadores, Tecnologia e Ciência	Fundação para Ciência e a Tecnologia - REF. PTDC/CCI-BIO/31356/2017	15/06/2018	14/12/2021	196 773,35	51 336,39
Proteínas Membranares - desenvolvimento de novas técnicas de modelação computacional e sua aplicação ao estudo dos recetores acoplados a proteína G (o Projeto) - COORDINATOR:	Fundação para Ciência e a Tecnologia - REF. PTDC/QUI-OUT/32243/2017	03/09/2018	04/06/2022	78 850,00	24 782,51

Irina Moreira - PROPONENTE: Instituto Superior Técnico - PARTICIPANTS: CNBC					
Alvejamento de transportadores de aminoácidos catiónicos para radioteranóstica do cancro: uma abordagem experimental e de quimica computacional - COORDINATOR: Irina Moreira - PROPONENTE: IST-ID - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/QUI-NUC/30147/2017	01/09/2018	31/08/2022	23 449,35	8 284,80
AI COVID _Ciência dos Dados e Intiligência Artificial na Administração Pública para reforçar o combate à COVID 19 e futuras pandemias - COORDINATOR: Irina Moreira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: IST-ID , INESC-ID/INESC/IST/ULisboa	Fundação para Ciência e a Tecnologia - REF. DSAIPA/DS/0118/2020	01/02/2021	31/01/2024	211 209,38	10 664,73
Vesículas extracelulares de Giardia lamblia na imunomodulação de células do hospedeiro: potencial aplicação terapêutica das EVs de Giardia na inflamação intestinal -	Fundação para Ciência e a Tecnologia - REF. PTDC/SAU-PAR/31506/2017	17/09/2018	16/09/2022	238 721,61	51 937,44

COORDINATOR: Maria do Céu Rodrigues de Sousa - PROPONENTE: - PARTICIPANTS:					
IF/00425/2015/CP1324/CT0001 - COORDINATOR: Manuela Ferreira	Fundação para Ciência e a Tecnologia - REF. IF/00425/2015/CP1324/CT0001	18/01/2021	31/12/2021	49 970,30	49 957,50
A MATURAÇÃO DA VESÍCULA SINÁPTICA E A SUA RELEVÂNCIA PARA A NEURODEGENERAÇÃO - COORDINATOR: Ira Milosevic	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/8030/2020	29/03/2021	28/03/2024	249 931,25	27 609,17
Sub-Total FCT Projects					**3 102 886,25**
Alemtuzumab therapy in Multiple Sclerosis: tracking immune cell trafficking, induced molecular mechanisms and aftermath effects - COORDINATOR: Inês Baldeiras -	Sanofi aventis, Lda. - REF. GZ-2017-11730	01/04/2019	31/12/2022	132 918,90	3 078,45
Examining Fyn/Src in Huntington`s disease cell models - COORDINATOR: Ana Cristina Carvalho Rego	The University Hospital of Ulm - REF. Examining Fyn/Src in Huntington`s Disease cell models	01/11/2021	31/10/2022	49 955,00	2 299,29
Role of NT3/TrkC in the regulation of fear - Project 85/18 - COORDINATOR: Monica Pinto dos Santos	Bial-Portela & Companhia, S.A. - REF. Role of NT3/TrkC in the regulation of fear - Project 85/18	01/03/2019	20/08/2022	43 790,32	9 155,15

Combination therapy synergistically accelerates diabetic wound - COORDINATOR: Eugénia Maria L. Carvalho	EFSD-Europ. Found. S. Diabetes - REF. EFSD-Microvascular Complicatio	09/11/2015	31/12/2022	70 000,00	-14,26
MATERA_5402 - COORDINATOR: Lino da Silva Ferreira	- REF. MATERA_5402	01/09/2010	31/12/2078	27 820,88	379,00
Promoting endothelial progenitor cell function in diabetic would healing - COORDINATOR: Ermelindo Carreira Leal	EFSD-Europ. Found. S. Diabetes - REF. EFSD:Promoting endothelial	01/01/2013	31/12/2022	50 574,27	551,16
Evaluate novel calpain inhibitors from Blade Therapeutics - COORDINATOR: Luis Pereira de Almeida	Blade Therapeutics - REF. Blade	19/07/2018	31/12/2025	140 000,00	35 989,56
Enable Sponsor to practice certain intellectual property rights of Institutions related to spinocerebellar ataxia type 3 (SCA3); more specifically, th - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: CNBC	PTC Therapeutics GT, Inc. - REF. miRSilencing	27/04/2020	31/12/2022	703 253,97	194 338,52
Machado-Joseph/Spinocerebellar ataxia type (MJD/SCA3) - COORDINATOR: Luis Pereira de Almeida	SERVIER - REF. Servier	05/07/2021	04/01/2023	225 002,02	26 607,59

Calpain Inhibition as Therapeutic Strategy in Machado-Joseph Disease - COORDINATOR: Luis Pereira de Almeida	Blade Therapeutics - REF. Calpain Inhibition as Therapeutic Strategy in Machado-Joseph Disease	16/09/2021	15/09/2022	90 000,00	0,00
MicroRNA-specific small molecule modifiers as a new and promissing therapeutic approach for Machado-Joseph disease/spinocerebellar ataxiatype 3 - COORDINATOR: Sonia Patricia Dias Duarte	National Ataxia Foundation - REF. MicroRNA-specific small molecule modifiers as a new and promissing therapeutic approach for Machado-Joseph disease/spinocerebellar ataxiatype 3	01/09/2021	20/08/2022	40 546,41	3 082,30
Coffee protects against NAFLD progression through preservation of intestinal permeability and inhibiton of liver fibrosis - COORDINATOR: John Griffith Jones - PROPONENTE: CNBC	Institute for Scientific Information on Coffee - REF. Coffee protects against NAFLD	01/07/2019	30/06/2022	112 905,00	6 175,04
Adenosine A2A receptors as a new opportunity to manage and detail the neurobiology of emotional distress. - COORDINATOR: Rodrigo Pinto S. A. Cunha	Fundación Bancaria Caixa d´Éstalvis i P. Barcelona - REF. LA Caixa - HR17-00523 - adostress	18/12/2019	14/12/2022	335 460,49	49 573,23
Potassium channel dysfunction in models of neurodevelopmental disorders - COORDINATOR: Ana Luisa Monteiro de Carvalho - PROPONENTE: Centro	Fundación Bancaria Caixa d´Éstalvis i P. Barcelona - REF. La Caixa - HR20-00904 - MStar	11/12/2020	10/12/2023	620 000,00	138 062,42

Neurociências e Biologia Celular - PARTICIPANTS: CNRS - Centre National de la Recherche Scientifiqu					
Towards personalized beta-cell mass imaging in type 2 diabetes - COORDINATOR: Hugo Agostinho Machado Fernand - PROPONENTE: Stichting Katholieke Universiteit	Stichting Katholieke Universiteit - REF. Zon Mw	06/08/2017	31/12/2023	128 059,00	2 300,69
The brain on stress vulnerability and plasticity of the prefrontal cortex over the life course - COORDINATOR: Paulo César da Silva Pinheiro	Fundación Bancaria Caixa d´Éstalvis i P. Barcelona - REF. LA Caixa_Iniciativa Ibérica_LCF_PR_HP 21_52310010_micr oSTRESS	01/12/2021	30/11/2024	492 304,49	0,00
Collaboration ITMO - CNC - MitoXT - COORDINATOR: Paulo Jorge G. S. S. Oliveira	ITMO University - REF. Collaboration ITMO - CNC - MitoXT	01/07/2021	30/06/2026	48 825,00	10 875,78
Development of a defined approach for respiratory sensitization hazard assessment - COORDINATOR: Isabel Cristina Ferreira	SOT Awards, Society of Toxicology - REF. Colgate_Palmolive Grant 2021	01/09/2021	30/09/2022	33 178,66	5 787,36
Optic Nerve Atrophy_Santhera - COORDINATOR: Maria Manuela Monteiro Grazina	Santhera Netherlands - REF. Optic Nerve Atrophy_Santhera	01/07/2018	30/06/2024	63 999,98	4 899,73
Palhaços d´Opital 2020 - COORDINATOR: Maria Manuela Monteiro Grazina -	Palhaços d´Opital - REF. Palhaços d´Opital 2020	09/07/2020	05/01/2022	20 632,20	4 478,54

PROPONENTE: CNBC					
SymbioReactor-Sustainable production of bioactive metabolites from microbial symbionts of marine sponges and corals - COORDINATOR: Maria da Conceição V. Egas - PROPONENTE: Instituto Superior Técnico - PARTICIPANTS: Universidade de Aveiro	IST-ID - REF. FA-05-2017-032	06/09/2019	30/12/2022	29 153,00	11 521,48
The social code in cingulate-hippocampal circuits: The role of memory in social contests - COORDINATOR: Emanuel Fernandes	Bial-Portela & Companhia, S.A. - REF. 074/2020	01/02/2021	31/01/2024	47 000,00	14 485,22
Intravenous delivery of the brain-targeting AAV-PHPeB encoding the cholesterol hydroxylase CYP46A1 into a mouse model of spinocerebellar ataxia type 3 - COORDINATOR: Rita C. Gonçalves Perfeito - PROPONENTE: CNBC	National Ataxia Foundation - REF. Intravenous delivery of the brain-targeting AAV-PHPeB	01/03/2020	08/07/2022	42 561,00	11 033,99
Optical fingerprinting as a new tool for stratification of Alzheimer's disease patients	Ilof - Intelligent Lab On Fiber, Unipessoal Lda - REF. Colloborative Project CNC/iLoF	29/06/2021	28/06/2022	34 516,42	20 837,01

using blood-derived samples - COORDINATOR: Inês Baldeiras					
A Saúde no Saber - COORDINATOR: Sara Varela Amaral	Ciência Viva - REF. A Saúde no Saber	01/07/2019	01/12/2022	20 000,00	5 989,61
A system approach to find a blood-based biomarker for Machado-Joseph Disease - COORDINATOR: Magda Santana	National Ataxia Foundation - REF. Machado-Joseph Disease_blood-based biomarker	01/03/2019	28/02/2021	43 399,05	1 611,76
COCKPI- T 2020 - COORDINATOR: Ana Luisa Colaço Cardoso	Takeda Pharmaceutical Company Limited - REF. COCKPI-T	16/02/2021	31/12/2022	69 960,02	41 446,58
Evaluating the impact of high-efficacy treatments on disease control in early MS: beyond NEDA - COORDINATOR: Isabel Santana	Roche Farmacêutica Química, Lda. - REF. Donativo Roche - Iniciativa	25/06/2021	31/12/2023	31 000,00	0,00
An investigation on the MeCP2-early life stress interaction effects in anxiety sensitivity later in life in a mouse model of Rett syndrome - COORDINATOR: Monica Pinto dos Santos	Fondation Jérôme Lejeune - REF. An investigation on the Mecp2-early life stress interaction effects in anxiety…_Mónica Santos	01/06/2021	31/05/2023	40 000,01	3 500,45
Deciphering the Rickettsia toolbox to hijack the host - COORDINATOR: Pedro Tiago Cardoso Curto - PROPONENTE: CNBC	ESCMID-European Society of Clinical Microbiology a - REF. Deciphering the Rickettsia toolbox to hijack the host	21/02/2020	31/12/2021	20 000,00	12 778,96

Bolsa Edgar Cruz e Silva - Inês Baldeiras - COORDINATOR: Inês Baldeiras	Grupo de Estudos de Envelhecimento Cerebral e Demê - REF. Bolsa Edgar Cruz e Silva - Inês Baldeiras	14/12/2020	29/12/2022	5 000,00	4 331,51
Novas terapias para Doença de Chagas: reposicionamento de drogas com efeito sinergístico com Benzonidazol para combater infecção por Trypanosoma cruzi - COORDINATOR: Miguel Luís Cunha Mano - PROPONENTE: - PARTICIPANTS:	Fundação para Ciência e a Tecnologia - REF. FCT/CAPES-2018/2019	16/04/2018	31/12/2021	9 000,00	0,00
3º Simpósio International PDBE - COORDINATOR: João Ramalho de Sousa Santos	- REF. 3º Simpósio International PDBE	01/07/2016	31/12/2078	2 195,64	0,00
Paula Isabel da Silva Moreira - COORDINATOR: Paula Isabel da Silva Moreira	L`Oréal - REF. Prémio L`Oréal Paula Moreira	01/11/2008	31/12/2022	20 000,00	817,15
Bolsa Edgar Cruz e Silva/SCML, edição 2016/17 - COORDINATOR: Armanda Emanuela Castro Santos	SCML - REF. Bolsa Edgar Cruz e Silva/SCML, edição 2016/17	01/07/2017	31/08/2025	5 000,00	0,00
V Simpósio da Portuguese Glial Network - COORDINATOR: Paula Maria Garcia Agostinho	CNC - REF. V Simpósio da Portuguese Glial Network	11/02/2020	31/01/2022	1 250,00	1 234,72
Modulation of autophagy as a novel therapeutic strategy for Machado-Joseph diseas - COORDINATOR:	REF. National Ataxia Foundation	01/01/2010	31/12/2021	10 400,01	179,66

Luis Pereira de Almeida					
Terapia Machado Josefh - COORDINATOR: Luis Pereira de Almeida	APAHE - Assoc. Portuguesa de Ataxias Hereditárias - REF. Terapia Machado Josefh	01/01/2012	31/12/2078	8 031,75	0,00
Richard Chin and Lily Lock Machado-Joseph disease Research Fund - COORDINATOR: Luis Pereira de Almeida	REF. Richard and Lily Machado-Josep	01/02/2017	31/12/2022	13 396,00	0,00
Mini-Simposyum 'Vaccines and A - COORDINATOR: Olga Maria Fernandes R. Borges	NOVARTIS FARMA S.A. - REF. Mini-Simposyum 'Vaccines and A	01/03/2011	31/12/2025	250,00	0,00
EFSD - European Foundation Study Di - COORDINATOR: Eugénia Maria L. Carvalho - PROPONENTE: CNBC	EFSD-Europ. Found. S. Diabetes - REF. Saldos Fundos EFSD transitados	09/01/2013	31/12/2022	28 398,85	3 371,95
AsHeCe - Marta Pereira - COORDINATOR: João Nuno Sereno de A. Moreira	- REF. AsHeCe - Marta Pereira	01/01/2013	31/12/2078	8 000,00	0,00
Bolsa Cient.LPCE2014 Miranda M - COORDINATOR: Carlos Jorge A. M. B. Duarte	Liga Port. contra Epilepsia - REF. Bolsa Cient.LPCE2014 Miranda M	31/03/2014	31/12/2025	3 500,00	1 384,65
Fundos FBG - COORDINATOR: Maria Manuela Monteiro Grazina	CNC - REF. Fundos LBG	10/12/2013	31/12/2078	47 617,00	27 023,33

Fundos Obesidade - COORDINATOR: Maria Manuela Monteiro Grazina	CNC - REF. Fundos Obesidade	01/06/2017	31/12/2025	22 600,00	4 929,34
Bial - REMANESCENTE - COORDINATOR: Inês Maria Pombinho de Araújo	- REF. Bial - REMANESCENTE	01/09/2014	31/12/2025	15 293,99	1 175,18
Exocord - REMANESCENTE - COORDINATOR: Lino da Silva Ferreira	- REF. Exocord - REMANESCENTE	01/01/2017	31/12/2078	32 458,67	3 077,23
Livro de Neurociências - COORDINATOR: Ana Cristina Carvalho Rego	European Commission - REF. Livro de Neurociências	01/01/2016	31/12/2022	2 400,00	0,00
EMBO - COORDINATOR: Ana Sofia Bregieiro Eulálio	EMBO - REF. EMBO	01/04/2017	30/10/2022	13 919,00	3 784,22
14º Edição do Programa Doutoral PDBEB - COORDINATOR: João Ramalho de Sousa Santos	Bluepharma - REF. 14º Edição do Programa Doutoral PDBEB	01/01/2018	31/12/2025	500,00	0,00
Prémio 2º lugar no concurso Janssen Inovação 2018 - COORDINATOR: Sara Matias Silva	Janssen-Cilag - REF. Prémio 2º lugar no concurso Janssen Inovação 2018	17/05/2018	31/12/2025	20 000,00	1 490,28
Astrazeneca - iMed Conference 10.0 - COORDINATOR: Rodrigo Filipe Nunes Ribeiro	Fundação Astrazeneca - REF. Astrazeneca - iMed Conference 10.0	01/11/2018	31/12/2078	3 000,00	0,00
Sleep4All - COORDINATOR: Ana Teresa Viegas - PROPONENTE: CNBC	ResMed Foundation - REF. Sleep4All	01/02/2021	31/12/2022	8 161,07	7 439,70

Prémio Thomé Villar SPP2020 - COORDINATOR: Ana Rita Álvaro	Sociedade Portuguesa de Pneumologia - REF. Prémio Thomé Villar SPP2020	21/12/2020	23/12/2022	10 000,00	458,57
Prémio EIT Health_Grupo Alexandrina Mendes - COORDINATOR: Alexandrina M. F. S. P. Mendes	European Institute of Innovation Tecnology EIT - REF. Prémio EIT Health_Grupo Professora Doutora Alexandrina Mendes	01/01/2019	31/12/2022	15 378,15	139,32
Bolsa SPOT João Pedro Moreira - COORDINATOR: Alexandrina M. F. S. P. Mendes	Sociedade de Ortopedia e Traumatologia - REF. Bolsa SPOT João Pedro Moreira	23/01/2018	31/12/2022	2 500,00	556,60
Bolsa de Investigação SPT-Seculo XXI - COORDINATOR: Eugénia Maria L. Carvalho	Sociedade Portuguesa de Transplantação - REF. Bolsa de Investigação SPT-Seculo XXI	01/03/2019	30/11/2022	10 000,00	1 428,28
Bolsa SPD-Gift_Ermelindo Leal - COORDINATOR: Ermelindo Carreira Leal	Ermelindo Carreira Leal - REF. Bolsa SPD-Gift_Ermelindo Leal	13/05/2020	31/05/2023	8 500,00	-775,53
BEB Day 2022	BEB Day 2022	01/12/2021	31/12/2022	0,00	0,00
CIBB Meeting 2019 - COORDINATOR: Ricardo Jorge A. Rodrigues	- REF. CIBB Meeting 2019	01/11/2019	31/12/2078	850,00	0,00
Embo Young investigator small grant - round 2019/2020 - COORDINATOR: Ana Sofia Bregieiro Eulálio - PROPONENTE: CNBC	EMBO - REF. EMBO_Round 2019/2020	01/02/2020	31/12/2022	10 001,00	0,00

New Trans-Synaptic Bridge: the study of the NMDA receptor Neurexin-2 interaction - COORDINATOR: Joana Isabel Simões Ferreira	European Commission - REF. IBRO Return Home Fellowship_Joana Ferreira	01/06/2021	31/05/2023	20 000,02	4 711,91
IBRO Early Career Awards 2020_João Peça - COORDINATOR: João Peça Silvestre	IBRO - REF. EARLY CAREER AWARD - PEÇA	01/10/2020	30/09/2022	5 001,00	-4,82
Zfra 1-31 peptide as a new candidate to fight type 2 diabetes - associated brain damage: a pilot study - COORDINATOR: Cristina Isabel M. M. Carvalho	ESCI - REF. ESCI - Zfra 1-31	01/06/2021	31/12/2022	10 000,00	4 697,10
EMBO 2020 - COORDINATOR: Sara Varela Amaral - PROPONENTE: CNBC	FENS - REF. BAW 2020	01/02/2020	28/02/2021	1 000,00	422,74
Brain Time - COORDINATOR: Sara Varela Amaral	FENS - REF. BAW 2021_Brain Time	01/02/2021	28/02/2022	1 000,00	898,46
Ocupação Científica de Jovens nas Ferias 2021 - COORDINATOR: Sara Varela Amaral	Ciência Viva - REF. Ocupação Científica de Jovens nas Ferias 2021	01/06/2021	30/09/2021	1 345,00	1 294,62
8ª Edição do EJIBCE 2021 - COORDINATOR: Irina Moreira	Wallfuture - REF. EJIBCE Workshop	01/12/2021	30/11/2022	500,00	500,01
Estarreja – Evaluation of the reproductive health of men living in a heavily industrialized area	Universidade Aveiro - REF. Projeto L`OHMI _DHM-E/2019/Proj.3	01/01/2020	31/12/2022	18 500,00	457,48

- COORDINATOR: Renata Tavares					
Prémio "Best Scientific Poster from the Innovative Competition- AstraZeneca Foundation" - COORDINATOR: João Miguel Esteves C.S. Cardoso	Fundação Astrazeneca - REF. Prémio_Best Scientific Poster from the Innovative Competition- AstraZeneca Foundation	01/01/2018	31/12/2022	1 000,00	0,00
Science engagement through videos: a new lens on biomedical research - COORDINATOR: Sara Varela Amaral	Biochemical Society - REF. Biochemical Societu Scientific Outreach Grants 2020	22/12/2020	31/12/2021	1 079,58	1 026,32
Mini-Simpósio StemmCell Technologies - COORDINATOR: Catarina Seabra - PROPONENTE: CNBC	Stemcell Technologies - REF. Mini-Simpósio StemmCell Technologies	07/02/2020	31/12/2023	750,00	0,00
IBRO Global Engagement Seed Grant - COORDINATOR: Catarina Seabra	IBRO - REF. IBRO Global Engagement Seed Grant	01/12/2021	30/11/2022	5 000,01	0,00
Brain Gain- À descoberta das Neurociências - COORDINATOR: Catarina Seabra	Sociedade Port. Neurociências - REF. Brain Gain - À descoberta das Neurociências	17/12/2020	31/12/2021	270,00	267,23
Mechanisms by which thiazolidinediones protect against hepatic steatosis induced by high sugar feeding - COORDINATOR: Ana Maria Reis Costa	Sociedade Port. Diabetologia - REF. Bolsa SPD-Gift_Ana Costa	01/01/2020	31/12/2078	5 000,00	3 345,54

CENTRO-04-3559-FSE-000141 - COORDINATOR: Luis Pereira de Almeida	IFDR - REF. CENTRO-04-3559-FSE-000141	01/04/2020	31/03/2023	512 236,13	91 039,60
Biotech Stars - COORDINATOR: Ana Catarina Cunha Santos - PROPONENTE: CNC - PARTICIPANTS: Biocant; IATV	AG PORCentro - REF. BIOTECH STARS_Centro-04-3560-FSE-072507	01/01/2021	31/12/2022	163 181,12	0,00
Foie Gras_722619 - COORDINATOR: Paulo Jorge G. S. S. Oliveira - PROPONENTE: - PARTICIPANTS: Fyziologicky Ustav, UNIBA, FFUL, NENCKI, UPORTO, INTITUT NATIONAL, CNR, HMGU, CSIC	European Commission - REF. Foie Gras - 722619	01/01/2017	30/06/2022	769 347,13	58 681,58
Rise Foie Gras_734719 - COORDINATOR: Paulo Jorge G. S. S. Oliveira - PROPONENTE: - PARTICIPANTS: CNR, FFUL, HMGU, CSIC, UNIBA, UPORTO, NENCKI, KCL, MEDIAGNOST, APDP, OROBOROS, microBiolytics	European Commission - REF. Foie Gras RISE - 734719	01/06/2017	31/08/2022	111 112,45	12 864,53
InnoCore - Core Technologies for Education and Innovation in Life Sciences - COORDINATOR: Carlos Jorge A. M. B. Duarte - PROPONENTE: University of Trento	University of Trento - REF. InnoCore	01/09/2019	31/08/2022	59 648,00	2 877,00

CAFFEIN - Cancer Associated Fibroblasts (CAF) Function in Tumor Expansion and Invasion - COORDINATOR: João Nuno Sereno de A. Moreira - PROPONENTE: University of Copenhagen	European Commission - REF. Marie Curie grant 316610	01/10/2012	31/12/2022	201 432,00	319,59
Functional high-throughput analysis of the role of microRNAs in cardiac ischemia-reperfusion injury - COORDINATOR: Miguel Luís Cunha Mano	European Commission - REF. 701096-microCardio-MSCA-IF-EF-ST	01/03/2016	31/12/2021	148 635,60	69,72
Training European Network: Metabolic Dysfunction associated with Pharmacological Treatment of Schizophrenia - COORDINATOR: Eugénia Maria L. Carvalho	Agencia Estatal CSIC - REF. TREATMENT-721236	01/01/2017	30/06/2021	428 904,72	2 502,88
Accelerating Research and Development for Advanced Therapies - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Univerity Sheffield	University of Sheffield - REF. ARDAT_945473	01/11/2020	31/10/2025	630 000,00	5 953,46
Synaptic Dysfunction in Neuropsychiatric Disorders - COORDINATOR: Ana Luisa Monteiro de Carvalho - PROPONENTE: - PARTICIPANTS: CNRS, EPFL,	European Commission - REF. Syn2Psy_813986	25/02/2019	28/02/2023	1 009 052,48	193 000,49

Imperial, UEDIN, H. Lundbeck AS, SMS, Eurotrials, CHUC, E.P.E, PIN - Progresso Infantil, Marionet - Associação Cultural					
DYNAMIC BRAIN FUNCTION: Towards the Understanding and Treatment of Brain Disorders - COORDINATOR: Ana Luisa Monteiro de Carvalho	European Commission - REF. DYNABrain_952422	01/12/2020	31/12/2025	2 499 989,01	20 092,88
Functional high-throuchput analysis of the role of microRNAs in regulating Staphylococcus aureus infection - COORDINATOR: Ana Sofia Bregieiro Eulálio -	European Commission - REF. 893942 - miRs4Staph	15/10/2020	14/10/2022	147 816,04	59 058,82
New nanomaterials for neural stem cells drug delivery - COORDINATOR: Lino da Silva Ferreira - PROPONENTE: Queen Mary and Westfield Colle	Queen Mary University (QMUL) - REF. NANOSTEM - 764958	01/06/2018	30/06/2022	715 069,08	160 465,26
Exploring the dendritic molecular machinery responsible for neuronal polarization — SortAx - COORDINATOR: Luís Filipe da Silva Ribeiro	European Commission - REF. 101031398 — SortAx	01/09/2021	31/08/2023	147 815,01	18 659,40

LIght-responsive GrapHene-based inTerfaces for Electrical Stimulation - COORDINATOR: Artur Filipe Cardoso Duarte Rodrigues - PROPONENTE: CNBC	Research Executive Agency - REF. 101003413 _Lightest	01/04/2020	30/04/2022	159 816,04	63 765,28
PPBI_Portuguese Platform of Biolmaging - COORDINATOR: Luisa Maria O. P. L. Cortes - PROPONENTE: Instituto de Biologia Molecular e Celular	IBMC - REF. Rede PPBI - PINFRA/22122/2016	01/06/2017	30/09/2021	275 180,00	77 635,10
GENetic Frontotemporal dementia Initiative (GENFI) - COORDINATOR: Isabel Santana	- REF. GENFI	15/02/2016	31/12/2022	14 138,08	0,00
Sub-Total Others National and International Projects					**1 467 472,95**
From Protein Structure to biological funtion through interactomics- an integrated view (2nd edition) - COORDINATOR: Bruno José F. O. Manadas	- REF. Cursos Bruno Manadas	01/01/2018	19/01/2025	10 350,00	89,14
Cursos de Verão Doutor Carlos Palmeira - COORDINATOR: Carlos Manuel Marques Palmeira	- REF. Cursos de Verão Doutor Carlos Palmeira	01/04/2019	29/04/2025	8 930,03	2 196,27
8º Workshop da Sociedade Europeia de Cálcio - COORDINATOR: Claudia Pereira	Entidade Desconhecida - REF. 8º Workshop da Sociedade Europeia de Cálcio	01/06/2019	31/12/2078	13 607,21	1 100,43

Curso Bioteria Teór/Prát_2015 - COORDINATOR: João António Nave Laranjinha	- REF. Curso Bioteria Teór/Prát_2015	01/08/2015	31/12/2025	8 298,50	0,00
Fórum Pós-docs - COORDINATOR: Ermelindo Carreira Leal	- REF. Fórum Pós-docs	01/02/2018	31/12/2025	1 505,00	0,00
Comunicação de Ciência e Transferência de Tecnologia - COORDINATOR: Ana Catarina Cunha	CNC - REF. Comunicação de Ciência e Transferência de Tecnologia	01/01/2017	30/12/2025	1 293,00	0,00
Curso FOIE GRAS - COORDINATOR: Paulo Jorge G. S. S. Oliveira	CNC - REF. Cursos de faturação Paulo Oliveira	01/09/2017	31/12/2025	1 993,40	0,00
Faturação Cursos Paula Mota II - COORDINATOR: Paula Cristina Cardoso R. Mota	- REF. Faturação Curso Janeiro 2019 - Paula Mota	01/11/2018	31/12/2025	23 750,00	214,50
Curso Faturação Paula Mota III - COORDINATOR: Paula Mota	CNC - REF. Curso Faturação Paula Mota III	01/09/2019	30/08/2025	22 300,01	3 211,16
Curso IVMLAS - COORDINATOR: Paula Cristina Cardoso R. Mota	CNC - REF. Curso IVMLAS	30/09/2020	30/09/2025	17 200,00	2 549,61
VMLAS 2021 - COORDINATOR: Paula Cristina Cardoso R. Mota	CNC - REF. VMLAS 2021	01/09/2021	10/09/2025	15 450,00	3 963,74
Stress, Resilience and Epigenetic alterations: Frontal cortex and Social dominance. - COORDINATOR: Ana Cristina Carvalho Rego	- REF. Consultancy Agreement - Sigma-Tau B.V. and UC_StREs-FSD	01/01/2018	31/12/2022	23 500,00	4 749,61

Assessing the Value of Serum Neurofilaments as biomarker of response to first-line oral treatments im Multiple Slerosis - COORDINATOR: Sónia Batista	Biogen Idec Portugal - REF. Estudo Neurofilamentos - Professora Sónia Batista	01/09/2021	01/10/2023	18 241,84	0,00
Faturação Biotério - COORDINATOR: Paula Cristina Cardoso R. Mota	- REF. Faturação Biotério CNC	01/01/2017	31/12/2025	373 337,31	122 793,62
AAV-miATXN3w, AAV-GFP reporter, and new to develop transgene-containing AAVs - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: UNIQURE Biopharma B.V. - PARTICIPANTS: CNBC; UC	- REF. Collaboration agreement_uniQure biopharma B.V.	17/12/2018	31/12/2025	52 187,50	2 604,54
Evaluation of MJD/SCA3 preclinical drug discovery model systems - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: CNBC - PARTICIPANTS:	- REF. MJD/SCA3 Models	01/09/2019	31/12/2025	43 508,00	35 954,82
European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: CNBC	- REF. ESMI project continuation	26/11/2019	31/12/2025	10 002,00	7 642,48

Targeting mutant ATXN3 for the treatment of Spinocerebellar Ataxia 3 (SCA3) - COORDINATOR: Luis Pereira de Almeida	Wave Life Sciences USA, Inc. - REF. Wave Collaboration_Luis Almeida	01/04/2018	31/12/2025	300 000,00	111 106,26
Proof of concept evaluation of the ATXN3 LNA in the homozygous YAC hATXN3 Q84.2 - COORDINATOR: Luis Pereira de Almeida	- REF. STUDY Proof concept evaluation ATXN3 LNA	26/10/2020	31/12/2023	200 000,00	0,00
Targeting mutant ATXN3 for the treatment of Spinocerebellar Ataxia 3 (SCA3) - COORDINATOR: Luis Pereira de Almeida	- REF. Wave_Targeting mutant ATXN3 for the treatment of Spinocerebellar Ataxia 3 (SCA3)	01/07/2021	30/06/2023	80 000,00	1 657,28
Magnetic Resonance Spectroscopy - COORDINATOR: John Griffith Jones -	German Diabetes Center - REF. DDZ Resonance Spectroscopy MRS	01/11/2020	30/11/2022	15 893,00	1 379,62
Pharmatex In vitro Studies Program - COORDINATOR: João Ramalho de Sousa Santos	Laboratoire Innotech - REF. INNOTECH 2015	31/12/2014	31/12/2022	218 086,76	15 390,86
Revascularização e angiogénese - COORDINATOR: João Ramalho de Sousa Santos	- REF. Revascularização e angiogénese, Merck	20/12/2016	31/12/2021	123 377,83	29 153,49
Docente unidade curricular "Biologia Celular e Histologia" - COORDINATOR: Ana Tiago	Instituto Politécnico Leiria - REF. Docente unidade curricular "Biologia Celular e Histologia"	04/11/2021	04/12/2023	162,00	0,00
Microbilogia e Parasitologia - Unidade Curricular - COORDINATOR: Susana Isabel Elias Alarico	Escola Superior de Enfremagem de Coimbra - REF. Microbilogia e Parasitologia - Unidade Curricular	09/03/2020	09/03/2023	24 273,81	9 875,66

Exploring the role of pridopidine on mitochondrial function and dynamics in Huntington`s disease models - COORDINATOR: Ana Cristina Carvalho Rego	TEVA Pharmaceutical Indust. - REF. Exploring the role of pridopid_TEVA	01/01/2017	31/12/2022	120 165,04	4 470,39
NIH - 75N95020P00076 - COORDINATOR: Attila Köfalvi	- REF. NIH_Attila	01/01/2017	31/12/2022	24 851,00	2 255,65
DDZ_FLAME_L_study - COORDINATOR: John Griffith Jones	German Diabetes Center - REF. DDZ_FLAME_L_study	01/06/2017	31/12/2021	19 056,81	1 985,79
Project Furan toxicity in human and rat hepatocytes - COORDINATOR: Carlos Manuel Marques Palmeira	- REF. Comparison the acute effects..	01/08/2017	31/12/2022	28 200,00	2 225,76
SPN2021 - COORDINATOR: Luisa Maria O. P. L. Cortes	Sociedade Port. Neurociências - REF. SPN2021	01/07/2021	31/12/2022	44 090,02	43 932,31
Faturação Matera - COORDINATOR: Lino da Silva Ferreira	- REF. Faturação Matera	01/01/2020	31/12/2022	7 246,25	2 070,13
Faturação Dr. Lino Ferreira - COORDINATOR: Lino Ferreira	Universidade de Coimbra - REF. Faturação Universidade Coimbra	01/01/2018	31/12/2025	29 191,37	799,20
Cosmetologia Aplicada - Unidade Curricular - COORDINATOR: Ludgero Canário Tavares	Instituto Politécnico Leiria - REF. Cosmetologia Aplicada - Unidade Curricular	23/09/2020	22/09/2023	1 698,86	0,00

Evaluation of TETO-OSKM lentiviral constructs in WT and APP/PS1 mice - COORDINATOR: Ana Luisa Colaço Cardoso	- REF. Evaluation of TETO-OSKM lentiviral constructs in WT and APP/PS1 mice	17/03/2021	31/05/2022	24 600,00	17 254,08
MSCellProdutction: Produção de Células Estaminais Mesenquimais em Conformidade com os requisitos de Boas Práticas de Fabrico - COORDINATOR: Mário Grãos	- REF. MSCellProduction	01/07/2019	31/12/2022	45 450,00	26 737,00
Atividades docência - Joana Mourão - COORDINATOR: Irina Moreira	Universidade do Algarve - REF. Atividades docência - Joana Mourão	18/11/2020	04/12/2021	3 658,54	4 429,66
Microscopia - COORDINATOR: Luisa Maria O. P. L. Cortes	CNC - REF. Microscopia	01/01/2012	31/12/2025	104 942,89	4 716,85
Sub-Total Others Services					**466 509,91**
Total					**8 252 373,15**

FUNDING AT iCBR

Title	Financing Agency	Principal Investigator	Starting Date	Ending Date	Budget (iCBR)	Expenditure 2021
ERAatUC - 669088	Commission Of The European Communit	João Malva	01/07/2015	31/03/2021	2 762 402.26 €	199.843,00€
NECSUS	European Society of Cataract and	Joaquim Murta	01/06/2016	28/02/2023	309 706.00 €	44.053,00€
20588-EPIDEMPREV	Eit Health E.V.	João Malva	01/01/2020	30/06/2021	200.800,00€	54.424,00€
20515-LONELINESS	Eit Health E.V.	João Malva	01/01/2020	31/12/2021	16.250,00€	-
IDIAL_NET	European Commission INTERREG	Ana Bela Sarmento	01/06/2019	31/12/2021	93.333.33€	26.323€
210892-SMASHMEDICINE II	EIT HEALTH	Carlos Robalo Cordeiro	01/01/2021	31/12/2021	19 994.33 €	-
Novartis	Novartis	Francisco Ambrósio	-	-	30.000,00€	-
Coordenação Nacional Cancro da Mama	Mecenato	Victor Rodrigues	01/01/2011	31/12/2021	-	-
GenomePT - Lab. Nacional Sequenciação	FCT POCI-01-0145-FEDER-022184	Henriqueta Coimbra Silva	01/06/2017	31/12/2021	593 489,91 €	32.800€
PPBI– Plataforma Portuguesa de Bioimagem	Agência Desenvolvimento e Coesão	Henrique Girão	01/06/2017	30/09/2021	218.906,00€	17.432€
A novel mechanism to re-pair	FCT RE-PAIR - 032179	Henrique Girão	22/06/2018	21/06/2022	233.434,48€	45.806€

HFpEF and endothelial damage						
Tailored microenCAPsulation technology for Extreme Oxygen-Sensitive BACteria with beneficial effects on gut microbiota: Production, stability and functionality enhancements in various carriers	FCT CAPEOSBAC - 031400	Flávio Reis	01/06/2018	31/10/2021	23.634,25€	21807€
Use of blueberry juice as a nutraceutical strategy targeting gut dysbiosis to prevent the progression from prediabetes to diabetes	FCT FRUTIFY - 031712	Flávio Nelson Reis	26/07/2018	31/05/2022	239.304,92€	66.810€
Speed, crash and run: exersomes boost neuroenergetics and mood in mice on speed	FCT MOOD EXERSOMES - 030786	Frederico G.S.C. Pereira	26/07/2018	25/07/2022	239.413,80€	55.206€
Modeling Angiogenesis in Type 2 Diabetes Mellitus - integrating experimental and	FCT ANGIODIA -031743	Raquel Seiça	26/07/2018	25/07/2021	33.125,00€	7.542€

theoretical approaches						
On the right side: unveiling the mechanisms of pulmonary hypertension reversability and the heart failure progression	FCT RIGHT-2H -032414	Rui Baptista	26/07/2019	25/07/2021	164648.20	49.980€
Environmental enrichment protects adult hippocampal neurogenesis and memory decline induced by systemic inflammation	FCT MercuMemory - 031699	Carlos Fontes Ribeiro	26/07/2018	25/07/2021	239.475,67€	50.030€
Contribution of olive polyphenols and olive oil for the prevention of cardiovascular diseases	FCT PHENOLIVA - 032492	Flávio Reis	07/072018	06/07/2022	238.115,29	3.271€
Brain metastases: uncovering the biomechanical between cancer cells and brain microenvironment	FCT BRAIN_METS - 030625	Ana Paula Martins	15/03/2019	14/03/2021	15.000,00€	4.438€
Mediterranean Enriched Diet for tackling Youth Obesity	FCT MED4YOUTH - PRIMA/0004/2018	Maria Filomena Botelho	01/12/2019	30/11/2023	93.815,00€	14.469€

Nova Terapêutica de RNA de Interferência para o Glaucoma	FCT siRNAGlau - 039743	António Francisco Ambrósio	01/10/2019	30/09/2021	215.064,98€	47.912€
3D DENTOFACIAL SURGERY FULL P LANNING	FCT ARTHUR - 039690	Francisco Caramelo	01/10/2019	30/09/2021	131.322,65€	11.276€
iPET - Sistema PET inteligente para imagiologia pré-clínica	FCT iPET – 039880	Ana Cristina Santos	11/09/2019	10/03/2022	161.898,78€	28.226€
Preservação do património natural e cultural e validação científica das práticas com plantas medicinais do Vale do Côa	FCT COA/BRB/0019/2019 - CÔAMEDPLANTS	Célia Cabral	01/07/2020	30/06/2023	241 509,67 €	67.996€
Human and ambient monitoring integrated sensors in firefighter workwear for increase safety	FCT- PCIF/SSO/0163/2019	António Jorge	20/03/2021	19/03/2024	21 055.00 €	-
Radiolabeled EXosomes - a nanotheranostic tool for lung micrometastasis in osteosarcoma	FCT- PTDC/BTM-SAU/4451/2020	Célia Gomes	29/03/2021	28/03/2024	191 852.90 €	21.049€

Boosting easyPET.3D imaging by integrating a new CT scanner approach	FCT- PTDC/EMD-EMD/2140/2020	Ana Cristina Santos	01/03/2021	29/02/2024	56 064.13 €	5.265€
Cerebrovascular hypothesis of stress-induced behavioral alterations	Bial 73/20_CEREBROVASCULAR	Ana Paula Martins	01/09/2021	31/08/2023	45 000.00 €	458€
Strategic Project	FCT UIDB/04539/2020- Base	Henrique Girão	01/01/2020	31/12/2023	881 437,90 €	142.231€
Strategic Project	FCT UIDB/04539/2020– Programático	Henrique Girão	01/01/2020	31/12/2023	943 792,55 €	131.916€

PUBLICATIONS

INTERNATIONAL PUBLICATIONS

1. A Bottom-Up Approach to Red-Emitting Molecular-Based Nanoparticles with Natural Stealth Properties and their Use for Single-Particle Tracking Deep in Brain Tissue. Rosendale, Morgane; Flores, Jessica; Paviolo, Chiara; Pagano, Paolo; Daniel, Jonathan; Ferreira, Joana; Verlhac, Jean-Baptiste; Groc, Laurent; Cognet, Laurent; Blanchard-Desce, Mireille. ADVANCED MATERIALS, **2021**, 33[22], 2006644. **DOI:** 10.1002/adma.202006644
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Catarina Carreira (MSc Student)

Catarina Daniela Gonçalves Rodrigues (Technician)

Catarina Domingues (PhD)

Catarina Isabel Costa Mestre (MSc Student)

Catarina Melim (Grant Tech.)

Catarina Mendes Morais (PhD Student)

Catarina Morais Seabra (PhD)

Catarina Neves, PhD Student

Catarina R. Oliveira (MD, PhD)

Catarina Rebelo (PhD)

Catarina Reis Gomes (PhD)

Catarina Sofia Oliveira Miranda (PhD)

Cátia Ferreira (MD)

Cátia João Monteiro da Santa (PhD)

Cátia Lopes (PhD Student)

Cátia Lourenço Marques (PhD)

Cátia Moreira de Sousa (PhD Student)

Celeste Alcobia (MD, PhD Students)

Célia Aveleira (PhD)

Célia Cabral (PhD)

Célia Gomes (PhD Student)

Célia Margarida Alcobia Gomes (PhD Student)

Célia Nogueira (PhD)

Celso Henrique Freitas Alves (PhD)

Chantal Fernandes, PhD

Clarissa Pérez Faria (PhD)

Cláudia Cavadas (PhD, Group Leader)

Cláudia Deus (PhD Student)

Cláudia Figueiredo (assistant technician)

Cláudia Loureiro (PhD)

Cláudia Pereira (PhD)

Cláudia Santos (UC-BIOTECH assistant technician)

Conceição Egas (PhD, Group Leader)

Cristiana Paulo (PhD)

Cristina Barosa (PhD)

Cristina Barroso (M.Sc., Sup. Technic)

Cristina Carvalho (PhD)

Cristina Teixeira (caretaker)

Cristina Uriarte (MD)

Daniel Alexandre Rodrigues Ramalhão (Technician)

Daniel Alexandre Sousa Henriques (PhD Student)

Daniel Ferreira (master)

Daniel Martins (PhD Student)

Daniel Santos (PhD Student)

Daniel Silva (Grant Tech.)

Daniela Almeida (PhD Student)

Daniela Calheiros (MSc)

Daniela Cristina Gonçalves Costa (Grant Technician)

Daniela Madeira (PhD Student)

Daniela Marinho Lopes (Grant Technician)

Daniela Mateus (PhD Student)

Daniela Nunes-Costa (PhD Student)

Daniela Oliveira (MSc)

Daniela Rosendo da Silva (MSc)

Daniela Saldanha (MSc)

Daniela Santo (PhD Student)

Daniela Santos Silva (MD, PhD Students)

Daniela Sofia Matias Simões (MSc)

Débora Justo Cerqueira (MSc)

Debora Mena (Grant Tech.)

Débora Serrenho (PhD Student)

Denisa Amado (Technician)

Deolinda Santinha (PhD Student)

Diana Adão (MSc)

Diana Bela da Luz Sequeira (MSc)

Diana Filipa Duarte Lobo (PhD Student)

Diana Filipa Ferreira da Silva (PhD)

Diana Gaspar (Technician)

Diana Gonçalves (Technician)

Diana Isabel da Silva Santos (PhD)

Diana Santos (PhD Student)

Diana Silva (PhD)

Diana Sousa (Technician)

Dina Maria da Silva Rodrigues Pereira (PhD)

Diogo André Afonso da Fonseca (PhD)

Diogo Cruz (MSc Student)

Diogo Ferreira (UC-BIOTECH assistant technician)

Diogo Pinho (PhD Student)

Dominique Fernandes (PhD)

Edgar Miguel Calvo Loureiro Tavares da Silva (MSc)

Edmilson Correia (PhD student)

Edna Filipa P. Soares (PhD)

Elena Rodriguez (PhD Student)

Eliana Fernandes (Grant Technician)

Eliana Rita Barbosa (MSc Student)

Eliane Sanches (PhD student)

Elisa Campos (PhD)

Elisa Corti (Grant Technician)

Elisabete Ferreiro (PhD)

Elisabete Jorge (MD, PhD)

Elisabete Resende (MD, PhD Students)

Elsa Fernanda de Sousa Henriques (PhD)

Emanuel Candeias (PhD Student)

Emanuel Ferreira Fernandes (PhD)

Emanuel Tahiri (MSc Student)

Emilia Duarte (PhD)

Ermelindo Leal (PhD)

Euclides Pires (PhD)

Eugenia Carvalho (PhD)

Eunice Virginia Valdez Faria Bidarra Palmeirao Carrilho (PhD)

Fabiana de Meneses Ribeiro (MSc)

Fábio de Jesus Ribeiro de Sousa (MSc)

Fátima Graça (FMUC/CNC caretaker)

Fátima Moreira (UC-BIOTECH Animal Welfare responsible and caretaker)

Fernanda Carrilho (MD, PhD Student)

Fernanda Daniel (PhD)

Fernando Cabral (Masters Student)

Fernando Davide de Sousa Caldeira Sampaio dos Aidos (PhD)

Fernando Regateiro (MD PhD)

Filipa C. Baptista (PhD)

Filipe Valente Duarte (PhD)

Flávia Rodrigues (PhD Student)

Flávio Reis (PhD, Goup Leader)

Francesca Tomatis (Grant Technician)

Francisca Silva (MSc Student)

Francisco Ambrósio (PhD, Group Leader)

Francisco Duarte (MSc Student)

Francisco José Santiago Fernandes Amado Caramelo (PhD)

Francisco Marques (MD, PhD Students)

Francisco Queiroz (PhD)

Francisco Tejo (MSc Student)

Frederico G. Pereira (PhD)

Frederico Pena (PhD Student)

Gabriela Conceição Duarte Jorge da Silva (PhD)

Gabriela Oliveira (PhD Student)

Gabriela S. Moço (MSc Student)

Gabriela Tavares (PhD Student)

Getachew Debas Belew (PhD Student)

Gianluca Masella (PhD Student)

Gil Correia, MD, PhD student

Gil Roberto Correia Lopes (MSc)

Giorgioo Belperio (MSc Student)

Gisela Filipa Assunção Santos (PhD)

Giuseppe Cammarata (MSc)

Gladys Caldeira (PhD)

Glória de Fátima da Silva Figueiredo (Technician)

Gonçalo Brites (PhD Student)

Guilherme Jerónimo (Technician)

Guilherme Ribeiro da Silva (Technician)

Gustavo Franco Ferreira da Costa (PhD)

Hans Christian Eickhoff (MD, PhD)

Heidi Maria da Silva Lopes Gonçalves (MSc)

Hélder Esperto (PhD Student)

Helena Aires (PhD Student)

Helena Leal (PhD Student)

Helena Maria Lourenço Carvalheiro (PhD)

Helena Sá (PhD)

Hélène Léger (PhD)

Heloísa Salguinho Gerardo (PhD Student)

Henrique Almeida (PhD

Henrique Alves (PhD)

Henrique Girão (PhD, Group Leader)

Henrique Manuel Santos Faneca (PhD)

Henrique Miguel Marques Bom Borges Alexandrino (PhD)

Henrique Silva (PhD)

Henrique Tavares (MSc student)

Henriqueta Breda (MD PhD)

Hugo Fernandes (PhD)

Iara Pratas (MSc Student)

Ildete Luisa Ferreira (PhD)

Inês Aires (PhD Student)

Inês Albino (Grant Technician)

Inês Alexandra Figueira Marques (MSc)

Inês Baldeiras (PhD)

Inês Caiado (PhD Student)

Inês Costa (MSc)

Inês Isabel Nunes Caramelo (MSc)

Inês Isabel Pires Serrenho (MSc)

Inês Lopes (PhD Student)

Inês Melo Marques (Technician)

Ines Moniz (collaborator)

Inês Pinto Fernandes (Technician)

Inês Preguiça (Msc)

Inês Roxo (PhD Student)

Inês Santos (MSc, PhD Students)

Inês Simões Pinto (Technician)

Inês Ventura (MSc Student)

Ingrid Gaspar (MSc Student)

Ira Milosevic (PhD)

Irina de Sousa Moreira (PhD)

Isabel Ferreira (PhD Student)

Isabel Maria de Oliveira Martins Dantas Fernandes (Technician)

Isabel Maria de Sousa Lopes da Silva (PhD)

Isabel Marques Carreira (PhD, Group Leader)

Isabel Nunes Correia (PhD)

Isabel Poiares Batista (MD PhD)

Isabel Santana (MD, PhD, Group Leader)

Isabel Vitória Figueiredo (PhD)

Isaura Simões (PhD, Group Leader)

Ivan Lalanda Salazar (PhD)

Ivo Machado (MSc Student)

Jane Dias (PhD Student)

Jane Dias (PhD Student)

Jani Sofia Jesus Almeida (PhD Student)

Jeannette Schmidt, (PhD Student)

Jennifer Duarte (Msc Student)

Jéssica Macedo (MSc Student)

Jéssica Margarida Mendes Costa (MSc)

Jessica Silva (PhD Student)

Jisette González Núñez (MSc)

Joana Barbosa de Melo, PhD

Joana Domingues (MSc Student)

Joana Ferreira, (PhD)

Joana Henriques (MSc Student)

Joana Margarida Verdasca Jorge (MSc)

Joana Margarido (Technician)

Joana Marques (PhD)

Joana Martins (MSc)

Joana Medeiros Vieira Marques (PhD)

Joana Oliveira, MSc

Joana Padrão (MSc Student)

Joana Padrão (Technician)

Joana Ribeiro Guedes (PhD)

Joana Ribeiro (MD, PhD Students)

Joana Silva (Grant Technician)

Joana Silva (MD)

Joana Silva (MSc Student)

Joana Silvestre Rodrigues Cipriano (Technician)

Joana Vanessa Cordeiro Melro Mourão (PhD)

João Braz (Grant Technician)

João Durães (MD)

João Eduardo Aleixo Rodrigues (PhD)

João Fernando Pereira Mendes (MSc)

Joao Gabriel Silva (Masters Student)

João Gonçalves (PhD Student)

João Laranjinha (PhD, Group Leader)

João Lourenço Ribeiro Alves (Technician)

João Magalhães (PhD Student)

João Malva (PhD, Group Leader)

João Miguel Peça Lima Novo Silvestre (PhD)

João Novo (PhD Student)

João Nuno Sereno de Almeida Moreira (PhD)

Joao Patricio (Masters Student)

João Paulo Oliveira (MD)

João Paulo Soeiro Terra Teodoro (PhD)

João Pedro Lopes (PhD)

João Pessoa (PhD)

João Pratas (Technician)

João Ramalho-Santos (PhD, Group Leader)

João Rocha (MSc Student)

Joaquim Moita (MD)

Joaquim Murta (PhD)

John D. Marugg (PhD)

John Jones (PhD, Group Leader)

Jorge António Ribeiro Salvador (PhD)

Jorge Silva (PhD Student)

Jorge Varandas Lindo (MD student)

José Carlo Cardoso (MD, PhD Students)

José Dionisio (PhD)

José Guilherme Lopes Rodrigues Tralhão (PhD)

José Manuel Nunes Carreira (Technician)

José Teixeira (PhD)

Judite Raquel Martins Coimbra (PhD Student)

Juliana Esgueirão (MSc student)

Juliana Simões (collaborator)

Julie Héléne Reis (Grant Technician)

Júlio Torres (Technician)

Karla Menezes Cardoso (MSc)

Kevin Costa Leandro (PhD Student)

Laetitia da Silva Gaspar (PhD Student)

Lara Ferreira (PhD)

Lara Ferreira (PhD)

Lara Franco (PhD)

Laura Alcântara (PhD)

Laura Francisca Martins Mendonça (Technician)

Lavínia Romera (PhD)

Lélita da Conceição dos Santos (PhD)

Leonor Almeida (PhD)

Leonor Barroso (MD, PhD Students)

Lia Carvalhais (Msc Student)

Lia Costa (MSc)

Lia da Costa Jordão Aparicio Lopes (MSc)

Lígia Fão (PhD Student)

Liliana Dias (PhD Student)

Liliana Letra (MD, PhD Student)

Liliana Simões Mendonça (PhD)

Lino Gonçalves (PhD)

Lino Silva Ferreira (PhD, Group Leader)

Lisa Rodrigues (PhD)

Lucas (MSc student)

Luciana Albuquerque (PhD)

Luciana Pinto (Ph.D, Sup. Technic)

Lucile Bonneau (Volunteer)

Ludgero Tavares (PhD)

Luís Estronca (PhD)

Luís F Ribeiro, (PhD)

Luis Fernando Morgado Pereira Almeida (PhD, Group Leader)

Luís Grilo (PhD Student)

Luís Henrique Costa Carvalho (Technician)

Luís Leite (Other)

Luís Maria Marques dos Santos Bimbo (PhD)

Luís Martinho do Rosário (PhD)

Luís Monteiro (PhD Student)

Luis Negrão (MD)

Luís Oliveira (PhD student)

Luis Pereira (PhD)

Luis Silva (Masters Student)

Luísa Cortes (PhD)

Luisa Santos (MD)

Luiz F. Piochi (MSc student)

Luiz Miguel Santiago (PhD)

Luiz Miguel Santiago (PhD)

Luiza Almeida (Technician)

Maria Teresa Sequeira (PhD)

Mafalda Sofia Laranjo Cândido (PhD)

Magda Matos Santana (PhD)

Manuel Maria Moura Neves Moreira Pires (MSc)

Manuel Marques Ferreira (PhD)

Manuel Santos (MD)

Manuela Ferreira (PhD)

Manuela Grazina (PhD)

Marcelo Flávio Jesus Queiroz (MSc)

Márcia Teixeira (Grant Tech.)

Marcos António dos Santos Rodrigues Gomes (MSc)

Marcos Divino Ferreira Junior (MSc)

Margarida Beatriz (Grant Technician)

Margarida Caldeira (PhD)

Margarida Sobral (PhD Student)

Maria Teresa Oliveira (PhD)

Maria Amália da Silva Jurado (PhD)

Maria Carmen Alpoim (PhD)

Maria Carminda Morais (PhD)

Maria Cristina Oliveira (PhD)

Maria da Conceição Lopes Lobo da Fonseca (PhD)

Maria da Conceição Monteiro Pedroso de Lima (Agregation)

Maria da Conceição Monteiro Pedroso de Lima (PhD)

Maria da Conceição Venâncio Egas (PhD)

Maria de Fátima de Sousa Martins Moreira (Technician)

Maria do Céu Rodrigues de Sousa (PhD)

Maria do Rosário Ferreira da Costa Faro (MSc)

Maria do Rosário Ferreira da Costa Faro (MSc)

Maria Emília de Oliveira Quinta Ferreira (PhD)

Maria Ester Freitas Barbosa Pereira Coutinho (PhD)

Maria Eugénia Campos (FMUC/CNC assistant technician)

Maria Filomena Rabaça Roque Botelho (PhD)

Maria Francisca Madeiran (Technician)

Maria Gomes (Technician)

Maria Helena Vieira Soares Loureiro (PhD)

Maria Inês Alfaiate (PhD Student)

Maria Inês Cristo (PhD student)

Maria Inês Morgado Oliveira Martins (PhD Student)

Maria Inês Santos (MSc)

Maria Inês Sousa (PhD)

Maria Inês Veiga de Almeida Barros (PhD Student)

Maria Isabel Gonçalves (Technician)

Maria Joana Guimarães Pinto (PhD)

Maria João da Silva Fernandes Leal Carvalho (PhD)

Maria João Leitão (PhD Student)

Maria João Santos (PhD Student)

Maria José Julião, MD

Maria Luísa Bonito (Technician)

Maria Luísa Carvalho Carreira (PhD Student)

Maria Madeira (PhD)

Maria Manuel Cruz Silva (PhD)

Maria Manuel Martins Pinto (MSc)

Maria Margarida Castel-Branco (PhD)

Maria Margarida Gonçalo (PhD)

Maria Margarida Ribeirinho Pereira (MSc)

Maria Margarida Serra Coelho (MSc)

Maria Moreira Soares (PhD Student)

Maria Rosário Almeida (PhD)

Maria Santiago (Technician)

Maria Teresa Cruz (PhD, Group Leader)

Maria V.-Cardoso (PhD Student)

Mariana Afonso, PhD student

Mariana Barradas Serrano Laranjo (MSc)

Mariana Biscaia Caleiras (MSc)

Mariana Diniz (Grant Tech.)

Mariana Ladeiro Afonso (MSc)

Mariana Machado (MSc student)

Mariana Martins (MSc)

Mariana Pereira de Magalhães (MSc)

Mariana Pires (MSc Student)

Mariana Sá Rocha (MSc Student)

MariaTeresa Sequeira (PhD)

Marija Petkovic (PhD Student)

Marina Rodrigues (PhD Student)

Mário Carvalho (PhD)

Mário Laço, MD, PhD

Mário Martins Rodrigues Grãos (PhD)

Mário Pedro Da Silva Marques (MSc)

Mário Pinto (PhD)

Marisa F. Marques (PhD Student)

Marisa Neves (PhD Student)

Marta Barão (Grant Technician)

Marta Laranjeiro Pinto (PhD)

Marta Simões (Technician)

Marta Susana de Oliveira e Silva Inácio de Sousa Henriques (PhD Student)

Matilde Jesus (MSc Student)

Matilde Sofia Guerreiro da Costa Rodrigues (MSc)

Micaela Figueiredo (MSc student)

Miguel Albano, MD

Miguel Ângelo Almeida Cardoso (MSc)

Miguel Lino (PhD)

Miguel Mano (PhD, Group Leader)

Miguel Maria Varandas Anão Rosado (MSc)

Miguel Monteiro Lopes (PhD Student)

Miguel Pereira (MD)

Miguel Pinto (Technician)

Milene Gonçalves (PhD Student)

Milene Ribeiro (UC-BIOTECH Animal Welfare responsible and caretaker)

Miranda Mele (PhD)

Mónica Morais (Technician)

Monica Santos (PhD)

Mónica Serrano (FMUC/CNC caretaker)

Mónica Teresa Parente Abreu (PhD)

Mónica Zuzarte (PhD)

Morten Bjerregaard-Andersen (PhD)

Mylene Carrascal (PhD)

Nadine dos Santos (PhD Student)

Natália António (PhD)

Nélio Gonçalves (PhD)

Neuza Luísa da Silva Domingues (PhD)

Nícia Filipa Rosário Ferreira (PhD Student)

Nilza Manadas (Technician)

Nuno Beltrão (PhD Student)

Nuno Coutinho (PhD)

Nuno David de Sousa Chichorro da Fonseca Ferreira (PhD)

Nuno Empadinhas (PhD, Group Leader)

Nuno Filipe Viegas das Neves Raimundo (PhD)

Nuno Miguel Beltrão Marques (MSc)

Olga Maria Fernandes Borges Ribeiro (PhD)

Orsolya Antal (PhD Student)

Pasqualino De Luca (PhD Student)

Patrícia Alexandra Rosado Albuquerque (PhD Student)

Patrícia Borges (PhD)

Patrícia Coelho (Grant Technician)

Patrícia Diogo (MD, PhD)

Patricia Martins (PhD)

Patrícia Moreira (PhD Student)

Patrícia Pitrez (PhD)

Patrícia Raquel Delgado Coelho (MSc)

Patrick Joel da Silva (PhD Student)

Paula Agostinho (PhD)

Paula Laranjeira (PhD)

Paula Martins (MD, PhD Student)

Paula Moreira (PhD)

Paula Mota (PhD)

Paula Veríssimo (PhD)

Paulo Felix (MSc student)

Paulo Matafome (PhD)

Paulo Oliveira (PhD, Group Leader)

Paulo Pinheiro (PhD)

Paulo Santos (PhD)

Pedro Afonso Valente (PhD student)

Pedro António Cruz Ferreira (MSc)

Pedro Barbosa (PhD Student)

Pedro Curto (PhD)

Pedro Fernandes (MSc)

Pedro Ferreira (PhD, Group Leader)

Pedro Figueiredo (PhD Student)

Pedro Fonseca (Technician)

Pedro Gomes (MD)

Pedro José Moreira Sobral (PhD Student)

Pedro Manuel Quelhas Lima Engrácia Antunes (PhD)

Pedro Rafael da Silva Álvaro Magalhães (PhD)

Pedro Ricardo Lucas Perdigão (PhD)

Pedro Valada (PhD Student)

Rafael Baganha (MSc)

Rafael Dias (MSc Student)

Rafael Silveira (MSc student)

Rafaela Ferrão (Grant Technician)

Rafaela Seabra (MSc Student)

Ramon Raposo (PhD)

Raquel Boia, PhD Student

Raquel Fernanda da Silva Alves (PhD)

Raquel Pina Gouveia (MSc)

Raquel Rodrigues, (PhD)

Raquel Santiago (PhD)

Raquel Seiça (MD, PhD)

Renata Tavares (PhD)

Ricardo Abreu (PhD Student)

Ricardo Amorim (PhD Student)

Ricardo Cunha (PhD Student)

Ricardo Jorge Marques Teixo (MSc)

Ricardo Leitão (PhD)

Ricardo Lorenzoni (PhD)

Ricardo Marques (PhD)

Ricardo Morais (MD)

Ricardo Moreira (PhD Student)

Ricardo Neves (PhD)

Ricardo Rodrigues (PhD)

Ricardo Romão Nazário Leão (PhD)

Ricardo Santos (Student)

Ricardo Silva (PhD Student)

Ricardo Vieira-Pires (PhD)

Rita Alves (PhD Student)

Rita Catarina Gonçalves Perfeito (PhD)

Rita Domingues, (MSc)

Rita Gaspar (PhD Student)

Rita Lavrador (master student)

Rita Manuela Palmeira de Oliveira (PhD)

Rita Pacheco (collaborator)

Rita Pereira (MSC Student)

Rita Sá Ferreira (PhD Student)

Rita Santos (PhD Student)

Rita Vilaça (PhD)

Rodrigo Cunha (PhD, Group Leader)

Rodrigo Ribeiro (PhD Student)

Rodrigo Ribeiro (PhD Student)

Rodrigo Taveira (MSc Student)

Romina Guedes (PhD)

Rosa Alexandra Fernandes (MSc)

Rosa Fernandes (PhD)

Rosa Maria Moreira Alves dos Santos

Rosa Resende (PhD)

Rosemeyre Amaral Cordeiro (PhD)

Rufino Martins da Silva (PhD)

Rui Barbosa (PhD)

Rui Jorge Gonçalves Pereira Nobre (PhD)

Rui O Costa (PhD)

Rui Pimenta (PhD)

Rui Tavares (PhD Student)

Rute Santos (MSc Student)

Rute Simões (Technician)

Samira Ferreira (PhD)

Sandra Amaral (PhD)

Sandra Catarina Oliveira Braz (PhD)

Sandra Cristina Campos de Jesus (PhD)

Sandra Freire (FMUC/CNC Animal Welfare responsible and caretaker)

Sandra Isabel dos Santos Anjo (PhD)

Sandra Jesus (PhD)

Sandra Luis (Technician)

Sandra M. Cardoso (PhD)

Sandra Mota (PhD)

Sandra Oliveira (PhD)

Sandra Pinhanços (PhD Student)

Sandra Reis (PhD Student)

Sara Amaral (PhD)

Sara Aparício Lopes (Technician)

Sara Gonçalves (Volunteer)

Sara Isabel Monteiro Lopes (PhD)

Sara Margarida dos Santos Domingues (PhD)

Sara Martins (Volunteer)

Sara Nunes (PhD Student)

Sara Patrícia de Sousa Pereira Moura (MSc)

Sara Pedroso (MD)

Sara Pego (Grant Tech.)

Sara Rebelo (PhD Student)

Sara Ribau (MSc Student)

Sérgio Abílio Teixeira Bernardo de Sousa (MD, PhD)

Sérgio Gonçalo Reis Mendes (MSc)

Sérgio Simões (PhD)

Sílvia Maria Esteves de Sousa (MSc)

Sílvia Raquel Monteiro Martins (PhD Student)

Simão Santos (Student)

Sofia Costa (Technician)

Sofia Galvão (MSc Student)

Sofia Isabel Domingues Combo (MSc)

Sofia Maia (MD, PhD)

Sofia Viana (PhD)

Solange Martins Nogueira (MSc Student)

Sónia Batista (MD, PhD)

Sónia Correia (PhD)

Sonia Guadalupe

Sónia Guadalupe dos Santos Ribeiro Neves de Abreu (PhD)

Sónia Patrícia Dias Duarte (PhD)

Sónia Pinho (PhD Student)

Sónia Pinho (PhD)

Sónia Santos, PhD

Soraia Faria (Technician)

Steve Catarino (PhD)

Susana Adelaide Rocha da Silva (Technician)

Susana Alarico (PhD)

Susana Cardoso (PhD)

Susana Costa (PhD Student)

Susana P. Pereira (PhD)

Susana Pedreiro (Grant Technician)

Susana Rosa (PhD)

Susana Simões (PhD)

Tânia Fernandes (PhD Student)

Tania Luísa Barbosa Barata (PhD Student)

Tânia Marques (PhD)

Tânia Milene Pires Lourenço (MSc)

Tânia Silva (MD)

Tarcísio Guerra Guimarães (MSc)

Tatiana Catarino (PhD)

Tatiana de Azevedo Paula (Technician)

Teresa Carla Oliveira (PhD)

Teresa Carmo Pimenta Dinis Silva Dinis Silva (PhD)

Teresa Dinis (PhD)

Teresa Gonçalves (PhD, group leader)

Teresa Maria Caldeira Martins (PhD)

Teresa Oliveira (PhD)

Teresa Raquel Tremoço Dias de Abreu (MSc)

Teresa Rodrigues (PhD Student)

Tiago Ôchoa-Pires (PhD Student)

Tiago Reis (PhD Student)

Tiago Rodrigues (PhD Student

Tiago Rondão (Grant Technician)

Tiago Ventura Lourenço Lima (MSc)

Tony Rolo, MD, PhD Students

Ulyana Motresku (MSc Student)

Valentin Fernandez (PhD Student)

Vanessa Costa (Grant Tech.)

Vânia Gonçalves (PhD)

Vânia Gonçalves (PhD)

Vania M Moreira (PhD)

Vasco Santos (Technician)

Vera Mónica Milheirão Mendes (MSc)

Vilma Marisa Arrojado Soares Sardão Oliveira (PhD)

Vítor Francisco (PhD)