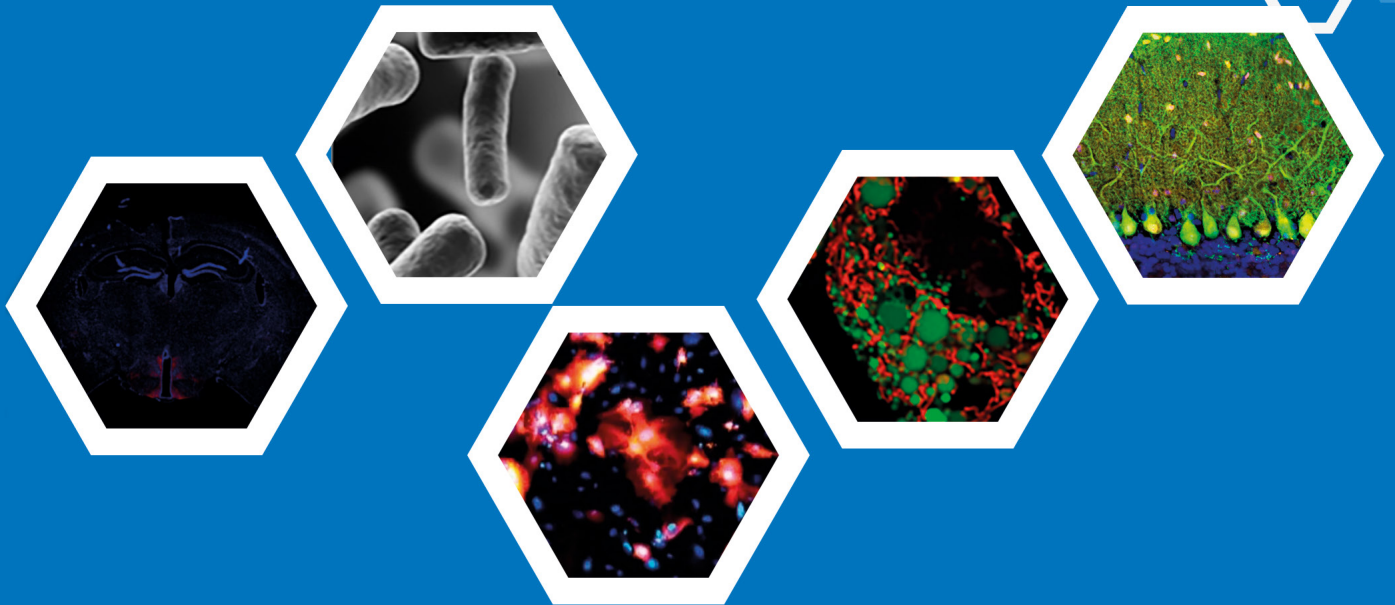


CIBB

ANNUAL REPORT

[2020]



CENTRE FOR INNOVATIVE
BIOMEDICINE
AND BIOTECHNOLOGY

CIBB

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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.

FACTS & FIGURES

From Year 2020

RESEARCH STAFF

Members holding Ph.D.	364
PhD Students	147
MSc Students	41
Grant Technicians	59

PUBLICATIONS

Scientific papers published	444
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THESIS CONCLUDED

Ph.D. thesis	26
MSc thesis	133

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 Group (Head: Paulo Oliveira)

Metabolic Control Group (Head: John Griffith 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)

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

Research activities at the Neuroscience and Diseases thematic line are dedicated to understanding brain function and the pathogenesis of diseases of the nervous system, and to developing novel therapeutic strategies.

Nine research groups contribute to this research line and researchers focus in the areas of molecular, cellular, circuits and behavioral neuroscience, to understand the brain at different levels, 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 that ligand-independent activity of the ghrelin receptor modulates AMPA receptor trafficking and supports memory formation (Ribeiro et al. *Sci Signaling* 2021), and revealed that social subordination induced by early life adversity rewires inhibitory control of the prefrontal cortex via enhanced Neuropeptide Y1 receptor signaling (Franco et al. *Neuropsychopharmacol* 2020). Research on neuromodulation by purines has been 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), as well as their function in autism spectrum disorders, by formatting long-term depression and memory strategies in a mouse model of Angelman syndrome (Moreira-de-Sá et al. *Neurobiol Dis*, 2020). Activation of the adenosine A3 receptor was found to protect retinal ganglion cell from degeneration induced by ocular hypertension (Boia et al. *Cell Death Dis*, 2020).

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, mitochondrial and redox modifications in Huntington's disease induced pluripotent stem cells have been rescued by targeting CAGs using CRISPR/Cas9 methodologies (Lopes et al., *Front Cell Dev Biol*, 2020).

Multiple studies on Alzheimer's disease pathogenic mechanisms have emerged: One found that chronic hyperglycemia impairs hippocampal neurogenesis and memory in an Alzheimer's disease mouse model (Ferreiro et al., *Neurobiol Aging*, 2020), and a collaborative publication between several CIBB groups revealed that miRNA-31 improves cognition and abolishes amyloid- β pathology in an animal model of Alzheimer's disease (Barros-Viegas et al. *Mol Ther Nucleic Acids*, 2020). Clinical studies have addressed the conversion of mild cognitive impairment to Alzheimer's disease, and discovered that the ApoE ϵ 4-TOMM40L haplotype increases risk for conversion (Cardoso et al. *J Alzheimer's Dis*, 2020) and the C-reactive protein can be used as a predictor of conversion (Fernandes et al. *Exp Gerontol*, 2020). The Biomarkers in Neuropsychiatric Disorders group led by Isabel Santana participates in the multicentric Genetic Frontotemporal Dementia Initiative (GENFI), and studies from this initiative have revealed abnormal pain perception associated with thalamo-cortico-striatal atrophy in mutation carriers in GENFI (Convery, et al. *J Neural Neurosurg Psychiatry*, 2020). One study led by the FTD Prevention Initiative, with the participation of the Biomarkers group, addressed age at symptom onset and death and disease duration in genetic frontotemporal dementia (Moore et al. *Lancet Neurol*, 2020).

Clinical studies are also very strong in the Ophthalmology field. One example of a significant contribution in the field is a five-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*, 2020).

Promising strategies for ameliorating senescence phenotypes have been investigated: Avelaira and colleagues showed that neuropeptide Y enhances progerin in human Hutchinson-Gilford Progeria Syndrome cells (Avelaira et al., *J Gerontol A Biol Sci Med Sci*, 2020), and 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).

Technological developments include the evaluation of a multi-site clinical depth recording electrode for monitoring cerebral tissue oxygen (Ledo et al. *Micromachines*, 2020), and the characterization of a ruthenium purple-modified carbon fiber microelectrodes for detection of hydrogen peroxide in the brain (Ledo et al., *Sensors and Actuators B: Chemical*, 2020). A collaborative project between two groups has led to an optimized spectrophotometric assay that allowed elucidating 2-arachidonoyl glycerol turnover in the cortex of a rat model of Alzheimer's disease (Rodrigues et al. *Eur J Neurosci*, 2020).

The Innovative Training Network Syn2Psy-Synaptic Dysfunction in Neuropsychiatric Disorders, coordinated by CNC/CIBB and funded by the European Commission through the MSCA, was launched late in 2019 and has recruited 14 Early Stage Researchers to develop joint research projects between Neuroscience and Disease groups in CIBB and other European research groups on the Syn2Psy consortium, focused on synaptic malfunction in neuropsychiatric disorders. Please check the Syn2Psy website (www.syn2psy.eu) for more information.

This is a brief summary of the main achievements in the Neuroscience and Disease research line, highlighting some of the important contributions from research groups in this area. Please refer to the individual group reports for other important studies during 2020.

Synapse Biology

Ana Luisa Carvalho (PhD, Group Leader)
 Ângela Inácio (PhD)
 Dominique Fernandes (PhD)
 Gladys Caldeira (PhD)
 Mariline Silva (PhD)
 Mário Carvalho (PhD)
 Paulo Pinheiro (PhD)
 Sandra Santos (MD, 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)
 Renato Macedo (MSc Student)
 Vera Pais (Msc Student)

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)
 Andreia Marques (MSc 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)
 Ana Teresa Viegas (PhD)
 Célia Avelaira (PhD)
 Fernando Judas (MD, PhD)
 M^a Manuel Cruz Silva (PhD)
 Sara Carmo Silva (PhD)
 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)
 Ana Catarina Franco (Grant Technician)
 Daniela Costa (Grant Technician)
 Rodolfo Águas (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)
 Giorgio Belperio (PhD Student)
 Pasqualino De Luca (PhD Student)
 Elisa Corti (Grant Technician)
 Emanuel Tahiri (MSc Student)
 Francisca Silva (MSc Student)

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)
 Nélcio Gonçalves (PhD)
 Paula Agostinho (PhD)
 Paula Canas (PhD)
 Ricardo Rodrigues (PhD)
 Samira Ferreira (PhD)
 Anna Pliássova (PhD Student)
 Ana Teresa de Sá (PhD Student)
 Daniela Madeira (PhD Student)
 Liliana Dias (PhD Student)
 Ana Sofia Figueira (MSc Student)
 Andreia Oliveira (MSc Student)
 Catarina Carreira (MSc Student)
 Joana Silva (MSc Student)
 João Rocha (MSc Student)
 Matilde Jesus (MSc Student)
 Rafael Dias (MSc Student)
 Cátia Lopes (Grant Technician)
 Vanessa Lourenço (Grant Technician)

Neuronal Circuits and Behavior

João Peça (PhD, Group Leader)
 Ana Luísa Cardoso (PhD)
 Catarina Seabra (PhD)
 Joana Guedes (PhD)
 Diana Bela Sequeira
 Marcos Gomes (PhD Student)
 Ana Rafaela Oliveira (PhD Student)
 Jéssica Costa (PhD Student)
 Mariana Laranjo (PhD Student)
 Marta Pereira (PhD Student)
 Pedro Ferreira (PhD Student)
 Giuseppe Camarata (Grant Technician)
 Solange Nogueira Volunteer

Mitochondria and Neurodegenerative Disorders Aging and Brain diseases: advanced diagnosis and biomarkers Group Alexandra F Cruz (Student)

Ana C. Rego	(PhD, Group Leader)	Isabel Santana	(MD, PhD, Group Leader)
Ildete Luisa Ferreira	(PhD)	Ana Paula S. Martins	(PhD)
Sandra Mota	(PhD)	Ana Rita S. Silva	(PhD)
Carla Nunes Lopes	(PhD)	Bruno Manadas	(PhD)
Ricardo Lorenzoni	(PhD)	Carlos A. F. Ribeiro	(MD, PhD)
Rita Vilaça	(PhD)	Catarina R. Oliveira	(MD, PhD)
Lúgia Fão	(PhD Student)	Catarina Reis Gomes	(PhD)
Daniela Lopes	(Grant Technician)	Edna Filipa P. Soares	(PhD)
Margarida Beatriz	(Grant Technician)	Filipa C. Baptista	(PhD)
Patrícia Coelho	(Grant Technician)	Frederico G. Pereira	(PhD)

Vision Diseases

António F. Ambrósio	(PhD, Group Leader)	João Rodrigues	(PhD)
Ana Raquel Santiago	(PhD)	João Freitas	(MD, PhD)
António C. Figueiredo	(PhD)	Joaquim Cerejeira	(MD, PhD)
Ana Rita Santos	(PhD)	Marcos Barbosa	(MD, PhD)
Andreia Rosa	(PhD)	M ^a João Martins	(PhD)
Celso Alves	(PhD)	M ^a Rosário Almeida	(PhD)
Elisa Campos	(PhD)	Mariana Almeida	(PhD)
Hélène Léger	(PhD)	Sandra Anjo	(PhD)
João Figueira	(PhD)	Sónia Batista	(MD, PhD)
Joaquim Murta	(PhD)	Ricardo Leitão	(PhD)
José Cunha-Vaz	(PhD)	Alexandre Marques	(MD)
M ^a C. Fonseca	(PhD)	Anabela Matos	(MD)
M ^a Luz Damasceno	(PhD)	Filipe Palavra	(MD)
M ^a Helena Madeira	(PhD)	Gustavo Santo	(MD)
M ^a João Quadrado	(PhD)	Inês Correia	(MD)
M ^a Luísa Ribeiro	(PhD)	João Durães	(MD)
Paulo Santos	(PhD)	Luis Negrão	(MD)
Rosa Fernandes	(PhD)	Luisa Santos	(MD)
Rufino Silva	(PhD)	M ^a Carmo Macário	(MD)
Cláudia Farinha	(MD)	Miguel Pereira	(MD)
Inês Marques	(MD)	Patrícia Regueira	(MD)
João Gil	(MD)	Ricardo Morais	(MD)
João Marques	(MD)	Sara Pedroso	(MD)
Jorge Henriques	(MD)	Tânia Silva	(MD)
Pedro Fonseca	(MD)	Ana Cristina Santos	(Graduate Technician)
Pedro Gil	(MD)	Diana Duro	(Graduate Technician)
Patrícia Barreto	(Pharmacist)	Vera Mendes	(Graduate Technician)
Inês Aires	(PhD Student)	Ana Catarina Neves	(PhD Student)
Joana Martins	(Researcher)	Anuschka Spínola	(PhD Student)
Raquel Boia	(Researcher)	Cátia Santa	(PhD Student)
Ana Rita Gaspar	(Grant Technician)	Diana Carvalho	(PhD Student)
Beatriz Martins	(Grant Technician)	Inês Isabel Caramelo	(PhD Student)
Flávia Rodrigues	(Grant Technician)	Marisa Neves	(PhD Student)
Miguel Teixeira	(Grant Technician)	M ^a João Leitão	(PhD Student)
Sara Nunes	(Grant Technician)	M ^a Margarida Coelho	(PhD Student)
Carolina Santos	(MSc Student)	Mariana Magalhães	(PhD Student)
Alexandra Cruz	(Volunteer)	Miguel Rosado	(PhD Student)
		Milene Gonçalves	(PhD Student)
		Ana Martinho	(MSc Student)
		Diana Gaspar	(MSc Student)
		Erika Muñoz	(MSc Student)
		Margarida Neves	(MSc Student)
		M ^a Manuel Santiago	(MSc Student)
		Alexandra Dinis	(Grant Technician)
		Julie Hélène Reis	(Grant Technician)

SYNAPSE BIOLOGY

Head: Ana Luisa Carvalho

OBJECTIVES

The Synapse Biology group is broadly interested 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 including primary cultures of dissociated neurons and brain slices, biochemistry, molecular and cellular biology, mouse molecular genetics, electrophysiology, and behavioural analysis, to address the role of molecular players that regulate 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. This fundamental research has strong implications to cognitive disorders, since genetic variants in multiple synaptic proteins are linked to intellectual disability, schizophrenia and autism spectrum disorder. Our cellular and molecular studies and the animal models that we are generating can also contribute to the rational development of therapies for these diseases. The group has been pursuing the following specific objectives:

1. **The membrane fusion machinery in physiology and disease**
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 neuronal development and synaptic function and how they may be linked to synaptic dysfunction in neuropsychiatric disorders. We are evaluating genetically modified mice lacking their expression for behaviour and for alterations in synaptic function and neuronal development.
2. **Mechanisms of chronic stress-induced microRNA-186-5p in cognitive dysfunction**
We have identified post-transcriptional regulation of AMPA receptors by miR-186-5p, which directly targets and bidirectionally modulates the expression of GluA2 AMPA receptor subunit (Silva et al., PNAS 2019). This miRNA is

upregulated by chronic stress in the prefrontal cortex (PFC). We are now interested in understanding how chronic stress-upregulated miR-186-5p affects AMPA receptor composition and synaptic transmission in the PFC 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.

3. **Synaptic dysfunction and alterations in neuronal excitability in disease-associated human mutations in CACNG2**
We are interested in understanding how disease-associated human mutations in the CACNG2 gene encoding for stargazin – an AMPA receptor auxiliary subunit- impact synaptic and cognitive function. Toward this, we have produced knock-in mice harbouring an intellectual disability- associated variant of the CACNG2 gene that reproduce alterations in cognitive and social behaviour reminiscent of the clinical symptoms found in patients, and knock-in mice harbouring a schizophrenia-associated variant of CACNG2. We are now characterizing neuronal excitability, synaptic transmission, plasticity and behaviour of these mice.

4. **Pathogenic mechanisms of CASPR2 antibodies in autoimmune synaptic encephalitis**
We previously found that Caspr1 and Caspr2, cell adhesion molecules of the neurexin family, regulate AMPA receptor function (Santos et al., J Biol Chem 2012; Fernandes et al., Cerebral Cortex 2019) and that anti-CASPR2 antibodies from autoimmune synaptic encephalitis patients block synaptic transmission in the visual cortex. We are now interested in understanding how antibodies targeting different CASPR2 epitopes impact synaptic physiology, including the synaptic abundance and functional properties of AMPA receptors.



Cover story in *Science Signaling*: No ligand needed for learning – blocking the constitutive activity of the ghrelin receptor impairs spatial and recognition memory. Image shows fluorescent probe signal used for measuring ligand-independent activity of the ghrelin receptor in hippocampal neurons

MAIN ACHIEVEMENTS

1. 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)

2. We have found that knock-in mice harboring an intellectual disability-variant of the *CACNG2* gene reproduce alterations in cognitive and social behavior reminiscent of the clinical symptoms found in patients. Morphological and electrophysiological analyses revealed that stargazin knock-in mice present abnormalities in neuronal morphology and synaptic function in the hippocampus, which constitute a potential disease mechanism (Caldeira, Inácio et al., *bioRxiv* 2021.06.08.447333; under review).

3. The M-current is a low-threshold K⁺ current that shapes neuronal excitability and firing. M-current dysfunction is a common epileptogenic mechanism, but little is known about how M-currents are regulated. We have identified

stargazin as a new interactor of the Kv7.2 M-channel subunit, and mutations in the stargazin-coding gene have been found in intellectual disability and schizophrenia patients. Our patch-clamp experiments now reveal that stargazin, but not its disease-associated variants, potentiates Kv7.2 currents. In addition, stargazin is required for activity-dependent plasticity of the axonal initial segment, where M-channels are highly concentrated. We are presently elucidating the stargazin-mediated mechanism of regulation of M-currents and neuronal excitability, and how its impairment contributes to hyperexcitability in models of intellectual disability and schizophrenia. We have obtained a €0.78M la Caixa/FCT Research grant (€0.62M for the Synapse Biology group), in collaboration with the University of Bordeaux (Laurent Groc and Joana Ferreira) to pursue this project.

4. We have found that long-term in vitro exposure of cortical neurons to glucocorticoids, a protocol mimicking chronic stress in vitro, increases miR-186-5p levels and results in decreased levels of synapses and synaptic AMPA receptors with altered subunit composition. These changes are hallmarks of chronic stress in the prefrontal cortex. Blocking the upregulation of miR-186-5p during chronic exposure to glucocorticoids prevents the changes in AMPA receptor subunit composition and the impairment of excitatory synaptic transmission. We have obtained a €0.5M la Caixa/FCT Research grant to pursue this project.

5. We have found that KO mice for SNAP47 display subtle cognitive alterations and we are currently performing

electrophysiological analysis of brain synapses. We also found that mice heterozygous for SNAP29 express about 50% of the protein, causing haploinsufficiency. The mice display cognitive deficits and electrophysiological analysis revealed 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 synapses.

6. 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.

REDOX BIOLOGY AND BRAIN SENSING

Head: João Laranjinha

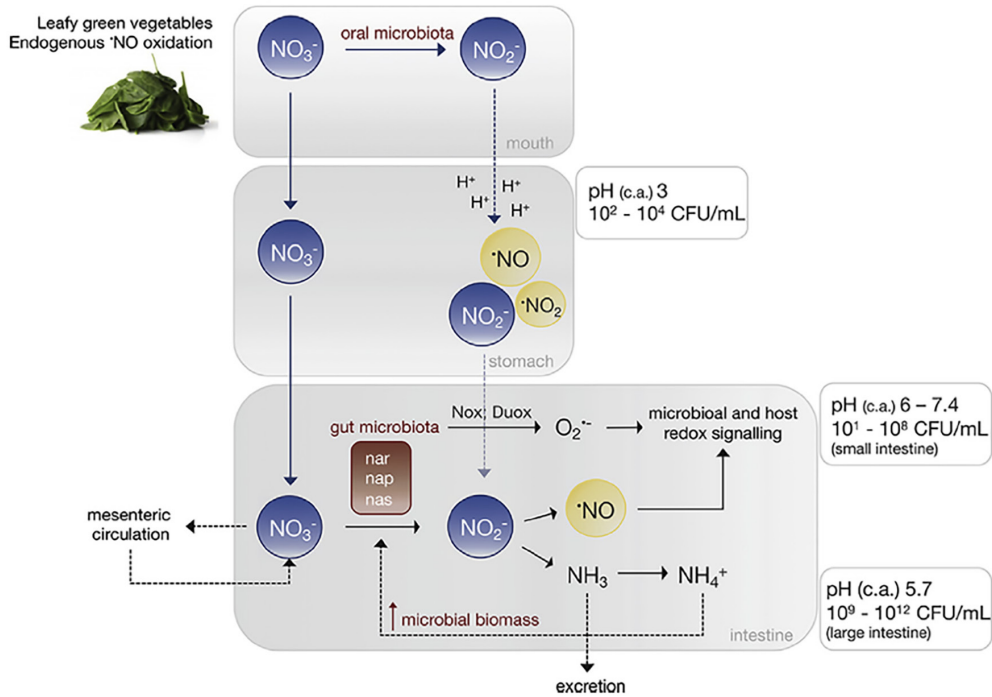
OBJECTIVES

The group's research programs address:

(a) The molecular mechanisms inherent in neuromodulation and aging under an umbrella that characterizes the bidirectional communication between neurons and microvasculature by addressing quantitatively, in vivo, and in real-time the role of nitric oxide as a diffusional intercellular messenger, coordinating the neurovascular and neurometabolic coupling axis. The study of the neurovascular-neurometabolic coupling axis, encompasses mechanistic as well nutritional approaches with potential to restore the functionality of neurovascular coupling and 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 conscious, freely behaving animals.

(c) The mechanisms of action of plant-derived dietary phenolic compounds in terms of protection against vascular endothelial dysfunction and anti-inflammatory properties, as well as their impact on nitrite-driven regulatory processes along the nitrate:nitrite:nitric oxide pathway, encompassing the non-enzymatic production of nitric oxide from dietary nitrite in the gastric compartment and the brain.



MAIN ACHIEVEMENTS

1) Humans are complex and highly dynamic holobionts. As superorganisms, we enclose mammalian and multispecies microbial cells confined in different physical compartments. Following previous work on the impact of microbiota in health, we have forwarded the concept that diet via the nitrate-nitrite-nitric oxide pathway fuels gut microbiota metabolic pathways and inter-kingdom communication. This concept rooted on the functional interdependency of mammalian-microbial ecosystems might establish a conceptual framework for future experiments addressing the modulatory role of diet in human health via the microbiome.

2) Hydrogen peroxide is now widely recognized as a signaling molecule involved in the redox regulation of cell functions. Thus, its measurement in vivo is a challenging task. We have developed and applied of ruthenium purple modified carbon fiber microelectrodes for measurement of hydrogen peroxide in brain tissue.

3) The intracranial measurement of local cerebral tissue oxygen levels-PbtO₂-has become a useful tool for the critical care unit to investigate severe trauma and ischemia injury

in patients. Our preliminary work in animal models supports the hypothesis that multi-site depth electrode recording of PbtO₂ may give surgeons and critical care providers needed information about brain viability and the capacity for better recovery. Based on the reported catalytic properties of Pt toward the electroreduction reaction of O₂, we proposed that these probes could be repurposed for multisite monitoring of PbtO₂ in vivo in the human brain.

4) Dietary polyphenols, such as anthocyanins, are multi-target compounds that have been considered promising candidates in strategies for the mitigation of neurological diseases, acting particularly through reduction of microglia-driven neuroinflammation. Our recent work provided new insights about the chemical changes observed in an anthocyanin extract obtained from Portuguese blueberries, after simulated digestion, and about its potential to combat microglia-driven neuroinflammation, using a stimulated microglia N9 cell line as a model. Although its markedly different chemical composition, the digested anthocyanin extract,

a mixture of diverse phenolic compounds, maintained a high efficiency in reducing the production of either key inflammatory markers or reactive oxygen species and in enhancing the reduced glutathione levels in activated cells, as compared with the original anthocyanin mixture. These protective effects seemed to be related to the reduction in the activation of NF- κ B pathway. Considering the obtained results and the literature data supporting the ability of many anthocyanins and phenolic acids to cross the blood-brain barrier, the anthocyanin mixture, isolated from blueberries, can be envisaged as a potential strategy to combat the neuroinflammatory process, which may be potentially useful in the prevention of neuroinflammation-related neurological disorders.

NEUROENDOCRINOLOGY AND AGING

•
Head: Cláudia Cavadas

OBJECTIVES

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 (metabolism dysfunction, osteoarthritis (OA), sleep dysfunctions, neurodegenerative diseases);
- To understand if and how obstructive sleep apnea (OSA), insomnia or obesity induce or accelerate molecular mechanisms of ageing;

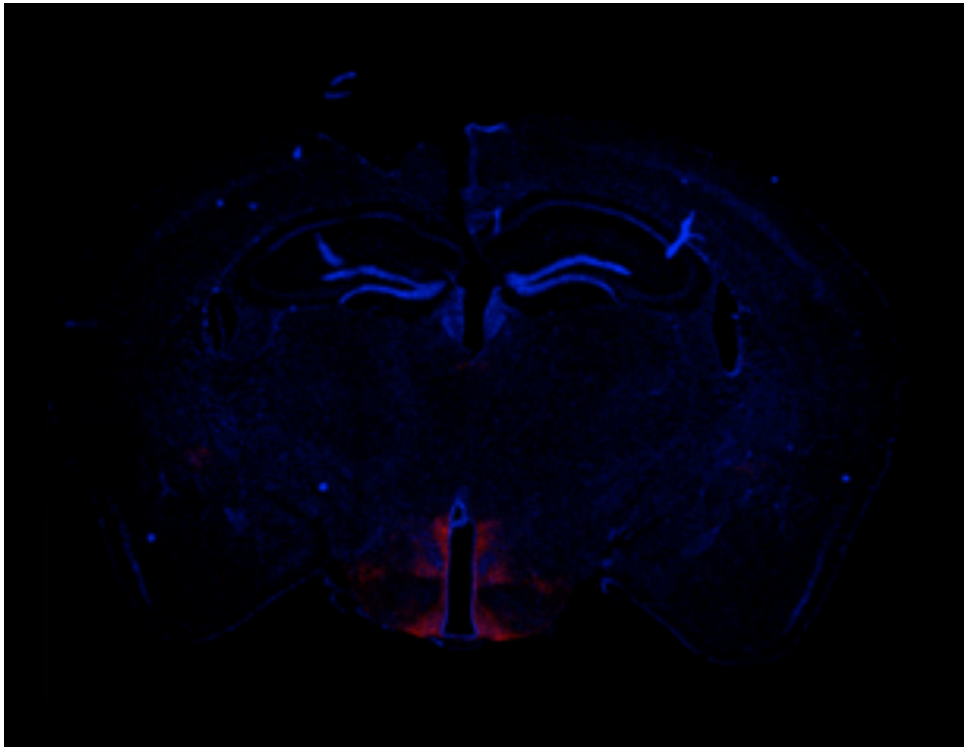


Fig. 1 - Neuropeptide Y immunoreactivity (red) in the hypothalamus of mouse brain. Nuclei (blue)

MAIN ACHIEVEMENTS

- We investigated the role of NPY and ghrelin in rescuing the aging phenotype in experimental models of ageing, using Hutchinson-Gilford Progeria Syndrome (HGPS) experimental models. The results obtained show that NPY and also ghrelin 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 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.
- Modulation of ataxin-2 in mice hypothalamus regulates energy balance and metabolism: including changes in body weight and response to insulin, through reestablishment of clock gene levels
- SIRTUIN 2 is abundantly expressed in major mouse hypothalamic nuclei and hypothalamic SIRT2 expression changes upon high fat diet (HFD), which triggers insulin resistance, suggesting that hypothalamic SIRT2 levels are modulated by nutrient availability.
- The preliminary data show that peripheral cells (PBMCs) from obstructive sleep apnea (OSA) patients present some hallmarks of aging.
- Long-term Continuous Positive Airway Pressure Treatment Ameliorates Biological Clock Disruptions in Obstructive Sleep Apnea.

NEUROTROPHIN SIGNALING AND 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 psychiatric disorders of the nervous system. In particular, the work in this research unit is focused on: 1) 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 contribute to several diseases of the nervous system; 2) the alterations in proteostasis coupled neuronal death in brain ischemia; and 3) how dysregulation of GABAergic synapses contribute to the increased neuronal excitability in epilepsy.

Regulation of glutamatergic synapses by BDNF (PI: Carlos B. Duarte)

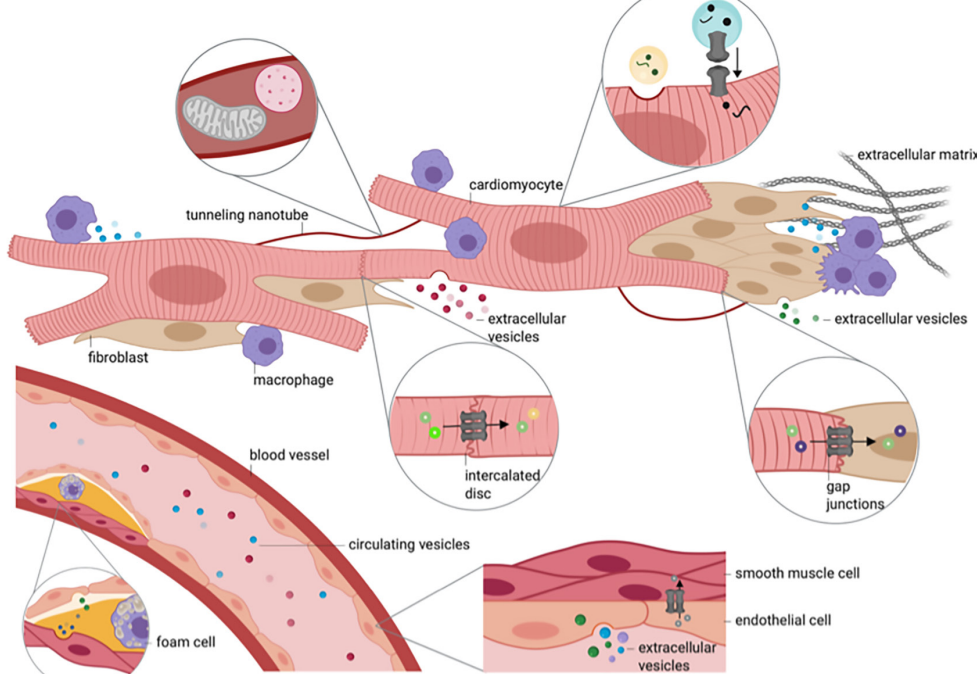
The neurotrophin brain-derived neurotrophic factor (BDNF) plays an important role in the functional and structural changes at synapses required for both early- and late phases of LTP in the hippocampus. These effects of BDNF are partly mediated by regulation of the synaptic proteome through regulation 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 fear (PI: Mónica Santos)

Anxiety disorders are marked by excessive fear (and avoidance) that is resistant to extinction. 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. Our current research line aims to investigate the role of NT3-TrkC pathway in the regulation of learned fear (and fear extinction) in physiologic conditions. To this end we use mice trained in the contextual fear conditioning paradigm to study where, when and how NT3-TrkC pathway modulates fear.

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.



Alterations of GABAAR trafficking in brain disorders.

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 fear (PI: Mónica Santos)

Using the contextual fear conditioning paradigm, we found that trained animals, when compared to control animals, show reduced levels of phospho-TrkC in the amygdala and prefrontal cortex at the consolidation phase, and in the hippocampus at the reconsolidation phase, suggesting that downregulation of TrkC signaling in the fear circuit is necessary for fear memory formation. In addition, using the fear

extinction training paradigm we found a striking disparity in extinction acquisition, which is highly correlated with extinction memory, with a subset of animals able to extinguish fear (EXT-success) and a subset of animals that failed to extinguish fear (EXT-failure). In the extinction consolidation phase, we found higher phospho-TrkC levels in the amygdala of EXT-success animals, when compared to EXT-failure and control groups. At the reconsolidation phase instead, we found lower phospho-TrkC levels in the hippocampus of the EXT-success animals, when compared to EXT-failure and control groups. By showing a differential pattern of TrkC activation in the fear network that is stage- and brain region-dependent, our data suggests a complex role of TrkC in the regulation of fear. We measured the levels of total NT3 by ELISA and we observed no differences among groups at the time-points and brain regions studied. This result might indicate a selective role of NT3 released by the regulatory versus the constitutive pathway. AMPA and NMDA receptors (AMPA and NMDAR) are important mediators of synaptic plasticity mechanisms in the CNS, which underlie certain forms of learning and memory. In cultured hippocampal neurons, stimulation with NT3 for 10 - 30 min increased the number of puncta of synaptic GluN2A and GluN2B containing NMDAR, and selectively decreased in a transient manner the intensity of GluN2A puncta. NT3 stimulation also increased the number of synaptic surface GluA1 puncta and decreased transiently the intensity of synaptic GluA2-containing puncta, thereby increasing the relative abundance of Ca²⁺-permeable receptors. Together, these results suggest that NT3 changes the synaptic composition NMDA receptors and the molecular composition of

synaptic AMPA receptors, which may have an impact on the synaptic responses mediated by these receptors.

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

Recent results from our laboratory showed a KCC2 dysfunction in epileptic conditions in vitro (transient incubation in a salt solution lacking Mg²⁺), which was correlated with GABAA receptor downmodulation. We hypothesized that the increase of [Cl⁻]_i in hippocampal neurons incubated in the absence of Mg²⁺ was due to the loss of KCC2 within the plasma membrane, with a consequent impairment of the mechanisms involved in Cl⁻ extrusion. To test this hypothesis, we used Clomeleon, a genetically encoded ratiometric probe that allows measuring variations of [Cl⁻]_i in live neurons. We evaluated the effect of a KCC2 activator, which prevented the SE-induced downregulation in the surface expression of the transporter, on [Cl⁻]_i by performing live imaging experiment. The results showed an increase in the [Cl⁻]_i in hippocampal neurons incubated in the absence of Mg²⁺, and this effect was abrogated by KCC2 activation. This result, together with our previous findings, supports the hypothesis that the KCC2 surface expression is essential to control the Cl⁻ gradient and hence to maintain the GABAAR-mediated inhibition during SE. This is in accordance with our recent findings showing an increased excitability in neurons expressing a phospho-mimetic form of GABAAR that reduces the endocytosis of the receptor. Currently we are investigating whether KCC2 activation is enough to counteract GABAA receptor downmodulation observed in epileptic condition.

NEUROMODULATION

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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 is implemented:

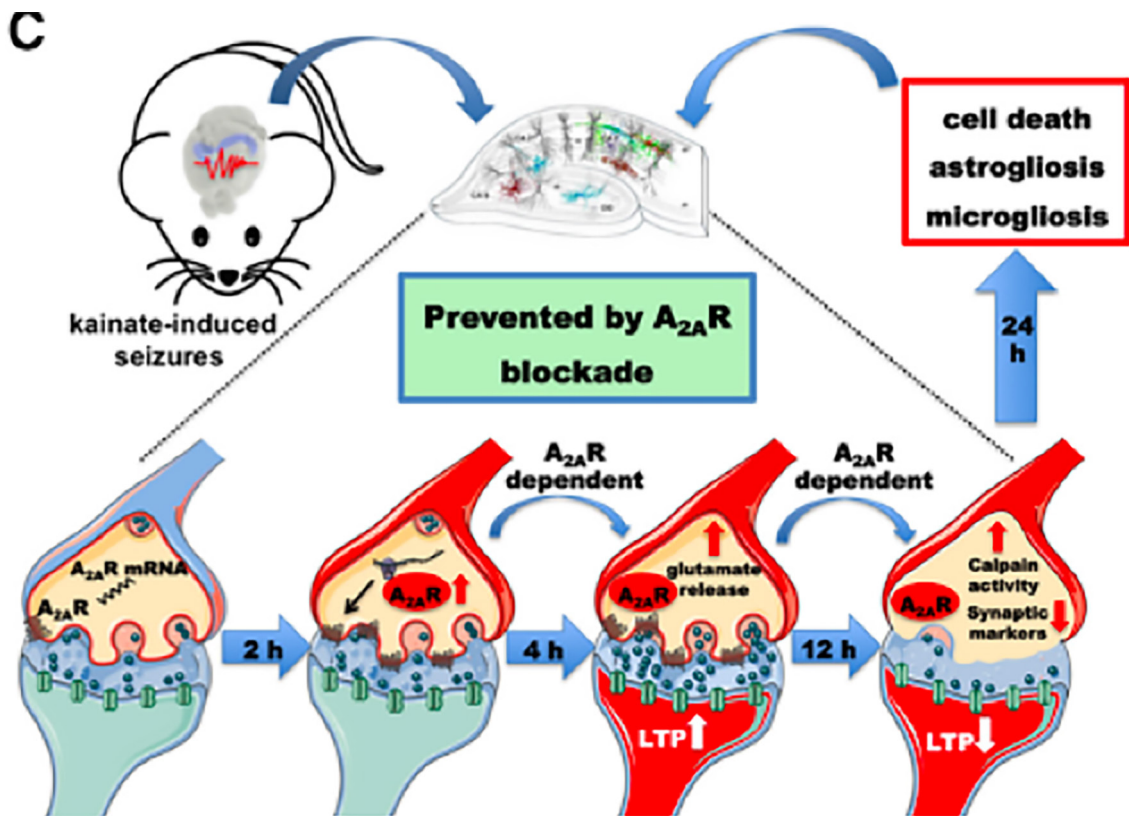
I-Group Purines@CNC (overall coordination by RA Cunha)

- 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)

- Altered corticostriatal neuromodulation in Willis-Ekbom Disease
- A2AR & brain glucoregulation
- Endocannabinoid receptor GPR55 & astrocytic glycolysis

III-Group Brain Development (RJ Rodrigues, J Marques, N Gonçalves)



MAIN ACHIEVEMENTS

1-Adenosine A_{2A} receptor ($A_{2A}R$) overfunction increases the susceptibility to brain damage

2-Brain neuronal $A_{2A}R$ are responsible for the ergogenic effects of caffeine

3- $A_{2A}R$ control the migration of principal neurons during brain development

4-Heteromers of cannabinoid and $A_{2A}R$ control glutamate release

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.

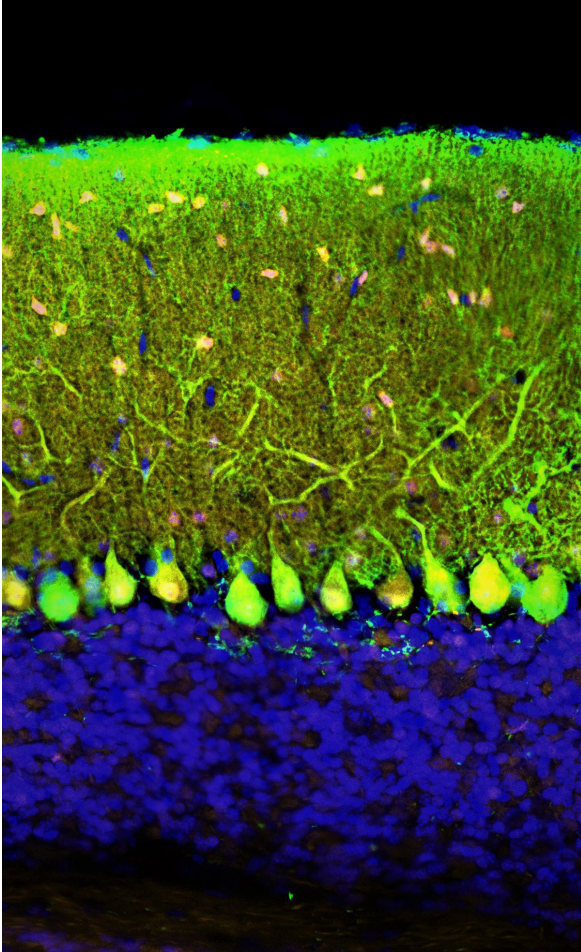
In this line of research, we incorporate advanced models, including novel genetic engineered mice, whole-cell patch clamp and brain organoids derived from patient cells.

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 subordination and alterations in the inhibitory system in the prefrontal cortex.

We recently established this line of research dedicated to understanding how environmental triggers, such as early-life stress and immune insults, may impact the function of microglia during the maturation of neuronal circuits. We hypothesize that alterations in physiological microglial phenotypes in critical periods of circuit maturation may impair neuronal function in adulthood and underlie behavioral deficits reminiscent of neurodevelopment disorders. 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 subdivision 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 behavioral testing facility, implementation of brain slice electrophysiology and the training of several students and postdocs in this techniques. We have also implemented optogenetic manipulation and optogenetic behavioral 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 journal 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 an 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. Using these samples, we are generating and characterizing brain organoids to assess the impact of ASD-linked mutations.

Despite being one of 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 2020 we were able to attract funding from several sources, including FCT, Takeda, Bial Foundation and IBRO. Additionally, we published a few high impact papers, including in *Nature*, *Neuropsychopharmacology* and *Science Signalling*.

MITOCHONDRIA AND NEURODEGENERATIVE DISORDERS

Head: Ana Cristina Carvalho Rego

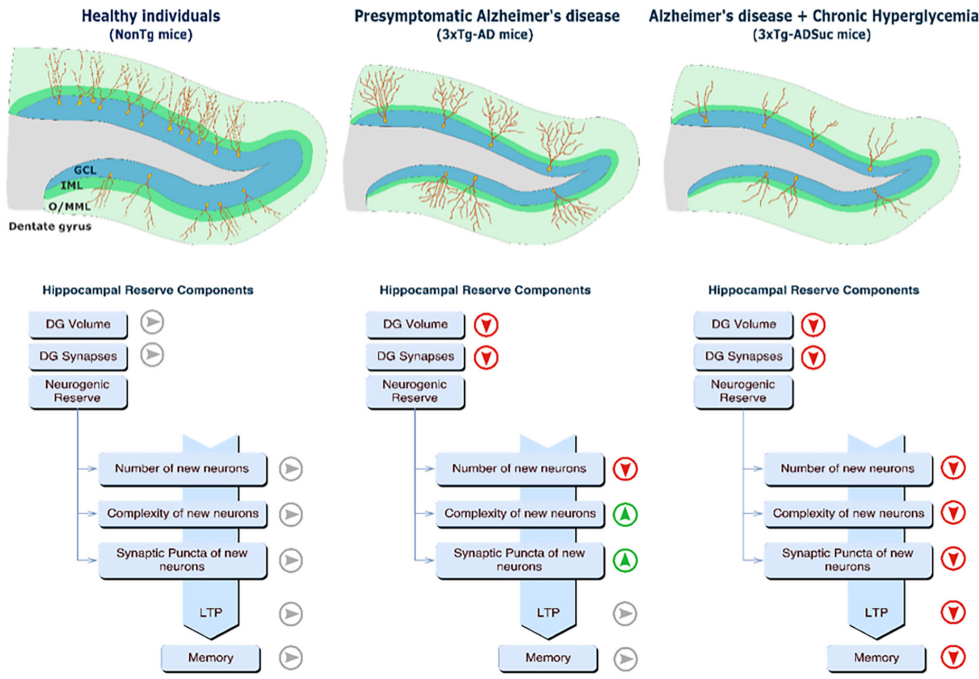
OBJECTIVES

The research group “Mitochondria and Neurodegenerative Disorders” aims to understand fundamental cell and molecular mechanisms in early stages of brain neurodegenerative disorders, namely in Huntington’s disease (HD) and Alzheimer’s disease (AD). These are chronic, debilitating, and age-related brain disorders, characterized by aggregation of misfolded proteins, early and selective brain neurodegeneration, exhibiting motor impairment and/or cognitive decline, and invariably leading to dementia. Misfolded proteins, due to posttranslational or oxidation modifications (among other processes) or pre-identified mutations, progressively 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 molecular, cellular, ex-vivo and in vivo/animal approaches, we aim to investigate early disease-related modifications affecting mitochondrial function and signaling processes linked to redox deregulation, glutamate postsynaptic dysfunction and/or modified neurogenesis in different models of neurodegenerative disorders and in peripheral human cells derived from patients and non-affected individuals. The last envisages a close interaction with neurologist at the local hospital. Identification of early disease mechanisms, involving early mitochondrial deregulation, are envisaged to uncover relevant molecular targets for therapeutic interventions. Therefore, the group aligns basic and potential translational research with a main interest in early disease stages, as well as investigation on neuroprotective therapies based on modifiers of mitochondrial function and dynamics or glutamatergic synapses using pharmacological compounds, modulation of protein expression and/or gene correction strategies.

In 2020 we focused our research in modulating adult hippocampal neurogenesis and verifying the influence of bacterial neurotoxin on the innate inflammatory response in AD models, and how mutant huntingtin (the protein affected in HD) elicits early features of mitochondrial dysfunction in human iPSC and NSC.

Thus, we investigated:

1. The impact of chronic hyperglycemia associated with type 2 diabetes on adult hippocampal neurogenesis and memory profile in AD mouse model; we showed that hyperglycemia evokes cellular and functional alterations that accelerate the onset of AD-related symptoms as memory impairment, which may impact on brain cognitive reserve.
2. The influence of microbial β -N-methylamino-L-alanine (BMAA) on mitochondrial function, innate immunity activation, and AD-like features in cortical neurons; we showed that alterations in mitochondrial metabolism and inflammation increased Tau phosphorylation and A β peptides production, two hallmarks of AD (collaborative study); and
3. Mitochondrial-based mechanisms in HD patient-derived induced pluripotent stem cells (iPSCs) and differentiated neural stem cells (NSC) and mito-phenotype rescue after CRISPR/Cas9 CAGs targeting of CAG repeat deletion.



Schematic representation of the detrimental effect of chronic hyperglycemia and Alzheimer's disease-related impairments on the hippocampal neurogenic reserve and memory.

Legend: DG, dentate gyrus; GCL, granular cell layer; IML, inner molecular layer; LTP, long term potentiation; O/ MML, outer and medial molecular layer. Hippocampal immature neurons are represented in brown.

In: Ferreiro et al., Neurobiol.Aging, 2020

MAIN ACHIEVEMENTS

In the context of Alzheimer's disease (AD) we assessed the impact of hyperglycemia on adult hippocampal neurogenesis and memory profile using the triple transgenic AD (3xTg-AD) mouse model (Ferreiro et al., 2020). During aging, lifestyle-related factors shape the brain's response to insults and modulate the progression of neurodegenerative pathologies such as AD. This is the case for chronic hyperglycemia associated with type 2 diabetes, which reduces the brain's ability to handle the neurodegenerative burden associated with AD. However, the mechanisms behind the effects of chronic hyperglycemia in the context of AD are not fully understood. In this study, we showed that newly generated neurons in the hippocampal dentate gyrus of 3xTg-AD mice presented increased dendritic arborization and a number of synaptic puncta, which could constitute a compensatory mechanism allowing the animals to cope with a lower neurogenesis rate. Contrariwise, chronic hyperglycemia decreased the complexity and differentiation of 3xTg-AD newborn neurons and reduced the levels of β -catenin, a key intrinsic modulator of neuronal maturation. Moreover, synaptic facilitation was depressed in hyperglycemic 3xTg-AD mice, accompanying the defective hippocampal-dependent memory. Our data suggested that hyperglycemia evokes cellular and functional alterations that accelerate

the onset of AD-related symptoms, namely memory impairment.

In collaboration with Dr. SM Cardoso, we showed how the microbial β -N-methylamino-L-alanine (BMAA), a bacterial neurotoxin, elicited mitochondrial dysfunction, innate immunity activation, and AD-like features in cortical neurons (Silva et al., 2020). BMAA is a neurotoxin produced by some microorganisms, namely cyanobacteria, previously detected in the brains of AD patients. Treatment with BMAA reduced O₂ consumption rates in isolated mitochondria and in primary cortical cultures, decreased mitochondrial potential and increased ROS production. The mitochondrial network was found to be fragmented, which resulted in cardiolipin exposure that stimulated inflammasome NLRP3, reinforced by decreased mitochondrial turnover, as indicated by increased p62 levels. BMAA treatment also activated neuronal extracellular TLR4 and intracellular TLR3, inducing p65 NF- κ B translocation into the nucleus and activating the transcription of NLRP3 and pro-IL-1 β . Increased caspase-1 activity resulted in elevated levels of mature IL-1 β . Of relevance, these alterations in mitochondrial metabolism and inflammation increased Tau phosphorylation and A β peptides production, two hallmarks of AD.

In Huntington's disease (HD) we studied mitochondrial and redox modifications in HD patient-derived induced pluripotent stem cells (iPSCs) (Lopes et al., 2020). In this study we thoroughly investigated mitochondrial-based mechanisms in HD-iPSC and differentiated neural stem cells (NSC) versus control cells, as well as in cells subjected to CRISPR/Cas9-CAG repeat deletion. We analyzed mitochondrial morphology, function and biogenesis, linked to exosomal release of mitochondrial components, glycolytic flux, ATP generation and cellular redox status. Mitochondria in HD cells exhibited round shape and fragmented morphology. Functionally, HD-iPSC and HD-NSC displayed lower mitochondrial respiration, exosomal release of cytochrome c, decreased ATP/ADP, reduced PGC-1 α and complex III subunit expression and activity, and were highly dependent on glycolysis, supported by pyruvate dehydrogenase (PDH) inactivation. HD-iPSC and HD-NSC mitochondria showed ATP synthase reversal and increased calcium retention. Enhanced mitochondrial ROS were also observed in HD-iPSC and HD-NSC, and decreased UCP2 mRNA levels. CRISPR/Cas9-CAG repeat deletion in HD-iPSC and derived HD-NSC ameliorated mitochondrial phenotypes. Thus, metabolic and mitochondrial dysfunction linked to transcriptional deregulation are early events in HD pathogenesis, which can be alleviated following CAG deletion.

VISION DISEASES

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Head: António Francisco Ambrósio

OBJECTIVES

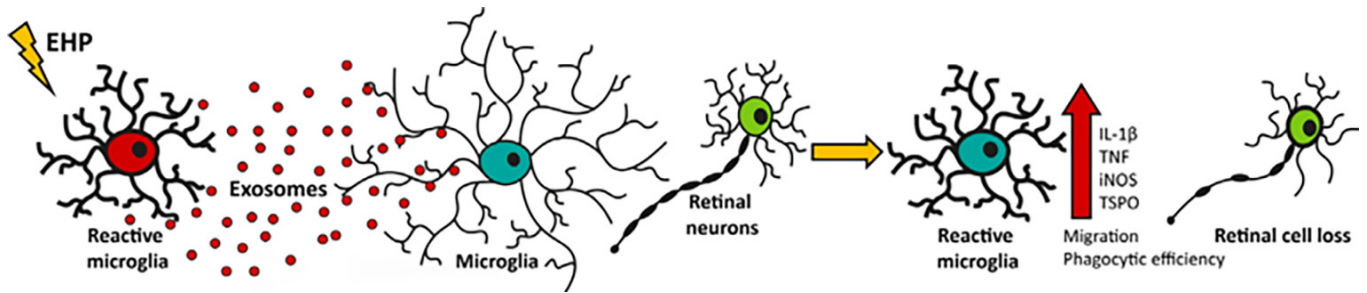
Retinal degenerative diseases, namely diabetic retinopathy, glaucoma and age-related macular degeneration (AMD) are our main research focus. The general goals are:

- 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.

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, exosomes, miRNAs and mitochondrial DNA, contribute to retinal neural, vascular and epithelial dysfunction and degeneration.

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. Moreover, we aim to identify tear fluid biomarkers for early detection and progression of diabetic retinopathy and biomarkers based on texture analysis of optical coherence tomography (OCT) retinal image data for the diagnosis of diabetic retinopathy and Alzheimer's disease. We have been also developing biodegradable intraocular implants and light sensitive nanoparticles for drug delivery systems.

We are also performing epidemiological studies to evaluate the incidence of AMD in the Portuguese population, namely the genetic characterization and association with structural alterations.



MAIN ACHIEVEMENTS

We demonstrated that exosomes derived from elevated pressure-induced reactive microglia amplify the inflammatory response in the retina (Aires, *Glia*, 2020).

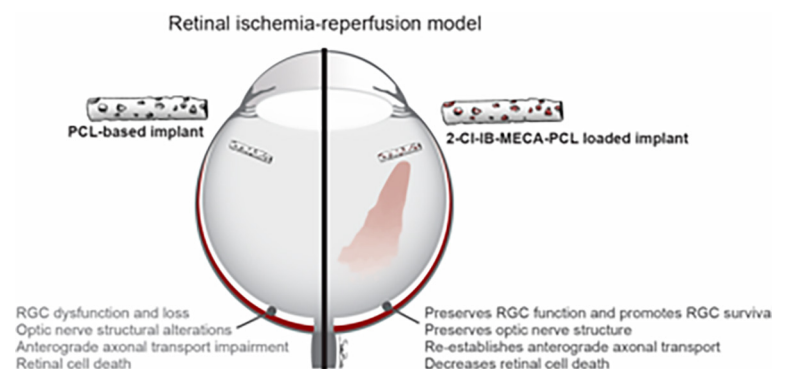
We identified adenosine A3 receptor (A3R) as a molecular target to afford protection to the retina. The activation of A3R protects retinal ganglion cells from degeneration induced by ocular hypertension and prevents microglia reactivity induced by elevated pressure, suggesting that A3R may be a therapeutic target for the treatment of glaucoma (Boia, *Cell Death Dis*, 2020; Ferreira-Silva, *Int J Mol Sci*, 2020).

We found that the loss of RhoA triggers microglia dysfunction disrupting neuronal physiology and leading to neurodegeneration (Socodato, *Cell Rep*, 2020).

We demonstrated that microglial cells are activated in the retina of a triple-transgenic Alzheimer's disease mouse model (3xTg-AD) (Salobar-García, *Int J Mol Sci*, 2020).

Using texture analysis of optical coherence tomography retinal images computed data we were able to identify retinal changes in different retinal layers in the 3xTg-AD mouse model (Ferreira, *Health and technology*, 2020).

We identified ocular biomarkers for risk of progression in diabetic retinopathy and evaluated the incidence of AMD in the Portuguese population.



BIOMARKERS IN NEUROPSYCHIATRIC DISORDERS: FROM MOLECULES TO DIAGNOSIS AND INTERVENTION

Head: Maria Isabel Santana

OBJECTIVES

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

- i) To investigate neuroinflammatory processes and blood-brain barrier dysfunction under the following conditions: psychostimulants abuse, attention-deficit/hyperactivity disorder, traumatic brain injury.
- ii) To pinpoint the role of lifestyle including physical exercise and drugs of abuse on brain health.
- iii) To assess the impact of maternal diabetes during development on offspring, with a focus on microglia cells and sex-specific alterations.
- iv) To study the role of peripheral immunity in Parkinson disease.
- v) To clarify the role of neuropeptide Y under several neuropathological conditions.

Regarding clinical studies, biomarker-based diagnosis and prognosis of neuropsychiatric disorders, as well as the study of their genetic components, are important areas of interest of our group.

During this year we have:

- i) Evaluated whether a poly-T polymorphism in the translocase of outer mitochondrial membrane 40 homolog (TOMM40) gene (TOMM40' 523) is associated with the risk and conversion time from Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD).
- ii) Participated in the study of the contribution of neuropsychological measures to predict time to conversion to dementia in patients with MCI due to AD
- iii) Been actively involved in Genetic Frontotemporal Dementia Initiative (GENFI), a multicentre cohort study of families with genetic frontotemporal dementia (FTD), with the objective of studying longitudinal biomarker trajectories in people with presymptomatic and symptomatic genetic FTD;
- iv) Investigated the potential of cerebrospinal fluid (CSF) lipocalin 2 (LCN2), a secreted glycoprotein that has been suggested as mediating neuronal damage in vascular brain injuries in the differential diagnosis of Vascular Dementia (VaD)
- v) Conducted a systematic review to (1) determine the overall frequency of delirium in older people undergoing noncardiac surgery; (2) explore factors explaining the variability of the estimates; and (3) determine the changing of the estimates over the past 2 decades.
- vi) Contributed to the development of a machine learning exploration framework concerning disease evolution in Multiple Sclerosis (MS), focused on predicting conversion from relapsing-remitting to secondary progressive course and disease severity with rapid accumulation of disability, concerning the 6th and 10th years of progression.
- vii) Investigated the different pathological and physiological repair mechanisms involved in blood-brain barrier (BBB) permeability through the different stages of ischemic stroke and their role in the development of hemorrhagic transformation (HT) and stroke recovery.

MAIN ACHIEVEMENTS

Results from the pre-clinical studies have shown that methamphetamine induces endothelial cell death and elicits the production of reactive oxygen species (ROS) by these cells, which were prevented by the activation of neuropeptide Y2 receptor (Y2R). In sum, with the present study we identified the NPY system, and particularly the Y2R subtype, as a promising target to protect against METH-induced neurovascular dysfunction. We have also demonstrated that maternal diabetes induces a delay in male and female offspring development and impacts offspring discrimination ability at memory test. Insulin treatment expedites offspring acquisition of developmental milestones while also inducing a hyper-ramification of hippocampal microglia. Moreover, we have shown that prenatal stress is determinant to stress resilience later in life, which is dependent on microglia morphologic plasticity and sex-specific.

Regarding clinical studies addressing conversion from MCI to AD, we have showed that lower performance in a test of non-verbal reasoning was associated with time to conversion to dementia, but we could not find any independent effect of TOMM40 poly-T on MCI to AD conversion since most of observed effects were due to Apolipoprotein (APOE)- ϵ 4 allele. In the multicentric GENFI study, the potential of neuronal pentraxin 2, a synapse-derived CSF marker; and plasma

glial fibrillary acidic protein, a marker of astrocytic activation, as promising progression markers of genetic FTD, was unveiled. In VaD, CSF LCN2 levels were significantly elevated compared to controls, other neurodegenerative dementias and cognitively unimpaired patients with cerebrovascular disease and neuropathological studies disclosed a high percentage of macrophages linked to subacute infarcts, reactive astrocytes, and damaged blood vessels in multi-infarct dementia when compared to AD.

Our studies on Delirium showed that postoperative delirium in noncardiac surgery has been increasing across the years, suggesting that more resources should be allocated to delirium prevention and management and also that type of anesthesia and preoperative cognitive status were significant moderators of delirium frequency.

The modeling study in MS demonstrated the possibility of predicting Multiple Sclerosis progression by using machine learning, and identified Expanded Disability Status Scale value, the majority of functional systems, affected functions during relapses, and age at onset as the most predictive features of disease progression.

Studies on BBB and stroke showed that BBB permeability seems to follow a multiphasic pattern throughout the different stroke stages associated with distinct biological substrates. In the

hyperacute stage, sudden hypoxia damages the BBB, leading to cytotoxic edema and increased permeability; in the acute stage, the neuroinflammatory response aggravates the BBB injury, leading to higher permeability and a consequent risk of HT that can be motivated by reperfusion therapy; in the subacute stage (1-3 weeks), repair mechanisms take place, especially neoangiogenesis. Immature vessels show leaky BBB, but this permeability has been associated with improved clinical recovery. In the chronic stage (>6 weeks), an increase of BBB restoration factors leads the barrier to start decreasing its permeability. Nonetheless, permeability will persist to some degree several weeks after injury.

RESEARCH ACTIVITY

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 for a more holistic understanding of cause-effect relationships between (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 area will work to understand those same mechanisms.

MAIN ACHIEVEMENTS

Despite being an atypical year due to the covid-19 pandemic, the MAD research line has provided several achievements during 2020. Several of its team members were in the frontline of the first pandemic wave, volunteering at the Clinical Analysis Lab of the University of Coimbra, specially restructured to allow SARS-CoV2 PCR detection and relieving the burden of the Coimbra Hospital and University Center; significantly processing and analysing very large amounts of samples. In terms of research outputs, the MAD area supplied important contributions to the study of mESC pluripotency regulation, cell quality control processes in embryonal carcinoma stem cells, disruption of cardiac circadian rhythms by anti-cancer agents, regulation of offspring intestinal immune system by maternal dietary exposure, to mycotoxins, development of novel potential therapies (including natural-based) against cancer, diabetes and its complications, non-alcoholic fatty liver, Parkinson, and Alzheimer diseases, the influence of the gut microbiota metabolites to neurotoxicity events, the role of ER-mitochondria communication and stress in human innate immune cells, the role of EHD-1 in gap

junction protein Cx43 lateralization in injured cardiomyocytes, the role Cx43 regarding the inter-cellular communication in cancer and cardiac diseases, identification of novel cellular and molecular mechanisms and human genome variability for new diagnostic/prognostic biomarkers in different tumors, the modulation of interactions between the microbiome, metabolome and immune system by dietary factors, the modeling of signaling kinetics of reactive oxygen species in vascular endothelial cells, the alterations in Nrf2 signaling activity and the associated mitochondrial dysfunction in the development of age-related disease processes, the cultural and linguistic validations of health outcomes measures into Portuguese, which were included in the repository of health measurement instruments validated in Portuguese (RIMAS), the role of protein glycation in diabetic complications, mechanisms of endothelial dysfunction in type-2-diabetes, mechanisms of neurotoxicity of environmental pollutants, including methylmercury, the strengthening of collaborative European networks in aging research, or the identification of relevant microbiome populations with relevance for environmental and health studies. A complete list of achievements is present in each group page. The global achievements of our area resulted in over 250 peer-reviewed scientific publications, as well as in a unique “from the bench to the clinical and to the industry” perspective.

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. 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. The MAD area also plans to increase its internationalization by multiple activities, including participating in research networks.

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MITOCHONDRIA, METABOLISM AND DISEASE

Head: Paulo Oliveira

OBJECTIVES

Since mitochondria are also active players in energy production, regulation of cell death, redox and calcium homeostasis, as well as in intermediate metabolism, the overarching objective of our group is to provide insights into the role of mitochondria in cellular metabolism, redox signaling, and stress responses associated with chemical toxicology, as well as on the pathophysiology of aging, lifestyle, and genetic diseases. The role of mitochondria in stem cell biology and 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:

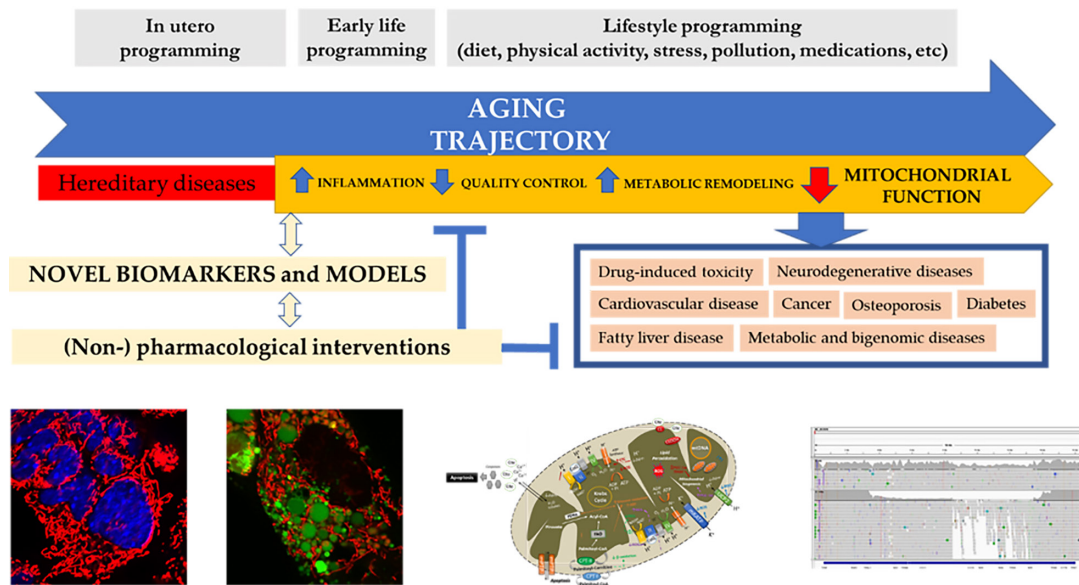
In this context, we investigated particular aspects of mitochondrial dysfunction in different conditions that are related to aging or incorrect lifestyles, including nonalcoholic fatty liver disease, diabetes, cardiovascular disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, cancer, or osteoporosis. We investigate how mitochondrial protective signaling pathways, metabolic remodeling, and oxidative stress are part of the pathophysiology of the different conditions above. Another objective is to 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) deletions 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 also 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 investigate 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

1 - We demonstrated mitochondrial and redox alterations in skin fibroblasts from sporadic Parkinson's disease (sPD) patients, uncovered when cells produce ATP mostly by oxidative phosphorylation. The results showed the relevance of using fibroblasts from sPD patients to study cellular and molecular changes characteristic of dopaminergic neurodegeneration and show that forcing mitochondrial ATP production uncovers hidden metabolic defects.

2 - We used a high-fat, high sugar dietary model of nonalcoholic fatty liver disease to demonstrate alterations in autophagic flux and increase the generation of reactive oxygen species at the peroxisomal level, contributing to mitochondrial degeneration and progress to steatohepatitis.

3 - We optimized a precise, simple, cost-effective microassay to measure catalase activity in small tissue samples and cell extracts with applications in different models of disease.

4 - We showed that P-cadherin, a poor prognostic factor in breast cancer, up-regulates carbon flux through the pentose phosphate pathway and decreases oxidative stress in matrix-detached breast cancer cells. These metabolic remodeling and antioxidant roles of P-cadherin can promote the survival of breast cancer cells in circulation and in metastatic sites.

5 - We compared cell quality control in P19 stem cells (P19SCs) before and after differentiation (P19dCs).

Differentiation of P19SCs resulted in alterations in cell survival and protein homeostasis parameters, including the redox system, cardiolipin, and lipid profiles, unfolded protein response ubiquitin-proteasome and lysosomal systems, and signaling pathways controlling cell growth. Our findings identified critical roles for the PI3K-AKT-MTOR pathway, as well as autophagic flux and apoptosis regulation in the maintenance of P19SCs pluripotency and differentiation potential. In the same subject, we found that 12R-hydroxy-bromosphaerol, extracted from red algae, specifically target cancer stem cells, and inhibit their formation in co-culture experiments in an IL-6 independent form.

6 - mtDNA copy number was evaluated in a Spanish population to assess its association with COVID19 symptoms severity. At the same time, a metabolic study carried out on drug addicts showed energy deficiencies and a decreased, although not statistically significant, mtDNA copy number in that group.

7 - Regarding the persistent cardiotoxicity of the anti-cancer agent doxorubicin (DOX), our results showed a delayed influence of DOX on gene expression, accompanied by changes in SIRT1-mediated cyclic deacetylation. The mechanism behind DOX interference included alterations of circadian-gene expression and increased BMALI

SIRT1-mediated deacetylation. We demonstrated that DOX treatment in juvenile mice disrupted oscillatory molecular mechanisms, including gene expression and acetylation profiles.

8 - We showed that vitamin A metabolite, retinoic acid (RA), regulates natural TCR $\alpha\beta$ Intraepithelial Lymphocytes (IEL) development and RA-regulated natural IELs are critical for gut protection against pathogen invasion. Thus, revealing that nutritional cues are essential for natural TCR $\alpha\beta$ IELs development and that these cells are required in host defense at early life.

9 - We showed that maternal dietary exposure to mycotoxins impacts offspring's intestinal immune system and leads to microbiota alterations.

10 - We showed RA is essential for iNKT lineage development by controlling proliferation and iNKT cell program in the thymus, while RA signaling-regulated iNKT cells prevented tumor growth. Our work establishes a novel metabolite-dependent pathway revealing new insights in iNKT cell biology.

12 - Our studies demonstrated that estradiol regulates osteoclast progenitors' differentiation through mitochondria complex I activity.

13 - We demonstrated that furan, a product of coffee beans roast, and its metabolic product, cis-2-butene-1,4-dial can cause toxicity on human hepatocytes for longer incubations.

METABOLIC CONTROL

Head: John Griffith Jones

OBJECTIVES

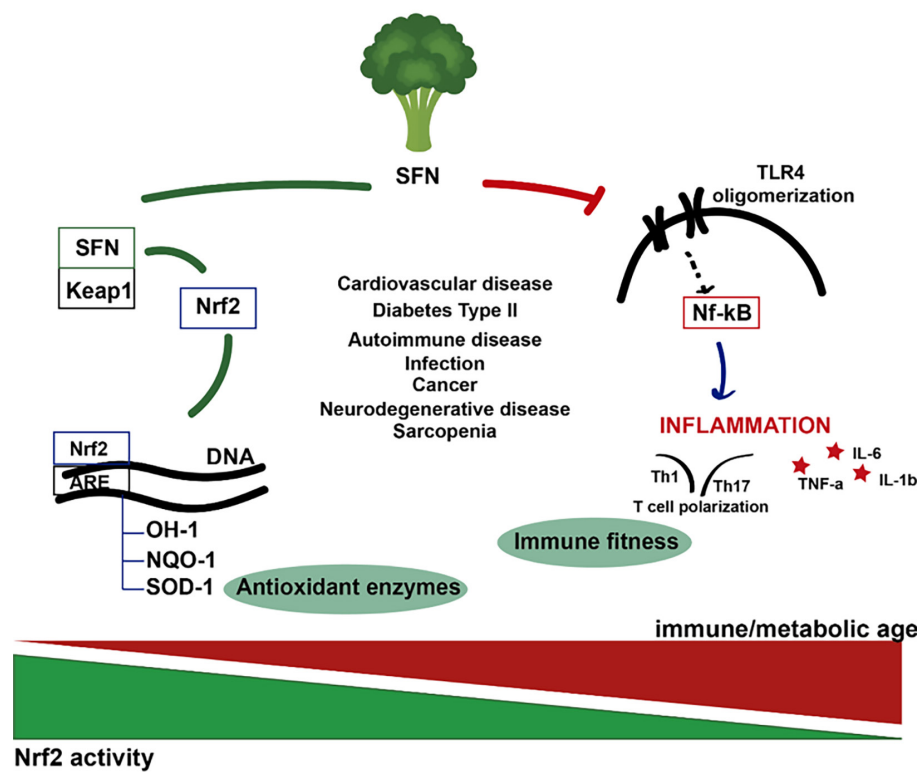
a) Developing ^{18}O -enriched water as a novel tracer of carbohydrate biosynthesis: Water enriched with oxygen- 18 (H_2^{18}O) is a potential tracer for evaluating the sources of glucose and glycogen synthesis since it is incorporated into specific sites of glucose-6-phosphate via specific enzyme-mediated exchange/addition mechanisms. Unlike deuterated water ($2\text{H}_2\text{O}$), ^{18}O does not experience significant isotope effects for any of these processes. Therefore, H_2^{18}O might provide more precise estimates of endogenous carbohydrate synthesis compared to $2\text{H}_2\text{O}$ provided that positional ^{18}O -enrichments of glucose or glycogen can be measured.

b) Relationship between nutrition and tissue mitochondrial function: Preliminary work suggests that overlapping mechanisms of metabolic dysregulation, including mitochondrial dysfunction, can impact cell and organ damage very early in life, much before symptoms can be measured, leading to several common diseases, including diabetes. Building on this work, I have begun to investigate whether nutrition may impact mitochondrial function and metabolism.

c) Organization principles of biochemical systems. The main goal of this research line is to discover, understand and exploit generic rules (organization principles) that (a) relate the design (i.e. naturally evolved molecular mechanisms) of biochemical systems to their function, and (b) hold across processes, cell types and organisms. We envisage that these network-structure / function relationships will play in biomedicine and bioengineering a role

analogous to that of QSAR in pharmacology. Objects of interest in our current research are metabolic networks, antioxidant defense and redox signaling. Our group has identified recurrent structural and functional motifs in all these biomolecular networks and derived design principles (relationships among kinetic parameters and component concentrations) that these motifs must fulfill so that they perform their function adequately. These predictions are thoroughly supported by experimental observations in a variety of organisms and permitted rationalizing the phenotypes of mutations and stress responses. We are working towards exploring translational implications of these design/function relationships in degenerative diseases. In parallel, we are developing novel experimental (fluxomics and synthetic biology) methodologies to determine critical parameters in these applications.

d) Computational tools for biomolecular systems. The main goal of this research line is to develop effective computational tools to simulate and analyze complex biomolecular systems and reaction networks. Namely, in support of the activities of the research lines described above. Developments range from fundamental computer-science methods that speed-up numerical computation in a broad range of computational biology applications, to tools for characterizing the relationship between design and performance of biomolecular reaction networks.



MAIN ACHIEVEMENTS

a) Proof-of-concept of metabolic ^{18}O enrichment of glucose-6-phosphate positions from H218O: H218O was incorporated into a well-characterized hemolysate model of sugar phosphate metabolism and ^{13}C NMR was applied to quantify positional ^{18}O -enrichment of glucose-6-phosphate oxygens. Human erythrocyte hemolysate preparations were incubated overnight at 37°C with a buffer containing sugar phosphate precursors and 20% ($n=5$) and 80% ($n=1$) H218O. ^{13}C NMR MAG spectra from hemolysate revealed resolved ^{18}O -shifted signals in positions 1-5. Mean ^{18}O enrichments were $16.4 \pm 1.6\%$ (P1), $13.3 \pm 1.3\%$ (P2), $4.1 \pm 1.1\%$ (P3), $12.6 \pm 0.8\%$ (P4), $10.7 \pm 1.4\%$ (P5), and no detectable enrichment of position 6. H218O is incorporated into positions 1-5 of glucose-6-phosphate in accordance with spontaneous aldose hydration and specific enzymatic reaction mechanisms. This provides a basis for its deployment as a tracer for glucose and glycogen biosynthesis.

b) Modulation of interactions between the microbiome, metabolome and immune system by dietary factors. Sulforaphane (SFN) exerts effects on aging, cancer prevention and

reducing insulin resistance. We have been able to show that SFN, a broccoli extract is able to prevent age-associated cardiac and muscular dysfunction through Nrf2 signaling in part by modulating the microbiome. Our studies in young and old mice revealed a significant drop in Nrf2 activity and mitochondrial functions, together with a loss of skeletal muscle and cardiac function in the old control mice compared to the younger age group. In the old mice, SFN restored Nrf2 activity, mitochondrial function, cardiac function, exercise capacity, glucose tolerance, and activation/differentiation of skeletal muscle satellite cells. Our results suggest that the age-associated decline in Nrf2 signaling activity and the associated mitochondrial dysfunction might be implicated in the development of age-related disease processes. Therefore, the restoration of Nrf2 activity and endogenous cytoprotective mechanisms by SFN may be a safe and effective strategy to protect against muscle and heart dysfunction due to aging.

c) Signaling kinetics of reactive oxygen species in vascular endothelial cells: In response to mechanical or other stimuli, vascular endothelial cells (EC) release superoxide ($\text{O}_2^{\bullet-}$) to the extracellular medium. Part of this $\text{O}_2^{\bullet-}$ is readily dismutated to hydrogen peroxide (H_2O_2), which is reabsorbed to the cellular cytosol, where it regulates multiple cellular processes. This extracellular loop in otherwise intracellular signaling pathways might assist intercellular coordination. But can $\text{O}_2^{\bullet-}/\text{H}_2\text{O}_2$ travel far enough in microcirculation for paracrine signaling? We addressed this question through a computational model that considered $\text{O}_2^{\bullet-}/\text{H}_2\text{O}_2$ release by EC and uptake by erythrocytes and EC, $\text{O}_2^{\bullet-}$ dismutation; $\text{O}_2^{\bullet-}/\text{H}_2\text{O}_2$ diffusion and transport by the blood flow. The results show that (i) signaling through $\text{O}_2^{\bullet-}/\text{H}_2\text{O}_2$ release to the circulation should be mostly autocrine in capillaries and mostly paracrine in arterioles; (ii) such signalling mechanisms must be sensitive to sub- μM extracellular H_2O_2 , which requires peroxiredoxins acting as H_2O_2 receptors.

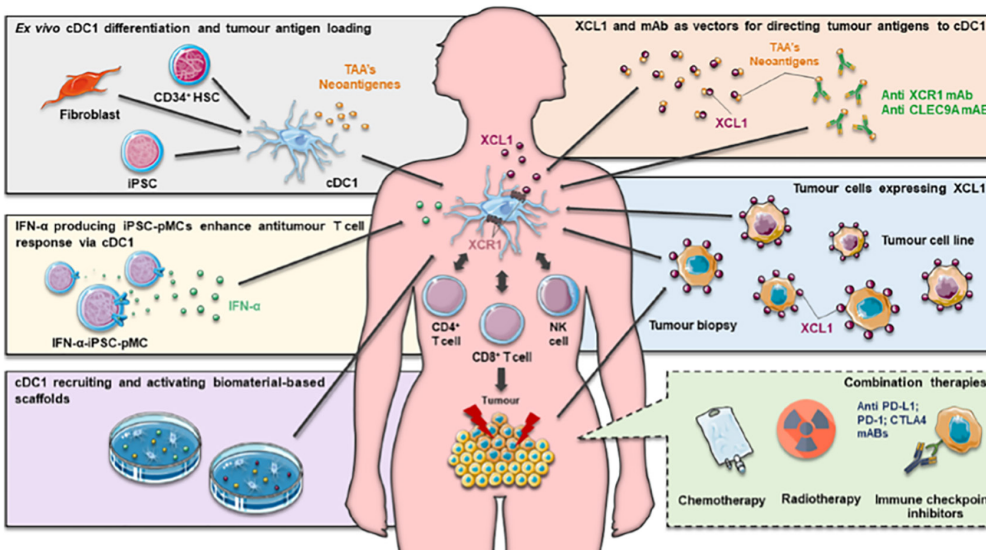
CELL SIGNALING AND METABOLISM IN DISEASES

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. The therapeutic potential of compounds obtained from Portuguese natural resources is another goal of our research group;
- 2) to develop a disease-modifying treatment for AD based on β -secretase (BACE)I inhibition;
- 3) to study the efficacy of repurposed drugs and non-pharmacological strategies in rodent models of AD;
- 4) to understand how mitochondrial damage-associated molecular patterns (DAMPs) trigger sterile pro-inflammatory responses that could drive AD and Parkinson's disease (PD) neurodegeneration;
- 5) to study the molecular mechanisms involved in peripheral and central inflammation with a special focus on macrophages and dendritic cells, aiming to: i) develop immunotherapy strategies based on dendritic cells for oncology; ii) screen anti-inflammatory drugs from natural endogenous resources; iii) develop non-animal approaches for immunotoxicity risk assessment.



Summary of current approaches exploring cDC1 in immunotherapy. Reproduced from (Calmeiro et al., 2020)

MAIN ACHIEVEMENTS

- We demonstrated that the APOE ϵ 4-TOMM40L haplotype increases the risk of mild cognitive impairment conversion to AD, by a mechanism that involves mitochondrial changes (Cardoso et al 2020).

- We developed new BACE1 chimeric peptide inhibitors that selectively prevent APP- β cleavage, decreasing A β 40/42 production and accumulation in AD models. These compounds showed to selectively inhibit APP- β cleavage while sparing the proteolysis of other BACE1 substrates. Thus, these compounds have the potential to be a disease-modifying therapy with minimal side effects.

- We demonstrated that PD and AD patients' mitochondrial pool triggers several pathogenic features observed in their brains, such as the generation of protein aggregates, microtubule disassembly, disruption of intracellular trafficking and accumulation of autophagosomes and autophagic substrates.

- We observed that NAD⁺ metabolism was altered in sporadic AD and PD patient-derived cells, contributing to SIRT-2 activation and subsequent decrease in acetylated- α -tubulin levels. Pharmacological inhibition of SIRT-2 deacetylase activity selectively enhanced α -tubulin acetylation and facilitated the trafficking and clearance of misfolded proteins. SIRT-2 knock-out mice neurons had no alteration in microtubule assembly after exposure to MPP⁺, allowing the maintenance of a normal autophagic flux. We provided strong evidence that mitochondrial deficit regulates SIRT-2 activation, thus controlling the functional ability of the autophagic system through acetylation

thereby highlighting the association between mitochondrial metabolism and neurodegeneration in sporadic AD and PD. We propose that SIRT-2 inhibition may improve microtubule assembly thus representing a valid approach as disease-modifying therapy.

- Since mitochondria are evolutionary descendants of alphaproteobacteria, we speculate that human gut microbiota may produce neuroactive toxins that target bacteria and, "collaterally", their endosymbiotic relatives, the mitochondria. Our results showed that certain bacterial neurotoxins alter mitochondrial function in cortical neurons. Additionally, a bacterial neurotoxin activated the inflammasome and induced the production of AD histopathologic features.

- We identified innovative molecules targeting the Nrf2 signaling pathway and concomitantly displaying anti-inflammatory properties with beneficial effects in AD cellular models. The potential therapeutic effect of those molecules is currently being validated using in vivo models of AD (Silva et al., 2020).

- Considering that AD and type 2 diabetes share several common features, we tested the efficacy of the antidiabetic drug liraglutide in mature AD female mice. We observed that liraglutide protects against brain A β 1-42 accumulation by partially rescuing oxidative/nitrosative stress and inflammation. Our results support the early use of liraglutide as a potential preventive/therapeutic agent against the accumulation of the first neuropathological features of AD (Duarte et al., 2020).

- Intermittent hypoxic conditioning (IHC) is a powerful non-pharmacological procedure known to enhance brain resilience. We observed that ICH rescues cognition and mitochondrial bioenergetic profile in a mouse model of AD. This study offers new insights to AD therapy and forces a reconsideration concerning the potential value of non-pharmacological interventions in clinical practice (Correia et al., 2021).

- We obtained evidence demonstrating that ER-mitochondria communication is involved in NLRP3 inflammasome activation under ER stress conditions 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) (Pereira et al, submitted). Furthermore, we have found that ER-mitochondria contacts are affected in fibroblasts obtained from BD patients and are associated with mitochondrial alterations (Marques et al, submitted).

- Our findings also support the bioactivity of Portuguese thermal waters from the Center region (Silva et al 2020a; Oliveira et al 2020a,b) as well as of forestry biomass (Oliveira et al 2020c).

- We evaluated the impact of different GMP serum-free media in the plasticity of dendritic cells for clinical use in cancer immunotherapy and we signaled the best one for this purpose (Calmeiro et al., 2021).

INSULIN RESISTANCE AND DIABETIC ANGIOPATHY

♦
Head: Flávio Reis

OBJECTIVES

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 are:

- 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

- Therapeutic strategies based on the modulation of the incretin GLP-1 are able to improve adipose tissue capillarization, insulin sensitivity and AGEs detoxification, as well as the evolution of microvascular diabetic complications (Pharmacol Res. 2020. doi: 10.1016/j.phrs.2020.105198);
- Perivascular adipose tissue of thoracic aortas presents a vasoconstriction phenotype that aggravates endothelial dysfunction through inflammation, oxidative stress and a reduction in antioxidant defence enzymes in a nonobese model of type 2 diabetes. Thoracic perivascular adipose tissue from diabetic animals exhibits macrophage infiltration thus explaining the proinflammatory phenotype (Free Radic Biol Med. 2020. doi: 10.1016/j.freeradbiomed.2019.11.002);
- Animal models of enhanced glycation and human type 2 diabetes share a striking similarity of cardiac phenotypic components and relation with metabolic changes, independently of fat content in the diet, which reinforces the role of glucose dysmetabolism in left ventricular dysfunction and provides a potentially useful approach for translational research in diabetes, in particular when testing new therapies early on during the natural history of this condition (J Diabetes Complications. 2020. doi: 10.1016/j.jdiacomp.2020.107554),
- The constituents of the aqueous extract of *Acrocomia aculeata* (Jacq.) Lodd. ex Mart. Leaves are able to upregulate Sirt1/NRF2 pathway, preventing oxidative stress in cellular and animal models (Oxid Med Cell Longev 2020. doi: 10.1155/2020/5238650);
- A rat model of high-fat and high-sugar-induced prediabetes can be a useful tool to study early features of diabetic nephropathy, namely crescent-like lesions, a premature signature that deserves in-depth elucidation (Nutrients. 2020. doi: 10.3390/nu12040881);
- Chronic blueberry supplementation challenges hepatic mitochondrial bioenergetics and elicits transcriptomics reprogramming in healthy Wistar rats. The beneficial or noxious consequences arising from this dietary trend should be carefully interpreted and claims future research (Pharmaceutics 2020. doi: 10.3390/pharmaceutics12111094).

BIOLOGY OF REPRODUCTION & STEM CELL

Head: João Ramalho-Santos

OBJECTIVES

A) Male infertility studies (PIs Sandra Amaral & Renata STavares)

A1) Searching for novel biomarkers in unknown origin male infertility (UOMI)

Clarify mechanism beyond UOMI [idiopathic (ID)/unexplained male infertility(UMI)], focusing on new aspects and suggest a biomarker that can be used to diagnose this infertility type, distinguish ID/UMI, and select better gametes. Influence of lifestyle and psychological factors will also be evaluated.

A2) The impact of anti-sperm antibodies on sperm function

Explain how antisperm antibodies impact sperm function/fertility, using an integrated approach. The analysis will be divided 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) Female infertility and fertility preservation (PIs Teresa Almeida-Santos & Ana Paula Sousa)

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 and therapeutic treatments to revert oocyte ageing. Use the knowledge about the role of age in fertility decline to develop prevention strategies to prevent the age related fertility decline.

C) Stem cell Biology (PI João Ramalho-Santos)

C1) Metabolic characterization of a novel pluripotent-paused state, induced by mTOR inhibition

Recreate a diapause-like state in cultured mESCs, through the inhibition of the mTOR pathway using INK-128, and to fully characterize this paused-like state from a metabolic standpoint.

C2) 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, through metabolic modulation, by culturing mESCs in a medium deprived of some specific amino acids.

C3) Inducing quiescent UC-MSCs through hypoxia

Achieve umbilical cord-mesenchymal stem cell (UC-MSC) cellular quiescence, through hypoxia modulation, by exposing cells to specific oxygen (O₂) levels, in order to improve survival, stemness and therapeutic function.

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

D1) Interdisciplinary studies on metabolism, communication and health promotion

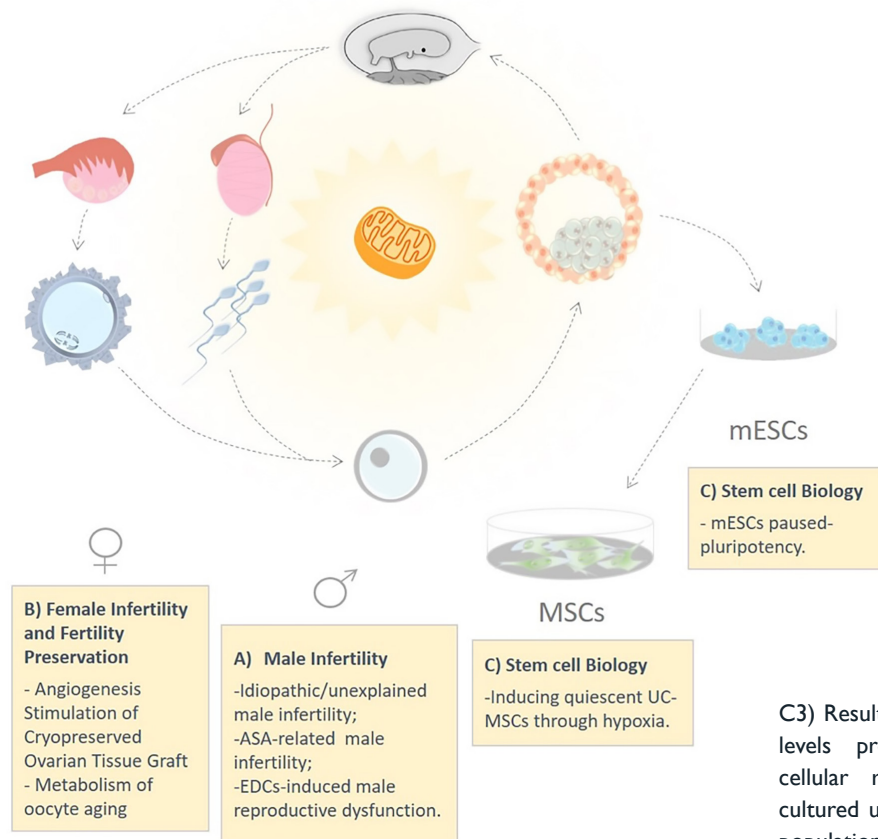
Explore how far comics/visual narratives can go in terms of communication and health promotion, joining biomedical, life/environmental and social sciences and humanities, and using both qualitative and qualitative approaches.

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

We aim to 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 diets and ecological sustainability.



MAIN ACHIEVEMENTS

A) Male infertility studies

A1) The ID group revealed a compromised function at several levels (viability, motility, morphology, acrosome integrity, capacitation, mitochondrial function). The proteomic analysis and the analysis of fertility outcomes is ongoing.

A2) The obtained results provide new information on the effects of ASA on sperm function, identifying new compromised aspects, such as capacitation, acrosome integrity and mitochondrial function. The molecular analysis to identify putative ASA-target proteins and sperm DNA genotyping is being started. The fertility outcomes of ASA patients will also be evaluated.

A3) Apart from capacitation and acrosome status, no differences were observed in other parameters and accessory glands function. Alone, neither As nor Hg exerted effects at environmental doses in vitro, but when combined, sperm viability, motility, mitochondrial function, capacitation and acrosome integrity were reduced. These pinpoint the need to reduce pollution herein, and monitor other places worldwide.

B) Female infertility and fertility preservation

B1) The preliminary 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) 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 H₂O₂ 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.

C) Stem cell Biology

C1) The results suggest that INK-128 can successfully induce a paused—like pluripotent state in naïve mESC in vitro culture, through cell cycle and metabolic modulation.

C2) The results obtained so far show that Leucine and Arginine withdrawal from mESC culture medium induces some of the features observed in paused-pluripotency, without affecting mESCs pluripotency status.

C3) Results show that different hypoxia levels promote different UC-MSCs cellular responses. While UC-MSCs cultured under 5% O₂ displayed higher population doubling than cells cultured in 21% O₂, UC-MSCs cultured under <1% presented a significant decrease in proliferation. Results also suggest that cells exposed to severe hypoxia present decreased biosynthesis.

D) Interdisciplinary studies on metabolism

D1) The involvement of patients, health providers, and researchers, from life sciences, biomedicine, psychology and sociology, resulted in new insights on NAFLD awareness within T2DM patients, and a baseline for creating a comic to raising awareness on NAFLD, and other non-communicable diseases, and health promotion.

D2) It was established 1) a *Pleurotus ostreatus* (PO) liquid culture with non-toxic concentration of zinc sulphate (ZnSO₄) to control growth and study metabolic pathways; and 2) a gastrointestinal tract (GIT) in vitro model with Caco-2 cells to study how Zn-PO interplays in GIT and liver in the scenario of high-fat diet and increased copper content.

D3) People-centred approaches highlight wider socioeconomic and natural environmental determinants reflecting health needs, expectations and capability. Cross-disciplinary research may also provide insights/innovation for more effective health-promoting changes in people and places.

MOLECULAR MECHANISMS OF CARDIOVASCULAR DISEASES

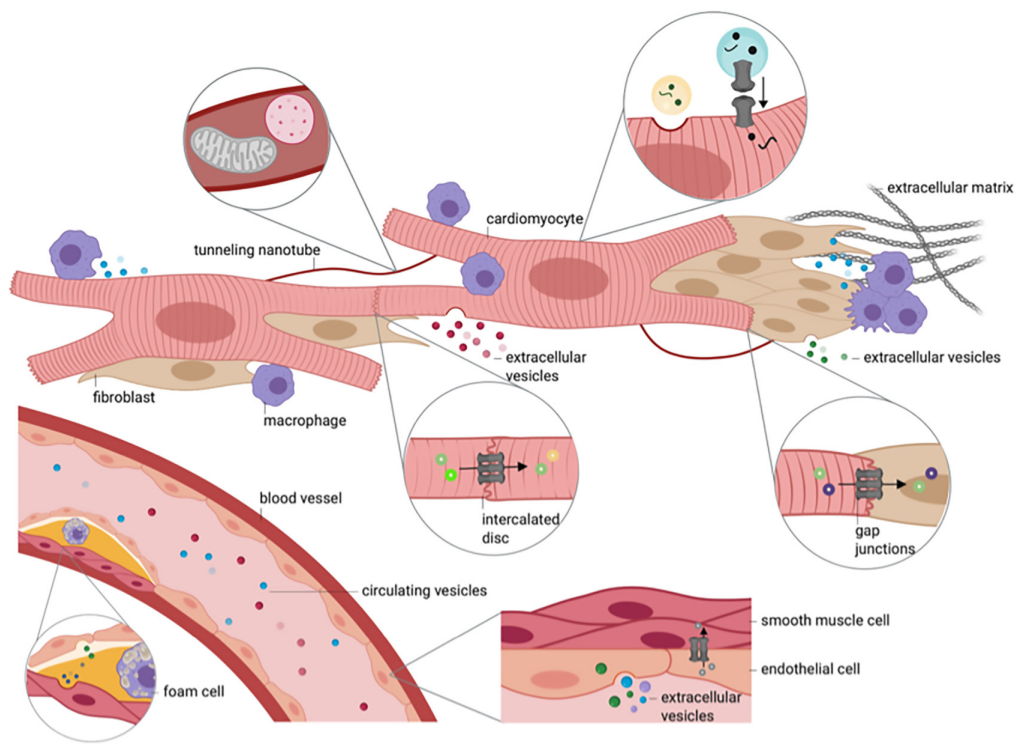
♦
Head: Henrique Girão

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

- . We unravelled the role of EHD-1 in gap junction protein Cx43 lateralization in injured cardiomyocytes
- . We established the molecular mechanisms and signalling pathways whereby Cx43 is incorporated into extracellular vesicles
- . We showed that ischemia modulates the sorting of Cx43 into extracellular vesicles secreted by cardiomyocytes
- . We demonstrated that the levels of Cx43 in circulation extracellular vesicles decrease after myocardial infarction, both in animal models and human beings
- . We established the presence of a LC3-interacting region (LIR) in Cx43 that mediates the interaction with LC3 and GABARAP without the need of ubiquitination and the autophagy adaptor p62
- . We unveiled the role of Cx43 in the formation of Tunneling Nanotube (TNT) between cancer cells
- . We demonstrated that ischemia induces the formation of TNT between cardiac cells
- . We disclosed the impact of elevated pressure on extracellular vesicles-mediated communication between microglia and retinal cells underlying inflammation propagation

MICROBIOMES, METABOLISM AND OMICS

Head: Conceição Egas

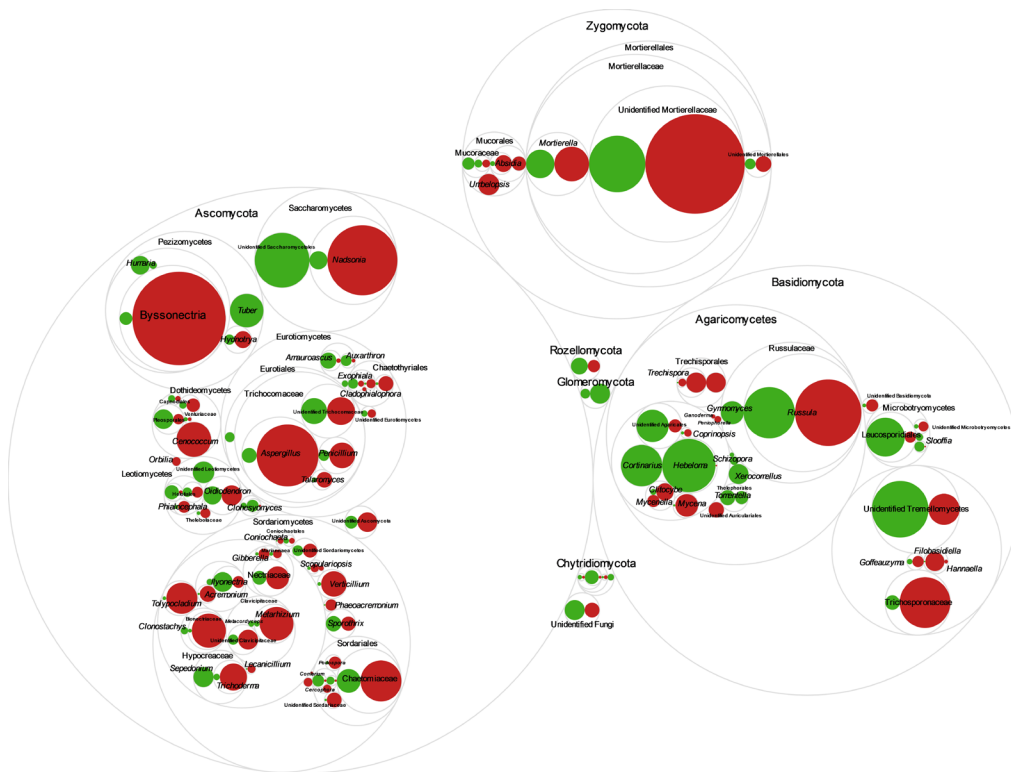
OBJECTIVES

Microbiomics, the genomic study of a population of microbes, is a recent field propelled by the rapid evolution of high-throughput sequencing. Microbiomics facilitates the study of the diversity and the role of microorganisms in diverse habitats. The study of microbial communities associated with hosts has received attention by the recognition of the important role of microbes in host development, homeostasis and the pathophysiology of chronic diseases including type 2 diabetes or non-alcoholic fatty liver disease.

The Advanced Microbiomics group takes advantage of the accumulated know-how in the field of bacterial genome sequencing, microbial community profiling (structure and dynamics) and metagenomics of the PI and her team and the available high-throughput DNA sequencing and HPC infrastructures at CIBB to address the following 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

The Microbiomes, metabolism and omics group established the baseline evidence for a role of the rhizosphere microbiome in acute tree decline (AOD). The study identified this microbial community as having an important role in health and decline in trees, contributing for the holobiont concept of plants, where microbes and trees interact to maintain homeostasis and health and paves the way to detailed identification studies on correlations between microorganisms and plants, mechanisms of interaction between the microbiome and the host, and disease biomarkers. Acidic pH was identified as a chemical marker for AOD, and several bacteria and fungi were found more abundant in the healthier trees, such as Acidobacteria of the subdivision 6, Chloroacidobacteria, members of the Nitrospirae phylum and N-sensitive ectomycorrhizal fungi. (Research objective 1, paper “Pinho D, Barroso C, Froufe H, Brown N, Vanguelova E; Egas C, Denman S. (2020) Linking tree health, rhizosphere physicochemical properties, and microbiome in acute oak decline. *Forests*. 11, 1153. doi:10.3390/f11111153”).

On the other hand, the study of extreme environments, such as hot springs, evidenced the presence of new genes encoding for enzymes with

biotechnology application, highlighting the huge potential of these environments for the discovery of new genes and functions. The functional metagenomes of the Portuguese springs, Chaves and S. Pedro do Sul, were analysed to identify genes involved in the biosynthesis of compatible solutes. These osmolytes are known for their protein and structure stabilizing activities and play important roles in cosmetics, food and health industries. In Chaves hot spring, several genes were identified for the synthesis of trehalose, mannosylglucosylglycerate and glucosylglycerate in microorganisms where these osmolytes have not yet been described, increasing the sequence space available to improve the biotechnology use of these important enzymes (Research objective 3). The study of the extreme environments also led to the identification of new microorganisms using taxonogenomics. The collaboration with other research groups in the research line of CNC and from other research institutions resulted in two research study publications (doi:10.1007/s00204-019-02626-z, doi:10.1016/j.syapm.2020.126083). The work developed by the group resulted in a total of 14 publications, 6 papers in peer-reviewed journals and 8 book chapters.

In 2020, the group has been involved in 8 projects with a budget of 120.000€. The projects are of several types and funding typologies: 1) two H2020 projects, Metafluidics: Advanced toolbox for rapid and cost-effective functional metagenomic screening - microbiology meets microfluidics, no. 685474 and 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-pine wood 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) one P2020 project: In2Genome - Integrative approach in the diagnosis of genetic diseases, no. 17800, and a 5) RNIE infrastructure: GenomePT, no. 01/SAICT/2016.

HUMAN GENOME VARIATION AND ENVIRONMENT IN HEALTH AND DISEASE

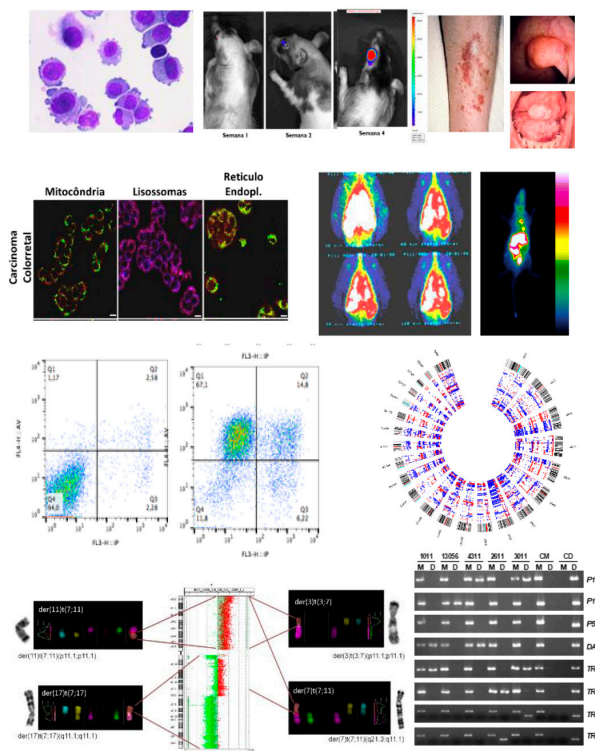
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Head: Isabel Marques Carreira

OBJECTIVES

- 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 copy number alterations and methylation status to characterize basal cell carcinoma samples (Cardoso JC et al 2020) and primary upper aerodigestive tract carcinoma (Ribeiro et al 2020) - Establishment of a proteomic signature between head and neck cancer patients with and without relapses or metastases (Ribeiro IP et al 2020) - Development of a method for the determination of copy number alterations based on segmented individual genomic profiles to establish disease profiles (Esteves L et al 2020) - Genotype – phenotype correlation in patients with intellectual disability and dysmorphisms by array-CGH detection of Copy Number Variants and delineation of critical genomic regions (Ferreira SI et al 2020) - Identification of cryptic rearrangements in patients with B-cell acute lymphoblastic leukemia by cytogenetic, molecular cytogenetic and array-CGH characterization of (Othman MAK et al 2020, Wafa A et al 2020) - Tyrosine kinase inhibitors (TKI), have an impact on immune system and when combined with IFN- α appears to be associated with increased immunosuppression (Alves R et al, 2020) - Acute myeloid leukemia cell lines reprogram their metabolism in order to overcome OXPHOS inhibition suggesting that glycolysis may be a

better therapeutic target in this kind of hematological neoplasias (Lapa B et al, 2020). - Blood-based specimens may be a potential source of non-invasive DNA methylation cancer biomarkers. Our results suggest that DNA methylation patterns measured in peripheral blood may have great potential as informative biomarkers of myelodysplastic syndromes (Jorge J et al, 2020). - Pladienolide B is a splicing inhibitor that showed high antitumor activity against erythroleukemia cell lines, being the cytotoxic effect independent of the spliceosome mutations syndromes (Jorge J et al, 2020). - In patient-derived bladder tumor specimens cultured ex vivo and bladder cancer cell lines with different photodynamic therapy (PDT) sensitivities, was found that the galactose-photosensitizer accumulates in bladder tumors expressing galactose-binding proteins. PDT sensitivity is correlated with caveolin-1 expression that increased the amount of GLUT1 at the cell membrane. (Parada B et al, 2020) - Dendritic cell (DC) phenotype and the capacity to activate autologous natural killer cells and to prime antigen-specific CD8+ T cells, are strongly influenced by the good manufacturing practice of serum-free media used during DC differentiation and correlate with evoked metabolic status. (Gomes C et al, 2020)

- The desmoplastic growth pattern of gastric carcinoma liver metastases is associated with improved outcomes and is an independent prognostic factor after hepatectomy in these tumors. (Cipriano MA et al, 2020) - The phospholipidome of patients with liver cancer was significantly modified after the tumor resection procedure. It was found an upregulation of some phosphatidylcholine and choline plasmalogens, and/or 1-O-alkyl-2-acylglycerophosphocholine in patients with liver cancer at T0 compared to the controls, and a downregulation after tumor resection. (Mart n-Sierra C et al, 2020) - An altered functional competence of monocyte subsets in hepatocellular carcinoma (HCC) and cholangiocarcinoma patients was found. In addition, the elevated serum levels of TNF α in G3-G4 compared to G1-G2 HCC patients point to a potential role of TNF α as a prognostic peripheral biomarker in HCC patients (Mart n-Sierra C et al, 2020) - The presence of Natrium-iodide symporter (NIS) in cholangiocarcinoma cell lines is crucial for the decreased cell viability and survival observed following the exposure of cholangiocarcinoma cells to I311. (Brito AF et al, 2020) - In vivo studies using a A375 melanoma mouse model, proved the extraordinary properties of the Pt(II) 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-fused chlorin as a luminescent probe having the ability to impair tumor growth, making image guided treatment and follow up a possibility (Laranjo M et al)

HEALTHY LIVING AND ACTIVE AGEING

♦
Head: João Malva

OBJECTIVES

The main objectives of Healthy Living and Active Ageing group for the reporting period included:

- To develop successfully one FCT-funded project (Mercumemory)
- To develop successfully the ERA Chair project (ERA@UC)
- To develop successfully EIT Health-funded projects, including EIT Health Healthyloneliness and EIT Health Ageing PhD School
- Develop contact with older people and interaction with the community and society on aging
- To deliver new publications to reinforce the impact of Mercumemory
- To secure new funded projects for 2021



ENVELHECIMENTO: ALÉM DA JUVENTUDE



João O. Malva, Investigador Coordenador na Faculdade de Medicina da Universidade de Coimbra



Shutterstock

MAIN ACHIEVEMENTS

In spite of Covid-19 the research group could achieve the main expected deliverables.

*Mercurumemory – We could reinforce the experimental work to further clarify the impact of methylmercury in neuroinflammatory response using microglial cell lines (BV2 and N9) as well as the effect of methylmercury in cell viability of neural stem cells using CB152 cell line. Related with this work, the research team could publish two manuscripts related with the neurotoxic effect of methylmercury and the neural stem cell niches. This work has been further reinforced by submitting two book chapters, both in collaboration with our collaborators in Fortaleza (Universidade Federal do Ceará).

*The implementation of EIT Health PhD School (first year of full program) has been highly successful. We could recruit 25 students eligible

to receive the EIT Label Certificate as a supplement to the PhD Diploma. The PhD School organized a portfolio of educational activities including Advanced Courses, Innovation and Entrepreneurship Activities and Mobility Schemes. The PhD School also organized a successful Annual Retreat with high-level scientific, pedagogic and entrepreneurial program. In 2020, the PhD School (coordinated by our research group) joined 12 European Universities and additional 6 Hospitals, Research Centers and Business Incubators).

*Our research group developed a new interdisciplinary tool (online questionnaire) to evaluate the impact of Covid-19 related loneliness in physical and psychological/social health in older adults. The innovative tool combines 12 different dimensions including health/medication, sleep,

food, physical activity, social support, literacy, digital literacy, among others. We collected 830 complete responses and plan to treat the results and publish data in 2021.

*Our team is also promoting the participation of the elderly population in the construction or strengthening of inclusive communities, helping to identify different types of needs and daily constraints of the elderly (physical, socio-emotional, cultural, etc)

We could successfully secure a new EIT Health funded project to continue the coordination of EIT Health PhD School in 2021 and a new ERASMUS+ project to continue the collaborative work started in EIT Health funded project Healthyloneliness.

HEALTH, MANAGEMENT AND ECONOMICS

Head: Pedro Ferreira

OBJECTIVES

The CEISUC researchers of the CIBB's research area Metabolism, Ageing & Disease aim at developing transdisciplinary research in the area of health systems and services, in particular in the Portuguese. Their activity also include participation in graduate programmes and national and international research networks.

Their main objectives are to contribute to the development of the field of applied health economics and research in health systems/ services.

The main research areas are (i) health systems, (ii) health value, (iii) people in health, and (iv) health trajectories.

In the 'health systems' research area, we address the global governance of the system, including the analysis of the definition of evidence-based health policies, through a comprehensive and rigorous analysis of the dynamics of the health system in Portugal, the new governance models for primary care and hospitals, the reconciliation of economic priorities with psychological well-being in health organizations, the assessment of equity in access to health services, as well as the monitoring of systems auditing.

In the 'value in health' research area, we share the idea that the main mission of health care is to achieve the greatest value for patients, while aiming at better sustainability of the health system. This area deals with the value that individuals attribute to the various health states through utility measures based on preference and through measures of effectiveness and health status/quality of life. However, in order to be administered, these measures must be culturally adapted and validated for the Portuguese language and culture. Thus, CEISUC maintains a project called RIMAS aimed at analyzing methodological issues in the assessment of quality of life and to constitute itself as a repository of health measurement instruments validated in Portuguese.

The research area 'people in health' addresses the human component of healthcare providers, including communities, users, informal and formal carers. Attention is increasingly being paid to how care users are involved in this same care. The immense literature on interaction between health systems and their beneficiaries allows us to outline a classification of numerous initiatives and mechanisms for the empowerment and involvement of citizens in the following three types: citizen participation, public consultation and public information. Satisfaction studies are included in the second of these items.

Finally, the research area 'trajectories in health' faces health over time by people, families or communities. It is assumed that the health of individuals is also dependent on the physical, social and economic environments to which they are exposed. At the same time, in Europe, there is also a growing need for end-of-life care and a definition of research priorities in this area of health and clinical practice.

These four research areas are reflected in several working groups. To achieve the general objective mentioned above, the CEISUC researchers of the CIBB's research area Metabolism, Ageing & Disease have the following strategies: carry out research projects, particularly with other CIBB colleagues and disseminate its results in prestigious international journals and conferences; be responsible or participate in national and international research projects and networks aimed at better knowing the reality of health in Portugal; host and support scientific meetings to discuss economic issues relevant to health; train human resources in this area of science; and cooperate with government agencies and other public and private organizations in the research of evidence for better health governance and decision making.

MAIN ACHIEVEMENTS

Because of the pandemic situation caused by the Covid-19, there was a significant decrease in research activities, in particular in research projects and in the organization and participation in conferences.

In fact, in the 'health systems' research area, the leadership of the Portuguese Observatory on Health Systems was also affected and no Spring Report was published this year. However, we initiated the leadership of the project 'CuidIn - Support and care for the informal caregiver', funded by the European Union POISE program, together with the Center for Studies and Development of Continuous and Palliative Care of the Faculty of Medicine of the University of Coimbra, with support from the Municipality of Cantanhede and Biocant. We also finished a project to create the health profile Figueira da Foz Municipality.

Regarding the research area 'value in health', we performed several cultural and linguistic validations of health outcomes measures into Portuguese, which were included in the repository of health measurement instruments validated in Portuguese (RIMAS).

In the research area 'people in health', we initiated some studies to assess satisfaction on health organizations, such as (i) users and professionals of the University of Coimbra Hospital; (ii) professionals of the Northern Regional Health Authority in central departments and primary health care units; and (iii) professionals of the Rehabilitation Medicine Center of the Central Region-Rovisco Pais. We also were involved in the measurement of health literacy levels of higher education community, within the National Academic Health Literacy Network, as well as in the project to assess literacy, empowerment and quality of life of diabetic individuals.

At last, in the research area 'trajectories in health' we initiated the project 'Health and Wellness - Impact of Covid-19' funded by the LaCaixa Foundation. We also led the Cost-effectiveness HTA Task Force (Subgroup 4) of the WG1 Prevention and treatment strategies for perinatal depression of the project 'Research Innovation and Sustainable Pan-European Network in Peripartum Depression Disorder' (Riseup-PPD) (CA18138).

During 2020, the CEISUC researchers of the CIBB's research area Metabolism, Ageing & Disease published 78 papers in peer reviewed journals and 5 papers in other international or national publications. They were also advisers in 13 PhD completed thesis and in 49 MSc completed thesis

RESEARCH ACTIVITY

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) to find drugs able to eradicate fungal and bacterial infections with a focus on yeasts and filamentous fungi affecting the respiratory system and the skin, (ii) to understand how purinergic metabolism and adenosine A2A receptors can be modulated to ameliorate pathological conditions of the elderly such as chronic inflammation of the gut, (iii) to investigate novel mechanisms for recycling and replication of polymethylated mycobacterial polysaccharides, (iv) to unravel the mechanisms by which chronic exposure to a dietary microbial neurotoxin may drive mitochondrial dysfunction, activation of neuronal innate immune responses, and neurodegenerative processes across the gut-brain axis in Parkinson's disease, (v) to identify microRNAs that regulate infection in the context of Salmonella Typhimurium and Shigella flexneri, (vi) to understand the mechanisms of disease and pathogenicity in the context of infection by Rickettsia, for future development of new biological drugs], neurosciences [(i) establishment of models of brain disease; (ii) study of disease mechanisms and (iii) 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 tumors], regenerative medicine [(i) to find miRNAs able to control cardiac fibrosis, (ii) to develop stem cell-based assays and in silico approaches for drug screening, (iii) to develop novel therapeutic compounds identified from high-throughput approaches using nanotechnology-based non-viral

vectors, (iv) to understand at the molecular level how hematopoietic cellular identities are specified employing cellular reprogramming and 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] and cancer [(i) to develop nanosystems for small drugs and nucleic acid delivery in the context of cancer; (ii) to identify and validate target proteins overexpressed in tumors, combined with the demonstration of their importance for the tumorigenic process].

Members of the Innovative Therapies thematic line were successful in attracting funding for the launching of a Collaborative Laboratory in Ageing (Colab4Ageing). The strategic vision of the Collaborative Laboratory, having CIBB as associated research center, is to enhance cooperation between companies, University of Coimbra, a technological interface center (IPN), hospitals (CHUC and IPO), primary care and social providers (Caritas and InfoSaude) and Municipalities in order to establish an integrated platform in the area of healthy ageing. The CoLab core activities will be dedicated to develop, test and implement innovative products and services on the following areas: (a) healthy ageing, (b) multimorbidities, (c) palliative care, and (d) brain dementias. In addition, members have initiated several projects to study (e.g. quantifying the SARS-CoV2 in indoors environments, especially in health care facilities) and control the SARS-CoV2 pandemic situation. Remarkably, the groups of the thematic strand published more than 100 peer-reviewed publications in 2020

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

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 Artur Rodrigues (PhD)
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 Henrique Almeida (PhD)
 Hugo Fernandes (PhD)
 Luís Estronca (PhD)
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 Ricardo Neves (PhD)
 Sérgio Sousa (MD, PhD)
 Sónia Pinho (PhD)
 Susana Rosa (PhD)
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 Deolinda Santinha (PhD Student)
 Helena Aires (PhD Student)
 Inês Ribeiro (PhD Student)
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Tumor Microenvironment and Targeted Therapies

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Cell Reprogramming and Developmental Hematopoiesis

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 Gabriela Silva (PhD)
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 Pedro Fernandes (PhD Student)
 Sara Moura (PhD Student)
 Tiago Lima (PhD Student)
 Ágata Lourenço (Grant Technician)
 Daniela Alho (Collaborator)
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Molecular Biotechnology and Protein Engineering

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 Carlos Faro (PhD)
 Euclides Pires (PhD)
 Paula Veríssimo (PhD)
 Pedro Curto (PhD)
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 Mariana Bexiga (PhD)
 Ricardo Silva (PhD Student)
 Flávia Rodrigues (PhD Student)

RNA & Infection

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Laura Alcântara	(PhD)
Inês Lopes	(PhD Student)
Jane Dias	(PhD Student)
Susana Costa	(PhD Student)

Molecular Microbiology and Microbiome

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John D. Marugg	(PhD)
Susana Alarico	(PhD)
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Inês Roxo	(PhD Student)
Ana Rita Fonseca	(Volunteer)
Sara Gonçalves	(Volunteer)

Medical Microbiology

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Célia Nogueira	(PhD)
Chantal Fernandes	(PhD)
Lisa Rodrigues	(PhD)
Marta Mota	(PhD Student)
Pedro Valada	(PhD Student)
Patrícia Diogo	(MD, PhD)
Gil Lopes	(MD)
José Baptista	(MD)
Rui Soares	(MD)
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Ana C. Almeida	(Student)
Daniela Calheiros	(Student)
Joana Oliveira	(Student)
Maria João Santos	(Student)
Rita Domingues	(Student)
Jorge Lindo	(Volunteer)
Mariana Almeida	(Volunteer)

ADVANCED THERAPIES

♦
Head: Lino Ferreira

OBJECTIVES

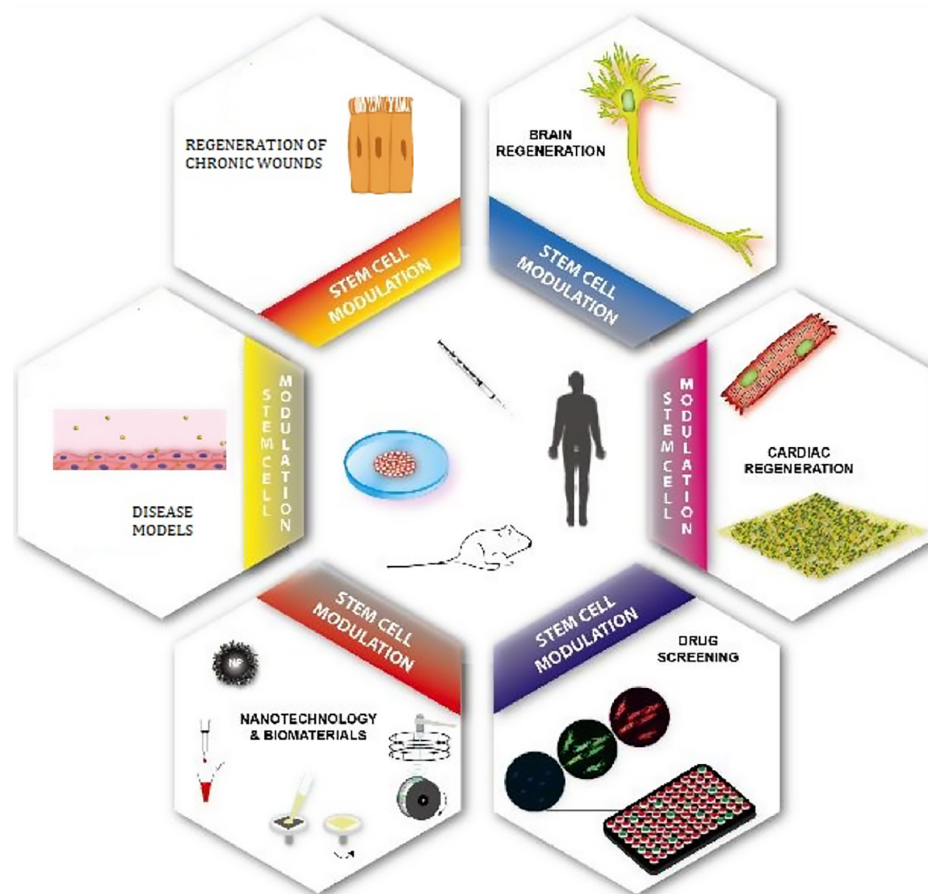
The main scientific objectives of the group are: (i) to use stem cell-based therapies for the treatment of ischemic diseases, (ii) to develop innovative strategies for cell reprogramming, (iii) to implement stem cell-based assays and in silico approaches for drug screening and (iv) to deliver novel therapeutic 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 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 2020 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 have generated a human in vitro model of ageing based on iPSC cells derived from patients with Progeria and we have studied the reasons of Progeria-smooth muscle cells vulnerability using iPSCs obtained from Progeria fibroblast patients, showing that the process is mediated by an upregulation of metalloprotease-13 (Pitrez et al, Nature Communications 2020).

We have successfully synthesized a light-activatable nanoparticle (NP) library and that some NPs can be used for controlled release of non-coding RNAs with higher efficiency (up to 500%) than commercially available lipofectamine in gene-knockdown activity (Blersch et al, Angew Chem Int Ed 2020), and the NPs showed to be very effective in the release of siRNA and miRNA. Light-activatable NPs offer a new strategy to topically deliver non-coding RNAs.

We have shown that small extracellular vesicles (SEVs) can be efficiently modulated with miRNAs of interest (we showed proof-of-concept using pro survival miRNAs, identified by the group using high-throughput screening strategies). Moreover, we showed that the miRNA-modulated sEVs were efficient delivery systems both in vitro as well as in vivo (using a mouse

model of diabetic wound healing) (manuscript submitted). We are currently exploring new strategies to modulate the sEVs cargo/surface with the final goal of developing a translational drug-delivery platform capable of playing a key role in Regenerative Medicine at large.

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.

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. 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 transverse 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 2020.

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

MAIN ACHIEVEMENTS

Regarding neurodegenerative diseases, we have generated lentiviral and adeno-associated viral vectors to study their pathogenesis focusing on Machado-Joseph disease/spinocerebellar ataxia type 3 (MJD). Development of lentiviral-based in vivo models of MJD, in which we are experts, allowed fruitful investigation of disease-modifying strategies involving gene silencing, interaction of ataxia-related proteins, autophagy activation, proteolysis inhibition and neural stem cell transplantation.

Regarding non-viral-mediated gene delivery, an extensive screening of a variety of cell penetrating peptides and for their capacity to generate efficient nucleic acid delivery systems has been carried out and structure-activity relationships have been successfully established. The introduction of chemical modifications in the structure of the S413-PV peptide, involving acylation (lauroyl group) and addition of five histidines to the N-terminus, remarkably improved its competence to carry siRNAs into glioblastoma cells.

A miRNA-based therapy addressing GBM cancer stem-like cells (GSCs) to tackle human GBM was successfully developed. In this regard, the modulation of the dysregulated levels of miR-128 and miR-302a, which are implicated in tumor progression, promoted GSC differentiation and sensitization to multiple tyrosine kinase inhibitors (MTKIs), impairing GSC proliferation through a senescence-associated mechanism. Combination of MTKIs with modulation of membrane lipid

composition of GBM cells, through the silencing of key enzymes of lipid metabolism, such as glucosylceramide synthase (GCS) and stearoyl-coA desaturase I (SCD1), also showed to be a highly promising therapeutic approach towards GBM. Thus, downregulation of GCS promoted alterations in the relative proportions of ceramide and ceramide glucosyl-derivatives and enhanced GBM cell sensitivity to axitinib, whereas SCD1 silencing promoted alterations both in the saturated to unsaturated fatty acids ratio and in the phospholipidome, rendering cells highly susceptible to sunitinib. Delivery of miR-144 and miR-200c, downregulated in GBM cells and involved in bioenergetic metabolism pathways, emerged as a promising strategy to fight GBM cell invasiveness and resistance to chemotherapy. Combination of the miR-144 modulation and treatment with the mitochondria-targeting drug dichloroacetate resulted in a significant decrease of tumor cell proliferation. On the other hand, overexpression of miR-200c combined with GBM cell exposure to temozolomide resulted in cell cycle arrest and induction of cell death.

Downregulation of the long non-protein coding RNA (lncRNA) MVIH, overexpressed in GBM cell lines and human GBM tumor samples, showed high efficiency in reducing tumor cell migration and invasion, as well as promoting cell death when combined with the MTKI cediranib.

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 demonstrated for the hepatitis B antigen by intranasal, oral and s.c. routes of administration in mice. It was concluded from vaccination studies, that the quality of the immune response depends on the polymer chosen. From the immunotoxicological studies we concluded that the deacetylation degree and molecular weight of the chitosan polymer and the size of Chit NPs influence the in vitro results. Moreover, the NPs are more cytotoxic than the corresponding polymers. Concerning Glucan NPs, the size matters when evaluating toxicity, the 130 nm presented greater ability to decrease PBMCs and macrophage viability, induce higher ROS production than 355 nm NPs. Both NP sizes caused hemolysis and induced lymphocyte proliferation, although the concentration required to observe such effect was lower for the 130 nm glucan NPs.

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.

Two new lines of research has started to be implemented: one relates with the use of Quality by Design tools for rational formulation and manufacturing of targeted nanosystems the group has been working on; another relates with the application of some of the generated knowledge on targeting the microenvironment of solid tumors to the design of CAR-T cells.

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. Regarding the polymer-based nanosystems, several cationic copolymers with block and statistical architecture of varying molecular weights and compositions were synthesized by ARGET ATRP, using 2- of 2- lactobionamidoethyl methacrylate (LAMA) and 2-aminoethylmethacrylate (AMA) as monomers, and fully characterized by: NMR, FTIR, MALDI-TOF, SEC, DSC and TGA. The obtained nanosystems presented small mean diameters, positive surface charge and high DNA protection. The cytotoxicity and transfection activity, both in terms of transgene expression and percentage of transfected cells, of nanocarriers were dependent on their charge ratio and on chain length and architecture of the cationic copolymers. On the other hand, the carbohydrate composition of cationic copolymers influence the

cellular internalization and specificity of nanosystems. Taking together, the data obtained in the biological activity and cytotoxicity assays demonstrated, in different cells lines, that PAMA114-co-PLAMA20 –based nanosystems are the best formulation, presenting high gene delivery efficiency and specificity to HCC cells.

In a different approach we have developed glycopolymer-coated mesoporous silica nanoparticles to simultaneously deliver chemotherapeutic agents and genetic material into HCC cells. The obtained results showed that these hybrid nanosystems exhibited small mean diameters, positive surface charge, high DNA protection and a significant drug loading capacity. These nanocarriers revealed high specificity to HCC cells and the ability to efficiently and simultaneously deliver nucleic acids and drugs into cells.

On the other hand, we generated a new formulation consisting of a polymeric

core of PLGA coated by a lipid bilayer containing GalNAc, a specific ligand to the asialoglycoprotein receptor, to deliver the combination of sorafenib with selumetinib. The obtained data showed that these hybrid nanosystems presented high stability and loading capacity of both drugs, and suitable physicochemical properties. Moreover, our results demonstrated that this new formulation allowed to circumvent drug resistance and present high specificity for HCC cells, promoting higher cell death in HCC cell lines, when loaded with both drugs, but not in non-tumor cells, when compared to the administration of the same amount of free drugs. This potentiation of the antitumor effect of the drugs when encapsulated in the new hybrid nanosystem was shown to be carried out by increasing the programmed cell death, a synergistic antitumor effect of the two drugs when encapsulated in the new hybrid nanosystems being observed.

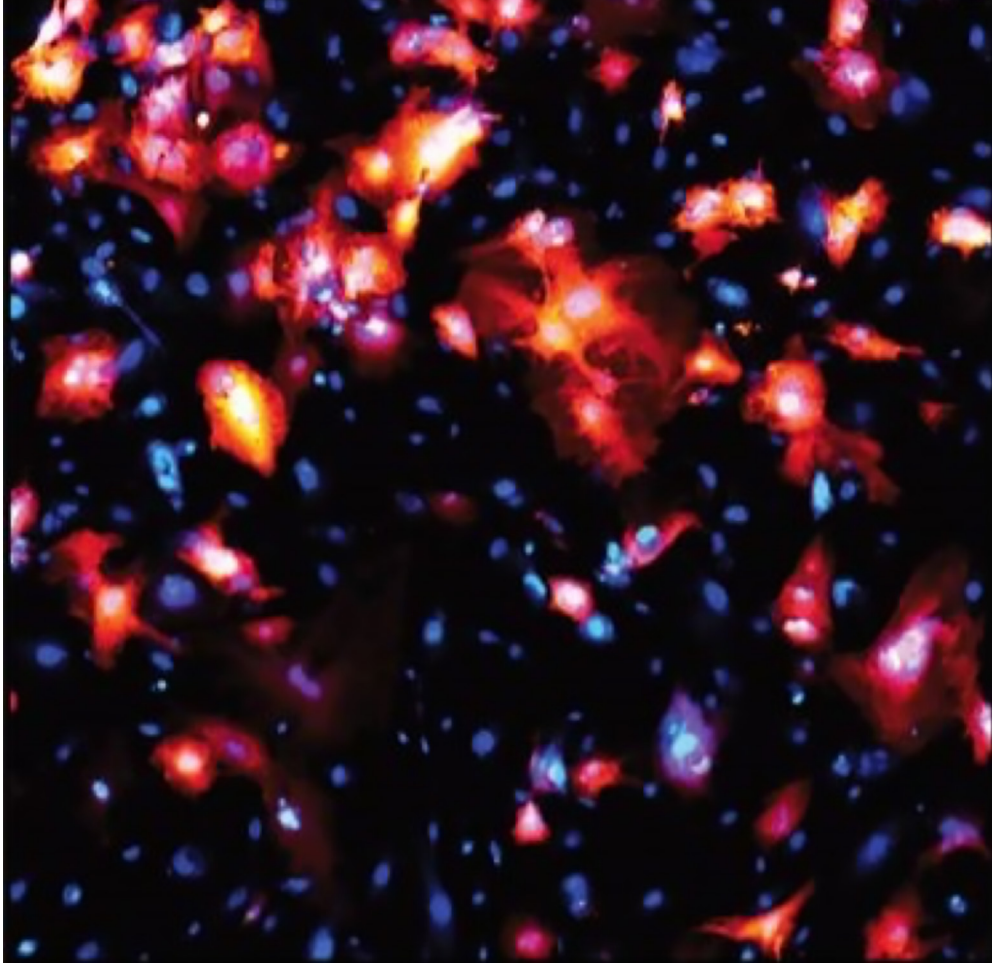
CELL REPROGRAMMING AND DEVELOPMENTAL HEMATOPOIESIS

•

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 3 papers in 2020 exploring these reprogramming approaches as well as a collaborative review paper in the regulation of mononuclear

phagocytes by transcription factors. In 2020 we have received a 3-year project from FCT to explore dendritic cell diversity with cellular reprogramming of approximately 200 000 euros.

MEDICINAL CHEMISTRY AND DRUG DISCOVERY

♦
Head: Jorge Salvador

OBJECTIVES

Research activities in center around 3 research lines (Microbial Pathways, Microbiome in Chronic Diseases, Public Health Microbiology):

Mycobacterial Pathways and biosynthesis of antimicrobials - Mycobacteria cause serious infections beyond tuberculosis (TB), mostly in the chronically ill and in the elderly. They are “a global priority for which innovative new treatments are urgently needed” (WHO, 2017).

We aim at deciphering pathways for mycobacterial polymethylated polysaccharides, regulators of their cell wall assembly and potential targets for rational drug design.

An emerging line of research aims at genetic, enzymatic and structural characterization of a novel secondary metabolite from a soil actinobacterium, known for being source of great chemical diversity and biological activities (antibacterial, antifungal, antiparasitic, antiviral, anticancer, anti-inflammatory) with potential biomedical and industrial applicability.

Public Health - We have

comprehensively screened domestic water distribution systems to assess the prevalence of some dangerous opportunistic nontuberculous mycobacteria increasingly reported to cause pulmonary infections in susceptible individuals. Ongoing genomic fingerprinting will allow understanding of the epidemiology and antimicrobial resistance determinants associated to this rapidly growing health threat.

Microbiome and Chronic Diseases – We are interested in understanding the contribution of neurotoxin-producing microbes found in dysbiotic gut microbiomes of Parkinson’s patients to neurodegeneration. Another objective in this line of research is to detect unique microbial signatures in diabetic skin microbiomes aiming at bacteriotherapeutic intervention. The unique and extensive DFU microbial biobank created recently in our group will be essential for research in this huge health problem.

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. Our results revealed that infection of THP-1 macrophages with these rickettsial species results in substantial alterations in a cluster of host proteins categorized as innate immune responses, particularly protein members of the RIG-I like receptor signaling pathway (RLR). We have also found an increase in the elongation of the mitochondrial network upon infection, which has been pointed as a hallmark of RLR activation. Moreover, our results also revealed alterations in the abundance of several proteins involved in pyroptosis. Further studies are currently ongoing to better understand this interplay between type I interferon production pathways and pyroptosis in rickettsial infections. (Manuscript in preparation)

We have further explored biocatalytic reactions, such as polyester synthesis by serine hydrolases. Here, we identified

structure-activity relationships that allowed us to increase the product yield of block polyesters and achieve a better control of their size. The reactions were tested in vitro and the products were characterized in collaboration with polymer chemists. We also started to work on enzymatic conjugation of polyesters to drugs and on the ligation of synthetic derivatives of nucleic acids with peptides using our developed enzymes. Other studies included the molecular characterization of an aspartic protease and the development of tools for biosynthetic pathways, including bacterial allosteric transcription factors (α TFs), such as UxuR.

We focused on characterizing Gram-negative outer membrane channel-tunnels of Type-I secretion systems (TISS) using bioinformatic analysis, with the aim to design immunotargeting strategies. Our analysis with more than 600 strains from 9 different Gram-negative genera revealed unique surface-exposed signatures for antibody targeting, while elucidated unique conservation profiles on such channels. We have continued the implementation and promotion of

a unique technological platform for production of antibodies in avian models (e.g. chicken, quails); the platform supports antibody discovery campaigns against multiple targets of interest (from microbial to human ones) and enables the development of novel immunotherapies and immunoresearch tools. The core logistics is the CNC Avian Technological Unit, the only of its kind in Portugal, holding IP on avian experimentation systems that enable core R&D activities (Modelo de Utilidade Nacional n.º 11936 - INPI submission date: 28-02-2020). We have also integrated the Editorial team of Springer book edition in the field of IgY Technology and participated as authors in 6 out of 18 chapters of the book. (Book manuscript submitted in December 2020).

We had two successful PhD Student applications to the special FCT call DOCTORATES 4 COVID-19.

FUNCTIONAL GENOMICS AND RNA-BASED THERAPEUTICS

♦
Head: Miguel Mano

OBJECTIVES

The research of the Functional Genomics and RNA-based Therapeutics laboratory is focused on two 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, and ii) the development and application of high-throughput and high-content screening technologies using genome-wide siRNA, miRNA and CRISPR libraries.

Cardiovascular diseases, including myocardial infarction, are the leading cause of death globally. In this context, the main topics of research are the identification and characterization of novel cellular factors that control regeneration and repair of cardiac tissue following injury, focusing on the process of cardiac fibrosis.

An additional area of research is the development of high-throughput screening (HTS) and high-content screening (HCS) technologies and their application to different areas of biomedical research (e.g. regenerative medicine, infection biology, intracellular signaling and cancer). The group has a particular interest in the development of improved strategies to increase the efficiency of precise genome editing based on CRISPR.

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. Future work aims 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.

The group also contributed to other achievements through collaborative work, including the identification and characterization of miRNAs relevant for infection by *Shigella* and *Salmonella*, the characterization of Che-I activity and the identification of FDA-approved compounds that counteract *Trypanosoma cruzi* infection in combination with Benznidazole.

RNA & INFECTION

♦
Head: Ana Eulálio

OBJECTIVES

The work in the RNA & Infection research group is mainly focused on the study of the role of host 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

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. While altered microRNA expression as part of the immune response to bacterial infections is a well-established phenomenon, considerably less is known regarding microRNAs that regulate bacterial infections and to which extent bacterial pathogens exploit host microRNAs to promote their own intracellular survival and proliferation.

We employed a comparative genome-wide microscopy-based functional screening approach to identify microRNAs controlling infection by two bacterial pathogens – *Salmonella Typhimurium* and *Shigella flexneri*. We selected these two pathogens as archetypes of intracellular bacteria, considering their disparate intracellular lifestyles despite being closely related. Following invasion, *Salmonella* replication occurs, to a large extent, confined to a vacuolar structure (*Salmonella*-containing

vacuole, SCV), whereas *Shigella* rapidly escapes the vacuole and replicates exclusively in the cytoplasm. In addition, *Shigella* exploits actin-based motility for intracellular and cell-to-cell spreading, a feature absent in *Salmonella*. We reasoned that the comparison of microRNAs controlling infection by these bacteria would enlighten new players relevant for their dissimilar intracellular lifestyles. Indeed, we found that microRNAs regulate various stages of infection, and that largely non-overlapping microRNA subsets regulate infection by these pathogens, seemingly reflecting different requirements prompted by their distinct intracellular lifestyles.

Through the characterization of a small subset of microRNAs chosen amongst the strongest inhibitors of *Shigella* infection, we discovered that miR-3668, miR-4732-5p and miR-6073 exert a selective effect on *Shigella* infection by impairing bacterial actin-based motility by down-regulating N-WASP. Additionally, through the identification of let-7i-3p miRNA as a strong inhibitor of *Salmonella* replication and an in-depth analysis of its mechanisms of action, we showed that this microRNA specifically inhibits *Salmonella* infection via modulation of endolysosomal trafficking and vacuolar environment by targeting the host RGS2 protein.

These findings illustrate two paradigms underlying microRNA-mediated regulation of bacterial infection, acting as part of the host response to infection, or as part of bacterial strategies to modulate the host environment and favor pathogenesis.

Our current work is focused on the characterization of other microRNAs with interesting phenotypes identified based on the high-throughput screening approach described. Moreover, we have been applying similar approaches to identify microRNAs controlling infection by other bacterial pathogens, namely *Campylobacter jejuni* and *Staphylococcus aureus*.

MOLECULAR MICROBIOLOGY AND MICROBIOME

•
Head: Nuno Empadinhas

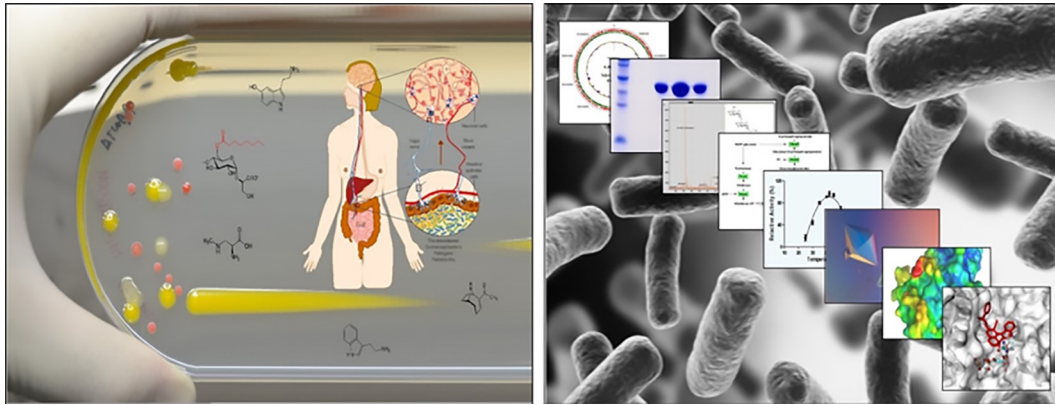
OBJECTIVES

The group is focused on 3 lines (Microbial Pathways, Microbiome in Chronic Diseases, Public Health Microbiology):

Microbial Pathways – The threat posed by nontuberculous mycobacteria (NTM), which are a cause of increasing numbers of lung infections worldwide, has been largely underestimated in Portugal and in the European Union. Our goal is to decipher pathways for intracellular mycobacterial polymethylated polysaccharides, vital regulators of cell wall assembly and potential targets for rational drug design. We have also been focused on the characterization of a gene cluster for a rare secondary metabolite in a soil actinobacterium from a family that has been source of many secondary metabolites (antibacterial, antifungal, antiviral, and anti-inflammatory), to decipher the biomedical potential of this unique secondary metabolite.

Public Health – NTM more often infect people with fragile immune systems or underlying chronic conditions namely cystic fibrosis, chronic obstructive pulmonary disease, diabetes, and the elderly. COVID-19 survivors may also enter the high-risk group list as consequence of damaged lung tissue and other organs. We are currently addressing municipal water microbiological quality to catalogue NTM distribution and diversity in household waters, a neglected problem on the rise. We aim at uncovering epidemiological links between the exposure to potable water NTM and the incidence of lung infections and other chronic diseases. We hope to influence public health policies in modernizing the screening protocols in place, to improve microbiological safety of drinking water and to ameliorate public health and economic burdens often leading to premature deaths and to irreparable social costs.

Microbiome and Chronic Diseases – We aim at the understanding of the contribution of a microbial neurotoxin to Parkinson's Disease. Public health authorities neglect the distribution and concentrations of this neurotoxin in foodstuffs of aquatic origin, but our results indicate that its chronic consumption promotes gut dysbiosis and inflammation, neuronal death, and motor alterations compatible with Parkinson's disease (collaboration with the Neuroscience and Disease line). Improved monitorization of food contamination with these neurotoxins will be essential. Another of our goals is to detect unique microbiome signatures in diabetic skin that may foster development of bacteriotherapeutic strategies to promote wound healing and ameliorate the burden of such complication (collaboration with the Metabolism, Aging & Disease line).



MAIN ACHIEVEMENTS

Microbial pathways – Building on previous achievements by the group, a novel mechanism for recycling and replication of polymethylated mycobacterial polysaccharides was recently comprehensively characterized (Ripoll-Rozada et al, 2019, PNAS; Maranha et al, submitted).

Parkinson's Gut Microbiome – We theorized on mechanisms by which chronic exposure to a dietary microbial neurotoxin may drive mitochondrial dysfunction, activation of neuronal innate immune responses, chronic low-grade inflammation, and neurodegenerative processes across the gut-brain axis in Parkinson's disease (Nunes-Costa et al, 2020). We proposed that mitoribosomes could be the earliest targets (Gonçalves et al, 2020). We confirmed that the microbial toxin elicits mitochondrial dysfunction, innate immunity activation and Alzheimer's Disease features in cortical neurons (Silva et al, 2020). Our animal studies revealed that chronic ingestion of the toxin led to selective erosion of a group of gut microbiota proposed to have anti-inflammatory effects and of another group that regulates mucosal immunity (Esteves, Munoz et al, submitted), which was associated with exacerbated inflammation, gut barrier impairment,

mitochondrial dysfunction, caudo-rostral protein aggregation and motor alterations compatible with Parkinson's. Our study confirmed that, although without major gut microbiota alterations, the specific ablation of certain gut bacterial groups had a pronounced impact locally and in the central nervous system.

Diabetic Wounds Microbiome – A large DFU biobank of strains was created from 200 diabetic patients. Typing and genome sequencing is ongoing. In a collaborative project mice DFU microbiomes were modulated toward healthier profiles by topical administration of natural and synthetic peptides. We isolated novel Mycobacterium species from diabetic patients' skin. Although they probably originated from shower water, the effects of colonization and persistence in diabetic skin remains unknown.

Public Health – After collecting water and biofilms from NTM-infected patients' homes and from showerhead biofilms we confirmed the ubiquity of mycobacteria and of pathogenic *M. chelonae*/*M. abscessus* and recommended urgent monitorization to health authorities. Some 17 different NTM species were isolated from households (7 different species from one). Genome

sequencing revealed at least 2 were members of 2 novel Mycobacterium species. We also found that Mycobacterium hassiacum, a species commonly found in municipal water although rarely a cause of infection, is extremely resistant to near-pasteurization temperatures (Alarico et al, 2020, distinguished with the Editor's Choice in the 2020 May edition). Revision of routine measures for disinfection of water distribution systems is urgent.

MEDICAL MICROBIOLOGY

♦
Head: Teresa Gonçalves

OBJECTIVES

The main interests of the group are centered in microbial agents of human disease, its biological traits relevant to infection and seeking for innovative therapies or preventive measures. Elderly, more susceptible to infection, is one of our major focus, including modulation of gut inflammation and chronic respiratory diseases.

During the period of this report (2020) our specific objectives were to seek for novel therapies to eradicate fungal and bacterial infections with a focus on yeasts and filamentous fungi affecting the respiratory system and the skin. We continue to pursue how the purinergic metabolism and adenosine A_{2A} receptors can be modulated to ameliorate pathological conditions of the elderly such as chronic inflammation of the gut. The scientific interest in the control of pandemics took us to initiate a project with the aim of quantifying the SARS-CoV2 in indoors environments, especially in health care facilities.



Bioactivity of a natural extract against filamentous fungi. Microdilution assay

MAIN ACHIEVEMENTS

- Antifungal activity of plant extracts
- Pyomelanin synthesis as a pathogenic trait in filamentous fungi
- Implementation of a surveillance system of indoors environmental SARS-CoV-2 in a transplant clinical facility and in a senior residence
- Oral microbiota modification associated with implants
- Neutrophils response to *Candida* spp.: influence of ectonucleotidases on NETs escape

INTERNATIONALIZATION

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

Projects in Collaboration

NEUROSCIENCE, AND DISEASE

SYNAPSE BIOLOGY

Coordination of the Innovative Training Network Syn2Psy-Synaptic Dysfunction in Neuropsychiatric Disorders [H2020-MSCA-ITN-2018 (813986)] – www.syn2psy.eu

Collaborative publications:

Ribeiro L.F., Catarino T., Carvalho M., Cortes L., Santos SD, Opazo P., Ribeiro L.R. Oliveiros B., Choquet D., Esteban J.A., Peça J., Carvalho A.L. (2021) Ligand-independent activity of the ghrelin receptor modulates AMPA receptors trafficking and supports memory formation. *Sci. Signal.* 14, eabb1953. DOI: 10.1126/scisignal.abb1953 (Cover story)

Ferreiro E, Lanzillo M, Canhoto D, Carvalho da Silva AM, Mota SI, Dias IS, Ferreira IL, Fontes AR, Mastrella G, Pinheiro PS, Valero J, Rego AC. Chronic hyperglycemia impairs hippocampal neurogenesis and memory in an Alzheimer's disease mouse model. *Neurobiol Aging.* 2020 Aug;92:98-113. doi: 10.1016/j.neurobiolaging.2020.04.003.

Gowrisankaran S, Houy S, Del Castillo JGP, Steubler V, Gelker M, Kroll J, Pinheiro PS, Schwitters D, Halbsgut N, Pechstein A, van Weering JRT, Maritzen T, Haucke V, Raimundo N, Sørensen JB, Milosevic I. Endophilin-A coordinates priming and fusion

of neurosecretory vesicles via intersectin. *Nat Commun.* 2020 Mar 9;11(1):1266. doi: 10.1038/s41467-020-14993-8

Invited talks at the international level:

- World Wide Neuro, September 2020, AMPA receptor dysfunction in cognitive disorders, Ana Luisa Carvalho
- European Neuroscience Institute Göttingen, January 2020, Synaptic dysfunction in neuropsychiatric disorders, Ana Luisa Carvalho

REDOX BIOLOGY AND BRAIN SENSING

Ongoing collaborations with Enrique Cadenas (LA, USA) and Jon Lundberg (Karolinska Inst. Sweden) regarding research planning and application to grants.

Ongoing collaboration with Greg Gerhardt (Univ. Kentucky, Lexington, USA):

Ana Ledo, Eliana Fernandes, Jorge Quintero, Greg Gerhardt and Rui Barbosa (2020) Electrochemical evaluation of a multi-site clinical depth recording electrode for monitoring cerebral tissue oxygen. *Micromachines (Basel)* 11, 632. doi: 10.3390/mi11070632

NEUROENDOCRINOLOGY AND AGING

Collaborative publications

Laetitia S. Gaspar, Janina Hesse, Müge Yalçın, 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 Alexandra 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/geron/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 Smith'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 (DYS)FUNCTION

The master theses: "GABAergic synapses reorganization and dysfunction in in vitro epilepsy" results from a collaborative work with Andrea Barberis (Ph.D) lab from the Italian Institute of Technology (IIT).

The experimental work for the master theses: "Novel roles for the KCC2 co-transporter in axons: regulation of chloride homeostasis and growth cone development" was performed by Giorgio Belperio during an international graduate training supported by the Erasmus+ program of the Università degli Studi del Sannio, Italy.

The experimental work for the master theses: "Role of NT3-TrkC signaling in fear memory and in the regulation of glutamatergic synapses" was performed by Gianluca Masella during an international graduate training supported by the Erasmus+ program of the Università degli Studi di Trieste, Italy.

VISION DISEASES

A subgroup of clinicians of Vision Diseases Group is a member of European Eye Epidemiology (E3) consortium, a cooperation between 31 groups from 13 different European countries, that aims to identify risk factors and pathways for eye diseases (lifestyle, vascular and metabolic factors, genetics, epigenetics and biomarkers).

Xandra Pereiro Díez - Post-Doc at Vision Diseases Group Fellow from the Basque Government "Ayudas nuevas para el programa posdoctoral Perfeccionamiento de Personal Investigador Doctor".

Collaborative publications

E.J. Campos, J. Martins, D. Brudzewsky, D.P.D. Woldbye and A.F. Ambrósio. Neuropeptide Y system mRNA expression changes in the hippocampus of a type I diabetes rat model. *Ann. Anat.* 2020, 227:151419. doi: 10.1016/j.aanat.2019.151419. PMID: 31563570.

E. Salobrar-García, A.C. Rodrigues-Neves, A.I. Ramírez, R. de Hoz, J.A. Fernández-Albarral, I. López-Cuenca, J.M. Ramírez, A.F. Ambrósio and J.J. Salazar. Microglial activation in the retina of a triple-transgenic Alzheimer's disease mouse model (3xTg-AD). *Int J Mol Sci.* 2020, 21(3)816. doi: 10.3390/ijms21030816. PMID: 32012676.

R.Boia,N.Ruzafa,I.DAires,X.Pereiro,A.FAmbrósio, E. Vecino and A.R. Santiago. Neuroprotective strategies for retinal ganglion cell degeneration: current status and challenges ahead. *Int. J. Mol. Sci.* 2020, 21(7).2262. doi: 10.3390/ijms21072262. PMID: 32218163.

R. Boia, M. Salinas-Navarro, A. Gallego-Ortega, C. Galindo-Romero, I.D. Aires, M. Agudo-Barruso, A.F. Ambrósio, M. Vidal-Sanz and A.R. Santiago. Activation of adenosine A3 receptor protects retinal ganglion cells from degeneration induced by ocular hypertension. *Cell Death Dis.* 2020, 11(5):401. doi: 10.1038/s41419-020-2593-y. PMID: 32461578.

R. Socodato, C.C. Portugal, T. Canedo, J.F. Henriques, S.H. Vaz, J. Magalhães, C.M. Silva, F.I. Baptista, R.L. Alves, V. Coelho-Santos, A.P. Silva, R. Paes-de-Carvalho, A. Magalhães, T. Summavielle, C. Brakebusch, A.M. Sebastião, A.F. Ambrósio and J.B. Relvas. Microglia dysfunction caused by the loss of RhoA disrupts neuronal physiology and leads to neurodegeneration. *Cell Rep.* 2020, 31:107796. doi: 10.1016/j.celrep.2020.107796. PMID: 32579923.

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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. Boon N, Alves CH, Mulder AA, Andriessen CA, Buck TM, Quinn PMJ, Vos RM, Koster AJ, Jost CR, Wijnholds J. *Int J Mol Sci.* 2021 Mar 30;22(7):3563. doi: 10.3390/ijms22073563. PMID: 33808129.

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Crumbs2 Mediates Ventricular Layer Remodelling to Form the Spinal Cord Central Canal. Tait C, Chinnaiya K, Manning E, Murtaza M, Ashton JP, Furley N, Hill CJ, Alves CH, Wijnholds J, Erdmann KS, Furley A, Rashbass P, Das RM, Storey KG, Placzek M. *PLoS Biol.* 2020;8 (3), e3000470. DOI: 10.1371/journal.pbio.3000470. PMID: 32150534.

Rosenblatt A, Udaondo P, Cunha-Vaz J, Sivaprasad S, Bandello F, Lanzetta P, Kodjikian L, Goldstein M, Habet-Wilner Z, Loewenstein A; ARTES Study Group. A Collaborative Retrospective Study on the Efficacy and Safety of Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema: The European DME Registry Study. *Ophthalmology.* 2020 Mar;127(3):377-393. doi: 10.1016/j.ophtha.2019.10.005.

De Breuk A, Acar EI, Kersten E, Schijvenaars MMVAP, Colijn JM, Haer-Wigman L, Bjorn Bakker, de Jong S, Meester-Smoor MA, Verzijden T, Missotten TOAR, Monés J, Biarnés M, Pauleikhoff D, Hense HW, Silva R, Nunes S, Melo JB, Fauser S, Hoyng CB, Ueffing M, Coenen MJH, Klaver CCW, I den Hollander A, EYE-RISK Consortium, Development of a Genotype Assay for Age-Related Macular Degeneration: The EYE-RISK Consortium, *Ophthalmology.* 2020 Jul 24;S0161-6420(20)30725-9. doi: 10.1016/j.ophtha.2020.07.037.

Jordan-yu JM, Teo K, Fan Q, Gana JC, Leopando AK, Nunes S, Farinha C, Barreto P, De Melo JB, Carreira I, Murta JN, Silva R, Cheung CMG.

INTERNATIONALIZATION

NEUROSCIENCE, AND DISEASE

Phenotypic and genetic variations between Asian and Caucasian polypoidal choroidal vasculopathy, *Br J Ophthalmol.* 2020 Oct 9;bjophthalmol-2020-317537.

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Larg-scale opacification of hydrophilic/hydrophobic intraocular lens. Costa JF, Bompastor-Ramos P, Marques M, Henriques J, Póvoa J, Lobo C, Alió JL, Werner L, Murta J. *Eur J Ophthalmol.* 2020 Mar;30(2):307-314.

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Higher Intake of Polyunsaturated Fatty Acid and Monounsaturated Fatty Acid is Inversely Associated With AMD. Roh M, Shin HJ, Lains I, Providência J, Caseiro-Alves M, Barreto P, Vavvas DG, Miller JB, Kim IK, Gaziano JM, Liang L, Silva R, Miller JW, Husain D. *Invest Ophthalmol Vis Sci.* 2020 Feb 7;61(2):20. doi: 10.1167/iov.61.2.20. PMID: 32058563

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García-Layana A, Recalde S, Hernandez M, Abalde 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

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

Research grants:

Joint project of the Association Nationale de Recherche 'ROle of Adenosine Receptors on synapse stabilization (ROAR)' with Sabine Levy (CNRS, Institut Fer à Moulin, Paris) and Christophe Bernard (INSERM, Univ. Méditerranée, Marseille).

Graduate training:

Co-supervision of a PhD student (Angela Patricia França) with Rui Prediger (Univ. Federal Santa Catarina, Brazil)

Co-supervision of a PhD student (Xinli Xu) with Nelson Rebola (Univ. Bordeaux, France)

NEURONAL CIRCUITS AND BEHAVIOR

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

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 27-31, 2020

International collaborative publications:

Lopes C, Tang Y, Anjo SI, Manadas B, Onofre I, de Almeida LP, Daley GQ, Schlaeger TM, Rego ACC. Mitochondrial and Redox Modifications in Huntington Disease Induced Pluripotent Stem Cells Rescued by CRISPR/Cas9 CAGs Targeting. *Front Cell Dev Biol.* 2020 Sep

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Ferreiro E, Lanzillo M, Canhoto D, Carvalho da Silva AM, Mota SI, Dias IS, Ferreira IL, Fontes AR, Mastrella G, Pinheiro P, Valero J, Rego AC. Chronic hyperglycemia impairs hippocampal neurogenesis and memory in an Alzheimer's disease mouse model. *Neurobiol Aging.* 2020 Aug; 92: 98-113. doi: 10.1016/j.neurobiolaging.2020.04.003. PMID: 32417750

Speaker(s) in international meetings:

Rego A. C. (2020) Strategies of rescuing mitochondrial function in Huntington's disease. SNCI_Society for Neurochemistry India 34th Annual Meeting. Symposium: 'Different Shades of Huntington's Disease', 11-13 de dezembro, 2020, online.

Beatriz M., Vilaça R., Rodrigues R., Schlaeger T., Daley G., Januário C., Lopes C. & Rego A. C. (2020) Human Huntington's disease iPSC-derived striatal-like neurons display altered maturation and mitochondrial dynamics. ESCI Virtual Meeting 2020 – Covid19 Edition, 20th September, 2020.

Lopes C., Castelhana J., Beatriz M., Fernandes C., Laço M., Januário C., Abrunhosa A., Castelo Branco M., Rego A. C. (2020) Overreduced intracellular state detected in Cu-ATSM brain imaging and fibroblasts from prodromal Huntington disease carriers. ESCI Virtual Meeting 2020 – Covid19 Edition, 20th September, 2020.

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 Ankarcróna (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

AGING AND BRAIN DISEASES: ADVANCED DIAGNOSIS AND BIOMARKERS

Dunya Selemangel (BSC in Biomolecular Research at University of Applied Sciences Utrecht, Netherlands), Erasmus programme (September 2020-February 2021).

Méndez-Couz M, Manahan-Vaughan D, Silva AP, González-Pardo H, Arias JL, Conejo NM. Metaplastic contribution of neuropeptide Y receptors to spatial memory acquisition. *Behav Brain Res.* 2021 Jan 1;396:112864. doi: 10.1016/j.bbr.2020.112864.

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González-Tablas Pimenta M, Otero Á, Arandia Guzman DA, Pascual-Argente D, Ruíz Martín L, Sousa-Casasnovas P, García-Martin A, Roa Montes de Oca JC, Villaseñor-Ledezma J, Torres Carretero L, Almeida M, Ortiz J, Nieto A, Orfao A, Tabernero MD. Tumor cell and immune cell profiles in primary human glioblastoma: Impact on patient outcome. *Brain Pathology* (2020); <http://dx.doi.org/10.1111/bpa.12927>.

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INTERNATIONALIZATION

METABOLISM, AGING AND DISEASE

MITOCHONDRIA METABOLISM AND DISEASE

a) Scientific collaborations:

Adrián Llerena, Extremadura Univ. Hospital, Spain
 Albert Rizvanov, Kazan Federal Univ., Russia
 Alessandro Valli, Centro Cardiologico Monzino, Italy
 Alfredo Sadun, Doheny Eye Institute, USA
 Anatoly Zhitkovich, Brown Univ., USA
 Bart Ghesquiere, VIB, Leuven, Belgium
 Clemens Steegborn, Univ. Bayreuth, Germany
 Daniel Dorta, Univ. São Paulo, Brazil
 David Sinclair, Harvard Medical School, USA
 Elmar Heinzle, Universität des Saarlandes, Germany
 Erich Gnaiger, Oroboros, Austria
 Fernando Scaglia, Baylor College of Medicine, USA
 Ignacio Vega-Naredo, Univ. Oviedo, Spain
 John Wise, Univ. Louisville, USA
 Jan Kopecky, Academy of Sciences, Czech

Republic
 Jeffrey Stuart, Brock Univ., Canada
 Jiiri Neuzil, Griffith Univ., Australia
 Joan Rosselo, CSIC, Spain
 Laurence Bindoff, Universitetet i Bergen, Norway
 Louise Dalgaard, Roskilde Univ., Denmark
 Maria Almeida, Univ. Arkansas, USA
 Maria Brizzi, Università degli Studi di Torino, Italy
 Maria Portillo, Univ. Basque Country, Spain
 Mariusz Wieckowski, Nenski Institute, Poland
 Massimo Zeviani, Università degli Studi di Padova, Italy
 Nika Danial, Dana-Farber Cancer Institute, USA
 Patricia Scott, Jon Holy, Kendall Wallace, Univ. Minnesota, USA
 Peter Nathanielsz, Univ. Wyoming, USA
 Piero Portincasa, Univ. Bari, Italy
 Pinchas Cohen and Changhan Lee, Univ. Southern California, USA

Rafael Artuch, Hospital Saint Joan de Déu, Spain
 Robert Taylor, Univ. Newcastle upon Tyne, UK
 Saber Hussain, Wright State Univ., USA
 Valerio Carelli, Univ. of Bologna, Italy
 Werner Koopman, Radboud Univ. Medical Centre, The Netherlands
 Zoraida Rello, Universidad Valladolid, Spain

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

Participation in other international networks:
 MetabERN (Rare Inherited Metabolic Diseases)
 Ibero-American Network of Pharmacogenetics and Pharmacogenomics studies
 Group study of Coenzyme Q10 deficits HACKING.HELP COVID-19

CELL SIGNALING AND METABOLISM IN DISEASES

Alves MI, Mena D, Silva DF, Seica R, Oliveira CR, Duarte AI, Moreira PI. Type 2 diabetes mitigates brain cortical energy metabolism in middle-aged female rats. *Eur J Clin Invest.* 2020;45:48.

Bernardes R, Ferreira H, Martins J, Moreira PI, Ambrósio AF, Castelo-Branco M, Serranho P. Characterization of the retina of the triple-transgenic mice model of Alzheimer's disease: onset and progression of the disease. *Neurology* 2020;95(15S):898.

Carvalho C, Moreira PI. 2020. Cognitive Impairment in Obesity and Diabetes. In: *Obesity and Diabetes*. Edited by Faintuch J., Faintuch S. Springer, Cham. Pp. 399-414. https://doi.org/10.1007/978-3-030-53370-0_29

Correia SC, Moreira PI, Perry G. 2020. Unraveling the Role of Mitochondria in Alzheimer's Disease. In: *Vascular Disease, Alzheimer's Disease, and Mild Cognitive Impairment: Advancing an Integrated Approach*. Edited by: David J. Libon, Melissa Lamar, Rodney A. Swenson, and Kenneth M. Heilman. OXFORD UNIV Press US, pp. 407-430. DOI:10.1093/oso/9780190634230.003.0017

Cortes L, Malva J, Rego AC, Pereira CF. Calcium Signaling in Aging and Neurodegenerative Diseases 2019. *Int J Mol Sci.* 2020 Feb 7;21(3):1125. doi: 10.3390/ijms21031125. (report)

Ferreira H, Martins J, Nunes A, Moreira PI, Castelo-Branco M, Ambrósio AF, Serranho P, Bernardes R. Characterization of the retinal changes of the 3x Tg-AD mouse model of Alzheimer's disease. *Health and Technology* 2020; 10(4):875-883.

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Mena D, Alves MI, Silva DF, Vaz D, Candeias E, Oliveira CR, Monteiro PF, Moreira PI, Duarte AI. Diet-induced high cardiovascular risk compromises brain hippocampal metabolism and long-term spatial memory in middle-

aged male rats. *Eur J Clin Invest.* 2020;50:46.

Mena D, Alves MI, Sjogren M, Silva DF, Oliveira CR, Moreira PI, Bjorkqvist M, Duarte AI. Co-administration of liraglutide and ghrelin ameliorates brain mitochondrial energy metabolism in the R6/2 mouse model for Huntington's disease. *Eur J Clin Invest.* 2020;50:30.

Neves B, Pereira CF, Krueger E (2020) "The Role of ER Stress and the UPR in Shaping Immunity" article collection. *Frontiers in Immunology* (edition of special issue)

METABOLIC CONTROL

Collaborative publication with German Diabetes Center: Sarabhai, T., Kahl, S., Szendroedi, J., Markgraf, D.F., Zaharia, O-P., Barosa, C., Herder, C., Wickrath, F., Bobrov, P., Hwang, J-H., Jones, J.G. and Roden, M. 2020. Monounsaturated fat rapidly induces hepatic gluconeogenesis and whole-body insulin resistance. *JCI Insight*. Article 134520.

Collaborative funding with University of Florida Advanced Magnetic Resonance Imaging and Spectroscopy Facility: National Science Foundation (PI7827) "High-sensitivity 13C NMR isotopomer analysis of triglyceride fatty acid enrichment from [U-13C]fructose".

Ongoing Collaborations with:

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.

Robert F. Anderson at the University of Auckland (New Zealand)

Project Title: Characterizing the kinetics and molecular mechanisms of human 2-Cys peroxiredoxins

Christine Winterbourn and Alexander Peskin at the University of Otago (New Zealand):

Project Titles:

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.

Flávia Meotti and Luiz F. de Souza at the University of São Paulo (Brasil)

Project Title: Characterizing the kinetics and molecular mechanisms of human 2-Cys peroxiredoxins.

Fook-Choe Cheah at the University Sains Islam, (Malaysia)

Project Title: Understanding the redox responses of erythrocytes of G6PD-deficient children

Hadley D. Sikes at the Massachusetts Institute of Technology (U.S.A.)

Project Title: Characterizing the mechanisms of H2O2-induced apoptosis in tumor cells

INTERNATIONALIZATION

METABOLISM, AGING AND DISEASE

INSULIN RESISTANCE AND DIABETIC ANGIOPATHY

Collaborations:

- Anindita Das, Virginia Commonwealth Univ., USA
- Abhay K. Pandey, Univ. Allahabad, India
- Joan Escarrabill, Hospital Clinic de Barcelona, Spain
- Orsolya Varga, Univ. Debrecen, Hungary
- Kely de Picoli, Federal Univ. Grande Dourados, Brazil
- Paulo Mathias, State Univ. Maringá, Brazil
- Rodrigo Mello-Gomes, Federal Univ. Goiás, Brazil
- Catalina Picó, Univ. Balearic Islands, Spain
- Thomas Efferth, Johannes Gutenberg Univ., Mainz, Germany
- Isabel M. Pires, University of Hull, UK
- Mohammad Sanad Abu-Darwish, Al-Balqa Applied Univ., Jordan
- Javad Sharifi-Rad, Semnan Univ. Medical Sciences, Iran
- Pamela Mayer, Salk Institute for Biological Studies, USA
- Cláudia Carbone, Univ. Catania, Italy

Special issues:

- Front Pharmacol – Ethnopharmacology. Combating redox imbalance-associated complications with natural products. Pandey AK, Kumar S, Pandey AK, Reis F.
- Front Pharmacol – Ethnopharmacology. Psychoactive natural products: potential in the treatment of brain diseases and strategies to improve delivery. Cabral C, Castelo-Branco M, Mayer P, Carbone C.
- Agronomy. Analysis of bioactive compounds from medicinal plants and promising applications. Cabral C, Campos E.

Publications:

- Free Radic Biol Med. doi: 10.1016/j.freeradbiomed.2019.11.002
- J Ethnopharmacology. doi: 10.1016/j.jep.2020.112803
- Oxid Med Cell Longev. doi: 10.1155/2020/5238650.
- Phytother Res. doi: 10.1002/ptr.6884
- Appl Materials Today. doi: 10.1016/j.apmt.2019.100501

- Nat Prod Bioprospecting. doi: 10.1007/s13659-020-00259-9

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.

INSULIN RESISTANCE AND DIABETIC ANGIOPATHY

Collaborations:

- Anindita Das, Virginia Commonwealth Univ., USA
- Abhay K. Pandey, Univ. Allahabad, India
- Joan Escarrabill, Hospital Clinic de Barcelona, Spain

BIOLOGY OF REPRODUCTION & STEM CELL

A) Male infertility studies (PI Sandra Amaral, PI Renata S Tavares)

A1) Collaboration with the Centre of Reproductive Medicine and Andrology (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.

A3) Collaboration with researchers both from the University of Padova and University of Campania Luigi Vanvitelli, Italy. This collaboration entails not only the publication of papers in aspects of common interest, as well as in the edition of relevant special issues on hotly debated topics. One of them published already in 2020:

"Endocrine Responses shaped by Ageing,

Diet, and Environmental Endocrine Responses". Chianese R, Tavares RS, Cescon M (eds). International Journal of Endocrinology (2020): <https://www.hindawi.com/journals/ije/si/375648/>.

E) Interdisciplinary studies on metabolism (PI Anabela Marisa Azul, PI João Ramalho-Santos)

-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; this partnership involves the joint research in i) science and health promotion, ii) insights on health benefits of mushrooms, and iii) but also and collective efforts for applying to national and international grants.

-European Institute of Innovation and Technology for Health (EIT Health), that allowed the joint cross-disciplinary research in European rural neighbourhoods, developed within the project Healthy Lifestyle Innovation Quarters for Cities and Citizens (HeaLIQs4cities).

-Collaboration with Hans Zischka at the Institute of Molecular Toxicology and Pharmacology (HMGU) and Institute of Toxicology and Environmental Hygiene from the Technical University Munich, Germany; this partnership involves the joint research in determining the beneficial therapeutic effects of mushrooms and collective efforts for applying to national and international grants.

-Collaboration with Walter Leal Filho from the Manchester Metropolitan University (UK) and Research and Transfer Centre "Sustainability and Climate Change Management", Hamburg University of Applied Sciences (Germany); this partnership involves the joint editorial project Encyclopedia of the UN Sustainable Development Goals.

MOLECULAR MECHANISMS OF CARDIOVASCULAR DISEASES

Klionsky DJ, (...), Girao H, (...), Tong C. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). *Autophagy*. 2021 Feb;1-382. doi:10.1080/15548627.2020.1797280

Tishchenko A, Azorín DD, Vidal-Brime L, Muñoz MJ, Arenas PJ, Pearce C, Girao H, Ramón Y Cajal S, Aasen T. Cx43 and Associated Cell Signaling Pathways Regulate Tunneling Nanotubes in Breast Cancer Cells. *Cancers (Basel)*. 2020 Sep 29;12(10):2798. doi: 10.3390/cancers12102798.

Rusiecka OM, Montgomery J, Morel S, Batista-Almeida D, Van Campenhout R, Vinken M, Girao H, Kwak BR. Canonical and Non-Canonical Roles of Connexin43 in Cardioprotection. *Biomolecules*. 2020 Aug 23;10(9):1225. doi: 10.3390/biom10091225.

Perrino C, Ferdinandy P, (...) Girao H, (...), Ytrehus K. Improving translational research in sex-specific effects of comorbidities and risk factors in ischaemic heart disease and cardioprotection: position paper and recommendations of the ESC Working Group on Cellular Biology of the Heart. *Cardiovasc Res*. 2020 Jun 02;117(2):367-385. doi: 10.1093/cvr/cvaa155.

Hernandez-Resendiz S, Prunier F, Girao H, Dorn G, Hausenloy DJ; EU-CARDIOPROTECTION COST Action (CA16225). Targeting mitochondrial fusion and fission proteins for cardioprotection. *J Cell Mol Med*. 2020 Jun;24(12):6571-6585. doi: 10.1111/jcmm.15384

Hausenloy DJ, Schulz R, Girao H, Kwak BR, De Stefani D, Rizzuto R, Bernardi P, Di Lisa F. Mitochondrial ion channels as targets for cardioprotection. *J Cell Mol Med*. 2020 Jul;24(13):7102-7114. doi: 10.1111/jcmm.15341.

Member of the Management Committee of the COST EU-CARDIOPROTECTION CA16225

European Research Concerted Action COST CA16225: Realising the therapeutic potential of novel cardioprotective therapies

MICROBIOMES, METABOLISM AND OMICS

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. The MMO group hosted the Ph.D student Cristiano M. Pedroso-Roussado for a 2 month internship. Cristiano is developing his Ph.D. thesis entitled “Whole gut microbiome research targeting health using nanopore sequencing”, with the supervision of Joao Inácio Silva, Lucas Bowler, and Fergus Guppy, under the DTA3/COFUND Marie Curie Early-Stage Researcher, in the University of Brighton.

The MMO consolidated the collaboration with the group of Sandra Denman, at the Forest Research, Centre for Ecology, UK. Sandra Denman has been dedicated to the study of Acute Oak Decline in the UK and has studied this tree disease from several aspects, one of which the role of tree-hosted microbiomes in AOD. The MMO Ph.D. student Diogo Pinho studied the relevance of the rhizosphere microbiome in *Q. robur* and found a correlation between rhizosphere microbiome and pH and AOD. The collaboration resulted in a publication “Pinho D, Barroso C, Froufe H, Brown N, Vangelova E; Egas C, Denman S. (2020) Linking tree health, rhizosphere physicochemical properties, and microbiome in acute oak decline. *Forests*. 11, 1153. doi:10.3390/f11111153

HUMAN GENOME VARIATION AND ENVIRONMENT IN HEALTH AND DISEASE

- European Board of Medical Genetics in the area of graduate training networks.
- 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.
- Perez-Ruiz E, Melero I, Kopecka J, Sarmiento-Ribeiro AB, García-Aranda M, De Las Rivas J. Cancer immunotherapy resistance based on immune checkpoints inhibitors: Targets, biomarkers, and remedies. *Drug Resist Updat*. 2020. 53:100718. doi: 10.1016/j.drug.2020.100718 (STRATAGEM COST action CA17104)
- 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)

INTERNATIONALIZATION

INNOVATIVE THERAPIES

ADVANCED THERAPIES

Nanomaterials for modulation of the Bone Marrow niche. Cristina Lo Celso (Imperial College of London, UK), Emanuel Quartin (CNC, Portugal), Delfim Duarte (I3S, Portugal), Lino Ferreira (CNC, Portugal), Ricardo Neves (CNC, Portugal)

Alternative splicing and Amyotrophic Lateral Sclerosis (ALS). Dora Brites (University of Lisbon, Portugal), Brian Kaspar (Ohio State University, USA), Laurent Roybon (Lund University, Sweden), Ricardo Neves (CNC, Portugal).

RESETEageing, a collaborative network between the University of Coimbra and three partners from high-performing countries with top expertise in ageing biology, cardiovascular biology and tools applied to the study of age-related diseases: Leibniz Institute of Ageing, Maastricht University, Newcastle University. Funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 952266.

Marie Curie ITN NanoStem is a Marie Skłodowska-Curie Innovative Training Network (ITN) funded by the European Commission through the Horizon 2020 Research and Innovation programme. The project started on June 2018. The network is coordinated by Prof Marina Resmini at QMUL and comprises 9 beneficiary partners and 5 partner organizations from the academic and the industrial sectors, from 7 countries (United Kingdom, Sweden, Portugal, France, Germany, Austria and Italy). The Nanostem project addresses brain drug delivery to target specifically neurogenic niches from a holistic approach.

VECTORS, GENE AND CELL THERAPY

Collaborative Publications:

- Carlo Wilke, Eva Haas, Kathrin Reetz, Jennifer Faber, Hector Garcia-Moreno, Magda M Santana, Bart van de Warrenburg, Holger Hengel, Manuela Lima, Alessandro Filla, Alexandra Durr, Bela Melegh, Marcella Masciullo, Jon Infante, Paola Giunti, Manuela Neumann, Jeroen de Vries, Luis Pereira de Almeida, et al. Neurofilaments in spinocerebellar ataxia type 3: blood biomarkers at the preataxic and ataxic stage in humans and mice. 2020. DOI: 10.15252/emmm.201911803.

International collaborations with joint publications (sub-group "Vaccines and Adjuvants")

- Gerrit Borchard - School of pharmaceutical sciences, Switzerland
- Fatouros Dimitrios - Department of Pharmacy, Aristotle University of Thessaloniki, Greece
- Peter Wick and Claudia Som - Federal laboratories for material science and technology, Switzerland
- Adley Rubira and Edvani Muniz - Chemistry department, University Maringa, Brasil

CELL REPROGRAMMING AND DEVELOPMENTAL HEMATOPOIESIS

Ulmert I, Oliveira LH, Pereira CF, Lahl K. Mononuclear phagocyte regulation by the transcription factor Blimp-1 in health and disease. *Immunology* 2020 August 16, IF: 5.016. doi: 10.1111/imm.13249.

MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Nanomaterials for modulation of the Bone Marrow niche. Cristina Lo Celso (Imperial College of London, UK), Emanuel Quartin (CNC, Portugal), Delfim Duarte (I3S, Portugal), Lino Ferreira (CNC, Portugal), Ricardo Neves (CNC, Portugal)

Alternative splicing and Amyotrophic Lateral Sclerosis (ALS). Dora Brites (University of Lisbon, Portugal), Brian Kaspar (Ohio State University, USA), Laurent Roybon (Lund University, Sweden), Ricardo Neves (CNC, Portugal).

MOLECULAR BIOTECHNOLOGY AND PROTEIN ENGINEERING

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

FUNCTIONAL GENOMICS AND RNA-BASED THERAPEUTICS

Functional screenings reveal different requirements for host microRNAs in Salmonella and Shigella infection. Aguilar, Carmen; Cruz, Ana Rita; Lopes, Ines Rodrigues; Maudet, Claire; Carmen; Cruz, Ana Rita; Lopes, Ines Rodrigues; Maudet, Claire; Sunkavalli, Ushasree; Silva, Ricardo Jorge; Sharan, Malvika; Lisowski, Clivia; Zaldivar-Lopez, Sara; Jose Garrido, Juan; Giacca, Mauro; Mano, Miguel; Eulalio, Ana. *NATURE MICROBIOLOGY*, 2020, 5, 192+. DOI: 10.1038/s41564-019-0614-3

Publication from collaborative work with Professor Juan Jose Garrido (Cordoba University, Cordoba, Spain) and Professor Mauro Giacca (ICGEB, Trieste, Italy).

he-I/AATF binds to RNA polymerase I machinery and sustains ribosomal RNA gene transcription. Sorino, Cristina; Catena, Valeria; Bruno, Tiziana; De Nicola, Francesca; Scalera, Stefano; Bossi, Gianluca; Fabretti, Francesca; Mano, Miguel; De Smaele, Enrico; Fanciulli, Maurizio; Iezzi, Simona. *NUCLEIC ACIDS RESEARCH*, 2020, 48, 5891-5906. DOI: 10.1093/nar/gkaa344

Publication from collaborative work with Professor Maurizio Fanciulli and Simona Iezzi (Regina Elena National Cancer Institute, Rome, Italy).

Collaboration with Professor Roderick Beijersbergen (Netherlands Cancer Institute, Amsterdam, The Netherlands) on genome-wide CRISPR screening for regulators of homologous-directed repair.

Collaboration with Professor Edecio Cunha-Neto (Heart Institute, Sao Paulo, Brazil) on repurposing of drugs with synergistic effect with Benznidazole to counteract Trypanosoma cruzi infection causing Chagas Disease.

RNA & INFECTION

Functional screenings reveal different requirements for host microRNAs in Salmonella and Shigella infection. Aguilar, Carmen; Cruz, Ana Rita; Lopes, Ines Rodrigues; Maudet, Claire; Sunkavalli, Ushasree; Silva, Ricardo Jorge; Sharan, Malvika; Lisowski, Clivia; Zaldivar-Lopez, Sara; Jose Garrido, Juan; Giacca, Mauro; Mano, Miguel; Eulalio, Ana. *NATURE MICROBIOLOGY*, 2020, 5, 192+. DOI: 10.1038/s41564-019-0614-3

This publication resulted from the collaboration with the research groups of Professor Juan Jose Garrido (Cordoba University, Spain) and Professor Mauro Giacca (ICGEB, Italy).

MOLECULAR MICROBIOLOGY AND MICROBIOME

Oriá RB, Empadinhas N, Malva JO (2020) Editorial: Interplay between Nutrition, the Intestinal Microbiota and the Immune System. *Frontiers in Immunology* 11:1758. <https://doi.org/10.3389/fimmu.2020.01758>. (collaboration with Reinaldo Oriá, Federal University of Ceará, Fortaleza, Brazil)

Silva MB, Lepzienj R, Ols S, Dahlbergh B, Grunewaldh J, Lore K, Smed-Sörensen A, Correia-Neves M, Empadinhas N, Färnert A, Källenius G, Sundling C (2020) Stabilization of blood for long-term storage can affect antibody-based recognition of cell surface markers. *Journal of Immunological Methods* 481-482:112792. <https://doi.org/10.1016/j.jim.2020.112792>. (collaboration with Gunilla Källenius and Christopher Sundling, Karolinska Institutet, Stockholm, Sweden)

Nuno Empadinhas. Evaluation of Grant Applications to the Programme REWIRE-Reinforcing Women in Research (<https://rewire.univie.ac.at/>), University of Vienna, Austria, COFUND Programme, Marie Skłodowska Curie Actions COFUND Project, European Commission (2020).

Nuno Empadinhas. Member of the Editorial Board of "Antibiotics", Section Board for 'Antibiotic Biosynthesis' since 2020.

Nuno Empadinhas. Member of the Editorial Board of "BMC Microbiology" since 2020

PARTICIPATION IN THE ORGANIZATION OF SCIENTIFIC MEETINGS

JANUARY 2020

Organizing of the meeting: MitoScreening Retreat 2020, Seminário Maior de Coimbra, Coimbra, Portugal

Date: January 21 2020

CIBB members involved in the organization: Paulo Oliveira

Organizing of the meeting: mini-symposium “The Neurobiology of Socio-Sexual Behavior”, Center for Neuroscience and Cell Biology, University of Coimbra, Portugal

Date: January 23-24 2020.

CIBB members involved in the organization: Carlos Duarte

Organizing of the meeting: “Desafios em Oncologia”

Date: January 30, 2020

CIBB members involved in the organization: Isabel Carreira

FEBRUARY 2020

Organizing of the meeting: Annual meeting of the Portuguese Society of Pharmacology

Date: February 5-7, 2020

CIBB members involved in the organization: Flávio Reis

Organizing of the meeting: 50th Meeting of the Portuguese Society of Pharmacology

Date: February 5, 2020

CIBB members involved in the organization: Maria Teresa Cruz

MARCH 2020

Organizing of the meeting: Concert and conferences “Rare Diseases and Events in the Universe”

Date: March 1 2020

CIBB members involved in the organization: Manuela Grazina

Organizing of the meeting: International Congress “Cuidados Continuados e Paliativos – O idoso no centro do cuidado, respostas e soluções”

Date: March 27-28, 2020

CIBB members involved in the organization: Marília Dourado

JULY 2020

Organizing of the meeting: 2nd CIBB Neuroscience and Disease 2020 Online Retreat”

Date: July 8, 2020

CIBB members involved in the organization: Ana Cristina Rego

SEPTEMBER 2020

Organizing of the meeting: - 1ª Reunião Virtual do Grupo de Estudos da Retina. Parte I

Date: September 5, 2020

CIBB members involved in the organization: José Henriques, Rufino Silva, Lilianne Duarte, Angelina Meireles, Ângela Carneiro, Rita Flores, Nuno Gomes, João Figueira, Inês Leal.

Organizing of the meeting: Scientific Committee of the “First Meeting of the Portuguese Network on Extracellular Vesicles” Porto, Portugal (Online event).

Date: September 13-13, 2020

CIBB members involved in the organization: Lino Ferreira

Organizing of the meeting: - Symposium on Mitochondrial Biology and Medicine, part of the 54th European Society for Clinical Investigation (ESCI) Virtual Meeting 2020 – COVID19 edition.

Date: September 23, 2020

CIBB members involved in the organization: Paulo Oliveira

Organizing of the meeting: - Co-organization of 54th European Society for Clinical Investigation (ESCI) Virtual Meeting 2020 – COVID19 edition

Date: September 23 - 25, 2020

CIBB members involved in the organization: Paulo Oliveira

Organizing of the meeting: - Symposium on Bioinformatics and Computational Biology for Biomedicine, part of the European Society for Clinical Investigation (ESCI) Virtual Meeting 2020 – COVID19 edition, online

Date: September 25, 2020

CIBB members involved in the organization: Paulo Oliveira

Organizing of the meeting: Organization of the 1st Symposium of Early Life Exposure to Mycotoxins and Health Impact.

Date: September 25, 2020

CIBB members involved in the organization: Paulo Oliveira

Organizing of the meeting: 34ª Reunião do Grupo de Estudos de Envelhecimento Cerebral e Demências (GEECD)

Date: September 25-26, 2020

CIBB members involved in the organization: M^a Isabel Santana

Organizing of the meeting: Coordination of the 2020 Summer School on Computational Biology, Coimbra (Portugal)

Date: September, 2020

CIBB members involved in the organization: Armindo Salvador

OCTOBER 2020

Organizing of the meeting: - 1ª Reunião Virtual do Grupo de Estudos da Retina. Parte II

Date: October 10, 2020

CIBB members involved in the organization: José Henriques, Rufino Silva, Lilianne Duarte, Angelina Meireles, Ângela Carneiro, Rita Flores, Nuno Gomes, João Figueira, Inês Leal.

Organizing of the meeting: - Conferences and concert under the scope of the UC730 Awarded project for the Promotion of Scientific Culture from the University of Coimbra, "A composer's blindness and the science of a rare disease".

Date: October 11, 2020

CIBB members involved in the organization: Manuela Grazina

Organizing of the meeting: Cérebro e Ambiente – O Impacto da Pandemia” – Online session of Brain Awareness Week (BAW) 2020

Date: October 14, 2020

CIBB members involved in the organization: Ana Cristina Rego

Organizing of the meeting: 1ª Reunião Virtual do Grupo de Estudos da Retina. Parte II

Date: October 10, 2020

CIBB members involved in the organization: José Henriques, Rufino Silva, Lilianne Duarte, Angelina Meireles, Ângela Carneiro, Rita Flores, Nuno Gomes, João Figueira, Inês Leal.

Organizing of the meeting: 28th Portuguese Congress of Atherosclerosis

Date: October 12-16, 2020

CIBB members involved in the organization: Flávio Reis

Organizing of the meeting: Pillow talks: "Using intermittent hypoxia to understand obstructive sleep apnea" (Zoom Meeting)

Date: October 15, 2020

CIBB members involved in the organization: Neuroendocrinology and Aging Group

Organizing of the meeting: 2-week international seminars in celebration of the world food day

Date: October, 2020

CIBB members involved in the organization: Eugenia Carvalho

NOVEMBER 2020

Organizing of the meeting: Member of the scientific board of the IBERPHENOL International Congress "Advances in the role of phenols in health effects and other uses", Coimbra

Date: November 5-6, 2020

CIBB members involved in the organization: Maria Teresa Cruz

Organizing of the meeting: 2020: Pillow talks: "It's about time: exploring the role of the circadian clock in disease" (Zoom Meeting)

Date: November 19, 2020

CIBB members involved in the organization: Neuroendocrinology and Aging Group

DECEMBER 2020

Organizing of the meeting: Scientific Commission of the "XXVIII Reunião Anual de Estomatologia e Medicina Dentária de Coimbra. Coimbra". On-line Event

Date: December 2020

CIBB members involved in the organization: Isabel Carreira

Organizing of the meeting: EIT Health Ageing PhD School, Annual Retreat. Event online

Date: December 2020

CIBB members involved in the organization: João Malva

Organizing of the meeting: Pillow talks: "Glial-neuronal interplay in circadian rhythms from the healthy brain to dementia" (Zoom Meeting)

Date: December 17 2020

CIBB members involved in the organization: Neuroendocrinology and Aging Group

GRADUATE STUDIES PROGRAMME

During 2020 CIBB organized 5 Advanced Courses (inserted at the Doctoral Programme in Experimental Biology and Biomedicine - PDBEB at CNC) and hosted 36 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 26 Ph.D. and 133 M.Sc. theses were concluded.

ADVANCED COURSES 2020

Core Technologies @ CNC
January 20 - 31, 2020
Coordinator: Luísa Cortes

The Avenging Metabolism in Human Disease: End-game!
March 9 - 13, 2020
Coordinators: Paulo Oliveira & João Ramalho-Santos

Connecting Researchers with the Society @ CNC
February 17 - 21, 2020
Coordinator: Sara Varela Amaral

Drug development
May 18 - 29, 2020
Coordinators: João Nuno Moreira & Luís Almeida

Computational Biology
February 24 - 28, 2020
Coordinators: Irina S. Moreira & Alexandra P. Carvalho & Armindo Salvador

CIBB SEMINARS

JANUARY

08.01.2020 | Multiple sclerosis: current pathological and clinical concepts

Sónia Batista, Neurology Service, CHUC; Faculty of Medicine and CNC

Host: Mário Grãos

10.01.2020 | WildCard challenges: EIT health funding opportunities

Jorge Pimenta, IPN

Host: Elsa Henriques

22.01.2020 | Genomic Power to Redeem from Oblivion - High-throughput Applications in Ancestry and Evolution

Luísa Pereira, i3S – ipatimup

Host: Mariana Bexiga

24.01.2020 | The Maternal Brain as a Model to Study Aggressiveness

Carmen Agustin-Pavón, Universitat de Valencia

Host: Mónica Santos

28.01.2020 | “Rapid Progressive Dementias: general overview and new data”

Franc Llorens, IDIBELL, Barcelona, Spain

28.01.2020 | “MRI-pathological correlation in Multiple Sclerosis

Menno Schoonheim, Amsterdam UMC, The Netherlands

29.01.2020 | The Repository of Measurement and Assessment Instruments in Health

Pedro Ferreira, Faculty of Economy of University of Coimbra and CEISUC

Host: Paulo Oliveira

30.01.2020 | “Mitochondrial function and ER-mitochondria interplay in APP knock-in mouse models of Alzheimer's disease”

Maria Ankarcrona, Karolinska Institutet, Stockholm, Sweden

31.01.2020 | Innovation in Research Infrastructures from a Technical and Managerial Point of View

Nuno Moreno, Institute Gulbenkian of Science

Host: Luísa Cortes

FEBRUARY

03.02.2020 | Axon Pathfinder and Neurovascular Interactions in Motor System Development

Dario Bonanomi, Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy

Host: Ramiro Almeida

05.02.2020 | Beta-glucans from medicinal mushroom strains

Amin Karmali, Research Center of Chemical Engineering and Biotechnology, Superior Engineering Institute of Lisbon

Host: Elisabete Ferreiro

CIBB SEMINARS

17.02.2020 | Fundraising for Biomedical Research

Maria João Leão, Maratona da Saúde

Host: Sara Varela Amaral

19.02.2020 | Neuronal dysfunction in neuropsychiatric disorders

Patrícia Monteiro, ICVS, University of Minho

Host: Bruno Manadas

18.02.2020 | Scientists and Journalists

Teresa Firmino, Jornal Público

Host: Sara Varela Amaral

21.02.2020 | Science Communication Through Design and
Multimedia Projects

Nuno Coelho, DEIUC and CEIS20

Host: Sara Varela Amaral

28.02.2020 | Mathematical Modelling of Cell Movement and
Angiogenesis

Rui Travasso, CFisUC; Department of Physics, UC

Host: Irina Moreira & Alexandra Carvalho & Armindo Salvador

28.02.2020 | Vector B2B - the Service Provider for Drug

Discovery and Development in Portugal

Bibiana Sá Moura, Vector B2B - Drug Developing Association for
Research in Biotechnology

Host: Joana Branco

MARCH

03.03.2020 | Human Metabolic Studies that Led to the Submission
of an NIH R01

Eugénia Carvalho, CNC, University of Coimbra & University of
Arkansas for Medical Sciences

Host: Ermelindo Leal

04.03.2020 | Tumor intracellular bioavailability of doxorubicin
determines therapeutic efficacy of GLP grade nanoparticle
targeted to nucleolin

Nuno Fonseca, CNC

Host: CIBB PostDoc Representatives

09.03.2020 | Functional Metabolomics

Barry Bochner, Biol, USA

Hosts: João Ramalho-Santos and Paulo Oliveira

10.03.2020 | Mitochondria: When Does Friend Turn Foe?

Zofia Chrzanowska-Lightowers, Newcastle University

Hosts: João Ramalho-Santos and Paulo Oliveira

10.03.2020 | The Public and Researchers: It's Complicated

Pedro Russo, Dep. Science Communication & Society; Astronomy
& Society Group Leiden Observatory Leiden University, the
Netherlands

Hosts: João Ramalho-Santos and Paulo Oliveira

10.03.2020 | Lactate Beyond a Waste Metabolite: Metabolic Affairs
and Signaling in the Tumour Microenvironment

Fátima Baltazar, University of Minho

Hosts: João Ramalho-Santos and Paulo Oliveira

25.03.2020 | Neural circuits of reward and aversion & the impact
of prenatal stress

Ana João Rodrigues, ICVS - School of Medicine, University of
Minho

Hosts: Filipa Baptista and António Francisco Ambrósio, iCBR

JUNE

19.06.2020 | Sustainable Healthy Diets: Back to Nature with
Consciousness,

The Experience of Montado do Freixo do Meio

Alfredo Cunhal Sendim, Coordinator of Cooperativa de Usuários
do Freixo do Meio

Hosts: Anabela Marisa Azul, CNC

19.06.2020 | Evaluation of nanoparticle immunotoxicity: Lessons
learned from the Nanotechnology Characterization Laboratory
assay cascade

Marina A. Dobrovolskaia, Nanotechnology Characterization Lab.,
Leidos Biomedical Research Inc., Frederick National Laboratory
for Cancer Research

Hosts: Sandra Jesus & Olga Borges, CNC

26.06.2020 | Native Scientist: Societal change through science and
language outreach

Sara Marques, Native Scientist

Hosts: Sara Varela Amaral, CNC

CIBB SEMINARS

JULY

03.07.2020 | The patents in Biotechnology
Susana Armário, Instituto Nacional da Propriedade Industrial
Hosts: Ana Catarina Santos, CNC

10.07.2020 | How circadian rhythms and sleep interact with
physiology
Amita Sehgal, Perelman School of Medicine at the University of
Pennsylvania
Hosts: Cláudia Cavadas & Ana Rita Álvaro, CNC

NOVEMBER

03.11.2020 | Western Blot Tech Day
Eduardo Lopes, Bio-Rad
Host: Isabel Nunes-Correia, CNC

06.11.2020 | Mental disorders – searching for the (un)known
Bruno Manadas, Center for Neuroscience and Cell Biology
(CNC), University of Coimbra
Host: Rosa Resende, CNC

11.11.2020 | Preexisting “prediabetes” and the severity of
COVID-19 complications: - World Diabetes Day - Nov 14th
Eugenia Carvalho, Center for Neuroscience and Cell Biology
(CNC), University of Coimbra
Host: Ermelindo Leal, CNC

20.11.2020 | New tool from the immunotherapy toolbox for
colorectal cancer patients
Noel de Miranda, Leiden University Medical Center
Host: João Nuno Moreira, CNC

27.11.2020 | Kainate Receptors, Circuit Imbalance and Mental
Diseases
Juan Lerma, Instituto de Neurociencias CSIC-UMH. San Juan de
Alicante, Spain
Host: Ricardo Rodrigues, CNC

DECEMBER

04.12.2020 | From the Bench to Corporate America
Rocio Rivera, Vice President of Marketing, Scientific
Communications, L'Oreal Paris, USA
Host: Joana Marques, CNC

11.12.2020 | Coordinated excitatory and inhibitory synaptic
plasticity at dendritic glutamatergic and GABAergic synapses
Andrea Barberis, Italian Institute of Technology
Host: Miranda Mele, CNC

PHD THESIS CONCLUDED IN 2020

Ana Coelho

Molecular Mechanism of Mitochondrial Transfer from Stromal cells to cancer cells with damaged mitochondrial DNA

May 4, 2020

Supervisor: Paulo Oliveira

Ana Rita Santos

Functional and Structural Characterization of the Response to the Treatment of Diabetic Macular Edema with Intravitreal Anti-VEGF Therapy

September 2020

Supervisor: António Francisco Ambrosio

Ana Soares

A new mechanism for selective protein loading into exosomes

Supervisor: Henrique Girão

António Campos de Figueiredo

Study on the contribution of the choroid to the pathophysiology of diabetic retinopathy

November 2020

Supervisor: António Francisco Ambrosio

António José dos Santos Gabriel

Avaliação do sistema colinérgico na doença de Alzheimer

Supervisor: Isabel Santana

António Cruz Ferreira

Lesões desportivas no rugby de sete português. Avaliação da incidência no primeiro e segundo patamar competitivo masculino, do seu impacto, recorrência, tipo e fatores de risco associados, bem como de estratégias para a sua redução

Supervisor: Luiz Santiago

Dina Pereira

The role of ageing in polyglutamine-induced neurodegeneration. A study in Machado-Joseph disease model

Supervisor: Luis Almeida

Cláudia Pereira

Monóxido de Carbono contra a isquémia cerebral: Função da mitofagia, da mitocôndria e do metabolismo celular

Supervisor: Henrique Girão

Filipe Prazeres

Multimorbidity in Primary Care

Supervisor: Luiz Santiago

Hugo Moreiras

Mecanismos moleculares de internalização e processamento de melanossomas por queratinócitos

Supervisor: Henrique Girão

Ilda Maria Horta Pedro

Alumni in a relationship marketing perspective: the alumni-alma mater commitment relationship

July 14, 2020

Supervisor: Luís Pereira

Joao C.P. Silva

Sugar, Intestine & Metabolic Syndrome: High fructose feeding and hepatic fatty liver disease inflammation: the role of intestinal microbiota

Supervisor: John Jones

Josephine Blersch

Biocompatible nanoparticles to modulate cell activity

Supervisor: Lino Ferreira

Maria del Carmen Martin Sierra

Avaliação lipidómica e do sistema imune no carcinoma hepatocelular e no colangiocarcinoma

Supervisor: Maria Rosario Domingues; Co- Supervisors: Artur Augusto Paiva, Paula Margarida dos Santos Laranjeira

Maria Helena Vieira Soares Loureiro

Influência do Exercício Físico e da Nutrição na Sarcopenia em idosos.

Supervisor: Manuel Veríssimo

Maria Inês R de A. e Sousa

Metabolic modulation in paused-like pluripotency

Supervisor: João Ramalho-Santos

Mário Carvalho

MIT-Portugal PhD Defence

Supervisor: João Peça

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

Supervisor: Anabela Marisa Azul, João Ramalho-Santos

PHD THESIS CONCLUDED IN 2020

Olga Marisa da Silva Pereira

Papel da autofagia (macroautofagia) na predisposição de pacientes diabéticos a doenças infecciosas e cancro

Supervisor: Henrique Girão

Paula Cristina Correia Martins

Impact of antiretroviral therapy used in the fetal and neonatal period on the cardiovascular development of children and adolescents.

Supervisor: Flávio Reis

Pedro Brito

Evaluation of the Systemic Pro-Inflammatory Response Associated with Diabetic Retinopathy as a limit factor on the efficacy of current intravitreal treatment agents for diabetic macular edema

Supervisor: António Francisco Ambrosio

Pedro Simões

Deprescribing: a self-portrait about the reduction of polypharmacy in Portugal

Supervisor: Luiz Santiago

Raquel Fernanda da Silva Alves.

Sensitivity and resistance in chronic myeloid leukaemia to tyrosine kinase inhibitors: insights into molecular mechanisms

Supervisor: Ana Bela Sarmiento Ribeiro. Co- Supervisor: António Medina Almeida

Susana Seca

Effects of acupuncture in the pain and function of the hands of selected patients with rheumatoid arthritis. Supervisor: Maria Filomena Botelho, António Cabrita.

Tânia Martins Marques

Heart ischemia gives a second life to Cx43: novel roles ascribed to Cx43 that go beyond gap junction intercellular communication

Supervisor: Henrique Girão

Xinli Xu

The role of purinergic receptors in hippocampal mossy fiber sprouting during epileptogenesis

February 28, 2020

Supervisor: Ricardo Rodrigues

MSC THESIS CONCLUDED IN 2020

A Ferreira

Gestão da esquizofrenia em tratamento no domicílio: o caso da Unidade Local de Saúde da Guarda

Supervisor: Sandra Oliveira

Adelaide Catarina Campos Barbosa

Renal effects of blueberry juice in a prediabetic rat model induced by hypercaloric diet

Supervisor: Flávio Reis

Adriana António Lemos Gonçalves Malheiro

Crosstalk between perivascular adipose tissue and blood vessels in obesity and type 2 diabetes

Supervisor: Flávio Reis

Adriana Isabel Batista Cruz

A problemática das listas e tempos de espera para cirurgia: o caso dos tempos superiores a 365 dias na Região Centro

October 2020

Supervisor: Carlota Quintal

Alexandra Cruz

Adenosine A2a receptor ability to retrieve microglia morphology and behavior upon brain masculinization of females prenatally exposed to dexamethasone

Alexandra Lopes Ramos Rodrigues

Dysfunctional dendritic and axonal activity in Alzheimer's Disease – identifying possible therapeutic targets

March, 20 2020

Supervisor: Ana Cristina Rego

Alexandre Miguel Figueiras Estevam

Ruxolitinib and pimozone as new therapeutic approaches in acute lymphoblastic leukemia

Supervisor: Ana Bela Sarmiento Ribeiro, Co- Supervisor: Raquel Alves

Alexandro Azevedo

Theranostic nanosystems combining gene therapy and imaging agents for cancer treatment

Supervisor: João Nuno Moreira

Ana Catarina da Silveira Ramos

Tradução e validação para a população portuguesa do "The Schedule of Attitudes Toward Hastened Death (SAHD)

February 19, 2020

Supervisor: Pedro Lopes Ferreira, Marília Dourado

Ana Daniela Esteves Oliveira.

Phenotypic characterization of cellular and animal models of Machado-Joseph Disease

Supervisor: Luis Almeida

Ana Beatriz Santos Amaral

Mestrado de Geriatria da UC

Supervisor: António Veríssimo

Ana Maria Vasconcelos

Exploring the pathogenic mechanisms elicited by antibody-mediated loss of Caspr2 in autoimmune synaptic encephalitis

Supervisor: Dominique Fernandes and Ana Luísa Carvalho

Ana Osório Petrucci

Cuidados Paliativos e Terapia da Dignidade: o que sabem os Portugueses?

July 3, 2020

Supervisor: Marília Dourado

Ana Reis Costa

The impact of different lipogenic diets on direct and indirect pathway contributions to hepatic glycogen synthesis

Supervisor: John Jones

Ana Rita Matos

Stress oxidativo e estratégias terapêuticas no contexto das doenças neurodegenerativas

Supervisor: António Veríssimo

Analúcia Pereira Matera Machado

A relação entre o capital social e a saúde autoavaliada e o impacto de variáveis contextuais: uma análise com base no European Social Survey 2018

October 2020

Supervisor: Carlota Quintal

André Monteiro Dinis

Famílias monoparentais com paciente identificado com toxicod dependência

July 23, 2020

Supervisor: Sónia Abreu

Andreia Filipa Nunes de Melo

Photodynamic therapy with glucoconjugated porphyrins for age-related macular degeneration

December 2020

Supervisor: Antonio Francisco Ambrosio

Ângela Costa Henriques de Freitas

Gestão das inovações em saúde na área da oncologia: uma análise comparativa entre países. Mestrado em

December 17, 2020

Supervisor: Vitor Raposo

Artur Miguel Quaresma Pereira Miler

Saúde oral em idosos nos cuidados de saúde primários

Supervisor: António Veríssimo

Bárbara Daniela Araújo Pinheiro Teixeira
Elucidating autoprocesing activity and function of the rickettsial retropepsin APRc in mammalian cells

Beatriz Vinhas Maio
GABAergic synapses reorganization and dysfunction in in vitro epilepsy
Supervisor: Carlos Duarte

Bernardo Rafael Ribeiro Cavadas.
Alterações visuais subjetivas pós-trombose venosa cerebral

Bruna Mónica Baptista Moreira
Importância e desafios de comunicar ciência numa empresa de base biotecnológica

Bruno Miguel Sequeira dos Santos
Mitochondrial dynamics and mitophagy in cellular models of Parkinson's
November 15, 2020
Supervisor: Ana Cristina Rego

Brigite Margarete de Jesus Ferreira.
Experiência numa unidade de medicina geriátrica
Supervisor: António Veríssimo

C. Rodrigues
Perceção dos utentes de uma Unidade Local de Saúde sobre o projeto Follow up +Saúde
Supervisor: Sandra Oliveira

Carla Maria Belo Mourato
Incidência e Prevalência da Doença Tiroideia Autoimune na Diabetes Mellitus Tipo I
Supervisor: Ilda Masano-Cardoso

Carla Sofia Vaz Marques
Contributo para a validação da versão portuguesa do instrumento de medição Lymphoedema Quality of Life (LYMQOL)
July 9, 2020
Supervisor: Rui Pimenta

Carlos Pita
Papel dos lisossomas danificados nas células endoteliais durante o desenvolvimento da insuficiência cardíaca com fração de ejeção preservada
Supervisor: Henrique Girão

Carolina Matos Carola
Heavy metal exposure and its effects in male reproductive health: an in vivo and vitro study
Supervisor: Sandra Amaral, Renata S.Tavares

Catarina Lopes Belo Baptista
Próteses mnésicas como estratégia de otimização do funcionamento da memória em pessoas com problemas cognitivos: perspetiva dos profissionais de saúde

Catarina de Jesus Pedreira Cascais
Pediatric optic neuritis

Catarina Campos Pinto
Avaliação da Função Diastólica em Atletas em Idade Pediátrica
Supervisor: Francisco José Caramelo, Patrícia Oliveira e Silva

Catarina da Silva Miranda
Uma nova abordagem para monitorização não invasiva utilizando termografia de infravermelhos, testada num modelo murino de choque séptico
Supervisor: Ana Salomé Pires, Nuno Franco

Catarina Isabel Areias Silva Gouveia
Avaliação da Qualidade de Vida e da Literacia em Doentes Oncológicos Submetidos a Radioterapia
January 2020
Supervisor: Carminda Morais

Catarina Vinhas
Impact of human iPSC-derived NESC transplantation in MJD-associated neuropathology and motor impairments
Supervisor: Luis Almeida

Cátia Maria Dias Oliveir.
Identificação das dificuldades no acesso e utilização dos medicamentos pelos idosos
Supervisor: Ilda Masano-Cardoso

Daniela Rosendo Silva
Unravelling the mechanisms of ghrelin-mediated regulation of adipose tissue angiogenesis
Supervisor: Flávio Reis

Daniele Ciampi
Lipidomic alterations in the Mitochondria-Associated Membranes (MAMs) in Alzheimer's disease: analysis of biosynthetic enzymes in APPswe-overexpressing cells

David Duarte Machado Gomes de Moura
Fisiopatologia da dor crónica

Diana Fonseca da Silva
Mestrado de Geriatria da UC
Supervisor: António Veríssimo

Diogo Banha;
LPS induction of innate immunity in PD cells

Diogo José Carvalho Roque
Mecanismos moleculares associados à resistência adquirida a inibidores do proteasoma em mieloma múltiplo
Supervisor: Ana Bela Sarmento Ribeiro, Co- Supervisor: Raquel Alves

E. Mendonça
A satisfação dos clientes seniores das organizações de Economia Social: O papel da participação em programas de turismo social
Supervisor: Sandra Oliveira

MSC THESIS CONCLUDED IN 2020

Elizabeth Santos Ribeiro

Validation of psychometric characteristics validity and reliability of Portuguese version of Identification of Functional Ankle Instability (IdFAI)
November 24, 2020

Supervisor: Ilda Rui Pimenta

Eva Mesquita Rodrigues

Equidade na utilização dos cuidados de saúde em Portugal: uma análise de internamento hospitalar e meios complementares de diagnóstico com base no Inquérito Nacional de Saúde 2014
February 2020

Supervisor: Carlota Quintal, Micaela Antunes

Eurico José Gonçalves Pereira

Plasma frio atmosférico no tratamento do cancro da bexiga
Supervisor: Maria Filomena Botelho, Ana Salomé Pires.

Filipa Raquel Santana Correia Zacarias

Oferta e procura de cuidados a idosos em Portugal
December 3, 2020

Supervisor: Pedro Lopes Ferreira, Aida Isabel Tavares

Francisco Gandra Ferrer Antunes

Imunomodulação pré-natal, células da microglia e alterações comportamentais

Gianluca Masella

Role of NT3-TrkC signaling in fear memory and in the regulation of glutamatergic synapses

Supervisor: Carlos Duarte

Giorgio Belperio

Novel roles for the KCC2 co-transporter in axons: regulation of chloride homeostasis and growth cone development

Supervisor: Carlos Duarte

Gonçalo Afonso

Impact of Rebaudioside A in Cancer Cell Metabolism: Potential as a Safe Chemotherapeutic Adjuvant

December 9, 2020

Supervisor: Paulo Oliveira

Gonçalo de Manha Passos Troca Favinha

Immunotherapy in pediatric Guillain-Barré Syndrome: intravenous immunoglobulin, plasmapheresis or both?

Gonçalo Chaves da Silva Neves

O Impacto social e económico da doença de Alzheimer precoce numa amostra de doentes e cuidadores informais do Serviço de Neurologia dos CHUC

Gonçalo Dinis Duarte Sousa

Patologia Inflamatória da Cavidade Oral: Relevância na Oncogénese Oral

Supervisor: Teresa Sequeira, Augusta Silveira

Hanna Sion

Ácido Hialurónico: metabolismo, síntese e reabsorção

Supervisor: Teresa Sequeira

Inês Catarina da Fonseca Elias

Evaluation of potential markers for the diagnosis and prognosis of CADASIL patients

Inês Fontainhas

Systematic analysis of clinical trials on multiple sclerosis and dementias in a neurology service

Supervisor: Flávio Reis

Irina Sofia Reis Gomes Santos

Alterações socio-emocionais no CADASIL e seus correlatos com dados de neuroimagem: revisão da literatura e dados de um estudo piloto

Isabel Dutra Rafael

Fragilidade e Demência – Mecanismos Causais

Supervisor: António Veríssimo

Ivana Martins

Oral Cancer: exploring the potential of liquid biopsies in diagnosis and follow-up

Supervisor: Ilda Ribeiro

Jacqueline Monteiro de Freitas Pinto Cid Cruz

Avaliação da qualidade de vida dos pacientes vivendo com VIH/SIDA
August 13, 2020

Supervisor: Pedro Lopes Ferreira, Artur Correia

Jean-Philippe De Mota

Mitochondrial function in permeabilized cardiac and skeletal muscle fibers - by high resolution respirometry

Jeremie Cozin

White Spots: discussão sobre etiologia e fenómenos histológicos associados – uma revisão narrativa

Supervisor: Teresa Sequeira

Joana Andreia Silva Moleiro Barros

Estudo de Mercado sobre a atividade da compra online e da app Auchan – Hipermercado Auchan de Faro
July 21, 2020

Supervisor: Luís Pereira

- Joana Araújo da Silva
Diabetes Mellitus - custo da doença no contexto português
Mestrado em Gestão e Economia da Saúde da FEUC
July 17, 2020
Supervisor: Vitor Raposo, Luiz Miguel Santiago
- Joana Rebelo Correia
A intervenção da radioterapia em doentes paliativos no controlo da dor - revisão sistemática da literatura
December 11, 2020
Supervisor: Marília Dourado
- Joana Rita Brito Matos
Fatores preditores de sobrecarga do cuidador informal em cuidados de saúde primários
December 18, 2020
Supervisor: Marília Dourado
- Joana Rita Ramos Paiva
Dificuldades e necessidades do cuidador informal: um estudo no Município de Cantanhede
December 2, 2020
Supervisor: Pedro Lopes Ferreira, Marília Dourado
- Joana Daniela Alves
Mestrado de Geriatria da UC
Supervisor: António Veríssimo
- Joana Mafalda Coelho Oliveira
Interaction of Filamentous Fungi Extracellular Vesicles with Respiratory tract Epithelium
Supervisor: Teresa Gonçalves
- João Manuel Rosa Simões
Satisfação dos utentes num serviço de imagiologia
November 26, 2020
Supervisor: Pedro Lopes Ferreira
- João Pedro Gomes de Oliveira Braz
Tras-A2B-corróis são fotossensibilizadores superiores para cancro do pulmão
Supervisor: Maria Filomena Botelho, Susana Martins Lopes
- João Pedro Leite Guerra
Papel moderador da autocompaixão na relação entre dor e depressão em doentes paliativos
December 9, 2020
Supervisor: Marília Dourado
- José Baptista
Biological activity of Brassica by-products in cell models of oxidative stress and lipid toxicity
December 4, 2020
Supervisor: Paulo Oliveira
- José Luís Lima Spencer
Avaliação da qualidade de vida em crianças e adolescentes com asma na Ilha de São Vicente
December 4, 2020
Supervisor: Pedro Lopes Ferreira
- L. Monteiro
A retinopatia diabética e a adoção de estilos de vida: a realidade de uma consulta de oftalmologia em contexto hospitalar
Supervisor: Sandra Oliveira
- Leonor Santos Martins
Reavaliação imagiológica pré-trombectomia no acidente vascular cerebral isquémico de doentes transferidos de centro primário
- Luis Miguel Guilherme Marques
Desafios em Famílias Monoparentais nas Diferentes Etapas do Ciclo Vital
July 23, 2020
Supervisor: Sónia Abreu
- Luísa Barão Vaz
Contributo para a validação da versão portuguesa do instrumento de medição Lymphoedema Quality of Life (LYMQOL) Leg.
July 9, 2020
Supervisor: Rui Pimenta
- Lydia Marchã Portela
Mestrado em Análises Clínicas
- Magali Ester Knorst
Atresia maxilar e respiração bucal: A importância do diagnóstico precoce
Supervisor: Teresa Sequeira
- Madalena Henriques Monteiro
Abordagem multidisciplinar em cuidados geriátricos
Supervisor: António Veríssimo
- Madania Gafur Amorim
Tear fluid biomarkers for early detection of diabetic retinopathy
December 2020
Supervisor: Antonio Francisco Ambrosio
- Margarida Sobral
Effects of Extended Passaging on the BEAS-2B Cell Line, an In Vitro Model of Human Lung Epithelium Established for the Study of Lung Carcinogenesis
December 3, 2020
Supervisor: Paulo Oliveira
- Maria Cardoso
Descobrir o papel dos enzimas deubiquitinantes na reparação da membrana plasmática
Supervisor: Henrique Girão
- Maria Inês Costa
The role of micronutrients in the DNA damage response: The case of zinc in acute myeloid leukemia
Supervisor: Ana Cristina Gonçalves. Co-Supervisor: Ana Bela Sarmiento Ribeiro

MSC THESIS CONCLUDED IN 2020

Maria Inês Sousa Cristo

Sperm quality in patients with unknown origin male infertility

Supervisor: Sandra Amaral, Renata S. Tavares

Maria Inês Santos

MicroRNA profiling in human cell-based models of Machado-Joseph Disease

Supervisor: Luis Almeida

Maria Manuel Martins Pinto

Brain-enriched plasma-derived extracellular vesicles as biomarkers for Machado-Joseph Disease

Supervisor: Luis Almeida

Mariana Ladeiro Afonso

Involvement of the purigenic system in the Host-Microbe interaction

Supervisor: Teresa Gonçalves

Mariana Muga

Methyphenidate- Induced alterations in Astrocytes: A comprehensive Characterization

Mariana Macieira Ferreira

Os glucocorticoides na terapêutica pré-natal: efeitos a longo prazo no neurodesenvolvimento

Mariana Pires de Carvalho Coimbra

Literacia em cuidados paliativos de profissionais e não profissionais de saúde

December 18, 2020

Supervisor: Marília Dourado

Marina Gerales

Acompanhamento farmacoterapêutico pós-enfarte agudo do miocárdio

Marisa Aparecida Tolentino

Governança clínica, gestão de risco e a segurança em cuidados de saúde para os doentes em Angola

December 17, 2020

Supervisor: Vitor Raposo

Marisa Daniela Pereira Ferreira

Advances in the Immunotherapies for Alzheimer's Disease

Marta Telo Pinto

Depressão no Idoso e Hábitos de Vida Saudáveis

Supervisor: António Veríssimo

Marta Sofia Ribeiro Martins

Avaliação de custos e satisfação dos doentes com a criação de um Hospital de Dia em Ortopedia Oncológica no Centro Hospitalar e Universitário de Coimbra

January 2020

Supervisor: Carlota Quintal, Isabel Cruz

Matilde S. Rodrigues

Hypoadenosinergic Pathologies In A Rat Model Of The Willis-Ekbom Disease

December 3, 2020,

Supervisor: Rodrigo Cunha

Matilde Isabel Ribeiro Pina

Terapias Génica e Celular na Doença de Alzheimer

Miguel Ângelo Almeida Cardoso

Efeito do Adper™ Scotchbond™ 1 XT, Clearfil™ SE Bond 2 e Scotchbond™ Universal na atividade de células tipo odontoblasto

Supervisor: Ana Sofia Coelho, Eunice Carrilho, Mafalda Laranjo

Natalina dos Reis da Cruz Spencer

Relação da perceção de suporte organizacional, envolvimento e segurança do doente

December 2, 2020

Supervisor: Pedro Lopes Ferreira

Nisa Tamara Silva Magalhães

Potencial terapêutico de moduladores do NRF2 na leucemia linfoblástica aguda- Estudos in vitro

Supervisor: Ana Cristina Gonçalves, Co-Supervisor: Joana Jorge

Nuna Raquel de Sá Lemos Gonçalves

Cuidados Continuados e Paliativos Pediátricos: O Impacto da Leitura na Família, na Fase de Agonia

December 16, 2020

Supervisor: Marília Dourado

Nuno Renato Amorim de Lima

Modeling of lung metastases from osteosarcoma in mice

Supervisor: Flávio Reis

Patrícia Isabel Francisco Rita

Burnout e satisfação profissional: disparidades nos cuidados de saúde primários

November 25, 2020

Supervisor: Pedro Lopes Ferreira

Pedro Miguel Dias Vieira.

Blueberries effects on diet-induced prediabetic nephropathy – an in vivo experimental approach

Supervisor: Flávio Reis

R. Gueifão

Determinantes na escolha das unidades de saúde privadas em Portugal: um estudo exploratório

Supervisor: Sandra Oliveira

Rafael Baganha
Development of single-step affinity chromatography protocols for the purification of adeno-associated viral vectors
Supervisor: Luis Almeida

Renata Maria Matias da Silva de Sousa Freire Saraiva.
Biomarcadores do envelhecimento - Uma visão global
Supervisor: Anabela Mota Pinto

Renato André Saraiva Santos
A influência do alelo épsilon 4 do gene da apolipoproteína E na predisposição para o desenvolvimento da doença de Alzheimer

Renato Macedo
Hippocampal dysfunction in animal models of neurodevelopmental disorders
Supervisor: Ângela Inácio, Ana Luísa Carvalho

Ricardo Casqueiro
Development of nanoparticles to target senescent cells
Supervisor: Lino Ferreira, Vitor Francisco

Ricardo Filipe Silva de Oliveira.
Assessment of benefits and risks of sodium-glucose co-transporter 2 inhibitors in metabolic complications
Supervisor: Flávio Reis

Ricardo Portugal
Dados do mundo real do tratamento com pembrolizumab de doentes com cancro com pulmão de células não-pequenas em estadio avançado previamente tratados

Rita Isabel Simões Clemente
A sobrecarga e a qualidade de vida dos cuidadores informais: um estudo no Município de Cantanhede
December 2, 2020
Supervisor: Pedro Lopes Ferreira, Marília Dourado

Rita Maria Mendes Silveira de Almeida Martins
Development and characterization of silica nanoparticles to mediate an antitumoral strategy involving drug and recombinant protein

Rita Martins
A new nanosystem-mediated antitumor strategy involving chemotherapeutic agents and recombinant proteins
Supervisor: João Nuno Moreira

Rita Sousa
Plasma Rico em Plaquetas na Harmonização Orofacial
Supervisor: Teresa Sequeira

Rosana Martins
Avaliação do efeito dos regimes clássicos de quimioterapia e imunoterapia no perfil metabólico de linhas celulares de cancro de pulmão de não pequenas células

Rui Bento Félix Buzaco
Mestrado de Geriatria da UC
Supervisor: António Veríssimo

Rute Alexandra Gomes Monteiro
O impacto do envelhecimento na resposta
Supervisor: Anabela Mota Pinto

S. Ferreirinha
A Gestão do desperdício em contexto hospitalar: o projeto Crivest
Supervisor: Sandra Oliveira

Sara Canário
Orchestrating Osteoclast Differentiation Through ROS and Mitochondrial Regulation: Developing new approaches for osteoporosis treatment
February 27, 2020
Supervisor: Paulo Oliveira

Sara Isabel da Silva Faria
Adaptação cultural e validação da versão portuguesa do “Western Ontario Shoulder Instability Index”. ESS-IPP
February 12, 2020
Supervisor: Rui Pimenta

Sara Sofia Bessa Magalhães
Familial multiple osteochondromatosis: literature review regarding a clinical trial

Sérgio Miguel Pedroso Azenha Cardoso.
Mestrado de Geriatria da UC
Supervisor: António Veríssimo

Sofia Lurdes Pereira Abreu
Os Cuidados Paliativos como Resposta às Necessidades das Pessoas com Doença Prolongada: A Realidade na Região Autónoma da Madeira
December 11, 2020
Supervisor: Marília Dourado

Solange Martins
Master's in Molecular and Cellular Biology
Supervisor: João Peça

Teresa Rajado
Computation meets experimentation to improve the catalysis and specificity of Cas12a genome editing enzyme

Tiago Moderno da Costa.
Estudo de compatibilidade química de um kit de extração: CASEWORK DIRECT KIT, PROMEGA
Supervisor: Francisco Manuel Andrade Corte Real Gonçalves,
Co-Supervisor: Filipa Silva Balsa de Sá

Zulmari Thais Dos Santos Betancourt
Avaliação da Citotoxicidade de Cimentos Endodônticos Biocerâmicos
Supervisor: Rita Noites, Co-Supervisor: Ilda P Ribeiro

TECHNOLOGY TRANSFER

Head: Ana Catarina Cunha Santos

The CIBB fosters innovation and entrepreneurship by translating the scientific and technological knowledge developed in our laboratories into answers to major societal challenges in healthcare. The biomedical nature of the research performed at CIBB brings an additional responsibility towards society. As such, 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 is the process of sharing knowledge, skills, facilities, and technologies among institutions for further development and exploitation. 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 socioeconomic development.

During 2020, CIBB consolidated the recently (in 2019) created Technology Transfer Office (TechTransfer) mainly through the implementation and assessment of procedures for protection and valorization of technological knowledge towards commercialization. The main achievements in Intellectual Property protection, management and valorisation in 2020 were the following:

- 7 patent applications (provisional and international through PCT);
- 1 utility model application;
- 4 international and national patent/utility model publications;
- 10 evaluated technologies (invention disclosure, search, patentability, and technology valuation reports);
- 1 successful licensing agreement of one technology for an international (USA) enterprise with capital revenue for CNC;
- 1 granted patent in USA.

Regarding projects in the topics related with the technology transfer and innovation, CIBB successfully concluded the execution of the project “LifeSciences ByCENTRO” funded by CENTRO2020 and applied for funding in promotion and training on bio-entrepreneurship as coordinator of a project in consortium with two other institutions of the CENTRO region of Portugal (currently in the final evaluation phase with CENTRO2020). The CIBB also applied to be recognized as a “Valorization and Technology Transfer Center” by Agência Nacional de Inovação (granted already in the year 2021).

Regarding scientific research projects, the Technology Transfer Officer of CIBB assisted researchers and participated as team member in the delineating of Intellectual Property protection and commercialization strategies for project applications in international (e.g. CaixaImpulse Consolidate) and national calls (e.g. 2020 FCT Call for Projects in all Scientific Domains). The TechTransfer of CIBB also engages with valorisation platforms such as Innospin and In-Part to get in contact with industrial partners and opportunities for further development and exploitation of the knowledge and technologies developed at our institute.

The TechTransfer of CIBB is committed with the training and education of researchers and students with the first MSc student supervised in the school year 2020-2021 with the thesis topic “Factors that influence valorization of technologies from R&D Centers”, the annual one-day training on the Course “Connecting Researchers with the Society” from the CIBB PhD Programme in Experimental Biology and Biomedicine, and other lectures and seminars in innovation and IP protection and entrepreneurship topics.

Through technology transfer, CIBB assures the application of the research developed here to the greater benefit of our local community and general society.

SCIENCE COMMUNICATION @ CNC / CIBB

Head: Sara Varela Amaral, PhD.

Team: João Cardoso, Lia Lopes, Marta Quatorze and Sara Varela Amaral

As a modern research institution where novel scientific and social challenges arise, CNC is strongly committed to science communication. Reach different groups of the society and develop innovative public engagement strategies are important hallmarks of the research center strategy.

Science Communication Office goals are:

- To foster dialogue between scientists and different groups of society - students, elderly, teachers, etc;
- To provide public accountability, ethically justified by the public nature of scientific funding;
- To engage society in research process;
- To spread our scientific findings through media (newspaper, radio, TV) and social networks;
- To create scientific culture through public engagement projects in order to construct a truly scientific citizenship and a more knowledgeable society;
- To consolidate CNC institutional image for the national and international scientific system, national and regional political decision-makers, public and private funders, and different types of publics;
- To inspire and engage scientist in science communication initiatives, give them tools that improve the public engagement;
- To evaluate our science communication strategies in order to improve and understand the best practices to engage community in science and scientific themes;
- To establish strategies that contributes to a better communication and team spirit inside the research center.

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.

Science in 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.

In 2020 CNC was in the news 694 times with an advertising value of 3.436.561 euros, reaching a total number of 39.193.254 audiences.

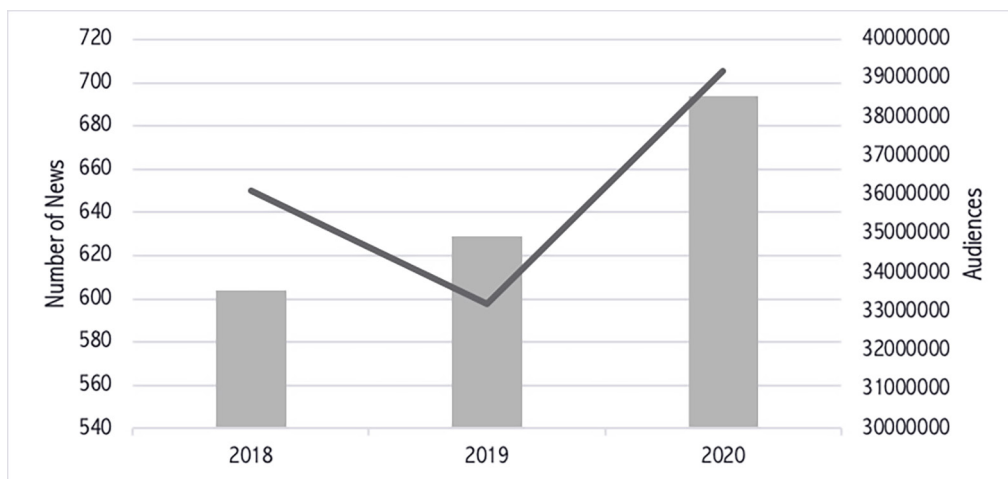


Figure 1 – CNC news and audiences in 2018, 2019, 2020.

To reach a wider population we improve our presence in social networks. At the end of 2020 we have more than 15.000 followers at different social networks: Facebook, Twitter, LinkedIn, Instagram and Youtube.

Public Engagement in Science

CNC 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.

RARE DISEASE DAY February 2020

During Rare Disease Day we organized an event at CNC dedicated to Machado-Joseph disease involving researchers, doctors, patients and caregivers. I received at CNC more than 20 patients and caregivers and promoted a lectures, lab visits and small conversations.



Figure 2 – Rare Disease Day participants

UNISTEM DAY MARCH 2020

UniStem Day is an initiative, launched by the Interdepartmental Stem Cell Research Center at the University of Milan (UniStem), which aims to disseminate research carried out in the area of stem cells. We received about 25 high-school students in our stem cell labs and promoted a discussion about stem cell research and applications.



Figure 3 – Program of UniStem day 2020 promoted by CNC

WORLD SLEEP DAY MARCH 2020

A health sleep habits campaign – Better Sleep, Better Life, Better Planet – organized by CNC with the collaboration of APS and Gaxozmed took place all over the country with animations and infographics in different supports:

- TOMI screens (Lisboa, Algarve, Figueira da Foz, Águeda, Évora, Tábua) | 615.000 exhibitions
- Outdoors (Lisboa, Porto, Coimbra and Faro) | 30 posters
- ATM machines (national level) | 933 machines
- Coimbra city council and buses TVs
- Social Networks | reach of 8015



Figure 4 – Some images of the national campaign Better Sleep, Better Life, Better Planet.

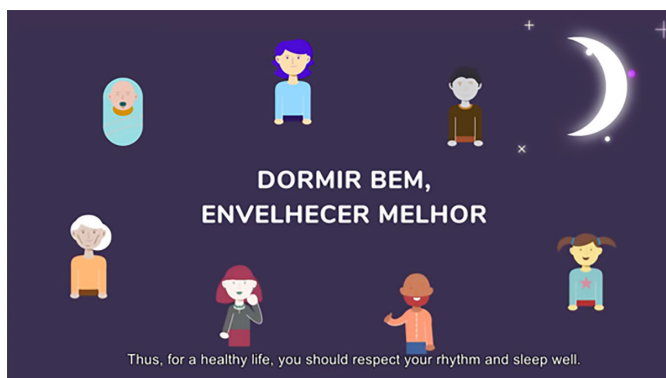


Figure 5 – Frame from the animation Sleep Hygiene Habits Throughout Life available here.

COVID-19 EDUCATIONAL MATERIALS
MARCH-MAY 2020

CNC joined UC against COVID-19 platform and contributed to the development and dissemination of several science communication contents:

- Videos



Figure 6 – Frame of an animated video about COVID-19 tests, available at <https://www.uc.pt/covid19/article?key=a-89d2d441a2>

- Research Q&A videos by CNC researchers (available at <https://www.uc.pt/covid19/repository?key=r-f724fdd35f>)

- Infographic



Figure 7 – Infographic about COVID-19

ZOOMING ON SCIENCE
JUNE-JULY 2020

Weekly youtube live sessions about different research carried out at CNC, with the participation of researchers from several areas of CNC: neuroscience, metabolism and biotechnology. Overall the sessions had more than 1000 views. The sessions are available at <https://www.youtube.com/watch?v=8ZxCEpnKbxs&list=PLMYLx4Ywr9u56rToerpAfajENMHenw42V>

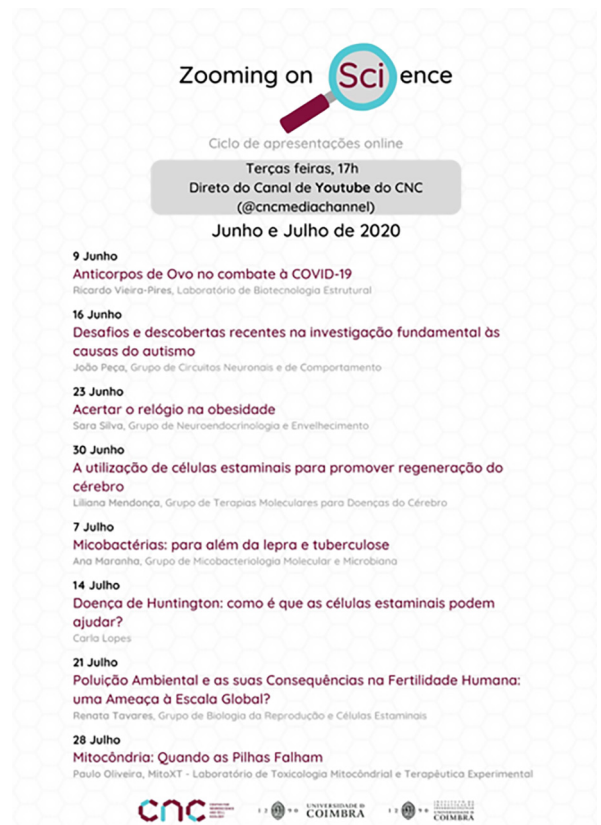


Figure 8 – Zooming on Science programme

BRAIN AWARENESS WEEK (BAW) | JOURNEY AROUND THE BRAIN
OCTOBER 2020 (POSTPONED DUE THE COVID-19 PANDEMIC)

Journey around the Brain challenged citizens to join a journey through the brain research that is being done at the CIBB. Due to the COVID-19 pandemic, the program was adjusted to fulfill all the restrictions imposed by health authorities. The BAW 2020 was supported by FENS, DANA Foundation, SPN and Ciência Viva.

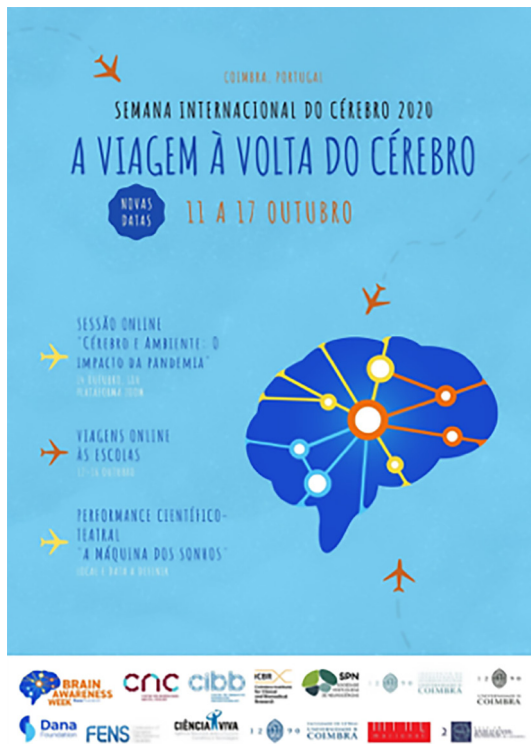


Figure 9 – Program of BAW 2020

Three main activities were organized:

• **Online debate**

On October 14th, the online debate entitled “Brain and Environment: The impact of the pandemic” aimed to discuss the role of the social, biological and natural environments in the COVID-19 pandemic, and its impact on the brain. This event was organized in collaboration with the Portuguese Society for Neuroscience, which coordinated the Brain Awareness Week in Portugal. We counted with the participation of an audience of 79 people and 7 speakers.

• **Online sessions with Schools**

From October 12th to 16th, several researchers presented their work, engaging around 214 high school students. We have discussed topics in neuroscience field such as Autism, Machado-Joseph Disease and the use of brain organoids to study brain disorders.

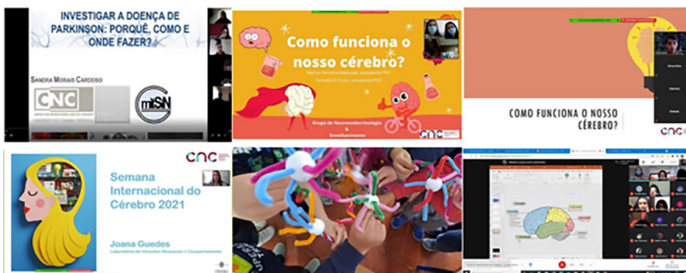


Figure 10 – BAW online sessions with schools

• **Art & Science Performance**

A Máquina dos Sonhos took place on October 27th and explored Sleep and Obstructive Sleep Apnea Syndrome (OSAS). This performance combined the artistic and scientific languages and was produced in collaboration with the theater company Marionet and the SleepApneaID – the CIBB research project that aims to study OSAS. This event was organized in the scope of the celebrations of the University of Coimbra 730th anniversary and had 60 viewers.



Figure 11 – A Máquina dos Sonhos theatre performance

EUROPEAN RESEARCHERS’ NIGHT (ERN)
SEPTEMBER 2020

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 CNC has been a partner of this event in Coimbra since 2009. This year we organized a live debate with the participation of researchers from several areas of the University (law, neuroscience, ecology, metabolism) with the moderation of a TV journalist.

Debate Online
Como é que a Ciência pode responder a problemas da sociedade?

NOITE EUROPEIA INVESTIGADORES
CNC UNIVERSIDADE DE COIMBRA

DIRETO | 27 DE NOVEMBRO
CANAL YOUTUBE UNIVERSIDADE DE COIMBRA | 18H - 20H

André Dias Pereira
CDB, FDUC

Cláudia Cavadas
IIIUC, UC, CNC-UC, FFUC

Dulce Freire
ReSEED, FEUC

Paulo Oliveira
CNC-UC

Moderação:
Ana Simões
TVI

Figure 12 – Debate organized at ERN 2020

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 2020: overall 155 people participated in the activities that involved 13 CNC researchers.

CNC 30TH ANNIVERSARY NOVEMBER 2020

In 2020 CNC celebrated 30 years. Within the commemoration of the CNC 3 decades, Luís Pereira de Almeida, CNC President, and Ana Luísa Carvalho and Paulo Oliveira, CNC Vice-Presidents, were interviewed by Diário de Coimbra, discussing topics such as the oviews and objectives for the Center led by the new Board of Directors, the CNC/UC answer to the COVID-19 pandemic, and the importance of accomplishing 30 years of biomedical research, among other topics.



Para a equipa: Luís Pereira de Almeida, Paulo Oliveira e Ana Luísa Carvalho - o edifício Biomed, no polo B, é fundamental para a actividade científica do CNC.

CNC quer colocar Universidade de Coimbra na primeira liga das universidades

Entrevista CNC assinala hoje três décadas ao serviço da investigação científica produzida por investigadores de excelência nas áreas da Biomedicina e da Biotecnologia. A nova equipa responsável pelo CNC nos próximos dois anos, liderada por Luís Pereira de Almeida, quer crescer, produzir mais e dar carreira aos investigadores. E já agora, dar um "empurrão" ao Biomed

um marco recente. Tem sido importante para ganhar escala? O CNC faz 30 anos e é um momento para analisar o que foi feito nos últimos anos. Mas já antes. Desde 1990, sob a forma de Centro de Biologia Celular, criado pelo professor António Patricio Carvalho, este sempre tem tido um papel preponderante na produção científica da região (em 2003, juntamos as forças com um outro centro, o ICB, formando um consórcio que passou a ser o financiamento da IEC e esse consórcio passou a ser o IEC - Centro de Inovação em Biomedicina e Biotecnologia. Se nos últimos anos o nosso centro, com este consórcio, tem dado mais frutos, o CNC tem um pouco mais de 200 investigadores, como o ICB tem cerca de 300. A unidade O centro foi criado pelo IEC, está em funcionamento e é financiada. É fundamental, eu acho, o modelo de laboratório associado, porque assim temos mais um local de trabalho que é essencial para a nossa actividade.

Falando da vossa actividade, como apresenta e define o CNC?
A missão principal do CNC é compreender os mecanismos da doença e encontrar estratégias para combater essas mesmas doenças. Estamos muito focados nos domínios da oncologia, mas também nas doenças metabólicas, cardiovasculares e ainda nas doenças associadas à infecção. O centro está organizado em três grandes áreas científicas: Neurociência, Oncologia e Biologia Celular. Metabolismo e Desenvolvimento, coordenada pelo professor Paulo Pereira de Almeida, e Biotecnologia, coordenada por mim.

Figure 13 – CNC 30th birthday interview at Diário de Coimbra.

We launched a comic that shows the different roles of CNC community based on the CNC's strategic objectives: research, education, technology transfer and science communication.

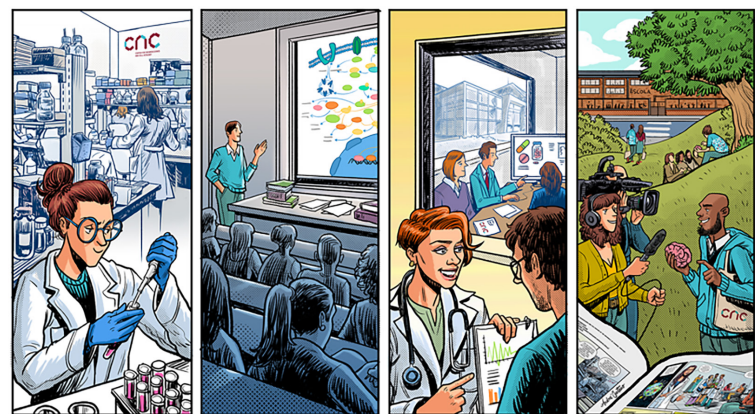


Figure 14 – CNC 30th birthday comic by André Caetano.

COMICS FEBRUARY AND JUNE 2020

In order to explore different languages to communicate scientific topics and to target wide audiences we developed a partnership with Jornal Público, one of the most prestigious daily newspaper in Portugal (daily circulation number: 33 000). In this context we produced two comics, involving different researchers and an illustrator: one about Machado-Joseph Disease (MJD) produced with APAHE (launched during Rare Disease Day) and other about Amyotrophic Lateral Sclerosis (ALS) produced with APELA (launched in ELA national day).

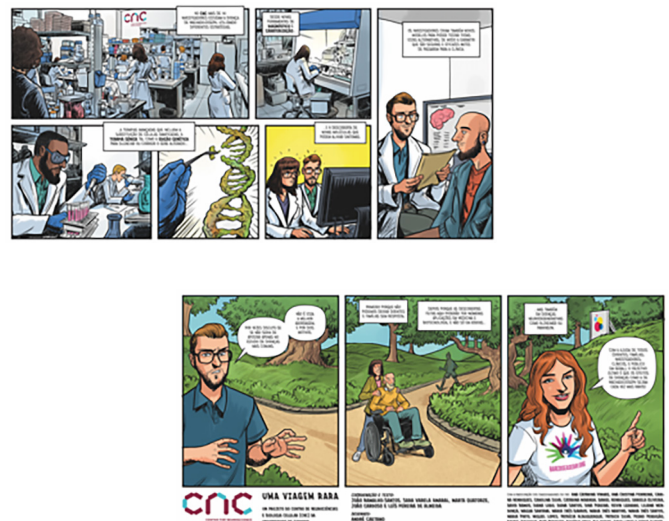


Figure 15 – MJD comic.

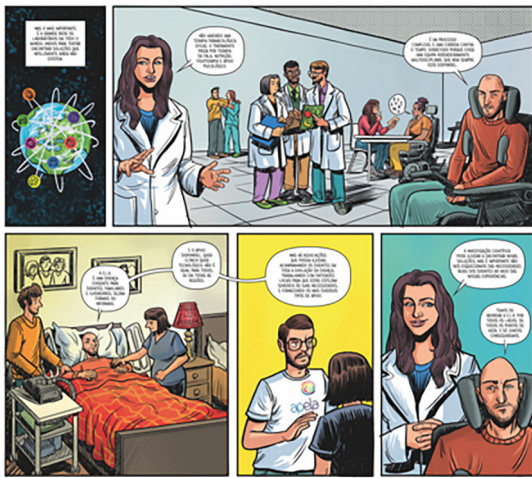
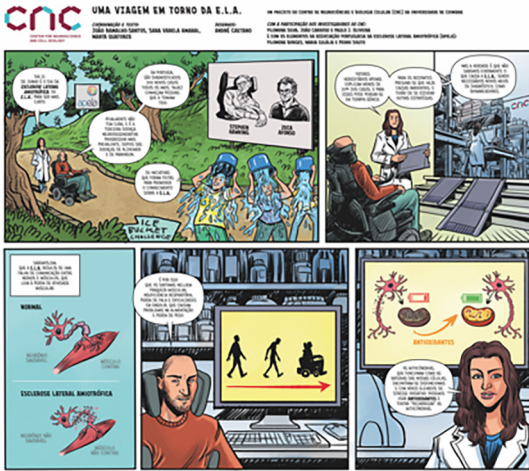


Figure 16 – ALS comic.

A SAÚDE NO SABER SINCE MAY 2020

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 will discuss 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 2019. In 2020 we launched the project and started the production of science communication materials at radio, newspaper, illustrations to start the campaign in January of 2021.



Figure 17 – Science communication materials that will be produced in the scope of Health in Knowledge project.

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. 17 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.



Figure 18 – Summary of SciComm at CNC in 2020.

CORE FACILITIES @ CNC

ANIMAL HOUSE

Head: João Laranjinha, PhD.

Staff:

Paula Mota (Designated Veterinarian and Animal Facilities Coordinator)

Carmen Semião (FMUC/CNC Animal Facility coordinator, Animal Welfare responsible and caretaker)

Fátima Graça (FMUC/CNC caretaker)

Mónica Serrano (FMUC/CNC assistant technician and caretaker)

Maria Eugénia Campos (FMUC/CNC assistant technician and caretaker)

Sandra Freire (FMUC/CNC Animal Welfare responsible and caretaker)

Tânia Ribeiro (UC-BIOTECH Animal Facility Coordinator and Animal Welfare responsible)

Fátima Moreira (UC-BIOTECH Animal Welfare responsible and caretaker)

Trainees:

Cristina Teixeira (caretaker)

Milene Ribeiro (caretaker)



Animal room – IVC cages (type I)

The Animal House Facilities are a shared resource that provides services in laboratory animal experimentation and husbandry, for all CNC and FMUC scientists using animals in their research.

At the present 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. The FMUC/CNC Animal Facility is a conventional type facility with the capacity to house about 4000 animals, mice and rats (*Mus musculus* and *Rattus norvegicus*). It has a “clean” area for animal production and an experimental area that includes animal rooms, procedures room and quarantine room.

The CNC_UC-BIOTECH Animal Facility has the capacity to house 1500 specific pathogen free (SPF) animals. It has a barrier area for animal production, a quarantine area and an experimental area. In the experimental area there is 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.

The animal facilities house rodents with wildtype phenotype, but also genetically altered strains, either due to spontaneous mutations or due to human manipulations. At this time the genetically altered strains are related to changes in the neurological system, immune system and in metabolic control and expression of reporter genes.

The animal facilities provide specialized animal services, namely breeding and housing of transgenic/knockout strains, production of rats/mice embryos and litters and support to animal experimentation procedures. 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 socioeconomic development.



Laminar flow chamber

CORE FACILITIES @ CNC

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.

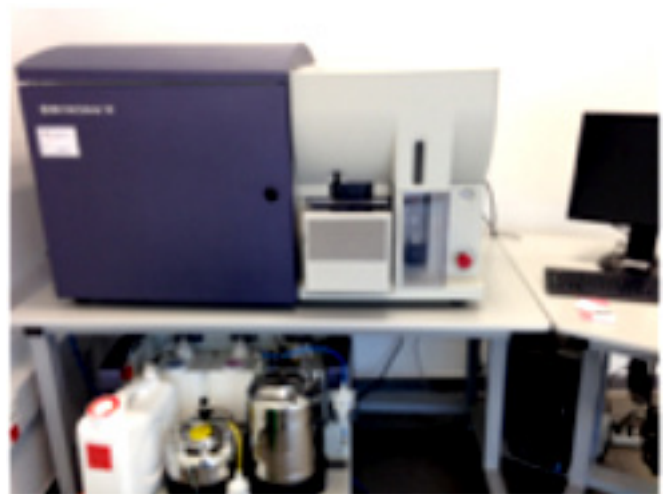
The Unit is divided between Polo I in Coimbra and in UC-Biotech in Cantanhede, that are currently equipped with a Becton Dickinson FACSCalibur cell analyser (4 colours) and a Partec CyFlow Space cell sorter (7 colours), and with a Becton Dickinson Accuri™ C6 cell analyser (4 colours) with auto-sampler 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.



FACSCalibur (Becton Dickinson) - 4 colours



FACSAriaTMIII (Becton Dickinson) - 12 colours

CORE FACILITIES @ CNC

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 2020, the MICC facility supported around 200 users from 58 research groups, with more than 25000 hours of equipment usage.

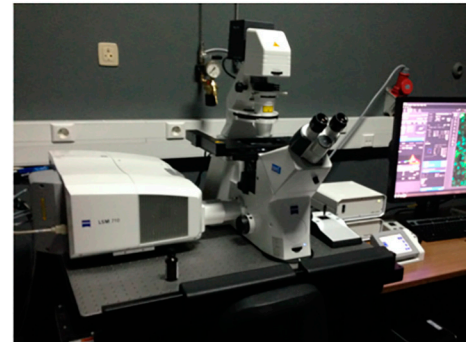
MICC-CNC is a well-established and renowned facility at the Portuguese scientific community which can be attested by the increase number of external services performed at the facility. External users are from different Portuguese research institutions: University of Coimbra, University of Algarve, University 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 20th- 31st). Cortes L co-organized the “Microscopy Imaging Analysis” Master course at the University of Valladolid (Online, May 4th-8th), the “Advanced Imaging Methods in Neuroscience” an EIT Health Aging PhD School (November 9th – 20th) and lectured at several post-graduation courses: PDBEB PhD courses, and MCB Master Programme from the University of Coimbra.

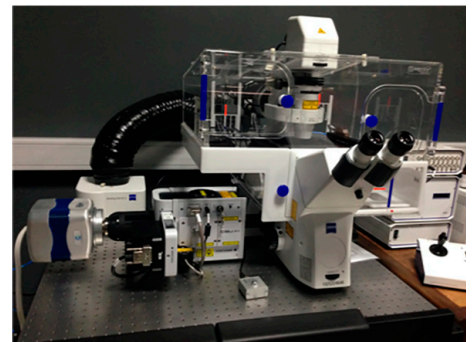
MICC-CNC is a Zeiss Labs@location Partner sharing and providing in depth knowledge and dedicated services, with expertise in specific applications of imaging technologies. In accordance with the Lab@location protocol agreement, MICC-CNC has performed external services for Carl Zeiss Microscopy.

Moreover, MICC-CNC is a node of the Portuguese Platform for Biolmaging (PPBI), a research infrastructure of the RNIE roadmap, Cortes L being the Coordinator for the Mondego & Beiras Pole. Importantly, in 2020, the PPBI network has become a Node of the prestigious EuroBiolmaging Research Infrastructure, which is an ESFRI initiative.

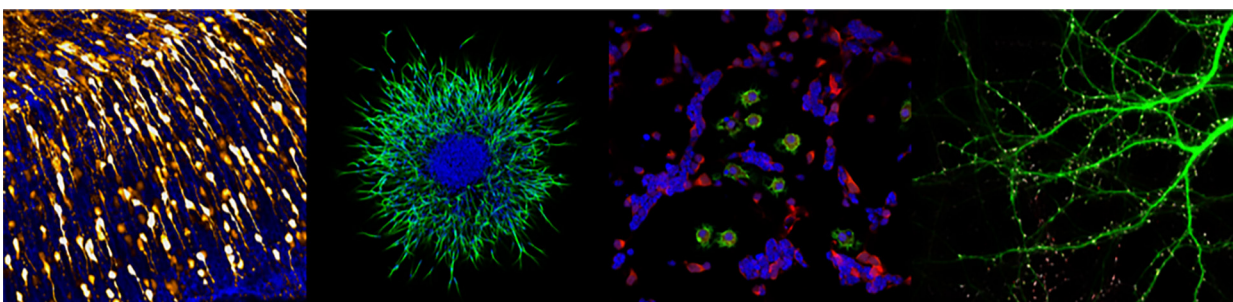
Finally, Cortes L. is an active member of the CTLS-Core Technologies for Life Sciences European association, and a team member of the Innocore Erasmus+ project.



Confocal LSM 710 (34 channels)



Confocal Cell Observer Spinning-Disk



CORE FACILITIES @ CNC

MASS SPECTROMETRY UNIT

Head: Bruno Manadas, PhD.

During 2020 the Life Sciences Mass Spectrometry lab developed several research projects coordinated by CNC, but also national and international collaborations. The research performed over the last years resulted in a significant number of publications, along with the continuation of an FCT project headed by the lab and several co-headed by the lab, all with a strong proteomics and metabolomics component. The certified services under the ISO 9001 compliance have been extended and new plans to cover the remaining laboratory research methods under this compliance have been implemented (being the only ISO 9001 certified research-based mass spectrometry lab in Portugal).

MAIN ACHIEVEMENTS:

Our strong technological capabilities, developed over the last years, are now resulting in higher biological impact research papers and demonstrating their potential to be transposed to biomarker research mainly in association with translational approaches. These indicators have contributed to increase the clinician's perception regarding the potential of the technology existent in the lab which resulted in the establishment of integrative screening projects for the search of new biomarkers for several diseases. We have dedicated special efforts on data processing and visualization tools to increase the visual impact of our research. We have also extended our sample collection for psychiatric disorders, neurodegenerative disorders, diabetes and thyroid cancer. Altogether this will put our lab in an interesting position in the next 3-5 years. Publications (Accumulated impact factor of 69.9, 13 publications, 8 in Q1 (2 in top 10%), 6 with impact factor above 6):

1. Ribeiro, I.P., et al, Proteomics-based Predictive Model for the Early Detection of Metastasis and Recurrence in Head and Neck Cancer: Cancer Genomics Proteomics, 2020. 17(3): p. 259-269. <https://www.ncbi.nlm.nih.gov/pubmed/32345667>

2. Mancio, J., et al, Influence of EPICardial adipose tissue in HEART diseases (EPICHEART) study: Protocol for a translational study in coronary atherosclerosis. Rev Port Cardiol, 2020. 39(11): p. 625-633. <https://www.ncbi.nlm.nih.gov/pubmed/33168363>

3. Mancio, J., et al, Epicardial adipose tissue volume and annexin A2/fetuin-A signalling are linked to coronary calcification in advanced coronary artery disease: Computed tomography and proteomic biomarkers from the EPICHEART study. Atherosclerosis, 2020. 292: p. 75-83. <https://www.ncbi.nlm.nih.gov/pubmed/31783201>

4. Lucena, S., et al, Changes in the salivary proteome of beagle dogs after weight loss. Domest Anim Endocrinol, 2020. 72: p. 106474. <https://www.ncbi.nlm.nih.gov/pubmed/32361424>

5. Lopes, C., et al, Mitochondrial and Redox Modifications in Huntington Disease Induced Pluripotent Stem Cells Rescued by CRISPR/Cas9 CAGs Targeting. Front Cell Dev Biol, 2020. 8: p. 576592. <https://www.ncbi.nlm.nih.gov/pubmed/33072759>

6. Ferreira, D., A. et al, FA-SAT ncRNA interacts with PKM2 protein: depletion of this complex induces a switch from

cell proliferation to apoptosis. Cell Mol Life Sci, 2020. 77(7): p. 1371-1386. <https://www.ncbi.nlm.nih.gov/pubmed/31346634>

7. Domingues, C., et al, Cofilin-1 Is a Mechanosensitive Regulator of Transcription. Front Cell Dev Biol, 2020. 8(678): p. 678. <https://www.ncbi.nlm.nih.gov/pubmed/32903827>

8. de Leeuw, F.A., et al, Specific Nutritional Biomarker Profiles in Mild Cognitive Impairment and Subjective Cognitive Decline Are Associated With Clinical Progression: The NUDAD Project. J Am Med Dir Assoc, 2020. 21(10): p. 1513 e1-1513 e17. <https://www.ncbi.nlm.nih.gov/pubmed/32001171>

9. Coelho, M., et al, The Potential of Metabolomics in the Diagnosis of Thyroid Cancer. Int J Mol Sci, 2020. 21(15). <https://www.ncbi.nlm.nih.gov/pubmed/32722293>

10. Anjo, S.I., et al, A different vision of translational research in biomarker discovery: a pilot study on circulatory mitochondrial proteins as Parkinson's disease potential biomarkers. Transl Neurodegener, 2020. 9: p. 11. <https://www.ncbi.nlm.nih.gov/pubmed/32266064>

11. Abrantes Dias, A.S., et al, Analytical methods to monitor dopamine metabolism in plasma: Moving forward with improved diagnosis and treatment of neurological disorders. J Pharm Biomed Anal, 2020. 187: p. 113323. <https://www.ncbi.nlm.nih.gov/pubmed/32470692>

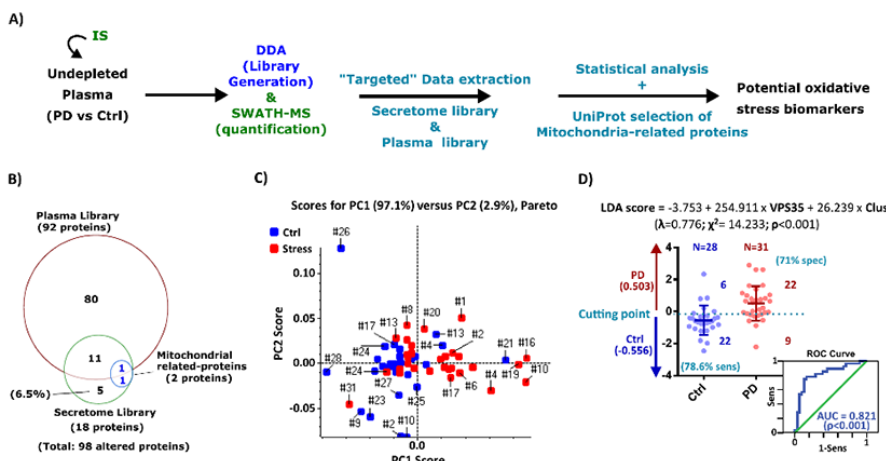


Fig. 1 - Evaluation of the capacity of the proposed pipeline to identify potential circulating biomarkers. a Workflow used to identify potential oxidative stress biomarkers in plasma samples from Parkinson's Disease (PD) and controls (Ctrl).

SERVICES @ CNC

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 COVID-19-related pandemic, the samples' income suffered 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) and Prof. Adrián Llerena (CICAB Clinical Research Centre at Extremadura University Hospital and Medical School, Universidad de Extremadura, Badajoz, 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 hospitals. Therefore, the cells were cryopreserved for future retests; they were simply harvested, or used to prepare some enriched mitochondrial samples, concerning those tests on fibroblasts towards the diagnostic evaluation, in three cases.

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.

A total of 8 patients suspected of mitochondrial cytopathies were

studied, corresponding to the analysis of 12 samples, including lymphocytes isolated of peripheral blood (7) and, muscular (2) and skin (3) biopsies. A MRC deficiency was detected in 4 patients (50%). Assayed ATP levels were lower than the reference normal values in two out of the three patients' samples analysed, reinforcing the association with energetic deficits according to the mitochondrial biochemical profiles and clinical phenotypes of the patients.

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 two patients, muscle and plasma. The coenzyme content was normal in both.

A sample of skeletal muscle is more specific for the CoQ10 deficit detection, and the fact that the muscle analyzed belonged to a boy with a heterozygous alteration in a gene coding for a CoQ10 biosynthetic protein, suggests that the tendency to deficiency in this patient has been hold out. Despite the low diagnostic yield for CoQ10 deficiency in mitochondrial disorders, the first step of patient's CoQ10 estimation may be based on plasma measurement, allowing discriminating between primary and secondary deficiency, once the muscle is analyzed. Muscle CoQ10 deficiency is relatively common in patients with mitochondrial disorders, although plasma CoQ10 values are often normal.

Biomarkers of well-being investigation

The group has proceeded with wellness's biomarkers setting, 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. The levels of biomarkers cortisol, oxytocin, serotonin and complemented with ATP levels were evaluated in saliva samples of controls and upon social interfaces with patients in clinical context (195 samples). The pilot study suggests the reduction of stress levels perceived by the biomarker cortisol, reinforcing the positive role of the social intervention for well-being in health outcomes.

Functional studies

Functional genomics' assays were performed, highlighting the reverse translational research nature of the work developed at LBioMiT.

During this year, the studied patients were, firstly, two relatives' patients 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, an adult with a phenotype of familiar dominant optic neuropathy, in whom novel genetic sequence variations were found with the need of clarifying pathogenicity. The preparations were initiated for the analysis of 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 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-seven samples (blood – 22, muscle – 3 and skin-derived fibroblasts - 2) were received for DNA extraction. Two DNA samples were also received for genetic analysis. Samples previously extracted were analysed for 76 genetic tests.

mtDNA genomes studies:

Molecular differential analyses of mitochondrial cytopathies have been performed by total mtDNA sequencing analysis using Next Generation Sequencing (NGS), covering all mtDNA sequence variations, including confirmed pathogenic mutations associated to MRC diseases. During 2020, 14 samples of 14 patients were analysed using this strategy and the findings included several benign sequence variations were identified in all samples. This method was also adapted for detection and characterization of mtDNA deletions, analysed in 5 samples.

The 24h testing of the Top 3 LHON primary mutations was implemented and screening allowed a clear positive result with identification of m.3460G>A point mutation in a male young patient suspected of LHON, which highlights the importance of a fast response, to quickly start treatment in order to prevent or to treat, if possible, the visual loss.

Copy number (mtDNA) assays are part of the genetic mitochondrial genome screening for diagnostics of Mitochondrial DNA depletion syndromes (MDS), which is caused by defects in intergenomic communication and comprising a heterogeneous group of diseases, namely due to nuclear genes mutations leading to severe reduction of mtDNA content, with energy failure. Concerning mtDNA copy number assays for depletion screening, 30 samples of 24 patients were investigated. Depletion (mtDNA content below 30%) was confirmed in one sample in two independent analysis (in triplicates).

Concerning the screening of nuclear genome (nDNA) defects causative of MRC diseases, 11 samples were screened for whole exome sequencing by NGS.

Additionally, POLG1 and POLG2 genes were also analysed in 4 (3 and 1) samples, allowing the detection of sequence variations, but

none was considered pathogenic.

Screening of OPA1 and OPA3 genes (6 and 4 samples, respectively), ANT, TWINKLE and MEN1 (1 sample each) also revealed sequence variations without pathogenicity.

Three samples were also analysed as part of a family study for screening sequence variations previously found in two probands. RNA integrity analysis, using capillary electrophoresis, was also performed as part of our Molecular Biology and Genetics Services. During the last year we have analysed 132 samples, divided in 11 RNA nano chips.

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 462 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 19 cases.

Regarding the Exome analysis, the bioinformatics 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 identification of the most probable cause of the disease. Among the samples in study, the full examination and application of the decision diagrams was completed in thirteen cases.

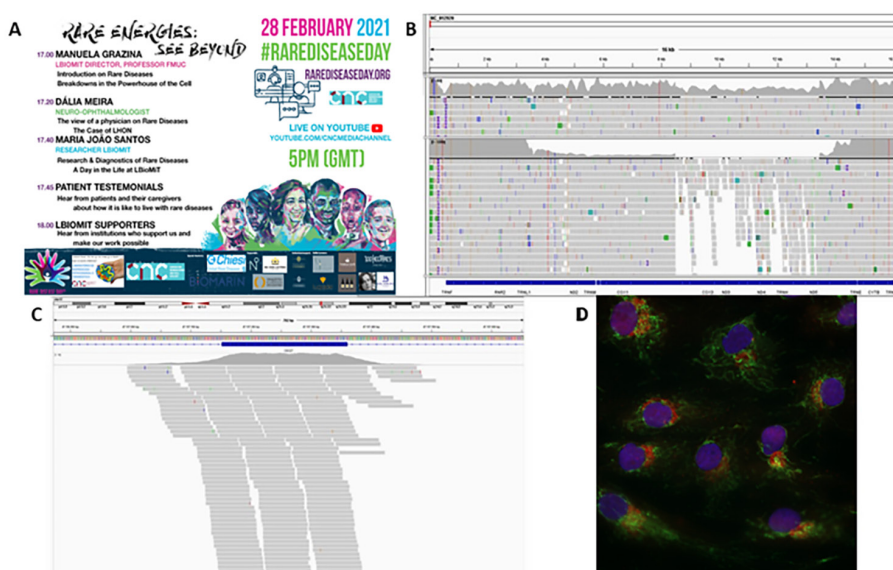


Fig. 1 – Illustration representative of activities occurring at LBioMiT.

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).

SERVICES @ CNC

LABORATORY OF NEUROGENETICS

Head of Unit: Maria Rosário Almeida

Team: Ana Cristina Santos

In 2020 the Neurogenetics Laboratory has pursued its main objective, namely the genetic analysis of patients with various Neurological diseases, mainly from the Neurology Department of Centro Hospitalar e Universitário de Coimbra (CHUC). In addition to the molecular diagnostic tests performed in affected individuals, this laboratory carried out predictive tests in asymptomatic relatives, followed in the genetic counseling at the Pediatric Hospital in Coimbra. The methodologies involved were mainly, Next Generation Sequencing technology (NGS) with subsequently Sanger sequencing, to confirm all the pathogenic variants identified. However, other techniques have also been used, such as: RP-PCR and ELISA assays, to detect the C9orf72 expansion and the low level of serum GRN, respectively, to study the patients with Frontotemporal lobar degeneration (FTLD) and/or Amyotrophic lateral sclerosis (ALS).

Last year, this laboratory expanded the range of genes studied such as: CECRI and SLC6A3 providing the diagnosis of patients with Deficiency of Adenosine Deaminase 2 and parkinsonism-dystonia, respectively. In addition, the number of cases referred with Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) increased markedly. As in previous years, the Neurogenetics laboratory has been focused in studying patients with the clinical diagnosis of Parkinson disease, Alzheimer disease, FTLD, Fatal familial insomnia, ALS, cerebral small vessel disease and cavernous malformations. Also, in 2020, patients with glioblastoma followed at the Neurosurgery unit of CHUC, continued to be referred to this laboratory to be tested towards an

improvement of their diagnosis and clinical management. Other main focus of activity concerned the bioinformatic analysis performed in this laboratory in the reading, alignment and variant calling process.

The identified variants were evaluated for coverage and visually inspected using the Integrative Genomics Viewer. Variant annotation was performed using a multistep process workflow to individually assess variants pathogenicity, based on the use of population databases and in silico prediction tools, according to the currently guidelines. Population databases included 1000 Genomes (1000G), exome aggregation consortium database (ExAC) and genome aggregation database (GnomAD). The in silico prediction tools included SIFT, PolyPhen, Mutation Taster, MUTPred and CADD. To investigate the effect of the different variants found, other databases and tools have been employed such as: dbSNP, HGMD, ClinVar, ENSEMBL, VarSome and UMD-Predictor. Thus, with this procedure, several pathogenic variants underlying different conditions, were identified, some of which were novel, expanding both the disease spectrum mutations and also the patient's clinical phenotype.

SERVICES @ CNC

CELLULAR MECHANOBIOLOGY

Head of Unit: Mário Grãos

In 2020, the laboratory continued its 2 main services. One service allows the simultaneous determination of several bio-molecules using the multiplex xMAP technology. The other assesses the viability and the differentiation capacity of Mesenchymal Stem/Stromal Cells (MSCs) obtained from cryopreserved tissue samples (ISO 9001-2015 certification for Cell and tissue culture).

Overall, within the two services, 176 samples were processed, generating over 1,100 data points.

During the year, 2 new design & development processes were successfully implemented within the Cell and tissue culture certified service.

The laboratory continued to provide advanced training, hosting 1 post-doctoral researcher, 3 PhD students, 1 Master student and several lab rotation students from MSc programs from the University of Coimbra.

We have been focusing on understanding the molecular details and intracellular signaling pathways responsible for integrating biophysical and biochemical stimuli (through mechanotransduction) involved in cellular differentiation (Lourenço et al. 2016, doi: 10.1038/srep21563; Lourenço and Grãos 2016, doi: 10.3389/fncel.2016.00277); cellular potency, maintenance of undifferentiated state and reprogramming (Gerardo et al., 2019, doi: 10.1038/s41598-019-45352-3) and regulation of the cellular proteome (Domingues et al, 2020, doi: 10.3389/fcell.2020.00678). Our current models include adult and pluripotent stem cells, neural progenitors and other cell types relevant for neurodegenerative diseases (namely multiple sclerosis), regenerative and precision medicine.

Specifically, in 2020 we aimed at:

1. understanding the molecular mechanisms involved in the mechanoregulation of oligodendrocyte differentiation under the scope of the BrEin-MS project, which has a particular focus in Multiple Sclerosis (MS) and the mechanical changes reported to occur in the brain of MS patients.
2. evaluating the effect of biophysical stimuli in the a) intracellular and b) extracellular proteome of mechanosensitive cells, such as mesenchymal stem/stromal cells (MSCs). The specific objective of the former is to further understand the mechanisms involved in cellular mechanotransduction and its impact on cellular functions, and of the latter is the production of enhanced secretome for the rescue of neuronal cells subjected to oxidative stress insults.
3. understanding the impact of extracellular stiffness on mechanisms underlying Alzheimer's disease.

As part of our unpublished work, we identified one transcription factor (TF) that responds to mechanical stimuli in oligodendrocyte progenitor cells (OPCs), which has been described in the literature to play an important role during oligodendrocyte differentiation. We are currently characterizing this TF and have setup an expression reporter system to understand its role in the regulation of oligodendrocyte differentiation by mechanomodulation. Another part of this study (in collaboration with the laboratory of Gonçalo Castelo Branco at the Karolinska Institute) is focused on the epigenetic changes occurring during the differentiation of OPCs under distinct mechanical conditions mimicking physiology and disease (namely MS). We identified a subtype of epigenetic modifications that are modulated in response to mechanical factors in OPCs, whose mechanistic details are currently being characterized. The aforementioned studies take advantage of mechanically defined platforms (that mimic mechanical and biochemical components of the extracellular matrix) which allow to perform ex vivo studies, suitable for culturing primary cells and cell lines.

We identified Cofilin-1 as a mechanosensitive protein (Domingues et al., 2020). The mechanical properties of the extracellular environment are interrogated by cells and integrated through mechanotransduction. Many cellular processes depend on actomyosin-dependent contractility, which is influenced by the microenvironment's stiffness. We explored the influence of substrate stiffness on the proteome of proliferating undifferentiated human umbilical cord-matrix mesenchymal stem/stromal cells (MSCs). The relative abundance of several proteins changed significantly by expanding cells on soft (3 kPa) or stiff substrates (GPa). Many such proteins are associated with the regulation of the actin cytoskeleton, a major player of mechanotransduction and cell physiology in response to mechanical cues. Specifically, Cofilin-1 levels were elevated in cells cultured on soft compared with stiff substrates. Furthermore, Cofilin-1 was de-phosphorylated (active) and present in the nuclei of cells kept on soft substrates, in contrast with phosphorylated (inactive) and widespread distribution in cells on stiff. Soft substrates promoted Cofilin-1-dependent increased RNA transcription and faster RNA polymerase II-mediated transcription elongation. Cofilin-1 is part of a novel mechanism linking mechanotransduction and transcription.

3. As part of our unpublished work, we identified several proteins (by performing quantitative and unbiased proteomics analyses in collaboration with the group of Bruno Manadas, CNC) whose levels change significantly in the extracellular medium of MSCs cultured on substrates with distinct degrees of stiffness. We used the conditioned medium (CM) of these cells and compared its ability to rescue neurons challenged with oxidative stress agents. We found an enhanced rescuing capacity of the CM obtained from cells cultured on substrates with specific mechanical conditions in comparison with that obtained from cells cultured in standard conditions (polystyrene tissue culture plates). This suggests that the distinct mechanical properties of cell culture substrates, which resulted in changes in the composition of the conditioned media, in fact has a significant functional impact on the neuronal rescuing ability of the CM.

4. Our preliminary data indicate that extracellular stiffness has an impact on distinct pathways involved in the establishment and progression of Alzheimer's disease (AD). This encouraged us to proceed such studies, to understand the still underexploited impact of mechanobiology in AD.

SERVICES @ CNC

LABORATORY OF GENOME SEQUENCING

Head of Unit: Conceição Egas

Staff:

Cristina Barroso | Graduate Technician

Filipe Alves | Bioinformatician

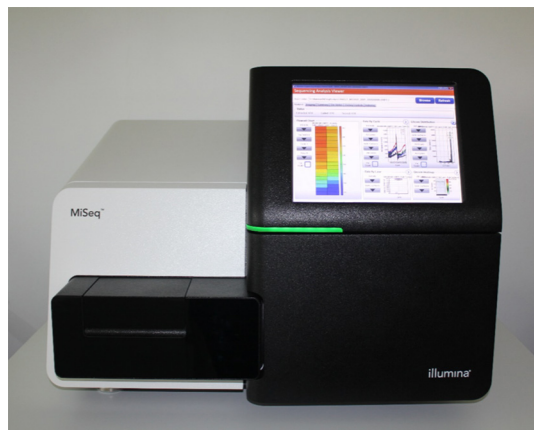
The genome sequencing unit - Genoinseq – is specialized in the field of omics. The Unit grants access to the full potential of the state-of-the-art of next generation sequencing equipment and bioinformatics data analysis. The Unit has a multidisciplinary team of experts in sequencing and bioinformatics, 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 in 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.



Illumina MiSeq

In 2020 the Laboratory sequenced 1,273 samples for external clients, in a total of 101 Gb. Sequencing services and bioinformatics were additionally provided for CNC users, with 493 samples sequenced in a total of 331 Gb.

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.
- In2Genome – Integrative approach in the diagnosis of genetic diseases. P2020 ref. 17800. Co-promotion project with the company Coimbra Genomics and Centro Hospitalar da Universidade de Coimbra. 2017-2020.
- Metafluidics- microbiology meets microfluidics, H2020, ref. 685474. 2016-2020.

OUTREACH

Genoinseq presented the core facility, sequencing applications and research results in 6 external events.

RESEARCH PAPERS:

- Ferreira LL, et al. Doxorubicin persistently rewires cardiac circadian homeostasis in mice. Arch Toxicol. 2020;94(1). doi:10.1007/s00204-019-02626-z
- Albuquerque L, et al. Hydrotalea. In: Kämpfer P, ed. Bergey's Manual of Systematics of Archaea and Bacteria. Wiley; 2020:1-8. doi:10.1002/9781118960608.gbm01442
- Varandas R, et al. Potato cyst nematodes: New solutions to an old problem. Crop Prot. 2020;137:105303. doi:10.1016/j.cropro.2020.105303
- Albuquerque L, et al. Oceanicella. In: Dedysh SN, ed. Bergey's Manual of Systematics of Archaea and Bacteria. Wiley; 2020:1-8. doi:10.1002/9781118960608.gbm01899
- Albuquerque L, Egas C. Heliomonas. In: Bergey's Manual of Systematics of Archaea and Bacteria. Wiley; doi:10.1002/9781118960608.gbm01903
- Albuquerque L, et al. Cavicella. In: Bergey's Manual of Systematics of Archaea and Bacteria. Wiley; doi:10.1002/9781118960608.gbm01904
- Albuquerque L, et al. Schleiferia. In: Bergey's Manual of Systematics of Archaea and Bacteria. Wiley; doi:10.1002/9781118960608.gbm01901
- Albuquerque L, et al. Schleiferiaceae. In: Bergey's Manual of Systematics of Archaea and Bacteria. Wiley; 2020:1-2. doi:10.1002/9781118960608.fbm00369
- Albuquerque L, et al. Raineyaceae. In: Bergey's Manual of Systematics of Archaea and Bacteria. Wiley; :1-1. doi:10.1002/9781118960608.fbm00370
- Albuquerque L, et al. Comparative genome sequence analysis of several species in the genus tepidimonas and the description of a novel species tepidimonas charontis sp. Nov. Int J Syst Evol Microbiol. 2020;70(3):1596-1604. doi:10.1099/ijsem.0.003942
- Young TL, et al. SVEPI as a genetic modifier of TEK-Related primary congenital glaucoma. Invest Ophthalmol Vis Sci. 2020;61(12). doi:10.1167/IOVS.61.12.6
- Pinho D, et al. Linking tree health, rhizosphere physicochemical properties, and microbiome in acute oak decline. Forests. 2020;11(11):1-19. doi:10.3390/f11111153

SERVICES @ CNC

MITOXT SERVICES LABORATORY: PREDICTIVE MOLECULAR TOXICOLOGY BASED ON MITOCHONDRIAL FUNCTION

Coordinator: Vilma A. Sardão

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

CNC FINANCIAL REPORT 2020

♦

In 2020 funding of “Laboratório Associado – Centro de Neurociências e Biologia Celular” ascended the amount of 7.959.043,08€.

The main financing contribution was made by “Fundação para a Ciência e Tecnologia (FCT)”, concerning global institution programs and national projects, namely amount of 6.330.232,96€ distributed as follows:

Strategical Project: UIDB/04539/2020	1.496.076,59€
Science Program:	1.805.747,77€
FCT Projects:	3.028.408,60€

The related items supported the main part of Center for Neuroscience and Cell Biology expenses during 2020.

Besides Center for Neuroscience is financed by other national and international agencies. In 2020 Center for Neuroscience received the amount of 1.328.711,35€, whereas other services had expenditure of amount 300.098,77€.

Main Services, not listed, is another important vector of our institution which ascends 443.303,59€ in 2020.

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 2020

TITLE	FINANCING AGENCY	STARTING DATE	ENDING DATE	BUDGET €	EXPENDITURE € 2020
Financiamento Base UIDB/04539/2020 - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. UIDB/04539/2020	01/01/20	31/12/23	4 145 331,20 €	1 491 008,47 €
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	01/01/20	31/12/23	449 982,45 €	5 068,12 €
Sub-Total Strategical Project					1 496 076,59 €
Norma transitória-DL 57 - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. Norma transitória-DL 57	04/01/19	31/12/25	8 811 340,96	1 127 209,02 €
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	15/02/19	28/02/25	2 798 759,33	375 175,43 €
Programa Investigador FCT_4ª edição - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. Programa Investigador FCT_4ª edição	01/11/16	25/11/21	2 065 304,67	303 363,32 €
Sub-Total Science Program					1 805 747,77 €
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	01/01/17	30/06/21	774 925,51 €	248 111,11 €
Alterações no proteoma sináptico e excitabilidade neuronal num modelo de epilepsia do lobo temporal induzido por administração de pilp carpina - COORDINATOR: Carlos Jorge A. M. B. Duarte	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/28656/2017	01/07/18	31/03/22	238 747,12 €	55 958,01 €

O transportador de K ⁺ - CL- (KCO) como alvo para manter a neurotransmissão GABAérgica: uma nova estratégia terapêutica para a epilepsia - COORDINATOR: Miranda Mele	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-FAR/30659/2017	01/06/18	30/05/21	237 446,83 €	50 174,84 €
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	26/07/18	25/04/22	234 226,71 €	66 920,72 €
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	01/06/18	31/12/21	203 025,00 €	73 807,65 €
Distúrbios afetivos: biomarcadores e deteção precoce - COORDINATOR: Bruno José F. O. Manadas	Fundação para Ciência e a Tecnologia - REF. PTDC/MEC-PSQ/30943/2017	26/07/18	25/07/21	238 743,45 €	68 818,24 €
POINTERS - Interações nemátode da madeira do pinheiro-árvore hospedeira: à descoberta de alternativas sustentáveis para a gestão da doença da murchidão do pinheiro - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/ASP-SIL/31999/2017	26/07/18	25/07/22	53 749,75 €	7 155,92 €
Impacto da agregação 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	01/06/18	31/05/22	26 250,00 €	3 458,26 €
Além do Beta-Amiloide - 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	01/09/18	31/08/22	106 997,37 €	17 111,07 €

Melhoria cognitiva no cérebro idoso e demência vascular em humanos através da funcionalização do acoplamento neurovascular: uma estratégia mecanística - COORDINATOR: João António Nave Laranjinha - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: CHUC, UC	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/29099/2017	26/07/18	25/07/22	100 955,61 €	16 115,02 €
Influência das antocianinas extraídas de mirtilos cultivados em Portugal na conexão entre o intestino e o cérebro nas perturbações do espectro 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	01/06/18	30/11/21	238 694,84 €	60 702,51 €
Monitorização in vivo de marcadores neurometabólicos com biossensores baseados em microelétrodos - COORDINATOR: Rui Manuel Silva G. Barbosa - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/28261/2017	25/07/18	24/07/22	106 478,94 €	11 136,61 €
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	01/07/18	30/06/21	238 749,59 €	127 317,79 €
O papel dos grânulos de stress nas doenças de poliglutaminas: da patogénese à terapia molecular - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Universidade do Algarve - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/29480/2017	13/10/18	12/10/21	57 000,00 €	36 672,10 €
ViraVector4Covid-Viral - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. 587 - ViraVector4Covid	09/07/20	08/01/21	45 000,00 €	42 452,54 €
Papel da desregulação dos microRNAs na doença de Machado - Joseph: Desenvolvimento de uma estratégia terapêutica baseada em microRNAs - COORDINATOR: Sonia Patricia Dias Duarte	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/32309/2017	06/07/18	05/07/22	239 947,00 €	68 977,93 €

O impacto do transplante de células estaminais neuroepiteliais derivadas de células estaminais pluripotentes induzidas na doença de Machado-Joseph - COORDINATOR: Liliana Mendonça	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-ORG/30737/2017	15/06/18	14/06/22	238 600,73 €	62 269,14 €
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	01/06/18	30/11/21	185 084,57 €	60 707,48 €
Recetores A2A da adenosina como desencadeadores de disfunção mnemónica na doença de Alzheimer: Mecanismos e possibilidade terapêutica - COORDINATOR: Rodrigo Pinto S.A. Cunha	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/31274/2017	01/07/18	30/06/21	236 326,73 €	66 505,24 €
Iniciativa Europeia para a doença de Machado-Joseph / Ataxia Espinocerebelosa do tipo 3 - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. JPCOFUND/0001/2015	01/05/16	31/03/20	174 992,03 €	- €
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	01/06/18	31/05/22	237 976,10 €	51 291,55 €
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	06/07/18	05/07/22	236 679,82 €	48 741,10 €
Desenvolvimento de novos antioxidantes dirigidos para as mitocôndrias na melhoria do fenótipo da Esclerose Lateral Amiotrófica familiar SOD1 - COORDINATOR: Ana Isabel Marques Duarte - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-FAR/29391/2017	01/05/18	28/02/22	148 765,17 €	55 372,29 €
Doenças cognitivas como sinaptopatias: Impacto de mutações humanas no gene CACNG2 - COORDINATOR: Ana Luisa Monteiro de Carvalho	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/28541/2017	01/07/18	31/12/21	236 245,47 €	36 149,76 €

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	01/07/18	31/12/21	38 600,01 €	17 300,17 €
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	15/06/18	31/12/21	236 222,74 €	55 976,17 €
Os altos e baixos do stress celular: "a hipótese MAM" para a fisiopatologia da doença Bipolar - COORDINATOR: Cláudia Maria Fragão Pereira	Fundação para Ciência e a Tecnologia - REF. PTDC/ MED-NEU/28214/2017	26/07/18	25/07/22	237 822,11 €	54 920,64 €
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	01/07/18	31/10/21	20 125,00 €	2 082,20 €
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	01/06/18	31/12/21	238 646,90 €	60 208,43 €
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	06/07/18	31/12/21	237 109,13 €	72 207,53 €
Cartilfactory - Desenvolvimento e Construção de um Sistema Automatizado de Fabricação em Larga Escala de Engenharia de Cartilagem Combinado Eletrofação 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	01/06/18	31/05/21	70 234,46 €	32 941,29 €

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	01/07/17	31/10/21	50 000,00 €	2 628,88 €
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	01/10/18	30/09/21	234 410,41 €	74 634,76 €
Eficácia pré-clínica do sulforafano ou do extrato total de Brássicas: Uma 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	Fundação para Ciência e a Tecnologia - REF. PTDC/ASP-HOR/29152/2017	01/06/18	28/02/22	41 577,40 €	16 615,80 €
MitoCIN .: Desenvolvimento de antioxidantes mitocondriais baseados em derivados do ácido cinnamico - COORDINATOR: Paulo Jorge G. S. S. Oliveira	Agência de Inovação, S.A. - REF. CENTRO-01-0145-FEDER-037586	12/01/18	31/12/20	48 161,27 €	4 584,42 €
MitoBEN - COORDINATOR: Paulo Jorge G. S. S. Oliveira	Agência de Inovação, S.A. - REF. CENTRO-01-0145-FEDER-037892	01/01/18	31/12/20	47 140,37 €	1 094,70 €
Uso de fitoquímicos redox-ativos para desencadear a hormesis mitocondrial: Desenvolvimento de uma nova geração de ingredientes para a cosmética - COORDINATOR: Marta Sofia Marques Simões - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-MOL/28607/2017	26/07/18	25/07/21	159 005,00 €	62 822,10 €
Desenvolvimento e validação de métodos inovadores da saúde mitocondrial. - COORDINATOR: Maria Teresa M. C. Oliveira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UC	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/29297/2017	06/07/18	05/12/21	166 749,26 €	56 176,62 €
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	15/06/18	14/12/21	224 839,21 €	92 651,29 €

Staphylococcus aureus intracelular: identificação de factores bacterianos e celulares envolvidos na invasão do hospedeiro por estirpes clinicamente relevantes para definição de novas abordagens terapêuticas. - COORDINATOR: Miguel Luís Cunha Mano	Fundação para Ciência e a Tecnologia - REF. Infect-ERA/0001/2015	01/10/16	30/09/20	106 233,00 €	28 246,34 €
Pequenas moléculas inibidoras do proteossoma: um passo em frente na descoberta de fármacos antitumorais - COORDINATOR: Jorge Salvador - PROPONENTE: FARM-ID - Associação da Faculdade de Farmacia - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/QEQ-MED/7042/2014	01/07/16	30/06/20	60 636,00 €	9 345,62 €
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	26/07/18	25/07/22	236 788,94 €	64 276,95 €
IF/01182/2015 - COORDINATOR: Vilma A. Sardão	Fundação para Ciência e a Tecnologia - REF. IF/01182/2015	01/07/17	30/06/21	50 000,00 €	- €
IF/01272/2015 - COORDINATOR: Alexandra Teresa Pires Carvalho	Fundação para Ciência e a Tecnologia - REF. IF/01272/2015	01/07/17	31/08/22	49 589,26 €	15 499,82 €
IF/01492/2015 - COORDINATOR: Paula Canas	Fundação para Ciência e a Tecnologia - REF. IF/01492/2015	01/07/17	31/12/21	49 950,00 €	9 970,08 €
IF/00825/2015 - COORDINATOR: Célia Alexandra F.O.Aveira	Fundação para Ciência e a Tecnologia - REF. IF/00825/2015	01/07/17	31/12/21	50 000,00 €	905,39 €
Alergénios cutâneos: moléculas com uma aplicação terapêutica improvável para a doença de Alzheimer - COORDINATOR: Maria Teresa T. Cruz Rosete	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-FAR/29369/2017	26/07/18	25/07/22	235 872,07 €	65 395,45 €
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	26/07/18	25/07/22	26 015,63 €	8 459,08 €

Um polissacarídeo intrigante de micobactérias: reciclagem, replicação e aplicações. - COORDINATOR: Nuno Miguel Silva Empadinhas - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: IBMC; UM	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-TEC/29221/2017	15/06/18	14/06/21	133 068,00 €	38 769,61 €
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	25/07/18	24/07/21	29 849,56 €	8 326,32 €
Os receptores A2A para a adenosina controlam a formação de axónios durante o desenvolvimento neuronal: novas estratégias para prevenir a epileptogénese - COORDINATOR: Joana Medeiros Vieira Marques	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/28160/2017	06/07/18	31/12/21	238 108,56 €	80 354,91 €
Identificação e caracterização funcional de microRNAs que regulam a infecção por estirpes de Staphylococcus aureus clinicamente relevantes. - COORDINATOR: Ana Sofia Bregieiro Eulálio	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-MIC/29999/2017	26/07/18	25/05/22	234 226,71 €	55 188,99 €
Desenvolvimento de um nanossistema inovador para mediar uma estratégia terapêutica combinada e multi-alvo para o carcinoma hepatocelular. - COORDINATOR: Henrique Manuel S. Faneca	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-MAT/30916/2017	01/07/18	31/12/21	238 634,37 €	70 562,35 €
Um modelo vascular de Progeria para identificar mediadores da perda de células do músculo 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	26/07/18	25/05/22	213 487,06 €	47 911,10 €
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	01/06/18	31/03/22	24 375,00 €	2 158,91 €

BrainEdition:controlo remoto da edição genética em células estaminais neurais. - COORDINATOR: Sónia Luzia Claro de Pinho	Fundação para Ciência e a Tecnologia - REF. PTDC/NAN-MAT/28060/2017	22/06/18	21/01/22	239 947,07 €	72 874,92 €
Uma biblioteca de nanopartículas activáveis por acção da luz para a libertação de terapias baseadas em RNA - COORDINATOR: Vitor Francisco	Fundação para Ciência e a Tecnologia - REF. PTDC/EQU-EQU/29414/2017	06/07/18	05/05/22	238 697,08 €	54 389,86 €
"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	24/08/20	23/08/23	66 189,34 €	1 611,54 €
Vacina Terapêutica para a Hepatite B crónica: Desenvolvimento de nanopartículas à base de glucano com o objectivo de direccionar os antígenos para as células imunitárias e induzir actividade antiviral - COORDINATOR: Olga Maria Fernandes R. Borges	Fundação para Ciência e a Tecnologia - REF. PTDC/MEC-GAS/30331/2017	15/07/18	14/04/22	234 902,55 €	72 360,46 €
EXO-HEART: Protecção e regeneração cardíaca mediada pela administração sistémica e direccionada de exossomas. - COORDINATOR: Hugo Agostinho Machado Fernandes	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/29919/2017	01/07/18	30/06/22	237 289,21 €	59 596,09 €
Indução de Células Apresentadoras de Antígeno por Reprogramação Celular Direta - COORDINATOR: Carlos Filipe R. L. Pereira	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-CEL/30013/2017	01/06/18	31/12/21	238 471,74 €	66 773,57 €
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	01/07/18	30/06/21	56 250,06 €	1 212,95 €
Translação da reprogramação celular direta em células dendríticas na imunoterapia do cancro. - COORDINATOR: Carlos Filipe R. L. Pereira	Fundação para Ciência e a Tecnologia - REF. CENTRO-01-0145-FEDER-039473	01/04/18	31/03/21	48 925,50 €	- €

Imunoterapias contra sistemas de efluxo para modulação de bactérias multiresistentes - COORDINATOR: Ricardo Simão Vieira Pires - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UNL	Fundação para Ciência e a Tecnologia - REF. PTDC/BTM-SAL/30550/2017	15/11/18	14/11/21	220 849,74 €	48 864,98 €
Propriedades viscoelásticas do cérebro em Esclerose Múltipla e implicações em mecanomodulação de oligodendrócitos: uma abordagem celular e clínica - COORDINATOR: Mário Grãos - PROPONENTE: CNBC - PARTICIPANTS: UNIVERSIDADE DE COIMBRA	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/29516/2017	26/07/18	25/07/21	192 669,05 €	71 937,64 €
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	15/06/18	14/12/21	196 773,35 €	59 110,63 €
Proteínas Membranares - desenvolvimento de novas técnicas de modelação computacional e sua aplicação ao estudo dos recetores acoplados a proteína G (o Projeto) - COORDINATOR: Irina Moreira - PROPONENTE: Instituto Superior Técnico - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/QUI-OUT/32243/2017	03/09/18	02/09/21	78 850,00 €	- €
Alvejamento de transportadores de aminoácidos catiónicos para radioteranóstica do cancro: uma abordagem experimental e de química computacional - COORDINATOR: Irina Moreira - PROPONENTE: IST-ID - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/QUI-NUC/30147/2017	01/09/18	31/08/21	23 449,35 €	1 237,13 €

Vesículas extracelulares de Giardia lamblia na imunomodulação de células do hospedeiro: potencial aplicação terapêutica das EVs de Giardia na inflamação intestinal - COORDINATOR: Maria do Céu Rodrigues de Sousa	Fundação para Ciência e a Tecnologia - REF. PTDC/SAU-PAR/31506/2017	17/09/18	16/09/21	238 721,61 €	70 296,03 €
Sub-Total FCT Projects					3 028 408,60 €
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	01/04/19	31/07/22	90 213,90 €	49 603,95 €
Modifying Machado-Joseph disease progression by caffeine blockage of Adenosine A2A receptors - COORDINATOR: Luis Pereira de Almeida	National Ataxia Foundation - REF. Caffeine MJD/SCA3-Ataxia	01/01/13	31/12/25	11 186,27 €	- €
Prémio Mantero Belard 2017 - COORDINATOR: Carlos Jorge A. M. B. Duarte - PROPONENTE: IMM - PARTICIPANTS: CNBC	SCML - REF. Prémio Mantero Belard 2017	01/01/18	31/12/20	5 093,25 €	2 987,82 €
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	01/03/19	28/02/22	43 790,32 €	11 534,34 €
Combination therapy synergistically accelerates diabetic wound - COORDINATOR: Eugénia Maria L. Carvalho	EFSD-Europ. Found. S. Diabetes - REF. EFSD-Microvascular Complication	09/11/15	31/12/21	70 000,00 €	3 199,25 €
MATERA_5402 - COORDINATOR: Lino da Silva Ferreira	MATERA, LDA	01/09/10	31/12/21	27 820,88 €	87,50 €
Promoting endothelial progenitor cell function in diabetic wound healing - COORDINATOR: Ermelindo Carreira Leal	EFSD-Europ. Found. S. Diabetes - REF. EFSD: Promoting endothelial progenitor cell function	01/01/13	31/12/20	50 000,00 €	560,88 €
Evaluate novel calpain inhibitors from Blade Therapeutics - COORDINATOR: Luis Pereira de Almeida	Blade Therapeutics - REF. Blade	19/07/18	31/12/25	140 000,00 €	21 521,28 €

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	PTCTherapeutics GT, Inc. - REF. miRSilencing	27/04/20	26/12/21	658 751,00 €	137 438,51 €
"Mitochondrial Trafficking In Alzheimer Disease: Revealing the Role of Hummr." - COORDINATOR: Paula Isabel da Silva Moreira	Alzheimer's Association - REF. NIRG-13-282387_Mitochondrial	01/11/13	31/12/20	71 495,56 €	4 851,79 €
Coffee protects against NAFLD progression through preservation of intestinal permeability and inhibition of liver fibrosis - COORDINATOR: John Griffith Jones	Institute for Scientific Information on Coffee - REF. Coffee protects against NAFLD	01/07/19	30/06/21	112 904,00 €	42 025,23 €
Adenosine A2A receptors as a new opportunity to manage and detail the neurobiology of emotional distress. - COORDINATOR: Rodrigo Pinto S. A. Cunha - PROPONENTE: CNBC - PARTICIPANTS:	Fundación Bancaria Caixa d'Éstalvis i P. Barcelona - REF. LA Caixa - HR17-00523 - adostress	18/12/19	14/12/22	335 460,49 €	81 299,52 €
Bolsa PMJMCD2017 - COORDINATOR: Rodrigo Pinto S. A. Cunha	Fundação Amélia de Mello - REF. Bolsa PMJMCD2017	01/01/18	31/12/20	25 000,00 €	- €
Ghrelin: a novel therapeutic intervention to rescue the phenotype of Hutchinson-Gilford progeria syndrome - COORDINATOR: Célia Alexandra F.O. Aveleira	Progeria Research Foundation - REF. Progeria syndrome	01/04/15	31/12/20	60 853,05 €	5 294,64 €
Novel cerebrospinal fluid and serum biomarkers for Multiple Sclerosis - COORDINATOR: Carlos Jorge A. M. B. Duarte	National Multiple Sclerosis - REF. Multiple Sclerosis_RG-1601-075	01/10/16	30/09/20	149 586,13 €	5 484,23 €
The toxinogenic gut microbiome in sporadic Parkinson's Disease: a quest for "antiPDbiotics - COORDINATOR: Sandra Morais Cardoso	SCML - REF. Prémio Mantero Belard'2016	01/01/17	30/06/20	199 098,00 €	7 418,33 €
Potassium channel dysfunction in models of neurodevelopmental disorders - COORDINATOR: Ana Luisa Monteiro de Carvalho - PROPONENTE: Centro Neurociências e Biologia Celular - PARTICIPANTS: CNRS - Centre National de la Recherche Scientifiqu	Fundación Bancaria Caixa d'Éstalvis i P. Barcelona - REF. La Caixa - HR20-00904 - MStar	11/12/20	10/12/23	620 000,00 €	- €

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	06/08/17	31/12/23	128 059,00 €	12 347,65 €
Optic Nerve Atrophy_Santhera - COORDINATOR: Maria Manuela Monteiro Grazina	Santhera Netherlands - REF. Optic Nerve Atrophy_Santhera	01/07/18	30/06/22	63 999,98 €	11 716,14 €
Palhaços d'Opital 2020 - COORDINATOR: Maria Manuela Monteiro Grazina - PROPONENTE: CNBC - PARTICIPANTS:	Palhaços d'Opital - REF. Palhaços d'Opital 2020	09/07/20	09/12/21	20 632,20 €	15 322,40 €
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	06/09/19	05/09/21	29 153,00 €	13 441,38 €
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	National Ataxia Foundation - REF. Intravenous delivery of the brain-targeting AAV-PHPeB	01/03/20	31/10/21	42 561,00 €	8 549,61 €
Silencing the SCA3-causing gene ATXN3 through CRISPR interference - COORDINATOR: Carlos Adriano A. Andrade Matos	National Ataxia Foundation - REF. ATXN3 through CRISPR interference	01/03/19	30/09/20	12 914,00 €	4 893,60 €
A Saúde no Saber - COORDINATOR: Sara Varela Amaral	Ciência Viva - REF. 45-2019/478	01/07/19	01/12/21	20 000,00 €	1 720,06 €
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	01/03/19	28/02/21	43 399,05 €	18 561,19 €
Deciphering the Rickettsia toolbox to hijack the host - COORDINATOR: Pedro Tiago Cardoso Curto	ESCMID-European Society of Clinical Microbiology a - REF. Deciphering the Rickettsia toolbox to hijack the host	21/02/20	31/12/21	20 001,00 €	6 175,69 €

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	14/12/20	29/12/22	5 000,00 €	- €
Novas terapias para Doença de Chagas: reposicionamento de drogas com efeito sinérgico com Benzonidazol para combater infecção por Trypanosoma cruzi - COORDINATOR: Miguel Luis Cunha Mano	Fundação para Ciência e a Tecnologia - REF. FCT/CAPES-2018/2019	16/04/18	31/12/21	9 000,00 €	825,13 €
Prémio L'Oréal - COORDINATOR: Paula Isabel da Silva Moreira	L'Oréal	01/11/08	31/12/21	20 000,00 €	- €
Prémio Janssen Inovação - COORDINATOR: Cláudia Margarida G. Cavadas	Janssen-Cilag - REF. Prémio Janssen Inovação	01/10/16	31/12/20	20 000,00 €	- €
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	01/07/17	31/08/20	5 000,00 €	- €
V Simpósio da Portuguese Glial Network - COORDINATOR: Paula Maria Garcia Agostinho	CNC - REF.V Simpósio da Portuguese Glial Network	11/02/20	31/12/21	1 050,00 €	- €
Terapia Machado Josefh - COORDINATOR: Luis Pereira de Almeida	APAHE - Assoc. Portuguesa de Ataxias Hereditárias - REF. Terapia Machado Josefh	01/01/12	31/12/20	8 031,75 €	1 894,04 €
Mini-Symposium 'Vaccines and A - COORDINATOR: Olga Maria Fernandes R. Borges	NOVARTIS FARMA S.A. - REF. Mini-Symposium 'Vaccines and A	01/03/11	31/12/20	250,00 €	- €
Qren Cogumelos - REMANESCENTE - COORDINATOR: - PROPONENTE: CNBC - PARTICIPANTS:	- REF. Qren Cogumelos - REMANESCENTE	01/01/17	31/12/20	2 975,62 €	- €
APU/ASTELLAS 2011 - COORDINATOR: João Nuno Sereno de A. Moreira	APU - REF.APU/ASTELLAS 2011	25/07/12	31/12/20	7 000,00 €	- €
EFSD - European Foundation Study Diabetes - COORDINATOR: Eugénia Maria L. Carvalho	EFSD-Europ. Found. S. Diabetes - REF. Saldos Fundos EFSD transitados	09/01/13	31/12/21	23 398,85 €	829,79 €

AsHeCe - Marta Pereira - COORDINATOR: João Nuno Sereno de A. Moreira	AsHeCe	01/01/13	31/12/21	8 000,00 €	64,27 €
Bolsa Cient.LPCE2014 Miranda M - COORDINATOR: Carlos Jorge A. M. B. Duarte	Liga Port. contra Epilepsia - REF.Bolsa Cient.LPCE2014 Miranda M	31/03/14	31/12/20	3 500,00 €	317,34 €
Fundos FBG - COORDINATOR: Maria Manuela Monteiro Grazina	Fundos LBG	10/12/13	31/12/21	37 755,95 €	3 966,97 €
Fundos Obesidade - COORDINATOR: Maria Manuela Monteiro Grazina	CNC - REF. Fundos Obesidade	01/06/17	31/12/25	22 600,00 €	7 705,46 €
Bial - REMANESCENTE - COORDINATOR: Inês Maria Pombinho de Araújo	- REF. Bial - REMANESCENTE	01/09/14	31/12/20	15 293,99 €	100,00 €
Exocord - REMANESCENTE - COORDINATOR: Lino da Silva Ferreira	Exocord	01/01/17	31/12/21	32 458,67 €	628,88 €
Livro de Neurociências - COORDINATOR: Ana Cristina Carvalho Rego	European Commission - REF.Livro de Neurociências	01/01/16	31/12/21	2 400,00 €	- €
Brain Buskers - COORDINATOR: Sara Varela Amaral	Liga Port. contra Epilepsia - REF. Brain Buskers	29/11/17	31/12/20	1 664,30 €	320,25 €
EMBO - COORDINATOR: Ana Sofia Bregieiro Eulálio	EMBO - REF.EMBO	01/04/17	31/12/21	13 919,00 €	3 568,56 €
14ª Edição do Programa Doutoral PDBEB - COORDINATOR: João Ramalho de Sousa Santos	Bluepharma - REF. 14ª Edição do Programa Doutoral PDBEB	01/01/18	31/12/20	500,00 €	- €
Prémio 2º lugar no concurso Janssen Inovação 2018 - COORDINATOR: Sara Matias Silva	Janssen-Cilag - REF. Prémio 2º lugar no concurso Janssen Inovação 2018	17/05/18	31/12/20	20 000,00 €	1 001,01 €
Astrazeneca - iMed Conference 10.0 - COORDINATOR: Rodrigo Filipe Nunes Ribeiro	Fundação Astrazeneca	01/11/18	31/12/21	3 000,00 €	- €

Prémio Thomé Villar SPP2020 - COORDINATOR: Ana Rita Álvaro	Sociedade Portuguesa de Pneumologia - REF. Prémio Thomé Villar SPP2020	21/12/20	23/12/21	10 000,00 €	- €
Prémio EIT Health_Grupo Alexandrina Mendes - COORDINATOR: Alexandrina M. F. S. P. Mendes	European Institute of Innovation Technology EIT - REF. Prémio EIT Health	01/01/19	31/12/21	15 378,15 €	1 187,64 €
Bolsa SPOT João Pedro Moreira - COORDINATOR: Alexandrina M. F. S. P. Mendes	Sociedade de Ortopedia e Traumatologia - REF. Bolsa SPOT João Pedro Moreira	23/01/18	31/12/21	2 500,00 €	- €
Bolsa de Investigação SPT-Seculo XXI - COORDINATOR: Eugénia Maria L. Carvalho	Sociedade Portuguesa de Transplantação - REF. Bolsa de Investigação SPT-Seculo XXI	01/03/19	30/11/21	10 000,00 €	5 830,29 €
Bolsa SPD-Gift_Ermelindo Leal - COORDINATOR: Ermelindo Carreira Leal	Ermelindo Carreira Leal - REF. Bolsa SPD-Gift_ Ermelindo Leal	13/05/20	31/05/23	8 500,00 €	7 124,06 €
CIBB Meeting 2019 - COORDINATOR: Ricardo Jorge A. Rodrigues	CIBB Meeting 2019	01/11/19	31/12/21	850,00 €	- €
Embo Young investigator small grant - round 2019/2020 - COORDINATOR: Ana Sofia Bregieiro Eulálio	EMBO - REF. EMBO_ Round 2019/2020	01/02/20	31/12/21	10 000,00 €	- €
IBRO Early Career Awards 2020_João Peça - COORDINATOR: João Peça Silvestre	IBRO - REF. EARLY CAREER AWARD - PEÇA	01/10/20	30/09/21	5 001,00 €	2 812,92 €
EMBO 2020 - COORDINATOR: Sara Varela Amaral	FENS - REF. BAW 2020	01/02/20	28/02/21	1 001,00 €	476,75 €
Estarreja – Evaluation of the reproductive health of men living in a heavily industrialized area - COORDINATOR: Renata Tavares	Universidade Aveiro - REF. Projeto L`OHMI _DHM-E/2019/Proj.3	01/01/20	31/12/21	6 500,00 €	132,05 €
Prémio "Best Scientific Poster from the Innovative Competition-AstraZeneca Foundation" - COORDINATOR: João Miguel Esteves C.S. Cardoso - PROPONENTE: CNBC	Fundação Astrazeneca - REF. Prémio_Best Scientific Poster from the Innovative Competition-AstraZeneca Foundation	01/01/18	31/12/22	1 000,00 €	- €

Science engagement through videos: a new lens on biomedical research - COORDINATOR: Sara Varela Amaral	Biochemical Society - REF. Biochemical Societu Scientific Outreach Grants 2020	22/12/20	31/12/21	1 079,58 €	- €
Mini-Simpósio StemmCell Technologies - COORDINATOR: Catarina Seabra	Stemcell Technologies - REF. Mini-Simpósio StemmCell Technologies	07/02/20	31/12/20	500,00 €	- €
Brain Gain- À descoberta das Neurociências - COORDINATOR: Catarina Seabra	Sociedade Port. Neurociências - REF. Brain Gain - À descoberta das Neurociências	17/12/20	17/12/21	270,00 €	- €
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	01/01/20	31/12/21	5 000,00 €	441,30 €
LifeSciences ByCENTRO: Valorização do Conhecimento em Ciências da Vida - COORDINATOR: João Ramalho de Sousa Santos	IFDR - REF. LifeSciences ByCENTRO	27/03/17	26/03/20	169 804,60 €	57 706,55 €
CENTRO-04-3559-FSE-000141 - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: CNBC - PARTICIPANTS:	IFDR - REF. CENTRO-04-3559-FSE-000141	01/04/20	31/03/23	512 236,13 €	2 330,68 €
Advanced toolbox for rapid and cost-effective functional metagenomic screening - microbiology meets microfluidics - COORDINATOR: Conceição EGAS - PROPONENTE: Universidade Madrid	Univ. Autónoma Madrid - REF. GA 685474 B I O T E C - 6 - 2 0 1 5 Metafluidics	01/06/16	31/11/2020	407 590,00 €	86 765,45 €
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	01/01/17	30/06/21	793 616,79 €	126 394,72 €
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	01/06/17	31/05/22	102 400,00 €	4 693,66 €

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	01/09/19	31/08/22	59 649,00 €	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	01/10/12	31/12/21	201 432,00 €	2 874,06 €
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	01/03/16	31/12/21	148 635,60 €	3 381,71 €
Training European Network: Metabolic Dysfunction associated with Pharmacological Treatment of Schizophrenia - COORDINATOR: Eugénia Maria L. Carvalho	Agencia Estatal CSIC - REF. TREATMENT-721236	01/01/17	31/12/20	428 904,72 €	79 273,64 €
Accelerating Research and Development for Advanced Therapies - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: University Sheffield	University of Sheffield - REF. ARDAT_945473	01/11/20	31/10/25	630 000,00 €	- €
Synaptic Dysfunction in Neuropsychiatric Disorders - COORDINATOR: Ana Luisa Monteiro de Carvalho - PROPONENTE: - PARTICIPANTS: CNRS, EPFL, Imperial, UEDIN, H. Lundbeck AS, SMS, Eurotrials, CHUC, E.P.E, PIN - Progresso Infantil, Marionet - Associação Cultural	European Commission - REF. Syn2Psy_813986	25/02/19	28/02/23	1 045 802,48 €	202 325,87 €
Functional high-throughput analysis of the role of microRNAs in regulating Staphylococcus aureus infection - COORDINATOR: Ana Sofia Bregieiro Eulálio	European Commission - REF. 893942 - miRs4Staph	15/10/20	14/10/22	147 816,04 €	11 176,79 €
"New nanomaterials for neural stem cells drug delivery - COORDINATOR: Lino da Silva Ferreira - PROPONENTE: Queen Mary and Westfield College"	Queen Mary University (QMUL) - REF. NANOSTEM - 764958	01/06/18	31/05/22	715 069,08 €	166 135,12 €
Production and Testing of human-derived Neurons and brain organoids: advanced model probing in neurodevelopment disorders - COORDINATOR: João Peça Silvestre	European Commission - REF. ProTeAN-799164	07/05/18	06/05/20	148 638,60 €	30 534,92 €

Light-responsive GrapHene-based inTerfaces for Electrical Stimulation - COORDINATOR: Artur Filipe Cardoso Duarte Rodrigues	Research Executive Agency - REF.101003413_Lightest	01/04/20	30/04/22	159 816,04 €	39 599,48 €
PPBI_Portuguese Platform of Bioluminescence Imaging - COORDINATOR: Luisa Maria O.P.L.Cortes - PROPONENTE: Instituto de Biologia Molecular e Celular	IBMC - REF. Rede PPBI - PINFRA/22122/2016	01/06/17	30/09/21	275 180,00 €	7 380,00 €
Sub-Total Others National and International Projects					1 328 711,35 €
From Protein Structure to biological function through interactomics- an integrated view (2nd edition) - COORDINATOR: Bruno José F. O. Manadas	- REF. Cursos Bruno Manadas	01/01/18	19/01/20	10 350,00 €	441,32 €
Cursos de Verão Doutor Carlos Palmeira - COORDINATOR: Carlos Manuel Marques Palmeira	- REF. Cursos de Verão Doutor Carlos Palmeira	01/04/19	29/04/20	8 930,03 €	1 430,00 €
8º Workshop da Sociedade Europeia de Cálculo - COORDINATOR: Claudia Pereira	8º Workshop da Sociedade Europeia de Cálculo	01/06/19	31/12/20	13 607,21 €	- €
Curso Bioteria Teór/Prát_2015 - COORDINATOR: João António Nave Laranjinha	- REF. Curso Bioteria Teór/Prát_2015	01/08/15	31/12/20	8 298,50 €	- €
Fórum Pós-docs - COORDINATOR: Ermelindo Carreira Leal	- REF. Fórum Pós-docs	01/02/18	31/12/20	1 505,00 €	- €
Brain without borders - COORDINATOR: Luis Pereira de Almeida	Brain without borders	01/09/16	31/12/20	574,20 €	- €
Formações do Gab. Comunicação - COORDINATOR: Sara Varela Amaral	- REF. Angariação fundos Gab. Comunicação da Ciência	01/01/17	30/12/20	140,00 €	- €
Curso FOIEGRAS - COORDINATOR: Paulo Jorge G. S. S. Oliveira	- REF. Cursos de faturação Paulo Oliveira	01/09/17	31/12/20	1 993,40 €	- €
Faturação Cursos Paula Mota II - COORDINATOR: Paula Cristina Cardoso R. Mota	- REF. Faturação Curso Janeiro 2019 - Paula Mota	01/11/18	31/12/20	23 750,00 €	- €
Curso Faturação Paula Mota III - COORDINATOR: Paula Mota	CNC - REF. Curso Faturação Paula Mota III	01/09/19	30/08/25	22 300,01 €	1 571,66 €
Curso IVMLAS - COORDINATOR: Paula Cristina Cardoso R. Mota	CNC - REF. Curso IVMLAS	30/09/20	30/09/25	17 200,00 €	84,21 €

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	01/01/18	31/12/21	23 500,00 €	2 008,82 €
Faturação Biotério - COORDINATOR: Paula Cristina Cardoso R. Mota - PROPONENTE: CNBC - PARTICIPANTS:	- REF. Faturação Biotério CNC	01/01/17	31/12/20	272 556,95 €	55 808,58 €
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.	17/12/18	31/12/25	52 187,50 €	10 268,91 €
Evaluation of MJD/SCA3 preclinical drug discovery model systems - COORDINATOR: Luis Pereira de Almeida	- REF. MJD/SCA3 Models	01/09/19	31/12/25	43 508,00 €	6 518,21 €
European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative - COORDINATOR: Luis Pereira de Almeida	- REF. ESMI project continuation	26/11/19	31/12/25	10 002,00 €	2 350,10 €
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	01/04/18	31/12/25	300 000,00 €	105 485,12 €
Proof of concept evaluation of the ATXN3 LNA in the homozygous YAC hATXN3 Q84.2 - COORDINATOR: Luis Pereira de Almeida	- REF. STUDY Proof of concept evaluation ATXN3 LNA	26/10/20	31/01/22	200 000,00 €	- €
Magnetic Resonance Spectroscopy - COORDINATOR: John Griffith Jone	German Diabetes Center - REF. DDZ Resonance Spectroscopy MRS	01/11/20	01/11/21	15 893,00 €	- €
Pharmatex In vitro Studies Program - COORDINATOR: João Ramalho de Sousa Santos	Laboratoire Innotech - REF. INNOTECH 2015	31/12/14	31/12/21	218 086,76 €	2 261,08 €
Revascularização e angiogénese - COORDINATOR: João Ramalho de Sousa Santos	- REF. Revascularização e angiogénese, Merck	20/12/16	31/12/21	123 377,83 €	45 999,38 €
Nanodrug 3rd Summer School&Int - COORDINATOR: Lino da Silva Ferreira	- REF. Nanodrug 3rd Summer School&Int	01/04/14	31/12/20	19 984,00 €	100,00 €
Study: Evaluation of Gecko polymer ability to inhibit bacterial growth by direct contact - COORDINATOR: Lino da Silva Ferreira	- REF. Evaluation of Gecko polymer	17/07/17	31/12/20	2 000,00 €	1 175,68 €

Microbiologia e Parasitologia - Unidade Curricular - COORDINATOR: Susana Isabel Elias Alarico	Escola Superior de Enfremagem de Coimbra - REF. Microbiologia e Parasitologia - Unidade Curricular	09/03/20	09/03/23	16 215,02 €	6 338,22 €
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	01/01/17	31/12/21	120 282,00 €	17 294,05 €
NIH - 75N95020P00076 - COORDINATOR: Attila Köfalvi	- REF. NIH 75N95020P00076	01/01/17	31/03/22	24 851,00 €	8 270,81 €
DDZ_FLAME_L_study - COORDINATOR: John Griffith Jones	German Diabetes Center - REF. DDZ_FLAME_L_study	01/06/17	31/12/21	12 056,81 €	2 798,42 €
Project Furan toxicity in human and rat hepatocytes - COORDINATOR: Carlos Manuel Marques Palmeira	- REF. Comparison the acute effects.	01/08/17	31/12/21	28 200,00 €	- €
Faturação Matera - COORDINATOR: Lino da Silva Ferreira	- REF. Faturação Matera	01/01/20	31/12/21	5 543,75 €	4 348,94 €
Faturação Dr. Lino Ferreira - COORDINATOR: Lino Ferreira	Universidade de Coimbra - REF. Faturação Lino Ferreira	01/01/18	31/12/20	27 651,92 €	6 476,57 €
Cosmetologia Aplicada - Unidade Curricular - COORDINATOR: Ludgero Canário Tavares	Instituto Politécnico Leiria - REF. Cosmetologia Aplicada - Unidade Curricular	23/09/20	22/09/23	820,80 €	- €
MSCellProduction: Produção de Células Estaminais Mesenquimais em Conformidade com os requisitos de Boas Práticas de Fabrico - COORDINATOR: Mário Grãos	- REF. MSCellProduction	01/07/19	31/12/21	26 950,00 €	8 544,97 €
Atividades docência - Joana Mourão - COORDINATOR: Irina Moreira	Universidade do Algarve - REF. Atividades docência - Joana Mourão	18/11/20	04/12/21	3 658,54 €	365,00 €
Microscopia - COORDINATOR: Luisa Maria O. P.L. Cortes	- REF. Microscopia	01/01/12	31/12/20	103 792,89 €	10 102,08 €
Citometria de Fluxo - COORDINATOR: Isabel Maria Nunes Correia	- REF. Citometria de Fluxo	01/01/18	31/12/20	940,00 €	56,64 €
Sub-Total Others Services					300 098,77 €
Total					7 959 043,08 €

ICBR FINANCIAL REPORT 2020

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TITLE	FINANCING AGENCY	PRINCIPAL INVESTIGATOR	STARTING DATE	ENDING DATE	BUDGET (ICBR)	EXPENDITURE 2020
ERAatUC - 669088	European Commission H2020 - Societal Challenges	João Malva	01/05/2019	30/06/2020	2.762.404,48€	354.548,87€
20588-EPIDEMPREV	Eit Health E.V.	João Malva	01/01/2020	30/06/2021	200.800,00€	54.423,53€
20515-LONELINESS	Eit Health E.V.	João Malva	01/01/2020	31/12/2021	16.250,00€	0,00€
ExoSwitch - Understanding the switch between dry and wet AMD: role of exosomes	BAYER -GOAP	Rosa Fernandes	01/11/2018	31/10/2020	43.478,00€	5.892,58€
IDIAL_NET	European Commission INTERREG	Ana Bela Sarmento	01/06/2019	31/12/2021	93.333,33€	23.528,87€
CALMA (ID 20565)	Eit Health E.V.	Carlos Robalo Cordeiro	01/01/2020	31/12/2020	6.870,00€	492,00€
SMASHMEDICINE	Eit Health E.V.	Carlos Robalo Cordeiro	01/01/2020	31/12/2020	19.991,86 €	2.475,07€
Novartis	Novartis	Francisco Ambrósio	-	-	30.000,00€	2.013,88€
BrainHealth2020	CCDRCCENTRO-01-0145-FEDER-000008	Luis Almeida/ Francisco Ambrósio	01/01/2017	31-12-2020	1.599.829,61€	65.245,14€.
HealthyAging2020	CCDRCCENTRO-01-0145-FEDER-000012	João Ramalho/ Henrique Girão	01/01/2017	31/12/2020	1.795.810,88	

GenomePT - Lab. Nacional Sequenciação	FCT P O C I - 0 1 - 0 1 4 5 - FEDER-022184	Henriqueta Coimbra Silva	01/06/2017	30/04/2021	593 489,91 €	200.951,63€
PPBI–Plataforma Portuguesa de Bioimagem	A g ê n c i a Desenvolvimento e Coesão	Henrique Girão	01/06/2017	30/05/2020	218.906,00€	60.009,74€
A novel mechanism to re-pair HFpEF and endothelial damage	FCT RE-PAIR - 032179	Henrique Girão	22/06/2018	21/06/2021	233.434,48€	36.419,97€
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	31/05/2021	23.634,25€	1.357,43€
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	25/07/2021	239.304,92€	69.510,29€
Speed, crash and run: exersomes boost neuroenergetics and mood in mice	FCT MOOD EXERSOMES - 030786	Frederico G.S.C. Pereira	26/07/2018	25/07/2021	239.413,80€	52.965,50€
Modeling Angiogenesis in Type 2 Diabetes Mellitus - integrating experimental and theoretical approaches	FCT ANGIODIA -031743	Raquel Seica	26/07/2018	25/07/2021	33.125,00€	12.235,49€
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	57.139,80€
Environmental enrichment protects adult hippocampal neurogenesis and memory decline induced by systemic	FCT MercurMemory - 031699	Carlos Fontes Ribeiro	26/07/2018	25/07/2021	239.475,67€	60.681,30€
Contribution of olive polyphenols and olive oil for the prevention of cardiovascular diseases	FCT PHENOLIVA - 032492	Flávio Reis	07/07/2018	06/07/2021	238.115,29	3.863,20€

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€	0,00€
Mediterranean Enriched Diet for tackling Youth Obesity	FCT MED4YOUTH - PRIMA/0004/2018	Maria Filomena Botelho	01/12/2019	30/11/2021	93.815,00€	20.801,63€
Nova Terapêutica de RNA de Interferência para o Glaucoma	FCT siRNAGlau - 039743	António Francisco Ambrósio	01/10/2019	30/09/2021	215.064,98€	
3D DENTOFACIAL SURGERY FULL PLANING	FCT ARTHUR - 039690	Francisco Caramelo	01/10/2019	30/09/2021	131.322,65€	
iPET - Sistema PET inteligente para imagiologia pré-clínica	FCT iPET - 039880	Ana Cristina Santos	11/09/2019	10/03/2022	161.898,78€	
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 €	
Strategic Project	FCT UIDB/04539/2020-Base	António F. Ambrósio	01/01/2020	31/12/2023	881 437,90 €	35.098,00€
Strategic Project	FCT UIDB/04539/2020	António F. Ambrósio	01/01/2020	31/12/2023	943 792,55€	100.104,00€

PUBLICATIONS

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- Agostinho P, et al. (2020) Purinergic signaling orchestrating neuron-glia communication. *Pharmacological Research* 105253. doi: 10.1016/j.phrs.2020.105253
- Aires ID, et al. Microglial exosomes in retinal neuroinflammation: focus in glaucoma. *Neural Regen Res.* 2021 Sep;16(9):1801-1802. doi: 10.4103/1673-5374.306084. PMID: 33510084
- Aires ID, et al. Exosomes derived from microglia exposed to elevated pressure amplify the neuroinflammatory response in retinal cells. *Glia.* 2020 Dec;68(12):2705-2724. doi: 10.1002/glia.23880. Epub 2020 Jul 9. PMID: 32645245
- Aguiar AS Jr, et al. (2020) Neuronal adenosine A2A receptors signal ergogenic effects of caffeine. *Scientific Reports* 10: 13414. doi: 10.1038/s41598-020-69660-1
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- Alves L, et al. Neuropsychological profile of amyloid positive versus amyloid negative amnesic Mild Cognitive Impairment. *Journal of Neuropsychology* 2020 e12218. DOI: 10.1111/jnp.12218. 2.333
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Ana Bela Sarmiento Antunes Cruz Ribeiro	0,3
António Carlos Miguéis	0,4
António Francisco Rosa Gomes Ambrósio	0,8
Ana dos Santos Carvalho	0,2
Akhilesh Rai	
Alcino Jorge Lopes Leitão	0,5
Alexandra Teresa Pires Carvalho	100%
Alexandre Marques Rodrigues	0,2
Alexandre Miguel Fernandes Gomes da Silva	0,5
Alexandrina Ferreira Mendes	0,8
Ana Branco Maranhã Tiago	
Ana Adelaide Caldeira Burgeiro	Collaborator
Ana Cristina Aguiar dos Santos	
Ana Cristina Carvalho Rego	0,8
Ana Cristina Pereira Gonçalves	0,4
Ana Cristina Rosa da Silva	
Ana dos Santos Carvalho	0,2
Ana Sofia Bregieiro Eulálio	0,8
Ana Faria	0,3
Ana Filipa Marques Brito	0,3
Ana Filipa Roque Branco	
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Ana Margarida da Cruz Ledo	
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Ana Maria Sequeira Cardoso	
Ana Patrícia Barreira Marques	
Ana Patrícia Ferreira Antunes	0,5
Ana Patrícia Simões	
Ana Paula Marques de Sousa	0,5
Ana Paula Pereira da Silva Martins	0,8
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Ana Raquel Sarabando Santiago	
Ana Rita Álvaro	
Ana Rita Esteves de Sousa e Silva	
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Anabela Baptista Pereira Paula	0,3
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António Joaquim de Matos Moreno	0,6
António Pedro Barros Gomes	
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Artur Augusto Paiva	0,3
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Bárbara Silva Rocha	0,6
Belmiro Ataíde da Costa Parada	0,3
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Lino da Silva Ferreira	
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Luís Manuel Neves da Silva Cavalheiro	0,2
Luís Martinho do Rosário	0,4
Luís Miguel Beicinha Branco Estronca	
Luiz Miguel Santiago	0,5
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Magda Matos Santana	
Manuela Cristina Fernandes Ferreira	
Marcos Barbosa	0,3
Manuel Marques Ferreira	0,3
Manuel Teixeira Marques Veríssimo	0,2
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Maria da Conceição Monteiro Pedroso de Lima	
Maria da Conceição Venâncio Egas	
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Maria Amália da Silva Jurado	0,65
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Maria João da Silva Fernandes Leal Carvalho	0,3
Maria Joao Capelo Quadrado	0,2
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Maria Manuela Monteiro Grazina	0,4
Maria Margarida Souto Carneiro	100
Maria Margarida Martins Gonçalves	0,2
Maria Manuel Silva	0,8
Maria Teresa de Teixeira Cruz Rosete	
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Mário Martins Rodrigues Grãos	
Marta Laranjeiro Pinto	
Miguel Luís Cunha Mano	0,5
Miguel Maria da Fonseca Miranda Ferreira Lino	
Miranda Mele	
Mónica Joana Pinto dos Santos	
Mónica Abreu	
Mónica da Rocha Zuzarte	
Mylène Adelaide do Rosário Carrascal	0,2
Natália Sofia António	0,3
Nélio da Mota Gonçalves	
Neuza Luiza da Silva Domingues	
Nuno André Carvalho da Fonseca	
Nuno David de Sousa Chichorro da Fonseca Ferreira	Collaborator
Nuno Gonçalo Costa Freitas Coutinho	0,3
Nuno Miguel da Silva Empadinhas	
Olga Maria Fernandes Borges Ribeiro	
Patricia Alexandre Teles Martins	
Patrícia Bastos Amador	Collaborator
Patrícia Diogo Nunes	0,4
Patrícia Raquel Pinheiro Pitrez Pereira	
Paula Cristina Cardoso Ramos Mota	
Paula Margarida dos Santos Laranjeira	0,4
Paula Cristina Silva Dias Sanches Pinto Alves	Collaborator
Paula Cristina Veríssimo Pires	0,4
Paula Isabel da Silva Moreira	0,6
Paula Margarida Gomes Canas	
Paula Margarida dos Santos Laranjeira	0,3
Paula Maria Garcia Agostinho	0,6
Paula Tavares	0,3
Paulo César da Silva Pinheiro	
Paulo Fernando Martins dos Santos	0,5
Paulo Jorge Gouveia Simões da Silva Oliveira	
Paulo Nuno Centeio Matafome	

Pedro Augusto de Melo Lopes Ferreira	
Pedro Filipe Lopes da Silva Monteiro	0,25
Pedro Ricardo Lucas Perdigão	
Pedro Tiago Cardoso Curto	
Ramiro Daniel Carvalho Almeida	Collaborator
Ramon da Silva Raposo	
Raquel Fernanda Da Silva Alves	
Renata Santos Tavares	
Ricardo Alexandre Gomes Leitão	
Ricardo Filipe Arinto Martins Rodrigues	0,5
Ricardo Jorge de Alves Rodrigues	
Ricardo Jorge Fernandes Marques	
Ricardo Lorenzoni	
Pedro Manuel Quelhas Lima Engrácia Antunes	0,2
Ricardo Neves Pires Das Neves	
Ricardo Romão Nazário Leão	0,3
Ricardo Simão Vieira Pires	
Rita Catarina Gonçalves Perfeito	
Rita Melo	Collaborator
Rita Manuela Palmeira de Oliveira	0,8
Rita Pereira Vilaça	
Rodrigo Pinto Santos Antunes Cunha	0,75
Rogério Paiva Cardoso Teixeira	0,2
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Rosa Maria Branco de Matos Costa Resende	
Rosa Maria Moreira Alves Dos Santos	0,4
Rosemeyre Amaral Cordeiro	
Rufino Martins da Silva	0,3
Rui da Assunção Esteves Pimenta	0,3
Rui Vasco Quintais Gradiz	0,3
Rui Jorge Gonçalves Pereira Nobre	
Rui Manuel Baptista Alves	0,2
Rui Manuel Silva Gomes Barbosa	0,5
Rui Miguel Monteiro Soles Gonçalves	0,2
Rui Miguel Terenas Lança Baptista	0,2
Rui Miguel Oliveira da Costa	
Rui Santos Cruz	0,2
Samira Cardoso Lopes Ferreira	
Sandra Catarina Gomes Amaral	
Sandra Catarina Oliveira Braz	
Sandra Cristina Campos de Jesus	
Sandra Isabel dos Santos Anjo	
Sandra Isabel Freitas Mota	
Sandra Morais Cardoso	0,6
Sandra Santos	0,2
Sandra Margarida Bernardes de Oliveira	0,3
Sara Margarida dos Santos Domingues	0,4
Sara Matias Carmo Silva	
Sara Varela Amaral	
Sérgio Abílio Teixeira Bernardo de Sousa	0,5
Sergio Paulo Magalhaes Simoes	0,35
Siri Folques Vicente de Paulo	Collaborator
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Sofia Ferreira Anastácio	0,2
Sónia Alexandra Pinto Ribeiro da Silva Santos	0,5
Sónia Catarina de Sousa Correia	
Sónia Luzia Claro de Pinho	
Sónia Patrícia Dias Duarte	
Sónia Raquel Marques Batista	0,5

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Susana Carvalho Rosa	
Susana Isabel Elias Alarico	
Teresa Fidalgo	Collaborator
Teresa Carla Trigo de Oliveira	0,4
Teresa do Carmo Pimenta Dinis Silva	0,5
Susana Margarida Neto Simões	
Susana Maria Batista Tieres Tomé Cardoso	
Tânia Sofia Martins Marques	
Teresa Maria Fonseca de Oliveira Gonçalves	0,4
Teresa Maria Caldeira Martins	0,8
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Vania Margarida de Oliveira Goncalves	
Vânia M. Moreira	0,85
Vilma Marisa Arrojado Soares Sardão Oliveira	
Vitor Manuel dos Santos Francisco	
Vitor Manuel dos Reis Raposo	0,5
Vitor Jose Lopes Rodrigues	0,3

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Adriana Marques Carvalho	
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Ana Catarina de Jesus Pais Pereira	100%
Ana Catarina Rodrigues Neves	
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António José Preto Martins Gomes	
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Beatriz Figueiredo Rodrigues	
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Cândida Marília das Neves Dias	
Carlos André Viegas Barreto	
Catarina de Barros Pinto Salvador Domingues	
Catarina Mendes Morais	
Cátia João Monteiro da Santa	
Cátia Moreira de Sousa	
Célia Margarida Alcobia Gomes	0,3
Cláudia Maria Carrudo de Deus	
Cristiana Ferreira Pires	
Daniel Ferreira dos Santos	
Daniel Eduardo Fernandes Martins	0,2
Daniela Costa Batista de Almeida	
Daniela Cristina Nunes Costa	
Daniela Filipa Domingues Santo	
Daniela Isabel Ferreira Madeira	

Débora Vanessa Lourenço Serrenho	
Deolinda Conceição Ribafeita Santinha	
Diana Filipa Coutinho Santos	
Diana Marisa Henriques Carvalho	
Dina Pereira Alves Farinha	
Elena Martinez-Rodriguez	
Emanuel Monteiro Candeias	
Fábio Alexandre Fiúza Rosa	100%
Flávia Sofia Maia Rodrigues	
Gabriela Pires Tavares	
Gabriela Lopes Oliveira	
Gianluca Masella	
Giorgio Belperio	
Gonçalo Sousa Brites	0,4
Helder Filipe da Cunha Esperto	0,1
Helena Isabel Reis Aires	
Helena Maria da Silva Leal	
Heloísa Salguinho Gerardo	
Inês Cravo Roxo	
Inês Alexandra Figueira Marques	
Inês Isabel Nunes Caramelo	
Inês Maria Nascimento Caiado	100%
Inês Preguiça	
Inês Rodrigues Lopes	
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Jane Risete Pires dos Santos Dias	
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Jéssica Margarida Mendes Costa	100%
Jessica Silva	
Joana Margarida Verdasca Jorge	
João David Panão da Costa	
João Duarte Magalhães	
João Miguel Calmeiro Pereira	0,4
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Laetitia Gaspar	
Lígia Vanessa Rocha Fão	
Liliana Pereira Santos	0,5
Lilica Sanca	
Liliana Rodrigues Dias	
Luís Filipe Fragoso Grilo	
Luís Miguel de Almeida Monteiro	
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Marcos António dos Santos Rodrigues Gomes	
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Maria Inês Ramalho de Almeida e Sousa	
Maria Inês Rodrigues Alfaiate	
Maria Inês Veiga de Almeida Barros	
Maria João Ferreira Canas dos Santos	
Maria João Nunes Vicente Mexia Leitão	
Maria Margarida Serra Coelho	
Maria Moreira Soares	
Mariana Barradas Serrano Laranjo	
Mariana Biscaia Caleiras	0,75

Mariana Pereira Magalhães	
Mariangela Natale	
Marisa Pedroso de Lima Marta Neves	
Marija Petkovic	
Marina Manuela Ventura Rodrigues	
Marisa Ferreira Marques	
Marta Isabel Ferreira Leite Pereira	
Marta Sofia Ereira Mota	0,4
Marta Susana de Oliveira e Silva Inácio de Sousa	0,6
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Mireia Alemany i Pagès	
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Nícia Filipa Rosário Ferreira	0,15
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Pedro Miguel Caniceiro Valada	
Pedro Miguel Pinto Fernandes	0,9
Pedro Miguel Reis Figueiredo	
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Ricardo Jorge Marques Teixeira	
Ricardo Jorge Carreira da Silva	
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Rita António dos Santos	
Rita Rodrigues Sá Ferreira	
Rodrigo Filipe Nunes Ribeiro	0,5
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Teresa Margarida Ribeiro Rodrigues	
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Tiago Maria Ochôa e Azevedo Pires	
Tiago Ventura Lourenço Lima	

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Ana Sofia Caride Gregório Barata Figueira	
Ana Maria da Graça Fernandes Vasconcelos	
Andreia Filipa Simões Oliveira	
Andreia Amaro	0,5
Andreia Margarida Silva Barro	
Bárbara Daniela Araújo Pinheiro Teixeira	
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Getachew Debas Belew	
Giada Di Nunzio	
Giuseppe Cammarata	
Inês Maria Cunha Albino	
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Jorge Lindo	Volunteer
Julie Héléne dos Reis	
Luís Filipe Henriques Oliveira	
Márcia Joana Nascimento Teixeira	
Margarida Fernandes Beatriz	
Mariana Raquel Antunes Colaço	
Mariana Isabel Duarte Almeida	Volunteer
Mariana Filipa Simões Diniz	
Miguel Ângelo Morgado Teixeira	0,2
Miguel Monteiro Lopes	
Marta Filipa Viegas Barão	
Patrícia Raquel Delgado Coelho	
Pedro Miguel Dias Vieira	
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Sara Raquel Ramalho Pereira Nunes	
Sónia Filipa Gomes dos Santos	
Susana Cristina Domingues Pedreiro	
Tamaeh Monteiro	
Teresa Raquel Tremeço Dias de Abreu	
Tiago Batista Abrantes Rondão	
Vanessa Filipa Rodrigues Costa	
Vanessa Simões Lourenço	
Vasco Lucas	0,5

OTHERS

Albina Bushmalyova	1
Alexandra Cruz	1
Alexandra Daniela Alves Cerca Seabra Dinis	0,3
Alexandra Fernandes de Carvalho	Collaborator
Alexandre Simão Vieira Pires	Collaborator
Alexandre Rebelo Marques	0,2
Alexandro Pereira Azevedo	1
Ana Cristina Franco Santos	1
Ana Esmeralda Oliveira Guedes Costa	0,2
Ana Filipa Rodrigues Ferreira	Collaborator
Ana Maria Reis Costa	1
Ana Rita Marques Fonseca	Volunteer
Ana Sofia Fernandes Pais	0,3
Anabela Peixinho Valente de Matos	0,3
Ana Teresa Santos Costa Gaspar	1
André Miguel Andrade Lázaro da Silva Correia	0,3
Andreia Sofia Reis Monteiro	Collaborator
Beatriz Maria Lemos Ormonde	1
Carlos Miguel Machado Marto	0,3
Carolina Matos Carola	Collaborator
Carolina Ferreira	1
Catarina Guilherme	1
Cátia Barra	0,2
Cátia Andreia dos Santos Ferreira	Collaborator
Cláudia Virgínia Louro Farinha	Collaborator
Christian André Fernandes Neves	0,2
Cristina Maria da Costa e Silva Barroso	1
Daniel Lopes Oliveira	1
Daniel José Vasconcelos Silvério	1
Daniela Pereira Santana Alho	0,2
Daniela Sofia Madama Santos Silva	0,2
Diana Bela da Luz Sequeira	Collaborator
Diana Filipa Dias Duro	0,3
Edgar Miguel Calvo Loureiro Tavares da Silva	0,2
Filipe Alves	1
Filipe Manuel Farto Palavra	0,2
Flávia Simões	0,2
Gil Roberto Correia Lopes	0,4
Gonçalo da Costa Rodrigues Ferreira	1
Gustavo António Pereira Rodrigues Cordeiro Santo	0,3
Henrique José Xavier Duarte	0,85
Inês Alexandra Ferreira Rodrigues	1
Inês Flores Amaro	0,2
Inês Martins Malva Correia	0,2
Inês Pereira Dias Marques	0,2
Joana Delgado Silva	0,2
Joana Mafalda Coelho Oliveira	1
Joana Margarida Cardoso Serra Martins	1
Joana de Jesus Ribeiro	0,2
João Gabriel Branco Silva	1
João Lourenço Ribeiro Alves	Volunteer
João Luís Oliveira Durães	0,5
João Fernando Pereira Mendes	0,7
João Manuel Beirão Cardoso Quadrado Gil	0,2
João Pedro Oliveira	0,5
João Pedro Teixeira Marques	0,2

Joaquim Moita	Collaborator
Jorge Filipe Silva Henriques	Collaborator
José G. Almeida	0,3
José Pedro Sousa Baptista	0,2
Karla Menezes Cardoso	0,5
Leonor Aurélio Barroso	Collaborator
Luis Leite	0,2
Luis Jorge Mendonça Peres Negrão	0,2
Luisa Nunes Dias Lagarto dos Santos	Collaborator
Manuel de Oliveira Santos	Collaborator
Maria do Carmo Ribeiro Reis Maio Macario	0,2
Maria Inês Nuno Alves	I
Maria Inês Sousa Cristo	Collaborator
Maria Mendes da Silva	I
Mariana Sá Rocha	0,4
Marta Isabel Pereira	0,35
Miguel António Tábuas da Cunha Pereira	0,5
Patrícia Sofia Soares Regueira	0,2
Patrícia Susana Correia Lopes Barreto	Collaborator
Paulo Rodrigues Santos	0,25
Pedro Luis Martins da Fonseca	0,3
Pedro Matos Filipe	0,3
Pedro Nuno Beirão Cardoso Quadrado Gil	0,2
Pedro Sobral	I
Raquel Sofia Freitas Boia	I
Raquel Fernanda Da Silva Alves	Collaborator
Raquel Pina Gouveia	I
Ricardo Jorge Teixeira Martins	Collaborator
Ricardo Manuel Ferreira Monteiro Félix de Moraes	0,5
Ricardo Pedro Moreira Martins Casqueiro dos Santos	I
Rita Maria Mendes Silveira de Almeida Martins	0,75
Rui Manuel da Costa Soares	0,4
Rui Miguel Rua Filipe Martins	0,3
Rui Pedro Caetano Moreira de Oliveira	0,2
Simao Correia Santos	I
Simaura Henriques	I
Sara Miguel Gonçalves	Volunteer
Sara Rita Rodrigues Pedroso	Collaborator
Solange Martins Nogueira	Volunteer
Tânia Raquel Vieira da Silva	0,2
Teresa Sofia Seara Sevivas	Collaborator
Tiago José Brasil Roquito	I
Vânia Marina Jorge Leal	Collaborator
Xavier Sá Castro Pinho	0,3

TECHNICAL / ADMINISTRATIVE SUPPORT

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Alda Maria de Oliveira Rodrigues	Basic Education	
Ana Filipa Gomes Oliveira Ensino	Secondary Education	
António José Azinhaga Teles Grilo	Degree Level	
Cândida Elsa Frias Mendes	Master degree	
Carla Andrea Pereira António Lopes	Secondary Education	
Carla Margarida dos Santos Verissimo	Master degree	
Carmen Lídia Graça Semião	Degree Level	
Catarina Alexandra Ferreira Gomes	Degree Level	
Cláudia Sofia Bastos Figueiredo	Secondary Education	
Claudia Patricia Garrote dos Santos	Secondary Education	
Elsa Henriques	PhD	
Fátima Cristina Dos Santos Graça	Secondary Education	
Filipe José Ribeiro Malta	Secondary Education	
Heidi Maria da Silva Lopes Gonçalves	Master degree	
Isabel Maria de Oliveira Dantas Fernandes	Degree Level	
Isabel Maria Nunes Correia	PhD	
João Miguel da Silva Pratas	Degree Level	
Lara Franco	PhD	
Lia da Costa Jordão Aparício Lopes	Master degree	
Luciana Costa de Albuquerque Pinto	Master degree	
Luisa Maria Oliveira Pinheiro Leitão Cortes	PhD	
Margarida Alexandra Vaz Caldeira	PhD	
Maria Adelaide Cunha Oliveira	Basic Education	
Maria de Fátima Sousa Martins Moreira	Master degree	
Maria do Céu Mendes Gomes	Basic Education	
Maria do Rosário Ferreira da Costa Faro	Master degree	
Maria Eugénia Alves da Silva Lopes Campos	Basic Education	
Maria Jose da Silva Glaziou	Basic Education	
Maria Isabel Mendes Gonçalves	Basic Education	
Maria Luísa Rocha Caldeira Bonito	Degree Level	
Marta Sofia Marques Simões	Master Degree	
Milene Vanessa Rodrigues Ribeiro	Master degree	
Mónica Alexandra Rodrigues Morais	Degree Level	
Mónica Alexandra Vilão Serrano	Secondary Education	
Nilza Clara Ferreira Marques Manadas	Secondary Education	
Rosa Alexandra do vale Folhas Fernandes	Master degree	
Rute Eliete Marques e Cruz Simões	Secondary Education	
Sandra Cristina Santos Luís	Degree Level	
Sandra Margarida Pinheiro Freire	Degree Level	
Sara da Costa Jordão Aparício Lopes	Secondary Education	
Sílvia Maria Esteves de Sousa	Master degree	
Susana Adelaide Rocha da Silva	Secondary Education	
Tânia Sofia Aguiar Ribeiro	Degree Level	
Tatiana Andreia Forjaz Amaral Catarino	PhD	
Tatiana de Azevedo Paula	Degree Level	
Telma Patricia Simões Graça	Secondary Education	
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