CNC.IBILI

ANNUAL REPORT [2019]

CNC.IBILI

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INTRODUCTION

CNC.IBILI is a multidisciplinary research consortium created at the University of Coimbra in 2015 that results from the fusion of two biomedical research institutes of excellence, CNC, recognized by FCT as a "Laboratório Associado" in 1990, and IBILI a researchinstitute of Biomedical Sciences at the Faculty of Medicine, University of Coimbra. CNC.IBILI incorporates the largest critical mass of biomedical investigators in the Center region of Portugal.

As stated in the project proposal, research at CNC.IBILI is organized in three Thematic Strands: The Neuroscience, Vision and Brain Diseases Strand, focused on understanding brain and visual function at the molecular and cellular levels focusing particularly in defects on synaptic processes, brain metabolism and biomarkers of brain diseases, in order to increase diagnosis accuracy and to design patient-tailored therapies; the Metabolism, Aging and Disease Strand, centered on unraveling the links between cellular dysfunction (namely mitochondrial activity, oxidative stress, endoplasmic reticulum dysfunction and protein folding), with metabolism-based changes in diabetes, neurodegenerative and aging-related disorders, aiming to identify possible molecular and cellular therapeutic targets, and provide novel non-invasive diagnostic strategies using metabolite tracers; the Stem-cellbased and Molecular Therapies Strand that aims at investigating translational advanced therapies for neurodegenerative, cardiovascular and infectious diseases, as well as cancer, taking advantage of stem cells and of molecular therapy strategies. The close connection to the Coimbra University Hospital Center (CHUC), one of the largest in Portugal, provides access to clinical know-how, patient samples, and patients themselves, fostering translational and clinical research and the participation in international consortia. On the other hand, collaboration with industry, namely in the biotechnology entrepreneurship campus created in Biocant Park, ensures that novel scientific ideas and methodologies will contribute to a more competitive knowledgebased economy in the region.

In 2019, CNC.IBILI pursued its main goal, the understanding of brain and vision function and disease mechanisms leading to the development of target-oriented therapies, supported by novel molecular biology approaches and by a tight interaction with Coimbra University Medical Center (CHUC).

CNC.IBILI was also strongly committed to post-graduate education and training, being involved in the coordination of master and PhD Programs at the University of Coimbra and also in international training networks (Marie- Curie and ITN).

Through the outreach program, innovative actions aiming to improve society scientific education have been developed in schools and in collaboration with "Ciência Viva" and "Instituto de Educação e Cidadania".

The specific objectives of each strand and of the respective research groups are described in detail in the respective reports of activity.

CATARINA RESENDE OLIVEIRA
CNC.IBILI Coordinator

FACTS & FIGURES

From Year 2019

RESEARCH STAFF

Members holding Ph.D.	204
Members holding MSc	197
Other members	77

PUBLICATIONS

Scientific papers published	354

THESIS CONCLUDED

Ph.D. thesis	14
MSc thesis	86

SCIENTIFIC AREAS AND RESEARCH GROUPS

At present, research programmes and projects are organized in 3 research scientific areas, each coordinated by a senior scientist. The programme for each area is implemented by small research groups each headed by a research leader in his field of study. In 2019, the research groups for Thematic Strand can be identified, according to the following organization:

Neuroscience, Vision and Brain Diseases Strand
Ana Luísa Carvalho

Synapse Biology Group (Head: Carlos B. Duarte)

Redox Biology and Brain Sensing Group (Head: João Laranjinha)

Neuroendocrinology and Aging Group (Head: Claudia Cavadas)

Vision, Brain Imaging and Cognitive Neuroscience (Head: Miguel Castelo-Branco)

Purines in brain diseases (Head: Rodrigo Cunha)

Mitochondrial Dysfunction and Signaling in Neurodegeneration Group (Head: A. Cristina Rego)

Aging and Brain diseases: advanced diagnosis and biomarkers (Head: Catarina Resende Oliveira)

New Targets and Therapeutics for Chronic Diseases (Head: António Francisco Ambrósio)

Metabolism Aging, and Disease Strand
João Ramalho Santos

Cell Metabolis and Quality Control Group (Head: Paula Moreira)

Mitochondria, Metabolism and Disease Group (Head: Paulo Oliveira)

Metabolic Control Group (Head: John Grifith Jones)

Stem Cell-Based and Molecular Therapies Strand
Luis Pereira de Almeida

Vectors and Gene Therapy Group (Head: M. Conceição Pedroso Lima)

Stem cell biotechnology Group (Head: Lino Ferreira)

Systems and Computational Biology Group (Head: Armindo Salvador)

Medical Microbiology Group (Head: Teresa Gonçalves)

Molecular Mycobacteriology Group (Head: Nuno Empadinhas)

Medicinal Chemistry & Drug Discovery Group (Head: Jorge Salvador)

Biotechnology

Microbiology of Extreme Environments Group (Head: Milton Costa)

Molecular Biotechnology Group (Head: Isaura Simões)

CNC.IBILI External Advisory Commitee: Fernando Lopes da Silva (NL); John Greenwood (UK); Rainer Goebel (NL); Marc Peschanski (FR); Xandra Breakefield (USA); Matthijs Vehage (NL)

RESEARCH ACTIVITY

NEUROSCIENCE, VISION AND BRAIN DISEASES
COORDINATOR: ANA LUÍSA CARVALHO

GENERAL OBJECTIVES
Research at the Neuroscience, Vision and Brain Diseases (NVBD) research area investigates brain function and the causes of diseases of the nervous system, and develops novel strategies for disease prevention and treatment. This research line comprises 8 research groups in the areas of molecular, cellular, circuits and behavioral neuroscience, along with brain imaging, to understand the brain at different scales, from the level of single cells to brain circuits and behavior.

In collaboration with the Coimbra University Hospital (CHUC), NVBD groups explore different potential candidates, such as altered synaptic neuromodulation, mitochondrial dysfunction, neurovascular coupling and neuroinflammation, in order to develop novel interventions and identify biomarkers for brain and vision disorders.

MAIN ACHIEVEMENTS
In 2019, researchers in the NVBD research line identified a post-transcriptional mechanism of regulation of synaptic transmission (Silva et al., 2019), and how the neurotrophin BDNF impacts NMDA receptors, by enhancing local translation (Afonso et al., 2019). They have also characterized an additional role for the cell adhesion molecule Caspr2 in regulating AMPA receptor-mediated transmission, which is disrupted by antibodies from patients with autoimmune synaptic encephalitis (Fernandes et al., 2019). A study led by the most recent group in the NVBD research line (coordinated by João Peça) revealed abnormal mGluR-mediated synaptic plasticity and autism-like behaviours in Gprasp2 mutant mice (Edfawy et al., 2019).

Studies on the neuromodulation by purines have continued in 2019. One group found that synaptic and memory dysfunction in Alzheimer's disease depends on increased formation of ATP-derived extracellular adenosine (Gonçalves et al., 2019), and that enhanced AT release and adenosine formation sustain adenosine A2A receptor activation in a model of Parkinson's disease (Carmo et al., 2019). In addition, adenosine A2A receptors in the prefrontal cortex were found to control delay-based cost-benefit decision making (Leffa et al., 2019). The role of adenosine receptor in the microglia has been explored. One study showed region-specific control of microglia by adenosine A2A receptors, and uncoupled its role in mediating anxiety and cognitive deficits in female animals (Duarte et al., 2019). A second study revealed that blockade of microglial adenosine A2A receptor suppresses elevated pressure-induced inflammation and cell death in retina cells (Aires et al., 2019).

One focus of the NVBD area is on neurodegeneration and aging. Age-related differences in event-related potentials and puppilary responses were found in cued reaction time tasks (Ribeiro et al., 2019). In young and older adults, neural correlates of anticipatory cardiac deceleration were described, and found to be associated with the speed of perceptual decision-making (Ribeiro et al., 2019). Longitudinal multimodal in vivo molecular imaging studies showed progressive early hippocampal volume decrease and taurine loss in a model of Alzheimer's disease (Chiquita et al., 2019), and that retinal thinning of inner sub-layers is associated with cortical atrophy (Chiquita et al., 2019). This last study supports the concept of the retina as a window to look into the brain or a mirror of the brain, and proposes that retinal alterations could constitute new reliable biomarkers to detect Alzheimer's disease at an early stage.

Our clinical studies have generated important data, in particular for identifying biomarkers of disease. A cross-sectional study showed an association between adipokines and biomarkers of Alzheimer's disease (Letra et al., 2019), the lumipulse G cerebrospinal fluid assays have been clinically validated for routine diagnosis of Alzheimer's disease (Leitão et al., 2019), and lower CSF Amyloid-Beta 1-42 has been found to Ppredict a higher mortality rate in Frontotemporal Dementia (Vieira et al., 2019).

Technical achievements include the characterization of oxSWATH, an integrative method for a comprehensive redox-centered analysis combined with a generic differential proteomics screening (Anjo et al., 2019), the validation of an LC-MS/MS method for the quantification of caffeine and theobromine (Mendes et al., 2019), and the characterization of a platinized carbon fiber-based glucose microbiosensor designed for metabolic studies in brain slices (Lourenço et al., 2019).

This summary of the main achievements in the NVBD line highlights some of the important contributions from research groups in this area. Please refer to the individual NVBD group reports for other important studies during 2019.

Synapse Biology Group

Carlos Duarte	PhD Head of Group)
Mónica Santos	PhD
Emília Duarte	PhD
Rui Costa	PhD
Miranda Mele	PhD
Ivan Salazar	PhD
Gladys Caldeira	PhD
Dominique Fernandes	PhD
Filipe Duarte	PhD
Pasqualino De Luca	PhD Student
Elisa Corti	Student
Ramiro Almeida	PhD
Mohamed Hussien	PhD
Jeannette Schmidt	PhD Student
João P. Silvestre	PhD
Ana L. Cardoso	PhD
Joana Guedes	PhD
Catarina Seabra	PhD
Mariline Silva	PhD Student
Ana Mª Vasconcelos	Student
Renato Macedo	Student
Marta Pereira	Student
Mariana Laranjo	Student
Ana R. Oliveira	Student
Giuseppe Cammarata	Student
Jéssica Costa	Student
Nuno Marques	Student
Pedro Ferreira	Student
Ana Silva	Student
Solange Nogueira	Student
Marina Rodrigues	Student
Orsolya Antal	Student
Beatriz Rodrigues	Student
Débora Serrenho	Student
Paulo Pinheiro	PhD
Vera Pais	Student
Ângela Inácio	PhD
Ana Luísa Carvalho	PhD
Joana Mourão	PhD
Pedro Filipe	Student
Carlos Barreto	Student
Agostinho Lemos	Volunteer
Xavier Pinho	Student
Nícia Ferreira	Student
Ricardo Pinheiro	Student
Raquel Gouveia	Student
Irina Moreira	PhD
José Almeida	Volunteer
António Gomes	PhD Student

Redox Biology and Brain Sensing Group

João Laranjinha	PhD (Head of Group)
Ana Ledo	PhD
Diana Serra	PhD
Leonor Almeida	PhD
Rui Barbosa	PhD
Teresa Dinis	PhD
Barbara Rocha	Post Doctoral Fellow
Catia Marques	Post Doctoral Fellow
Cândida Dias	PhD Student
João Gonçalves	PhD Student
Joana Henriques	PhD Student
Andreia Marques	Student

Neuroendocrinology and Aging Group

Cláudia Cavadas	PhD (Head of Group)
Laetitia Gaspar	PhD Student
Célia Aveleira	PhD
Ana Rita Álvaro	PhD
Joaquim Moita	MD
Sara Silva	PhD
Rodrigo Ribeiro	Student
Helena Leal	Student
Bárbara Santos	Student
Daniela Costa	Student
Rodolfo Águas	Student
Catarina Almeida	Student
Ana Franco	Student
Ana Carvalho	PhD
Marisa Marques	PhD Student
Maria Silva	PhD
Alexandrina Mendes	PhD
Fernando Judas	MD
Cátia Sousa	PhD Student
João Oliveira	MD

Vision, Brain Imaging and Cognitive Neuroscience Group

Miguel Castelo-Branco	PhD (Head of Group)
Aldina Reis	PhD
Andreia Rosa	PhD
Antero Abrunhosa	PhD
Barbara Oliveiros	PhD
Francisco Caramelo	PhD
Francisco Alves	PhD
Gabriel Costa	PhD
Guiomar Oliveira	PhD
Inês Violante	PhD
João Pereira	PhD
Joaquim Murta	PhD
Jorge Saraiva	PhD
José Domingues	PhD
José Sereno	PhD
Luís Alves	PhD
Mª Conceição Fonseca	PhD
Mª Cristina J Santos	PhD
Mª Fátima Silva	PhD
Mª João Vidigal	PhD
Nuno Ferreira	PhD
Otilia D´Almeida	PhD
Pedro Serrenho	PhD
Rufino Silva	PhD
Rui Bernardes	PhD
Sérgio Carmo	PhD
Bruno Leitão	Post Doctoral Fellow
Helena Pereira	Post Doctoral Fellow
Inês Bernardino	Post Doctoral Fellow
Inês TAlmeida	Post Doctoral Fellow
Joana Silva	Post Doctoral Fellow
Joana Gonçalves	Post Doctoral Fellow
João Martins	Post Doctoral Fellow
João Castelhano	Post Doctoral Fellow
Joao Figueira	Post Doctoral Fellow
Joao Duarte	Post Doctoral Fellow
José Teles	Post Doctoral Fellow
Mª José Ribeiro	Post Doctoral Fellow
Alexandre Sayal	PhD Student
Ana Rodrigues	PhD Student
Ana Baptista	PhD Student
Andreia Pereira	PhD Student
Carlosl Amaral	PhD Student
Carolina Alves	PhD Student
Filipa Júlio	PhD Student
Hélio Gonçalves	PhD Student
Hugo Quental	PhD Student
Marco Simões	PhD Student
Marta Teixeira	PhD Student
Nádia Canário	PhD Student
Susana Silva	PhD Student
Susana Mouga	PhD Student
Tarcícsio Guimarães	PhD Student
César Nunes	MD
Margarida Marques	MD
Maria Ribeiro	MD
Pedro Fonseca	MD
Ana Dionísio	Grant Technician
João Pereira	Grant Technician
Vitor Alves	Grant Technician
Isabel Duarte	Technician
Mª Fátima Machado	Technician

Neuromodulation Group

Rodrigo Cunha	PhD Head of Group)
Anna Pliássova	PhD Student
Attila Köfalvi	PhD
Paula Canas	PhD
Paula Agostinho	PhD
Ângelo Tomé	PhD
Cátia Lopes	Student
Ricardo Rodrigues	PhD
Joana Marques	PhD
Nélio Gonçalves	PhD
Xinli Xu	PhD Student
João Rocha	Student
Ana Sá	Student
João P. Lopes	PhD
Ana P. Simões	PhD
Francisco Gonçalves	PhD
Liliana Dias	Student
Henrique Silva	PhD
Matilde Rodrigues	Trainee

Mitochondrial Dysfunction and Signaling in Neurodegeneration Group

Ana C. Rego	PhD Head of Group)
Bruno Moraes	Research Assist.
Bruno Santos	Student
Carla Lopes	PhD
Daniela Lopes	Student
Ildete Ferreira	PhD
Laura Neves	Student
Lígia Fão	Student
Margarida Beatriz	Student
Patrícia Coelho	Student
Rita Vilaça	PhD
Sandra Mota	PhD

Aging and Brain diseases: advanced diagnosis and biomarkers Group

Catarina R. Oliveira	PhD Head of Group)
Bruno Manadas	PhD
Inês Baldeiras	PhD
Mª Rosario Almeida	Student
Mª Isabel Santana	PhD
Mª Manuela Grazina	PhD
Sandra Anjo	PhD
Sónia Batista	MD
Ana Silva	PhD
João Rodrigues	PhD
Helena Santiago	MD
Miguel Pereira	MD
Ricardo Morais	MD
Inês Caramelo	PhS Student
Cátia Santa	PhD student
Mª João Leitão	PhD Student
Mª Margarida Coelho	Student
Rémy Cardoso	PhD Student
Márcia Teixeira	Student
Anabela Matos	MD
Gustavo Santo	MD
Luis Negrão	MD
Diana Duro	Superior Technic.
Inês Correia	MD
Mª Carmo Macario	MD
Anuschka Spínola	Student
Miguel Rosado	Student
Diana Carvalho	Student
Sara Pêgo	Student
Vanessa Costa	Volunteer

New Targets and Therapeutics for Chronic Diseases Group

António F. Ambrósio	PhD (Head of Group)
Catarina Gomes	PhD
Ana Abrantes	PhD
Filipa Baptista	PhD
Célia Cabral	PhD
Flávio Reis	PhD
Eunice Carrilho	PhD
Elisa Campos	PhD
Bárbara Gomes	PhD
Célia Gomes	PhD
Belmiro Parada	MD
Ana Santiago	PhD
Fernando Mendes	PhD
Carlos Ribeiro	PhD
Ana Pires	PhD
Ana Brito	PhD
Ana P. Martins	PhD
João Malva	PhD
José Tralhão	PhD
Mafalda Cândido	PhD
Manuel Veríssimo	PhD
Manuel Ferreira	PhD
Marcos Barbosa	PhD
Mª Filomena Botelho	PhD
Mª João Carvalho	PhD
Natália António	PhD
Paulo Santos	PhD
Rosa Fernandes	PhD
Ricardo Leitão	Student
Sofia Viana	PhD
Sónia Santos	PhD
Ana Costa	MD
Ana Gaspar	Student
Ana Pais	Student
António Figueiredo	MD
Carlos Marto	MD
David Castelo	MD
Diogo Fonseca	PhD
Edgar T Silva	MD
Eurico Ribeiro	Student
João Lopes	PhD
José Ives	MD
Ana Santos	PhD
Leonor Barroso	MD
Filipe Palavra	MD
Raquel Boia	Student
Rui Martins	MD
Rui Oliveira	Student
Sara Nunes	Student
Beatriz Martins	Student
Inês Aires	Student
Inês Pita	Student
Joana Martins	Student
Luciana Fernandes	Student
Miguel Pinheiro	Student
André Alves	Student
Inês Preguiça	Student
Alda Gonçalves	Public Sector
Joana Cipriano	Public Sector
Ana Santiago	Student
Inês Ventura	PhD
Sofia Galvão	Student
Ana Ferreira	Student
Maria Cotrim	PhD
Isabel Pereira	PhD
Frederico Pereira	PhD

SYNAPSE BIOLOGY

Head: Carlos B. Duarte

OBJECTIVES

Research in the 'Synapse Biology' group aims at understanding the molecular pathways controlling synaptic activity at the postsynaptic level under normal physiological conditions. How dysregulation of synapses contributes to psychiatric and acute disorders of the nervous system is also investigated by this group.

Opioid receptors are present in the central nervous system and can induce several cellular responses such as: analgesia, euphoria, or reduced inflammation, being important receptors in pain relief studies. One additional goal of the group is to understand how these receptors couple with their partners to induce downstream cellular responses.

Synapse function and dysfunction in brain disorders

The ability of synapses to change their strength is thought to be the cellular correlate of learning and memory. Synaptic dysfunction is a hallmark of neuropsychiatric disorders, and it is an early event in neurodegenerative disorders. We use a combination of techniques such as primary cultures of dissociated neurons and brain slices, biochemistry, molecular and cellular biology, mouse molecular genetics, electrophysiology and behavior analysis to address the role of molecular players that regulate synaptic function. Furthermore, we investigate disease-related alterations in synaptic function, either genetic 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, bipolar disorder and autism spectrum disorders. An additional aim of the group is to identify how specific genetic and environmental factors alter circuit level properties, ultimately leading to anxiety disorders, affecting social interactions or causing autism and other neurodevelopmental defects. 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.

Understanding the contribution of the neuroimmune system to the establishment of neuronal circuits and the development of neuronal pathologies

In this line of research, we hope to unravel how microglia cells, responsible for innate immune responses in the brain, contribute to neuronal homeostasis and circuit establishment during neuronal development and throughout life and how they respond to environmental insults during the early life period. In addition, we are also interested in studying the biochemical processes through which microglia and other innate immune cells, such as macrophages and monocytes, potentiate neuronal damage in dementia-associated disorders, such as Alzheimer's disease and Frontotemporal Lobar Degeneration, and in neurodevelopmental diseases, such as Autism spectrum disorder and Attention Deficit and Hyperactivity Disorder (ADHD).

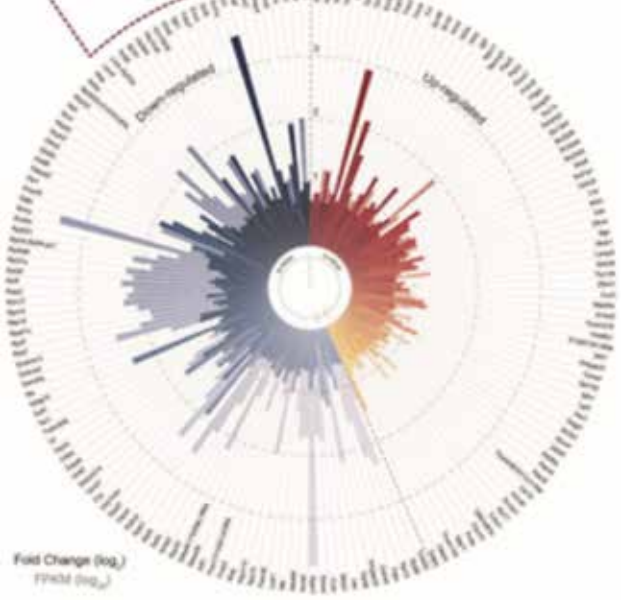
Targeting the K+-Cl- cotransporter (KCC2) to maintain GABAergic neurotransmission: a novel therapeutic strategy for epilepsy

Inhibitory neurotransmission in the CNS is largely mediated by GABA which plays an essential role in maintaining the excitatory/inhibitory balance required for correct brain function. Deficits in functional expression of GABAARs have been implicated in the pathogenesis of several neurological and psychiatric diseases, including epilepsy. In many patients with epilepsy, seizures are controlled with anti-epileptic drugs (AEDs) but 30% of epileptic patients do not respond to the treatment because of a progressive internalization of postsynaptic GABAARs and to a shift of the GABAAR reversal potential due to an alteration in chloride homeostasis (Mele et al., 2014).

Previous unpublished results from our laboratory have shown an enhanced internalization of GABAAR during Status Epilepticus (SE). Furthermore, SE is correlated with an impaired GABAAR recycling, indicating that GABAAR synaptic stability is compromised in this condition. The downregulation of GABA inhibitory activity may arise from a positive shift in GABAAR reversal potential, due to an alteration in chloride homeostasis. However, the contribution of alterations in the Cl– gradient in this phenomenon is not yet established. In this project we investigated the role of chloride homeostasis mechanisms in the alterations of inhibitory synapses induced by status epilepticus, focusing on the KCC2 K+-Cl-- cotransporter as a potential target for SE treatment.

Decoding Partner Specificity in G-Protein Coupled receptors

Opioid receptors are present in the central nervous system and can induce several cellular responses such as: analgesia, euphoria, or reduced inflammation, being important receptors in pain relief studies. Under constant opioid stimulation the receptors can be less internalized leading to the opioid tolerance, in other words, there is a never-ending increase of opioid doses to produce the same cellular response. This problem is described as the opioid crisis and is directly related to drug abuse. There are, currently, 13 structures deposited on online databases, 5 from mouse (Mus musculus) and 8 from human (Homo sapiens); 10 structures were solved by X-ray crystallography and the other 2 by cryo-electron microscopy; 4 structures are in an active state, the other 9 are inactive. The active structures are: 3 μ receptors from mouse and a k receptor from human. Although the number of structures had steadily increased in recent years, we are still far from understanding how these receptors couple with their partners and how the differences in the established interface influence their structure and function.



Global alterations in gene expression in the mPFC of maternal deprived mice.A Circos plot display of up-regulated transcripts in red (total of 78) and downregulated transcripts in blue (total of 102) in maternally deprived mice compared to CTR; solid bars represent fold change (log2) and transparent portion of each bar represents transcript abundance in Fragments Per Kilobase Million (FPKM in log10).

MAIN ACHIEVEMENTS

i) Synaptic function and dysfunction in brain disorders

PI: Ana Luísa Carvalho

1. We have identified a role for miRNA-186-5p in the regulation of AMPA receptor subunit composition, by targeting the GluA2 subunit of AMPA receptors (Silva et al., 2019). We also found that miRNA-186-5p mediates synaptic scaling in the hippocampus. We are presently studying abnormal upregulation of miRNA-186-5p levels in the brain during chronic stress, and whether it is implicated in chronic stress-related alterations in synaptic transmission.
2. We have described a new role for the cell adhesion molecule Caspr2 in regulating excitatory synaptic transmission (Fernandes et al., 2019). CASPR2 is also an auto-antigen in synaptic autoimmune encephalitis, and we found that anti-CASPR2 autoantibodies from patients disrupt the role of Caspr2 in regulating AMPA receptor function and synaptic transmission in the visual cortex. We are interested in understanding differential effects produced by anti-CASPR2 antibodies from patients targeting different epitopes, and with different antibody titers, and how those effects correlate with the clinical symptoms found in patients.
3. We have produced knock-in mice which express a human mutation in the CACNG2 gene (coding for stargazin) associated with intellectual disability. These mice 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., in preparation).

PI: João Peça

1. In collaboration with the group of Guoping Feng at MIT we have found that specific deletion of GPRASP2 in hypothalamic neurons is sufficient to induce obesity. We have also found that genetic ablation of GPRASP2 in parvalbumin (PV)-positive interneurons is sufficient to recapitulate severe memory deficits in mice.
2. Using behavioral studies, electrophysiology, and imaging, we have characterized the changes that emerge in juvenile, adolescent and adult rodents upon exposure to an early life stress paradigm that mimics maternal stress and neglect. Maternal separation induced long-term changes in social behavior and social hierarchy (Franco et al, 2020).
3. We concluded a study on the potential usability of miRNA-31 in Alzheimer's Disease progression by targeting APP and BACE1. This microRNA, previously found to be decreased in AD patients, simultaneously reduced the levels of APP and Bace1 mRNA in the hippocampus of 17-month-old AD triple-transgenic (3xTg-AD) female mice, leading to a significant improvement of memory deficits and a reduction in anxiety and cognitive inflexibility. In addition, lentiviral-mediated miR-31 expression significantly ameliorated AD neuropathology in this model, drastically reducing Aß deposition in both the hippocampus and subiculum (Viegas, et al. 2020)
4. In collaboration with MIT, we participated in a study on the regulation of thalamic information processing. The goal of this work was to gain a thorough understanding of the genetic, electrophysiological and network properties of the thalamic reticular nucleus, a key region involved in attention, sleep and sensory processing, with clear links to autism and ADHD (Li et al, Nature 2020).

PI: Mónica Santos

NT3/TrkC signaling in the regulation of fear. C57Bl6/J animals were trained in the contextual fear conditioning and extinction paradigms, as described previously (D'Amico et al., 2017), and sacrificed at timepoints that represent different phases of fear processing: fear conditioning, fear memory, fear extinction acquisition, fear extinction memory. For each test group, appropriate control groups were also included. All animals were previously tested in the elevated plus maze and open field paradigms to monitor anxiety and exploratory/locomotor activity. We found that only a subset of conditioned WT animals showed a reduction of 30% in their freezing levels, as compared to freezing levels at the fear retrieval phase, showing effective fear extinction. In a retrospective analysis of the data, animals in this "extinction-success" group also performed better in the extinction training phase, as compared to the "extinction-failure" animals, but no differences were observed between the two groups in fear retrieval or fear conditioning phases. We hypothesized that putative NT3 and TrkC levels in brain regions of the fear circuit could influence performance in CFC and CFExt and aimed at quantifying NT3 protein levels by ELISA, and pTrkC and TrkC by Western blot. Our first results with ELISA showed no differences among groups in the levels of NT3 in the PFC or in the amygdala, at the fear extinction retrieval phase.

PI: Carlos B. Duarte

1. Regulation of glutamatergic synapses by BDNF. We reported that BDNF induces synaptic delivery of GluN2B-containing NMDA receptors (NMDAR) by a mechanism mediated by activation of Pyk2 and dependent of protein synthesis (Afonso et al., 2019). Furthermore, BDNF upregulated dendritic Pyk2 protein levels by a mechanism dependent of hnRNP K, a ribonucleoprotein that binds the kinase mRNA. The results show a key role for Pyk2 synthesis at the synapse as a mediator of the effects of BDNF on the synaptic distribution of NMDAR, which may have an impact on LTP.
2. Targeting the K+-Cl- cotransporter (KCC2) to maintain GABAergic neurotransmission: a novel therapeutic strategy for epilepsy

The results obtained so far showed that exposure of hippocampal neurons to conditions that model Status Epilepticus (SE) in vitro downregulates KCC2 surface expression, by a mechanism sensitive to the inhibitor of clathrin dependent endocytosis dynasore, and this effect was correlated with an increase in the [Cl-]i. CLP257, a compound that enhances KCC2 activity, drastically reduced the SE effects on the distribution of KCC2, maintaining its surface expression much more stable when compared with the SE condition in absence of the KCC2 activator. These results suggest that activation of KCC2 may be considered a possible strategy to maintain the surface levels of the transporter in epileptic conditions, and indicate that KCC2 may be a new target for the treatment of epilepsy.

ii) Decoding Partner Specificity in G-Protein Coupled receptors

PI: Irina Moreira

An extensive characterization of opioid receptor (OR) family was carried out to create new knowledge about the physiological and pharmacological properties of these important drug targets. Homology modeling was used to generate reliable structures of complexes of OR bound to either G-protein or ARR.

A wide range of computational methods was applied to assess and provide a detailed description of the interaction interfaces of all members of the OR family (μ (MOR), δ (DOR), k (KOR), nociceptin (NOP), ζ (ZOR)) with their corresponding binding partners (ARRs: ARR2, ARR3; G-protein: Gi1, Gi2, Gi3, Go, Gob, Gz, Gq, G11, G14, G15, G16, Gs(sh), Gs(lo)). Moreover, dynamic analysis under the scope of Normal Mode Analysis (NMA) was also performed. The construction and analyse of these models involving OR, represents a novel and exciting big data analysis of OR-Partners interface determinants, and it constitutes a further step into the understanding of OR family functional specificity.

REDOX BIOLOGY AND BRAIN SENSING

Head: João Laranjinha

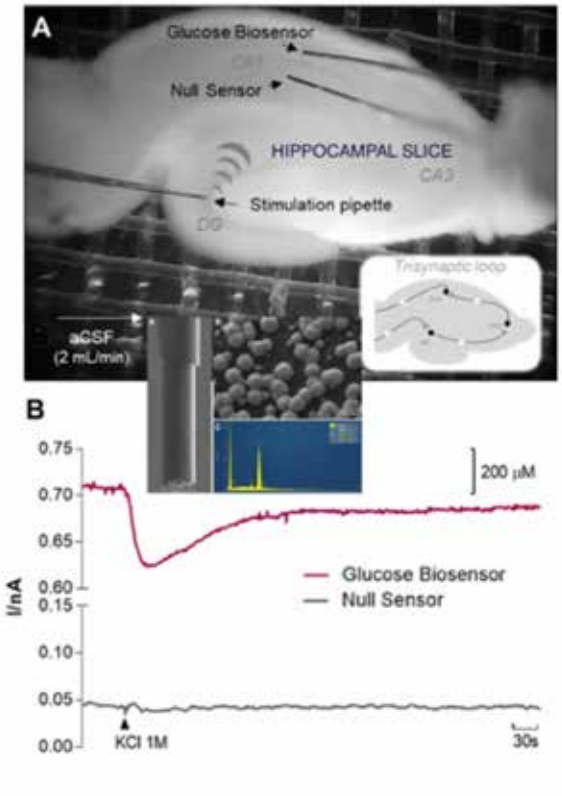
OBJECTIVES

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. This program is developed in collaboration with the Center for Microelectrode Technology, University of Kentucky (Lexington, USA).

(c) The mechanisms of action of plant-derived dietary phenolic compounds in terms of protection against vascular endothelial dysfunction, 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.

Funding sources:
European Regional Development Fund (FEDER) funds through the Operational Program for Competitiveness and Internationalization – COMPETE and national funds by FCT – Foundation for Science and Technology under the projects POCI-01-0145-FEDER-029099 (J. Laranjinha, PI); POCI-01-0145-FEDER-028261 (Rui Barbosa, PI) and PTDC/SAU-NUT/29089/2017 (Leonor Almeida, PI).



MAIN ACHIEVEMENTS

The main achievements incorporate both, technological and scientific components.

Technological developments:
We developed a glucose microbiosensor suitable for glucose measurement in vivo and validated their suitability by measuring evoked changes in extracellular glucose in brain slices. This is a valuable tool to investigate the complex nature of glucose utilization in brain tissue linked to neuronal activation both in physiological and pathological conditions, particularly during neurovascular coupling.

Scientific achievements:
Elaborating on ongoing research that is taking place in the lab for the last decades on the healthy benefits of dietary polyphenols, mitigating cardiovascular, metabolic and neurological diseases, during the current period:
1. We have identified molecular mechanisms by which polyphenols from red wine exhibit intestinal anti-inflammatory actions, supporting the notion that red wine polyphenolic extract might represent a readily available therapeutic intervention against intestinal inflammation and inflammatory bowel disease (IBD), promoted by cytokines and bacteria. In particular, the beneficial effects encompass.
a) prevention of the altered expression and subcellular distribution of tight junction proteins during cytokine-induced inflammation, thus averting dysfunction of intestinal barrier;
b) cyanidin-3-glucoside in particular was very effective in counteracting intestinal LPS-induced inflammation via, among others, inhibition of NF-kB and activactor protein-1 (AP-1) pathways;
c) providing evidences that the E. coli strain triggered the death of the intestinal epithelial cells through the production and release of a toxin and that the wine polyphenols through both, a direct interaction with bacterial exotoxin and the epithelial cells, prevented the action of the toxin on the cells, significantly reducing cell death.
In view of the increasing antibiotic resistance, this study might open new therapeutic avenues for development of polyphenols from red wine as natural antimicrobial agents.

2. In the past we have contributed to establish the notion that dietary nitrate undergoes stepwise reduction to the ubiquitous intercellular messenger, nitric oxide. We have now shown that dietary nitrate by impacting in intestinal microbiota, prevents the loss of tight junction proteins and modulates inflammatory events induced by broad-spectrum antibiotics. This is of foremost translational relevance ad led us to propose that nitrate consumption should be recommended during antibiotherapy to prevent overt intestinal inflammation and increased epithelial permeability which may elicit gastrointestinal side effects and dysbiosis.

3. Given the paramount importance of gut microbiota for the establishment of communication between the gut and the brain, the microbiota-gut-brain axis has been increasingly explored within the scope of neurosciences. We have reviewed key cellular signaling pathways underlying chronic intestinal inflammation and the influence of chronic intestinal inflammation and dysbiosis on brain disorders and have further developed the notion that polyphenols reach high local concentration in the intestine setting the conditions for modulating the "gut-brain axis" with impact in neurological disorders, notably autism spectrum disorders.

NEUROENDOCRINOLOGY AND AGING

Head: Cláudia Cavadas

OBJECTIVES

Our group has been contributing for the hypothesis that aging and age-related disorders are controlled by the hypothalamus or its related functions. This brain region regulates body homeostasis through specialized neurons that sense and integrate central and peripheral signals to properly coordinate several survival functions, including sleep, food intake, metabolism and neuroendocrine axis. The research developed by the group aims to answer to the following questions:

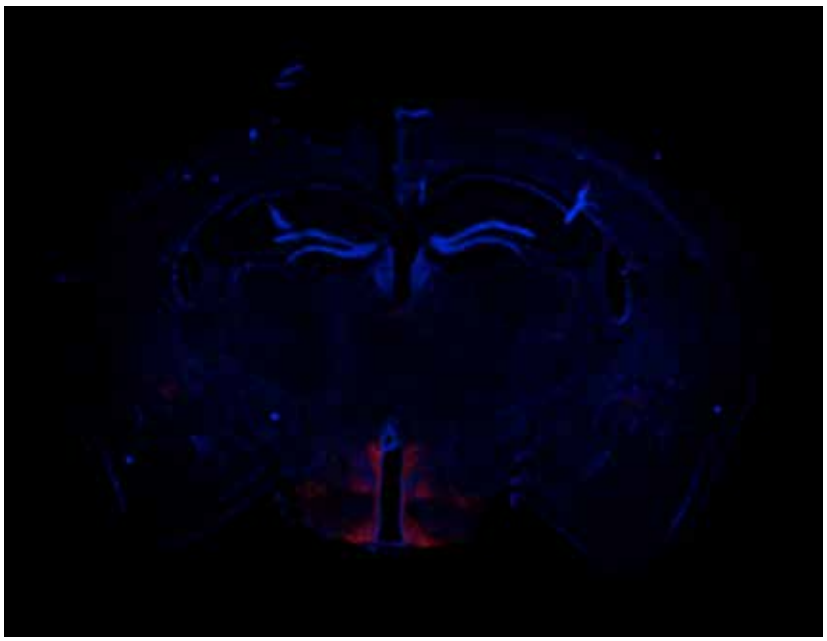
- How can we delay premature aging or natural aging by targeting the hypothalamus or by using hypothalamic related mechanisms?
- Do hypothalamic neuropeptides, as caloric restriction mimetic approaches, prevent peripheral aging and related dysfunctions? What are the underlying mechanisms?

- Does circadian rhythm dysfunction prevention protect against peripheral aging and age-related disorders?

More specifically the group has been investigating strategies and mechanisms aiming to delay ageing and age-related disorders: 1) Neuroendocrine strategies; 2) Circadian rhythm and biological clocks 3) molecular hallmarks of aging (senescence, inflammation, and dysfunction of intracellular communication, autophagy, sirtuins).

To address these questions the group has been using gene delivery approaches to modulate critical mechanisms or pathways in the hypothalamus (NPY, microRNAS, sirtuin-2, ataxin-2), and intranasal and peripheral administration of small molecules or neuropeptides (as NPY, ghrelin). The projects developed by the group have been contributing to emphasize the crucial role of hypothalamus in aging and potentially open new strategies to delay aging and aging related diseases.

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



MAIN ACHIEVEMENTS

a) We investigated the role of NPY and ghrelin in rescuing the aging phenotype in experimental models of ageing, using Hutchinson-Gilford Progeria Syndrome (HSPS) 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 HSPS mouse model. These results support that these peptides can be considered a promising strategy to delay or block the premature aging of HGPS.

b) 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

c) 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.

d) NPY and NPY receptors are present in chondrocytes of articular cartilage. New studies are needed to further investigate the role of NPY and its receptors in development and progression of cartilage aging related disease, the osteoarthritis.

e) The preliminary data show that peripheral cells (PBMCs) from obstructive sleep apnea (OSA) patients present some hallmarks of aging

VISION, BRAIN AND COGNITIVE NEUROSCIENCE

Head: Miguel Castelo-Branco

OBJECTIVES

Our group has further strengthened its work in vision research, cognitive neuroscience and medical imaging. Our vertical structure combines expertise in fundamental visual neurobiology, engineering approaches with a strong focus on signal/image processing and data mining, and visual and clinical neuroscience. This has allowed for interdisciplinary contributions in the fields of Cognitive Neuroscience, Human Neurophysiology, Visual Neuroscience, Human Psychophysics, Functional Brain Imaging and translational research in Neurology.

Our group has continued participation in Eurobioimaging and coordination of the core Infrastructure of National Brain Imaging Network, a consortium of 5 Universities with the leadership of the U. of Coimbra, where the main central equipment is located and which obtained funding within the scope of the National Program for Scientific Reequipment, after international evaluation.

We have continued work on Vision, Perception and Decision-making research streams. Our Clinical Neurosciences Pillar has continued to generate scientific production along the following Themes: 1. Normal Ageing: Cognitive Models and Neuroimaging 2. Neurodegenerative Disorders with a focus of mechanisms of disease, impaired neurotransmission and neurophysiology 3. Neurodevelopmental Disorders with a similar focus on multimodal explanatory approaches 4. Cortical plasticity in the maturing and adult brain: implications for neurorehabilitation 5. Neuropsychiatric disorders, with a focus on decision making and cognitive control.

Our hierarchical approach in fundamental visual neuroscience ranges from sensory biophysics to visual attention and high level processes in human neurophysiology. Our recent work in high level vision has addressed temporal dynamics of perceptual decision mechanisms and the role of context. This provides a thorough background for translational research approaches. These allowed to separate low vs. high level impairment in visual cognition neurodevelopmental models of impaired perception and decision making such as autism, and neurogenetic conditions such as Autism and Neurofibromatosis Type 1. We are studying parallel pathways to quantitatively analyze visual cognition, decision making and action control and motor aging in neurodegenerative disorders, in particular Parkinson Disease, and Huntington disease. Our expertise in Visual and Cognitive Impairment questions, and characterization of several disease models of genetic vs. acquired visual impairments, is allowing us to further refine novel models of visual neuroplasticity.

Our success in generating interdisciplinary work with scientists working in the field of cognitive neuroscience, neurology, medical imaging neuroinformatics and neuroengineering, is anchored on our national and international collaborations which also enabled proof of concept publications showing the effectiveness of brain computer interfaces and neurofeedback in normal and neurological populations. The ability to run collaborative work leading to recent publications in high level Journals can be well assessed by the cooperation with a broad set of international partners.

MAIN ACHIEVEMENTS

We continued to published a consistent flow of papers in prestigious journals in the fields of Ageing and Neurodegenerative Disorders, Neurodevelopmental Disorders and Vision Research. This group has therefore continued to publish in the fields of visual science, systems neurobiology, clinical neuroscience and biomedical Engineering with a focus on imaging. Basic science achievements and Translational Research Achievements: Clinical Neuroscience and Translational Research Achievements are highlighted by publications in the above mentioned fields.

Our translational work on integrating human and animal neurodevelopmental phenotypes has also progressed. Our work in the new IMI-2 H2020 initiative is in good progress. We also contributed publications in top journals in neuroimaging. Methodological Achievements can also be underlined by the successful publication of methodological papers.

In sum we were able to publish in leading journals in the following areas: Cognitive Neuroscience, Human Neurophysiology, Visual Neuroscience, Human Psychophysics, Functional Brain Imaging and translational research in Neurology. We are participating in European Projects and after achieving a worldwide patent together with IBA, our technology transfer approaches are also evolving steadily within the newly created clinical trial unit.

NEUROMODULATION

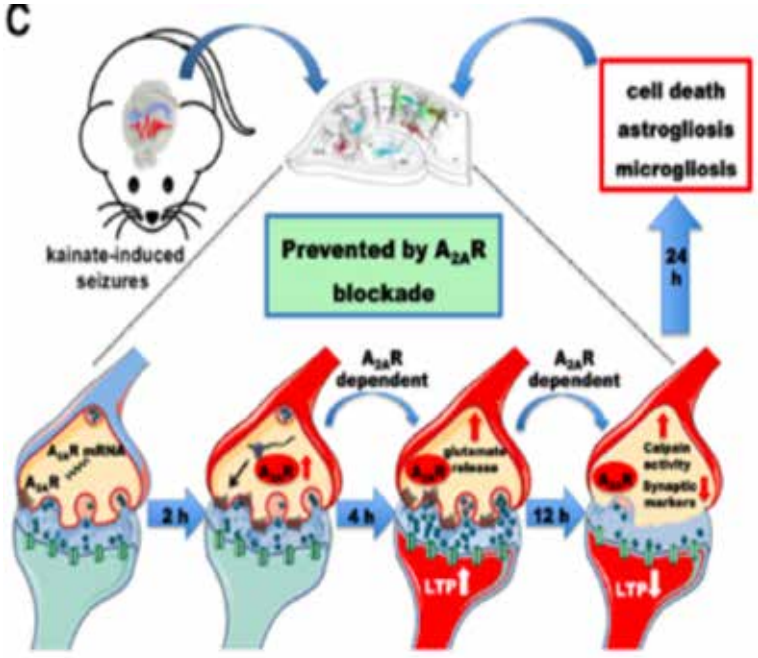
Head: Rodrigo Cunha

OBJECTIVES

The general objective of the group is to identify modulation systems that can be targeted to interfere with the evolution of neurodegenerative diseases, with a central focus on purines (adenosine and ATP). We concentrate on the initial stages of neurodegenerative disorders, under the working hypothesis that one of the key early features transversal to different such diseases is the dysfunction of synapses. This involves both neuronal and glial (astrocytes and microglia) maladaptive changes, with alterations of receptors, metabolic support and neuroinflammatory status, leading to abnormal synaptic plasticity and synaptic pruning that recapitulates features of neurodevelopment.

Our efforts over the years have identified a key role of adenosine A2A receptors (A2AR) in the control of neurodegenerative disorders. We have shown that their blockade prophylactically prevents alterations in animal models of Alzheimer's disease, epilepsy or diabetic encephalopathy; this is in remarkable agreement with the prophylactic benefit afforded by the regular consumption of caffeine (an adenosine receptor antagonist) against diseases such Alzheimer's or Parkinson's.

We post that A2AR up-regulation may actually be a causative factor of aberrant synaptic plasticity underlying abnormal phenotypic changes, through a combination of direct neuronal control of synaptic plasticity (Angelo R. Tomé and Henrique Silva), and glial control of synaptic function involving altered astrocyte-to-neuron communication (Paula Agostinho). In parallel, we are developing a new research line exploring the impact of purines in brain development and synaptic wiring under the assumption that features of brain development are aberrantly recruited to attempt restoring the diseased brain (Ricardo J. Rodrigues and Joana M. Marques). In parallel, four emergent lines within the group are exploring the role of purines and of cannabinoids in the control of brain metabolism (Attila Kofalvi), the role of extracellular ATP as a danger signal in brain diseases (Ricardo J. Rodrigues), the exploration of human brain samples collected during autopsy for translational efforts (Paula Canas) and the impact of A2AR in neurodegenerative (João Pedro Lopes) and neuropsychiatric disorders (Ana Patrícia Simões, Samira Ferreira).



MAIN ACHIEVEMENTS

1-The adenosine modulastion system mainly controls alostasis rather than homeostasis

2-Adenosine A2A receptor (A2AR) overfunction increases the susceptibility to brain damage

3-The overfunction of A2AR depends both of an up-regulation of A2AR and increased formation of ATP-derived extracelular adenosine

4-non-toxic concentrations of caffeine only affect information flow in brain circuits through the antagonism of A1R and A2AR

5-prefrontocortical A2AR control decision-making

MITOCHONDRIA AND NEURODEGENERATIVE DISORDERS

Head: Ana Cristina Carvalho Rego

OBJECTIVES

The research group "Mitochondria and Neurodegenerative Disorders" aims to understand fundamental cell and molecular mechanism in early stages of brain neurodegenerative disorders, namely in Huntington's (HD), Parkinson's (PD) and Alzheimer's (AD) diseases. These are chronic, debilitating, and age-related brain disorders, characterized by selective brain neurodegeneration and cognitive decline. Misfolded proteins due to posttranslational or oxidation modifications (among other processes) or pre-identified mutations acquired beta-sheet structures and tend to aggregate, progressively forming insoluble/fibrillary aggregates. In the form of oligomers, modified proteins interfere with neuronal function, potentially causing deregulated mitochondrial function and bioenergetics, and altered intracellular redox signaling, namely after activation of glutamatergic synapses, or lead to defective neurogenesis, which may impact on brain cognitive reserve. 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 closer interaction with neurologist at the local hospital, particularly in HD and AD. Identification of early disease mechanisms 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 2019 we focused our research in intracellular signaling pathways governing redox changes, in chronic stress conditions that may precipitate AD and the effect of amyloid-beta peptide (Aß) on neural stem cells (NSC) fate, and alpha-synuclein (a-Syn) role in the nucleus and the impact of protein phosphorylation.

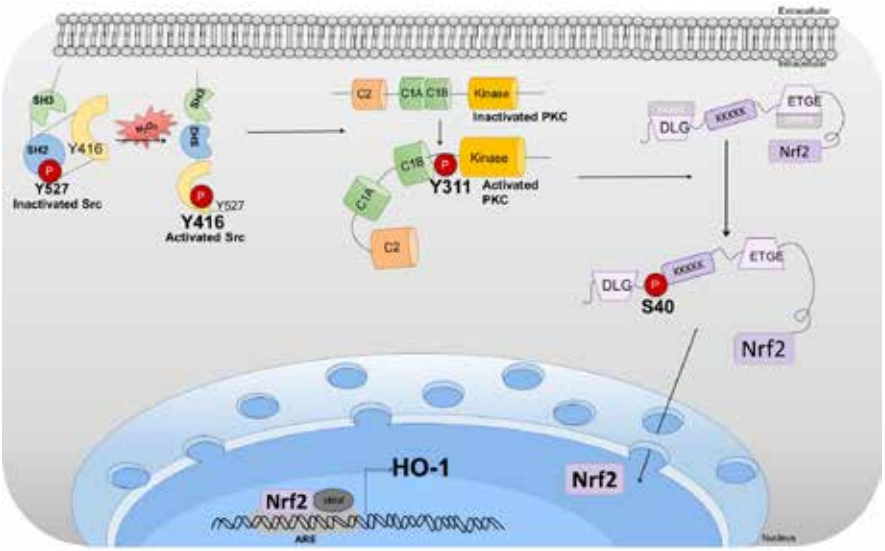
Thus, we studied:

1. The activation of cell survival-related signaling proteins, c-Src and Nrf2, and the influence of c-Src kinase on Nrf2 regulation after exposure to hydrogen peroxide (H2O2), demonstrating a novel c-Src/PKC□/Nrf2 interplay following oxidant stimulus;

2. The impact of chronic stress on dendritic development and structural maturation of newborn neurons in the dentate gyrus (DG) of the adult hippocampus (collaborative study);

3. Influence of Aβ on neurogenesis. NSC fate and mitochondrial parameters, including biogenesis, dynamics, and oxidative stress (collaborative study);

4. The mechanisms underlying aSyn-mediated transcription deregulation by assessing its effects in the nucleus and the impact of aSyn phosphorylation (collaborative study).



Representation of the Src/PKCδ/Nrf2 signaling pathway involved in heme oxygenase-1 (HO-1) expression after H2O2 exposure in mouse hypothalamic HT22 cells.

After H2O2 exposure, Src kinases are activated through Tyr416 phosphorylation. Src kinases-dependent phosphorylation of PKCδ Tyr 311 residue in the cytoplasm induces the activation of the protein, which can further phosphorylate Nrf2 at Ser40. Once phosphorylated, Nrf2 migrates to the nucleus, binds to the ARE element and regulates the transcription of target genes, namely HO-1.

In: Fão et al., Biochim Biophys Acta Mol Cell Res., 2019.

MAIN ACHIEVEMENTS

In the context of redox deregulation occurring in many neurodegenerative disorders, we demonstrated that the c-Src/PKCδ/Nrf2 pathway constitutes a novel signaling pathway stimulated by H2O2 (Fão et al., Biochim Biophys Acta Mol Cell Res, 2019). Cytosolic activation of Nrf2 (a transcription factor involved in expression of cell antioxidants) was modulated through phosphorylation by PKCδ, an enzyme controlled by Src Tyr kinases. Acute exposure of HT22 mouse hippocampal neural cells to H2O2 increased c-Src and Nrf2 phosphorylation/activation at Tyr416 and Ser40, respectively. Nrf2 P-Ser40, its nuclear accumulation and transcriptional activity involving heme oxygenase-1 (HO-1) expression were dependent on c-Src activation. Moreover, modulation of Nrf2 activity by c-Src occurred through PKCδ phosphorylation at Tyr311. The work supported that c-Src regulates Nrf2 activity through PKCδ after an oxidant stimulus, constituting a potential target for diseases involving redox deregulation.

In collaboration with Dr. Ioannis Sotiropoulos (ICVS, University of Minho, Portugal), we showed that chronic stress, a precipitant factor of several brain pathologies, such as depression and AD, triggers divergent dendritic alterations in immature neurons of the adult hippocampus (Dioli et al., Transl. Psychiatry, 2019). We showed that chronic stress differentially impacted on doublecortin (DCX)-positive immature neurons in distinct phases of maturation. Specifically, the density of the DCX-positive immature neurons whose dendritic tree reaches the inner molecular layer (IML) of DG was reduced in stressed animals, whereas the dendritic complexity was increased. DCX+ cells displayed complex and longer dendritic compartments located in the granular cell layer of the DG under stress conditions; on the contrary, their dendritic segments localized into the M/OML were shorter and less complex. Data highlight the complex and dynamic stress-driven neuroplasticity of immature neurons in the adult hippocampus.

In collaboration with Dr. Cecília Rodrigues (Faculty of Pharmacy, University of Lisbon, Portugal), we showed that Aβ compromises NSC by irreversibly disturbing mitochondrial oxidative state and blocking mitochondrial biogenesis and dynamics, bringing new perspectives for endogenous NSC-based strategies in AD (Ribeiro et al., Mol. Neurobiol., 2019). Aβ impaired NSC viability and proliferation and blocked neurogenic differentiation, by disrupting mitochondrial signaling of self-renewing NSCs. Aβ decreased ATP levels, generated oxidative stress, affecting radical scavenger system through SOD2 and SIRT3. Aβ also reduced mtDNA and mitochondrial biogenesis. Aβ compromised NSC commitment and survival by irreversibly impairing mitochondria and thwarting any neurogenic rescue through mitochondrial biogenesis, dynamics or radical scavenger system.

In the context of PD, and both as co-supervisor of Raquel Pinho (PhD student – defended in 2017) and in collaboration with Dr. Tiago Outeiro (University Medical Center Göttingen, Germany), we studied how nuclear localization and phosphorylation of aSyn modulated its pathological effects (Pinho et al., Hum. Mol. Genet., 2019). aSyn induced severe transcriptional deregulation, including the downregulation of important cell cycle-related genes. Transcriptional deregulation was concomitant with reduced binding of aSyn to DNA. In the presence of aSyn in the nucleus (aSyn-NLS), we found the accumulation of high molecular weight aSyn species, altered gene expression and reduced cytotoxicity, which were modulated by aSyn phosphorylation on Ser129. We hypothesize that the role of aSyn on gene expression and/or toxicity may be modulated by phosphorylation status and nuclear presence of different aSyn species. Data may open novel avenues for the design of future strategies for therapeutic intervention in PD and other synucleinopathies.

AGING AND BRAIN DISEASES: ADVANCED DIAGNOSIS AND BIOMARKERS

Head: Catarina Resende Oliveira

OBJECTIVES

The main objective of this Group is the identification of new biomarkers of aging and brain disorders, promoting the translation of knowledge generated in basic research to the clinic.

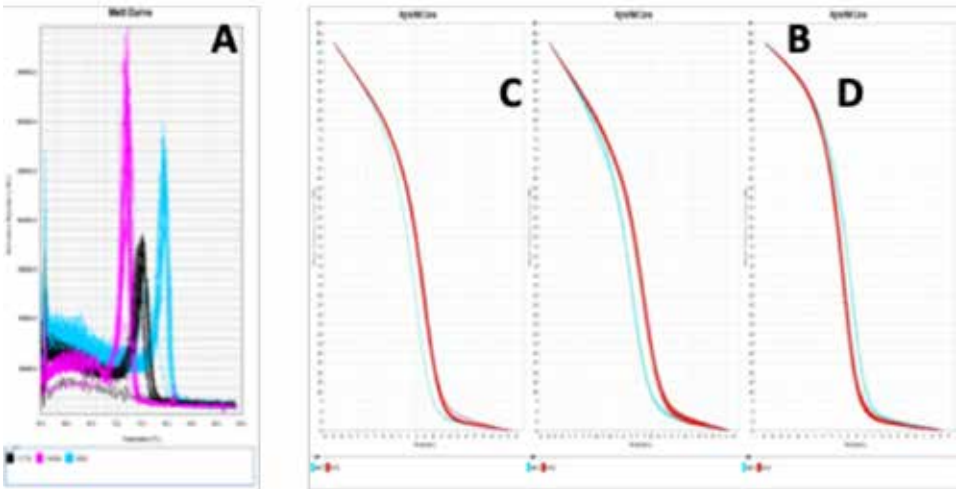
A close interaction with clinicians at Coimbra University Hospital (CHUC) has been shown to be relevant, allowing the access to human biological samples and clinical data, related with neurodegenerative and neuropsychiatric diseases, neurodevelopmental and bigenomic disorders and cancer.

Biomarker-based diagnosis and prognosis of neurodegenerative dementias is an important area of interest of this group. In 2019 we have: i) evaluated the analytical performance of a novel fully automated chemiluminescence enzyme immunoassays (Lumipulse) for the quantification of Alzheimer's Disease (AD) biomarkers in Cerebrospinal fluid (CSF); ii) participated in a modelling study, including people with mild cognitive impairment (MCI) from single-centre and multicentre cohorts in Europe and North America, aimed to establish robust prediction models of disease progression; iii) been actively involved in Genetic Frontotemporal Dementia Initiative (GENFI), which is a multicentre cohort study of families with genetic frontotemporal dementia across Europe and Canada, with the objective of studying longitudinal biomarker trajectories in people with presymptomatic and symptomatic genetic frontotemporal dementia (FTD); and iv) performed the genetic analysis of several patients with neurological diseases including early onset dementias.

"OMICS" methodologies have been applied, in a translational perspective, to the study of brain disorders, generating tools for diagnosis, prognosis and progression markers.

Bigenomic investigation of disorders aiming to find molecular and genetic risk factors in mitochondrial DNA (mtDNA) and nuclear genes associated with mitochondrial biology was also addressed. The group was updated in the latest developments in molecular genetics, including the analysis of exome by Next Generation Sequencing (NGS) technique, and other methodological assays that were developed to support functional genomics. These advances have made possible the functional studies for pathogenicity investigation of novel mutations identified in patients, which became more frequent with the application of NGS analysis.

Regarding the pharmacogenomics studies the main focus was the identification of genetic alterations and copy number variations that will determine the metabolic profile or targeting depending on genetics, to provide tools for more accurate diagnosis and more rationale treatments, managing risks and preventing drug adverse reactions, in the scope of theranostics.



Real-Time PCR analysis of a complete plate: (A) Derivative Melt Curve; Aligned Melt Curves, from the HRM Software, with variant calling (discriminated by color) – Representation per target (B) m.3460G>A; (C) m.11778G>A; (D) m.14484T>C. Harunt verferum volorit omnime pedipidunt hil iduciur.

MAIN ACHIEVEMENTS

Regarding biomarker-based diagnosis and prognosis of neurodegenerative diseases, the Lumipulse assays showed a very good analytical performance and an excellent diagnostic accuracy, therefore making them well-suited for CSF clinical routine measurements.

In the multicenter modelling study, we were able to generate risk models that were robust across cohorts, which adds to their potential clinical applicability. Such models could aid clinicians in the interpretation of CSF biomarker and hippocampal volume results in individuals with MCI, and help research and clinical settings to prepare for a future of precision medicine in Alzheimer's disease.

Regarding the GENFI, our findings showed the value of blood NfL as a disease progression biomarker in genetic frontotemporal dementia and suggested that longitudinal NfL measurements could identify mutation carriers approaching symptom onset and capture rates of brain atrophy.

The genetic analysis unveiled the pathogenic variants underlying different neurological conditions, providing the molecular diagnosis of several symptomatic individuals as well as offering predictive tests to other family members, still asymptomatic, in the context of genetic counseling. New proteomic methodologies were developed, to validate diagnostic categories and improve its boundaries and discrimination among neuropsychiatric disorders.

The contribution of nuclear gene variants in subunits and proteins involved in the mitochondrial protein import and processing of imported precursor proteins, as genetic modifiers in Leber's Hereditary Optic Neuropathy (LHON), was provided by a screening using whole-exome sequencing data. The variants c.280C>T and c.170delA/c.172_176delGGCAC, in MIPEP and TOMM20L, respectively, were identified in a LHON individual with m.14484T>C mutation. Regarding the identified variants, although promising for the outcome of mitochondrial assembly, they do not seem to be conditioning this level of impairment.

In a prospective observational study analyzing CYP2D6 pharmacogenetics in 55 Portuguese a adult women undergoing elective cesarean, the association with pain score, was studied. A positive association between alleles *4, *10 and pain was found and also between predicted reduced or null activity of CYP2D6 and increased pain. So, CYP2D6 genotyping was suggested useful for adjusting the needs for analgesia and opioid dose, in order to maximize clinical efficacy and avoiding adverse reactions

Under the scope of the "CEIBA.FP Consortium of the Ibero-American Network of Pharmacogenetics and Pharmacogenomics (RIBEF)", a collaborative study of a broad spectrum of Native American populations from different ethno-linguistic groups showed how autochthonous diversity shaped the distribution of pharmaco-alleles and gave insights on the prevalence of clinically relevant phenotypes associated with drugs, such as paroxetine, tamoxifen, warfarin, and clopidogrel .

By using genomic tools, the assessment of new biomarkers in different pathologies, namely in cancer, was performed. Furthermore, we contributed to detect a metabolomic signature in Urine of patients with Age-Related Macular Degeneration .

Under the scope of an international collaboration we also participated in the discussion regarding the rights and duties of Clinical Laboratory Geneticists in genetic healthcare systems.

NEW TARGETS AND THERAPEUTICS FOR CHRONIC DISEASES

Head: António Francisco Ambrósio

OBJECTIVES

The Group has been mainly focused in chronic disorders that affect the retina and brain, but also other organs such as the heart, kidney, nose and lungs, as well as on applied ageing research.
In general, our goals are:

- to elucidate the molecular and cellular mechanisms underlying the pathophysiology of chronic disorders affecting the retina, brain and other organs;
- to identify new potential drug targets and develop more efficient therapeutic strategies for the treatment of chronic disorders affecting those organs as well as evaluate the response to therapy.
- research on ageing with significant social impact in the elderly.

Particular objectives have been defined in different sub-areas, as follows:

Vision Sciences

We have a major focus on retinal degenerative diseases, namely diabetic retinopathy, glaucoma and age-related macular degeneration (AMD). We are particularly interested in clarifying the contribution of microglia-mediated neuroinflammation and the crosstalk between different cell types to retinal neural, vascular and epithelial dysfunction and degeneration. We have been exploring strategies that modulate adenosine receptors and dissecting the role of exosomes, PINK1/PARKIN and mitochondrial DNA. We also aim to clarify the protective mechanisms of incretin-based therapies and evaluate the role of α-adducin in the structure and function of the retina. In a translational perspective, we are trying to identify new biomarkers in the tear fluids for the diagnosis of retinal degenerative diseases and to develop biodegradable intraocular implants for drug delivery systems.

The concept of "the retina as a window to the brain" has emerged with possible implications in various pathologies, such as Alzheimer's disease (AD). We aim to understand when changes start appearing in the retina and brain, how changes progress, and if they are correlated, and also to investigate whether the retina can be used as a reliable tool to facilitate an early diagnosis of Alzheimer's disease.

Neuroscience

We intend to pinpoint the role of lifestyle, including diet, food supplementation, physical exercise, and drugs of abuse and CNS modifiers consumption, such as methamphetamine and methylphenidate, on brain health and cognitive dysfunction, giving a particular attention to neuroinflammation and blood-brain barrier dysfunction. We also intend to unravel the neurobiology behind Attention Deficit Hyperactivity Disorder (ADHD), the role of peripheral immunity in Parkinson's disease and the impact of glioblastoma multiforme on blood-brain barrier.

We are also investigating the impact of prenatal stress mediators, including diabetes during pregnancy and exposure to dexamethasone, on early neurodevelopment and mental health throughout life, namely the risk for anxiety and depression, giving a particular attention to microglial cells. Moreover, we aim to understand if sex differences in these cells underlie the differential clinical presentation of psychiatric disorders between men and women.

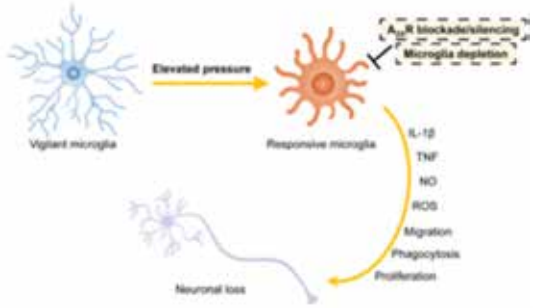
Experimental Therapeutics

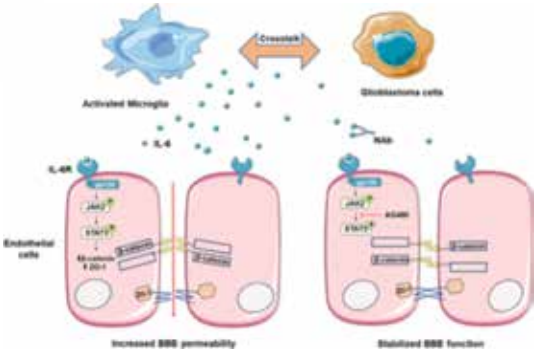
We are evaluating the impact of therapeutic and nutraceutic options in cardiometabolic and cardiorenal disorders, such as atherosclerosis, obesity, type 2 diabetes and its vascular complications, namely nephropathy and chronic renal failure.

Ageing Research

-To develop applied ageing research with significant societal impact focusing on: a) health literacy to support the adoption of healthy lifestyles by citizens; b) to develop and implement distance learning courses to capacitate formal and informal providers to better manage care for older people.

-To implement a successful ERA Chair project on ageing at the University of Coimbra and to launch a successful second stage application for the Teaming project of the Multidisciplinary Institute of Ageing (MIA-Portugal).





MAIN ACHIEVEMENTS

Vision Sciences

- The intravitreal injection of the A2AR antagonist controls neuroinflammation, affords protection against retinal cell loss and reduces vascular leakage associated with diabetes. Therefore, antagonists of A2AR could be envisaged as a therapeutic approach for the early complications of diabetes in the retina.

- Microglia are main contributors for retinal cell death during elevated pressure. A2AR expressed in microglia can be targeted to control retinal neuroinflammation and prevent neural apoptosis elicited by elevated pressure.

- Porous poly (ε-caprolactone) (PCL)-based intraocular implants are well tolerated by rats and can be envisaged for prolonged drug delivery applications.

- Quantification of TNFα at the picogram level in human tears using a rapid and sensitive biosensor technology based on electrochemical impedance spectroscopy (EIS).

- Similar neural changes can be found in the retina, hippocampus and visual cortex, i.e., retinal and brain thinning, in a triple transgenic mouse model of Alzheimer's disease (3×Tg-AD). The retinal physiology is also altered. These observations support the possibility of using the eye as an additional tool (noninvasively) for early AD diagnosis and therapeutic monitoring.

- Retinal texture biomarkers may help to discriminate between Alzheimer's and Parkinson's disease patients and healthy controls.

Neuroscience

- A lower dose of MPH in normal rats improves memory performance, being associated with the modulation of astrocytic morphology and synaptic machinery. However, a higher dose of MPH leads to BBB dysfunction and memory impairment.

- The cross-talk between microglia and glioblastoma multiforme cells trigger the release of IL-6 and the downstream JAK/STAT3 pathway activation, leading to endothelial barrier dysfunction and hyperpermeability.

- A dietary imbalance, related with hypoproteic or high-fat content impairs BBB properties potentially favoring the transmigration of peripheral immune cells and induces both a peripheral and central neuroinflammatory status.

- We identified differences in microglia cellular (and subcellular) morphology, portraying microglia as a unique cell type with a sex identity, which is locally determined according to the brain region. Moreover, there is a correlation between this morphologic plasticity and behavior with anxiety and depression.

Experimental Therapeutics

- The dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin inhibits oxidative stress and ameliorates glomerular lesions in a rat model of type 1 diabetes.

- Weight loss achieved by bariatric surgery modifies high-density lipoprotein subfractions and low-density lipoprotein oxidation towards atheroprotection.

- Adiponectin is protective in end-stage renal disease patients.

Ageing

The team successfully implemented the project HeaLiqs4Cities, funded by EIT Health. This project has implemented a vehicle equipped with an innovative concept and tools for lifestyle assessment of citizens in rural areas. Moreover, the team has been active in the implementation of three editions of the distance learning course on Active and Healthy Ageing for Care Providers, a project implemented by the University of Coimbra.

Our team is the leader of the EIT Health consortium EpiDEMPrev that implemented the preparatory year of the EIT Health Ageing PhD School, a network and educational portfolio awarded with the EIT Label Certificate, seal of excellence.

Giving continuity to the successful implementation of the ERA Chair (ERA@UC) project and the phase 1 of the Teaming project to launch the Multidisciplinary Institute of Ageing (MIA-Portugal), the team was successful in securing funding for the second stage and implementation of the new center of excellence in ageing research.

RESEARCH ACTIVITY

METABOLISM, AGING AND DISEASE
COORDINATOR: JOÃO RAMALHO-SANTOS

General Objectives

The general goal of the strand is to carry out excellent basic and translational research linking metabolic issues, notably mitochondrial function and intermediate metabolism-based pathways and biomarkers, with aging and disease, including neurodegenerative and neurobehavioral disorders, diabetes, infertility, immune-based disorders, cardio-vascular disorders, and fatty liver disease, and cancer. The goal was to create critical mass, and bring basic research closer to more interventional activities, as well as better diagnostics tools.
It should be reminded that the ImmunoMetabolic Pharmacology Group is no longer part of the CNC.IBILI Consortium, and was removed from the current report.

Main Achievements

One of the main achievements was the beginning of the successful European applications linked to three ETN training grants (FOIE_GRAS, TREATMENT, Rep-EAT) and a RISE action (mtFOIE_GRAS), that link metabolism research with liver disease, infertility and schizophrenia. Both FOIE_GRAS and mtFOIE_GRAS are coordinated by CNC.
The groups continued their work on targeting mitochondria for both diagnostic and therapeutic purposes with novel chemical entities based on dietary polyphenols and other molecules that may decrease cardiotoxicity of known drugs and alleviate menopause symptoms.
In terms of neurodegenerative disorders our data suggests that new BACE1 inhibitors have the potential to be a disease-modifying therapy in AD.
Furthermore, the stand has done innovative research in terms of both mitochondrial function and the microbiome of AD and PD patients, and continued to focus on sex-specific differences and the effects of diabetes. Some of these effects seem to be modulated by diet and the adipose tissue, and have consequences in terms of vascular and cardiac function, and influence wound healing, which could be potentiated using microRNAs and antimicrobial peptides.
In terms of novel methodologies, the strand also developed stable-isotope methodologies for quantifying liver and adipose tissue fatty acid and glycerol biosynthesis from specific precursors using a combination of deuterated water and 13C-enriched substrates. We were also able to certify a lab using the Good Laboratory Practices methodology, officially approved by INFARMED, Portugal using the international OECD guidelines, and have one of the few labs in Portugal in this field to have such a certification. This will be used to fulfil industry contracts.

Future Plans

The strand will continue to focus on the goals of linking basic with translational research, trying to move the field forward at different levels.
In terms of targeting mitochondria this will continue to be another key aspect of future research plans, in terms of aging, cancer and brain and improving liver mitochondrial bioenergetics during estrogen withdrawal in menopause or mitochondrial function affected by other toxic therapeutic interventions. In terms of the nutritional aspects noted, this work will be carried out in close association with the CNC Spinoff MitoDiets. Similarly the continued research on following metabolic pathways in vivo via non-invasive quantification of key metabolites will be carried out in close association with the SpinOff LifeTag. One of the goals of the Strand is to try to create opportunities for researchers beyond research. Future plans also involve submissions for competitive funding taking into account the successful ETN/RISE partnerships in the four funded actions, in order to expand the themes beyond the human resources funding that was made available.
The new BACE1 inhibitors we were developing last year will continue to be extended to preclinical models. The strand will also focus of characterizing and manipulating the microbiome in neurodegenerative disorders. Data from the strand also reinforced the need to establish sex/gender-specific preventive and/or therapeutic approaches and an appropriate time window for the efficient treatment against metabolic and neurodegenerative conditions and this will be followed up, also focusing on vascular and cardiac changes in metabolic-based disorders, in collaboration with the University Hospitals. We will also continue to follow our heart failure (HF) data in patients with and without diabetes given that epicardial adipocytes may be a possible therapeutic target for HF treatment. Finally we will make full use of our novel NMR-based methodology to animal models of non-alcoholic fatty liver disease in order to determine the contributions of glucose and fructose to lipid biosynthesis.

Cell Metabolis and Quality Control Group

Paula Moreira	PhD Head of Group)
Diana Silva	PhD
Daniela Silva	Volunteer
Sónia Correia	PhD
Tânia Fernandes	Student
João Magalhães	Student
Sandra Cardoso	PhD
Débora Mena	Student
Mª Teresa Rosete	PhD
Ana Silva	PhD
Mylène Carrascal	Superior Technic.
Isabel Ferreira	Student
João Pereira	Student
Gonçalo Brites	Student
Adriana Tavares	Student
Ana Duarte	PhD
Ana Esteves	PhD
Armanda Santos	PhD
Cláudia Pereira	PhD
Ana Marques	PhD
Patrícia Moreira	Student
Fábio Sousa	Student
Ana Pereira	Student
Cristina Carvalho	PhD
Emanuel Candeias	Student
Mª Inês Alves	Student
Mario Pinto	PhD
Paula Moreira	PhD
Ana Santos	Student
Rosa Resende	PhD
Susana Cardoso	PhD

Mitochondria, Metabolism and Disease Group

Paulo Oliveira	PhD Head of Group)
Adriana Carvalho	Student
Ana Castela	Student
Ana Coelho	Student
Anabela P. Rolo	PhD
Mª Carmen Alpoim	PhD
Cláudia Deus	PhD Student
Elisabete Ferreiro	PhD
Eurico Serrano	PhD Student
Filomena Silva	PhD
António Moreno	PhD
Carlos Palmeira	PhD
Gabriela Oliveira	Volunteer
Gonçalo Afonso	PhD Student
Helena Carvalheiro	PhD
Inês Santos	PhD
Ivo Machado	Student
João eodoro	PhD
José Baptista	Student
Luís Grilo	Trainee
Ricardo Amorim	PhD Student
Ricardo Marques	PhD Student
Sónia Pinho	PhD Student
Mª Teresa Oliveira	PhD
Vilma Oliveira	PhD

Metabolic Control Group

John G. Jones	PhD (Head of Group)
Mª Cristina Oliveira	PhD
Ludgero Tavares	PhD
Joao Rito	Student
Joao Silva	Student
Getachew Belew	PhD Student
Giada DiNunzio	PhD Student
Alejandra Torres	Student
Ana Costa	estudante
Carolina Carola	Student
Andreia Silva	Student
Mª Inês Alfaiate	Student
Eugénia Carvalho	PhD
Diana Santos	Student
Ana Figueiredo	Student
Marija Petkovic	Student
Aryane Pinho	Student
Ana Burgeiro	PhD
Jessica Silva	Student
Ermelindo Leal	PhD
Luciele Minuzzi	Student
Isadora Pombeiro	Student
Renata Tavares	PhD
Ana Almeida Santos	MD
Ana Branco	PhD
Sandra Amaral	PhD
Alexandra Carvalho	Superior Technic.
Mª Moreira Soares	Student
Mª Inês Sousa Cristo	Student
Rita Santos	Student
Ana P. Sousa	Health Sup. Technic.
Sara Rebelo	PhD

CELL SIGNALING AND METABOLISM IN DISEASES

Head: Paula Moreira

OBJECTIVES

Our research Group aims:

To investigate a) how cardiovascular risk factors contribute to Alzheimer disease (AD) (like) pathology, putting the focus on brain energy metabolism; b) how sex/gender modulates the risk for AD and c) the preventive and therapeutic potential of antidiabetic agents and mitochondrial modulators. To determine a) how mitochondrial damage-asssociated molecular patterns (DAMPs), which trigger sterile pro-inflammatory immune responses, drive AD and Parkinson disease (PD) neurodegeneration; b) how gut microbiota of AD and PD patients could trigger neuronal innate immunity activation through mitochondrial dysfunction; c) new therapeutic strategies to avoid mild chronic inflammation, thus preventing AD and PD relevant protein oligomers formation and mitochondrial damage.

To investigate the disturbance of the Endoplasmic Reticulum (ER) stress response and of ER-mitochondria contacts in neurodegenerative disorders such as 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.

To evaluate the molecular mechanisms involved in peripheral and neuroinflammation and changes in the cells of the immune system associated with the inflammatory response; and to develop methodologies to evaluate the ability of natural and industrial chemicals to modulate innate immunity, with a special focus on macrophages and dendritic cells. It is intended that the scientifically relevant data generated by the first aim may contribute to the development of efficient laboratory tests in screening for possible new drugs or potentially immunotoxic chemicals.

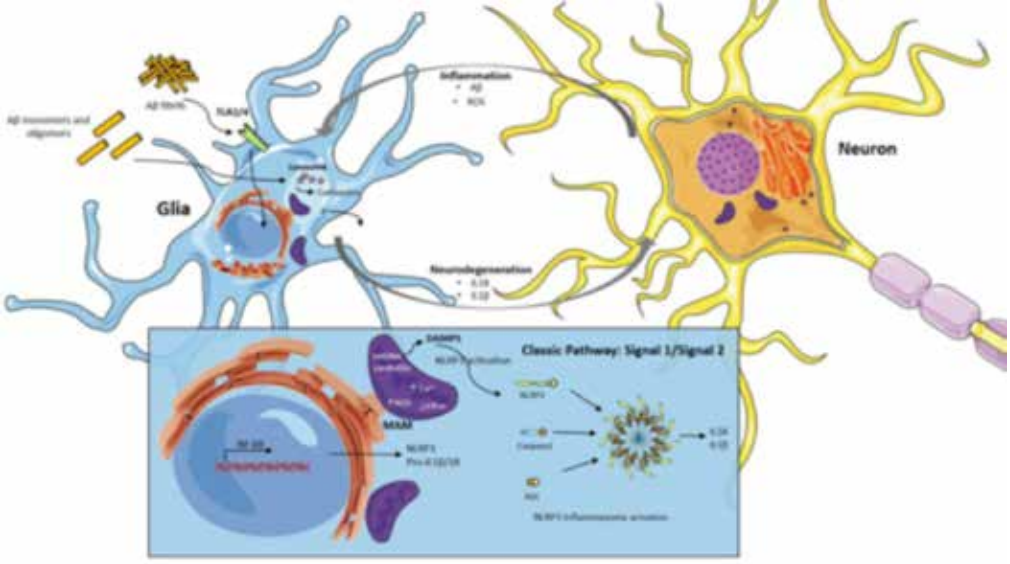


Fig. 1. Major players in NLRP3 activation in Alzheimer's disease. Aβ peptide is closely associated with inflammatory responses in the AD brain. Fibrillar Aβ species are agonists of pattern-recognition receptors, such as TLR 2 and 4, triggering NF-κB activation to upregulate the inflammasome component NLRP3 and prointerleukins, which are cleaved into their active forms upon assembly of NLRP3, ASC and pro-caspase-1 and subsequent activation of this pro-inflammatory caspase. Furthermore, phagocytosis of soluble Aβ also triggers lysosomal destabilization and consequent cathepsin leakage, leading to inflammasome activation. However, many other DAMPs, including production of ROS, mitochondrial membrane depolarization, release of mtDNA or cardiolipin externalization, as well as alterations in Ca2+ homeostasis have also been suggested as potential NLRP3 activating stimuli. Recent evidences support that ER-mitochondria contacts at MAMs are important sites of NLRP3 inflammasome activation. Glial cells are the main cells involved in inflammatory responses in the central nervous system, although neuronal cells can also have a role in the up-regulation of the immune response through the release of danger signals that recruit and activate local microglia. Chronic activation of NLRP3 inflammasome triggered by Aβ contributes to persistent neuroinflammation as evidenced by production and release of pro-inflammatory mediators, which ultimately leads to the neurodegenerative process and neuronal loss. Aβ: amyoid β-peptide; AD: Alzheimer's disease; ASC: Apoptosis-Associated Speck-Like Protein Containing CARD; DAMPs: Danger-Associated Molecular Patterns; ER: Endoplasmic Reticulum; MAMs: Mitochondria-Associated Membranes; mtDNA: mitochondrial DNA; NF-□B: factor nuclear kappa B; NLRP3: nucleotide binding and oligomerization domain–like receptor family pyrin domain-containing 3; TLR; toll-like receptor. (Pereira et al., 2019)

MAIN ACHIEVEMENTS

Using post-mortem human brain tissue, in vivo and in vitro models of AD, we observed that O-GlcNAcylation, the post-translational modification of intracellular proteins by O-GlcNAc, contributes to "mitochondrial pathology". A reduction in global O-GlcNAcylation levels was shown to be strongly correlated with hampered mitochondrial bioenergetic function, disruption of the mitochondrial network and loss of cell viability. Conversely, the pharmacological modulation of O-GlcNAcylation levels with Thiamet-G restored O-GlcNAcylation levels and cell viability (Pinho et al., 2019). Overall, these results suggest that O-GlcNAcylation is involved in AD pathology functioning as a potential link between mitochondrial energetic crisis and synaptic and neuronal degeneration. Findings from our laboratory also demonstrate that the antidiabetic drug liraglutide, a glucagon-like peptide 1 (GLP-1) mimetic, can be efficient against AD neuropathology.

We demonstrated that acetylation of Beclin-1 modulates autophagy in Alzheimer's disease cellular models (Esteves et al., 2019). Additionally, we proved that acetylation is a major determinant to microtubule-dependent autophagy in AD and PD. Since mitochondria are evolutionary descendants of endosymbiotic alphaproteobacteria, we speculate that human gut microbiota may produce neuroactive toxins to target bacteria and, "collaterally", their endosymbiotic successors, the mitochondria. Indeed, our results show that bacterial pathogen-associated molecular patterns (PAMPs) alter mitochondrial function in mesencephalic and cortical neurons, namely decrease mitochondrial membrane potential and increases mitochondrial reactive oxygen species (ROS) production. Additionally, bacterial PAMPs activate the inflammasome and induce the production of AD and PD histopathologic hallmarks both perceived as an "arm" of neuronal innate immune response.

We obtained evidences 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 (Pereira et al, in preparation). Our findings also support the bioactivity of Portuguese thermal waters from the Center region (Oliveira et al. 2019; Silva et al, under revision).

We demonstrated that thiol reactive skin allergens activate NLRP3 inflammasome through lysosomal destabilization and subsequent cathepsin leakage. Inhibition of cathepsin activity impaired NLRP3 activation and also allergen-induced maturation of dendritic-like cells, thus disclosing an innate immune mechanism crucial for the development of allergic contact sensitization.

MITOCHONDRIA, METABOLISM AND DISEASE

Head: Paulo Oliveira

OBJECTIVES

Mitochondria are critical organelles for cell physiology. Mitochondria are the cell energy powerplants, producing most of the chemical energy for cell metabolism, and playing a key role in cell death and quality control processes.

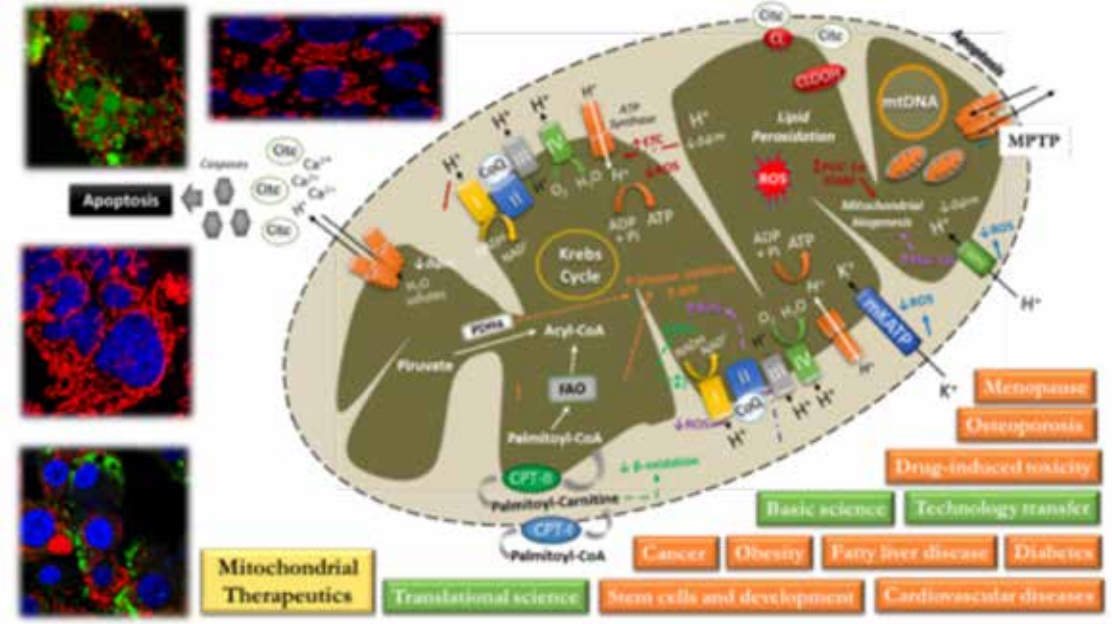
Since mitochondria are also active players in cellular redox and calcium homeostasis, as well as in intermediate metabolism, the overarching objective of our group is to provide insights into the role of mitochondria in cellular metabolism, redox signaling and stress responses associated with chemical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

The role of mitochondria in stem cell biology as well as the development of mitochondria-directed therapeutic agents are other of the group objectives. Specifically, the group is focused in various research lines:

1. Mitochondrial role in aging and lifestyle-diseases: a) molecular pathways behind CDCA's anti-obesogenic effects b) role of sestrin and sirtuin modulation as inducers of mitohormesis: preservation of mitochondrial function under pathologic stress, c) molecular mechanisms responsible for miRNA regulation in several biological and disease processes, particularly the miRNAs acting in mitochondria or in mitochondria-related mechanisms, d) mechanisms of mitochondrial disruption in non-alcoholic fatty liver disease and diabetes, e) mitochondrial metabolism and dynamics in non-neuronal cell samples from amyotrophic lateral sclerosis and Parkinson's disease patients, f) mitochondrial profiling in non-invasively obtained stem cells from young and old donors, g) mitochondrial remodeling and autophagy during cancer stem cell differentiation and carcinogenesis, h) interactions between the extracellular matrix (ECM), stromal and tumor cells and the various cytokines embedded in the ECM, and how that contributes to the neoplastic phenotype, i) involvement of exosomes on cytokines' release and inter-cellular communication, and role of human bronchial fibroblasts and their ECM in dedifferentiation, j) new strategies to block cancer stem cells formation and to modulate stromal cells phenotype to improve therapy's efficacy, k) mitochondrial metabolic profile in bone cells differentiation and function, in absence and presence of estradiol (E2) or selected phytoestrogens, evaluating their potential in bone anabolic (osteoanabolic) or anticatabolic (antiresorptives, with action on osteoclasts) treatment of postmenopausal osteoporosis and l) in utero programming of fetal energy deficit states in liver and heart, with impact in the development of adult diseases.

2. Mitochondrial Toxicology: a) mechanisms of drug-induced mitochondrial dysfunction caused by different xenobiotics, including drug-induced injury (e.g. anthracyclines) and nanoparticles, b) development of high-throughput methods to investigate mitochondrial function in the context of drug development and toxicology, c) identification of active compounds from different algae species with potential anti-tumor action.

3. Mitochondria-targeted therapeutics: a) intrinsic, pharmacological, or non-pharmacological (exercise or diet) regulation of mitochondrial biogenesis/metabolism and quality control to reduce organ injury during disease or chemical toxicity, b) novel mitochondrial-directed antioxidants based on dietary components in models for human diseases (cardiovascular/hepatic), c) new pharmacological conditioning strategies, resulting in the reduction of morbidity and mortality of liver resection surgery.



MAIN ACHIEVEMENTS

1. Mitochondrial role in aging and lifestyle-diseases: Related with cancer, and in a multi-institutional project we demonstrated recovery of respiration and tumor formation by mtDNA-depleted cells. We show that pyrimidine biosynthesis dependent on respiration-linked dihydroorotate dehydrogenase (DHODH) is required to overcome cell-cycle arrest, while mitochondrial ATP generation is dispensable for tumorigenesis. Still related with cancer, strategies to overcome chemotherapy resistance were developed based on the findings that resistance was due to the dedifferentiation of malignant cells to cancer stem cells as result of chemotherapy. Those strategies were based on the findings that inflammation sustained the cancer stem cell state, in a mechanism involving Toll-Like receptor 9. In the context of liver diseases and transplantation, our research has been looking into the development of new ways to preserve organs. We observed that mild hypothermia during reperfusion reduced the effect of ischemia-reperfusion injury on mitochondrial activity in liver tissue and promoted an increase in bioenergetic availability compared with normothermic reperfusion.

2. Mitochondrial Toxicology: Continuing our studies on the mechanisms of doxorubicin (DOX) cardiotoxicity, we showed that nanomolar DOX pretreatment of cardiomyoblasts induced a beneficial and possibly epigenetic-based mitochondrial adaptation, raising the possibility that an early sub-therapeutic DOX treatment can be used as a preconditioning and protective approach during anticancer therapies. By using an in vivo acute DOX cardiotoxicity study, by using an exploratory data analysis, we observed cardiac-specific alterations after DOX treatment for mitochondrial complexes III, IV, and preferentially for complex I. Interestingly, H2O2 production by the mitochondrial respiratory chain as well as loss of calcium-loading capacity, markers of subchronic toxicity, were not reliable indicators of acute DOX cardiotoxicity in this animal model. By using sequential principal component analysis and feature correlation analysis, we demonstrated for the first time alterations in sets of transcripts and proteins, but not functional measurements, that might serve as potential early acute markers of cardiac-specific mitochondrial toxicity, contributing to explain the trajectory of DOX cardiotoxicity and to develop novel interventions to minimize DOX cardiac liabilities.

3. Mitochondria-targeted therapeutics: Following previous work, and in collaboration with the University of Porto, we have developed novel multi-target agents designed to prevent progressive mitochondrial dysfunction, which act as mitochondria-targeted antioxidants with iron-chelating properties. Some of those molecules include derivatives from hydroxybenzoic and hydroxycinnamic acids and benzoic-acid-derived nitrones. Some of the new compounds were able to permeate a layer of hCMEC/D3 cells in a time-dependent manner, suggesting proper blood-brain barrier permeability activity, as well as serve as potential acetylcholinesterase inhibitors. The results validate the use of some of the new molecules in in vivo models of neurodegenerative diseases.

METABOLIC CONTROL

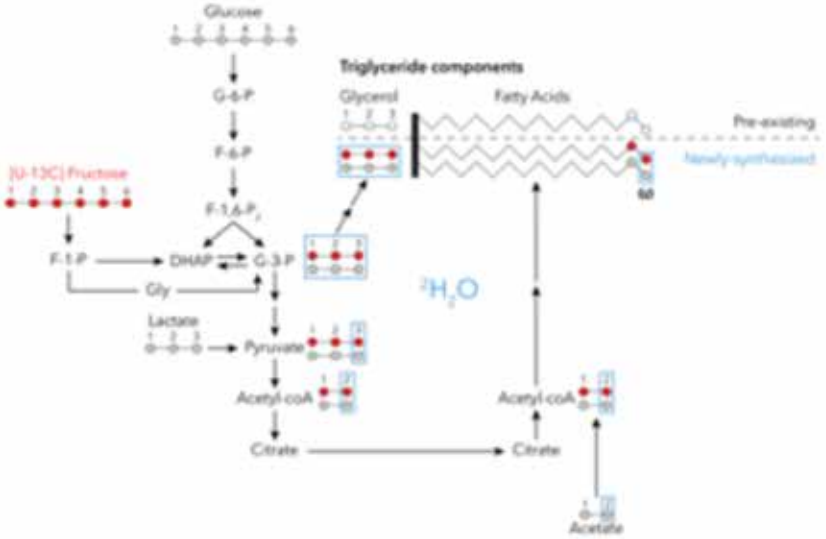
Head: John Grifith Jones

OBJECTIVES

a) Evaluating the effects of refined sugar intake on hepatic and visceral tissue intermediary metabolism: The increased consumption of sugar is implicated in the surge of nonalcoholic fatty liver disease (NAFLD) in Western societies. High sugar intake can modify intermediary metabolism of intestinal microbiota and visceral adipose tissues in addition to that of liver. Our group has developed stable-isotope tracer methodologies for quantifying glucose and fructose metabolism by liver and visceral fat using 13C-enriched fructose and glucose. These methods were applied to animal models of diet-induced NAFLD with the aim of improving our understanding of the role of extrahepatic sugar metabolism in the pathogenesis of NAFLD.

The effect of high fat intake on the metabolic disposition of these sugars is of particular interest since under normal conditions, lipid metabolites inhibit the main pathways of sugar metabolism including glycolysis, de novo lipogenesis and glycogen synthesis.

b) Mitochondrial dysfunction in early disease pathogenesis: My 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 mitochondrial function could be used to identify metabolic dysregulation locally in tissues and whether local tissue dysregulation can be picked up by measuring mitochondrial function in circulating cells and in specific tissues.



MAIN ACHIEVEMENTS

a) Obtained fundamental insights on the coupling of hepatic de novo lipogenesis with pentose phosphate pathway activity with glucose-6-phosphate as the provider of carbons for fatty acid synthesis as well as hydrogens for NADPH formation (Belew et al., 2019). This has important implications for the control of de novo lipogenesis in physiological and pathophysiological states such as non-alcoholic fatty liver disease and hepatocelluar carcinoma.

b) We demonstrated that dietary fructose carbons were incorporated into the glycerol and fatty acid components of mesenteric adipose tissue triglyceride but not into the triglyceride of subcutaneous adipose tissue (Silva et al, 2019). This indicates that the mesenteric adipose tissue has privileged access to dietary carbohydrate and is able to use fructose as a lipogenic substrate. This has important implications for visceral adipose tissue function and expansion in obesity and related complications such as non-alcoholic fatty liver disease and Type-2-diabetes.

c) mitochondrial function in tissues has been measured by high resolution respirometry using the Oroboros and circulating cells using the Seahorse technologies. Part of this work was funded by the Center for Childhood Obesity Prevention, an NIGMS COBRE (P20GM109096; JL Weber, PI) project where I was a primary research project leader. Preliminary data and findings being prepared for publication undergird my hypothesize that atypical mitochondrial respiration might be a protective and unresolved adaptation in response to stress. In addition, I believe that environmental factors, such as lifestyle and drugs, strongly influence this metabolic imbalance giving rise to insulin resistance early on that can easily be detected by important circulating mediators, including factors secreted by adipocytes, cytokines and microRNAs. Assessing circulating factors, including the microRNA profile of obese subjects, early, before any symptoms of disease arise, will be imperative for early diagnosis. So far 2 publications have results of these studies and several others are in preparation.

RESEARCH ACTIVITY

STEM CELL-BASED AND MOLECULAR THERAPIES
COORDINATOR: LUÍS PEREIRA DE ALMEIDA

General Objectives
The Stem Cell-Based and Molecular Therapies thematic strand brings together nine core research groups committed to the investigation and development of innovative tools and applications for prevention and treatment of target disorders, namely neurodegenerative, ischemic and infectious diseases, as well as cancer.
Being biotechnological in nature, the strand also accommodates a cluster of research groups devoted to structural biotechnology, computational modeling and protein engineering, as well as targeted biotechnological approaches.
Researchers in this strand are taking advantage of stem cells and of molecular therapy approaches in order to i) establish disease models to study molecular mechanisms of targeted diseases, ii) investigate new advanced nucleic acid-based therapies and viral and non-viral delivery vectors, iii) devise stem cell-based therapies for the ischemia treatment and wound healing, iv) develop novel methods for cell reprogramming and stem cell modulation/ differentiation and v) create stem cell-based assays and in silico approaches for drug screening.

Main Achievements
Overall, research efforts originated nearly 140 publications in peer-reviewed international journals and book series (not counting meeting abstracts), 52% of them including fruitful collaborations with institutions (academic and otherwise) from 34 different foreign countries. 20 of the publications involved hospital and healthcare units/entities (notably the Coimbra University Hospitals (CHUC)) and around 36% counted with the participation of other Portuguese institutions (including several companies) not affiliated with the University of Coimbra.
As for the international collaborations, the USA features the largest co-authorships (12%), followed by Italy and Germany. More than half the publications are Open Access.
The majority of the publications (80%) are Q1, and 45% are in Top 10% journals, including ACS Nano, Acta Neuropathologica, Biomaterials, Angewandte Chemie, Nature Communications, Seminars in Cancer Biology, PNAS, and Redox Biology, which puts in evidence not only the quality but also the diversity of addressed subjects and multidisciplinary nature of the ongoing research. They account for research achievements such as the development of a light-triggerable nanoparticle library for the controlled release of non-coding RNAs (Angewandte Chemie), the discovery of a novel mechanism for replication and recycling of a mycobacterial intracellular polysaccharide that modulates fatty acid metabolism (PNAS) or how restoring brain cholesterol turnover improves autophagy and has therapeutic potential for treatment of spinocerebellar ataxia (Acta Neuropathologica).
Indeed the areas of research of the publications range from Pharmacology & Pharmacy to Biotechnology & Applied Microbiology, to Genetics & Heredity, from Neurosciences & Neurology to Haematology. In terms of Category Normalized Citation Impact (InCites), it is worth mentioning the publications in the areas of Pharmacology & Toxicology (1.50) and Neuroscience & Behaviour (1.43).
The members of this thematic strand are also actively involved in advanced training, featuring several PhD students in doctoral programmes coordinated by CNC.IBILI researchers, notably the PhD Programme in Experimental Biology and Biomedicine (PDBEB) where advanced courses on Computational Biology, Drug Development or Advanced Therapies are the responsibility of this strand.
The implementation efforts of the new core facility ViraVector, for on-demand viral vector engineering and production, led CNC to be accepted in the National Hub of the EATRIS ERIC □the European Advanced Translational Research Infrastructure in Medicine, for the ATMP and Biological Biomarkers platforms of this network.

Future Plans
For the next 5-years, the Stem Cell-based and Molecular Therapies Thematic strand will be restructured to accommodate 11 groups and rebranding itself to Innovative Therapies.
It will focus on promoting interdisciplinary research translatable into the development of innovative tools and approaches for the prevention and treatment of disorders that are exacerbated in the aged population, such as neurodegenerative, ischemic, infectious and cancer diseases.
Capitalizing on the recently generated results and intellectual property, the groups in this thematic strand will use recent advances in high-throughput screening, deep sequencing, delivery formulations, medicinal chemistry, bioimaging and animal models to develop innovative therapies.
They will work in close collaboration with the other two strands of CIBB in the development of tools such as therapeutic biomolecules (miRNAs, protein, antibodies), in vitro models (e.g. in vitro blood brain barrier models) and bioinformatics models to explore large datasets (e.g. microbiome and metagenomes, etc).
The microbiology-driven groups will be paying particular attention to antimicrobial resistance and expand their interests to the intersection of molecular microbiology with neurodegenerative and chronic diseases so as to identify biomarkers associated to these pathologies that might be used for early detection.
The thematic strand will also continue to create translational and economical value for the Center Region of Portugal in the area of biotechnology/health sciences, benefiting from the long-standing links and collaborations with the BIOCANT biotechnology park (host of 40% of the biotech companies in Portugal) and the Coimbra University Hospitals (CHUC).

Vectors and Gene Therapy Group

Mª Conceição P. Lima	PhD Head of Group)
João Costa	Student
Alexandro Azevedo	Student
Catarina Morais	Student
Mª Amália Jurado	PhD
Dina Farinha	PhD Student
Henrique Faneca	PhD
Rosemeyre Cordeiro	PhD
Rita Martins	Student
Ana Cardoso	PhD
Daniela Santo	Student
Mariana Colaço	Student
Olga Ribeiro	PhD
Sandra Jesus	PhD
Anália Carmo	MD
Marta Pereira	MD
Nélio Gonçalves	PhD
Nuno Fonseca	PhD
Sérgio Simões	PhD
Vera Moura	PhD
Mariangela Natale	Student
Laura Carvalho	Student
Mariana Caleiras	Student
Ana Ribeiro	Student
Teresa Abreu	Student
Teresa Martins	PhD
Celeste Lopes	PhD
Ana Cruz	Student
João N. Moreira	PhD
Patrick Silva	Student
Mª Inês Martins	Student
Catarina Miranda	PhD
Sara Lopes	PhD Student
Magda Santana	PhD
Miguel Lopes	Student
António Ramos	PhD Student
Kevin Leandro	Student
Rui Nobre	PhD
Pedro Perdigão	PhD
Ana Silva	Student
Diana Santos	PhD
Rita Perfeito	PhD
Sónia Duarte	PhD
Ricardo Moreira	Student
Dina Pereira	PhD Student
Daniel Henriques	Student
Ana Oliveira	Student
Mª Manuel Pinto	Student
Mª Inês Santos	Student
Vanessa Fernandes	Student
Ana Ferreira	Student
Carina Henriques	Student
Diana Lobo	Student
Mª Inês Barros	Student
João Brás	Student
Patrícia Albuquerque	Student
Rafael Carreiras	Student
Liliana Mendonça	PhD
Luís P. Almeida	PhD
Mª Rosario Faro	Sup. Technic.
Catarina Vinhas	Student
Andreia Marques	Student

Stem cell biotechnology Group

Lino Ferreira	PhD Head of Group)
Luís Estronca	PhD
Carlos Jesus	Research Assist.
André Barbosa	Research Assist.
Susana Rosa	PhD
Patricia Pereira	PhD
Artur Rodrigues	PhD
Hugo Fernandes	PhD
Angela Sandoval	Student
Francesca Tomatis	Student
Inês Albino	Student
Sandra Pinhanços	Student
Inês Ribeiro	Student
Marta Barão	Research Assist.
Cristiana Paulo	PhD
Susana Simões	PhD
Rita Ferreira	Student
Catarina Rebelo	PhD
Deolinda Santinha	PhD Student
Ana Caetano	Student
Miguel Lino	PhD
Vitor Francisco	PhD
Rafaela Ferrão	Student
Akhilesh Rai	PhD
Arnab Banerjee	PhD
Helena Aires	Student
Tiago Rondão	PhD
Ricardo Abreu	Student
Luís Monteiro	Student
Andreia Vilaça	Student
Sonia Pinho	PhD

Systems and Computational Biology Group

Armindo Salvador	PhD (Head of Group)
Luís Loura	PhD
Mª João Silvestre	PhD

Medical Microbiology Group

Teresa Gonçalves	PhD (Head of Group)
Célia Nogueira	PhD
Chantal Fernandes	PhD
Lisa Rodrigues	PhD
Marta Mota	Student
Rui Soares	PhD
Patricia Nunes	MD
Gil Lopes	MD
Pedro Valada	Student
José Baptista	PhD
Mariana Afonso	Student
Joana Oliveira	Student
Jorge Lindo	Student

Molecular Mycobacteriology Group

Nuno Empadinhas	PhD (Head of Group)
Susana Alarico	PhD
Ana Tiago	PhD
John Marugg	PhD
Daniela Costa	Student
Inês Roxo	Student

Medicinal Chemistry & Drug Discovery Group

Jorge Salvador	PhD (Head of Group)
Pedro Fernandes	Student
Sara Moura	Student
Daniela Alho	Student
Sara Domingues	PhD
Sofia Anastácio	PhD
Alcino Leitão	PhD
Judite Coimbra	Student
Gabriela Silva	PhD
Tiago Lima	Student
Vânia Moreira	PhD
Ghada Hassan	Student
Tiina Ahonen	Student
Declan C. Mullen	Student
Ágata Lourenço	Student
Clarissa Faria	PhD
Mª Céu Sousa	PhD

Microbiology of Extreme Environments Group

Milton Costa	PhD (Head of Group)
Luciana Pinto	Superior Technic.
Gabriela Simões	Student
Nadine Santos	Student
Tiago Cravo	Student

Molecular Biotechnology Group

Isaura Simões	PhD (Head of Group)
Paula Pires	PhD
Carlos Faro	PhD
Euclides Pires	PhD
Pedro Curto	PhD
Andreia Barro	Student
Bárbara Teixeira	Student

VECTORS AND GENE THERAPY

Head: M. Conceição Pedroso de Lima

OBJECTIVES

The research in the Group of Vectors and Gene Therapy has been devoted to the design and development of carriers, including viral and nonviral vectors, for nucleic acid and drug delivery aiming at their application as technological platforms for 1) establishment of disease models, 2) study of disease mechanisms and 3) development of new molecular therapeutic approaches for cancer and neurodegenerative disorders and of prophylactic strategies.

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, as well as antisense oligonucleotides, siRNAs and anti-miRNA locked nucleic acids, aiming at promoting silencing of known oncogene proteins and both cancer-related and pro-inflammatory 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. In addition, non-viral vectors are currently being developed to study the role of miRNAs in neuroinflammation, aiming at promoting neuronal survival by targeting inflammatory and neurodegenerative pathways.

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

In addition, the fact that tumor survival and proliferation are largely dependent on the microenvironment, represents an opportunity to engineer novel therapeutic strategies to address unmet medical needs, upon choosing more than one target from the pool of tumor–stroma interactions. Therefore, the study of the functional contribution of tumor microenvironment on cancer progression and metastasis, aiming at identifying novel therapeutic targets is becoming an emergent area of research in our group. This is aligned with the design and understanding of the mechanistic basis of non-viral carriers aiming at targeting drugs and nucleic acids to the tumor microenvironment, in orthotopic murine models of cancer.

Viral vectors, particularly lentiviral and adeno-associated viruses are powerful technological platforms for gene delivery to the CNS, which we have been using for investigating the pathogenesis and modeling of neurodegenerative diseases, with a focus on Machado-Joseph disease/spinocerebellar ataxia type 3 (MJD). This knowledge is being used by our group to generate new induced pluripotent stem cells derived from patient fibroblasts and to develop new disease-modifying approaches for MJD therapy. Simultaneous we are interested in developing transplantation of neural stem cells as a new strategy to alleviate neurodegenerative disorders.

The group also addresses a therapeutic vaccine for hepatitis B (oral and subcutaneous) using antigens (protein or DNA) encapsulated in polymeric nanovectors. In this regard, new glucan-based delivery systems able to target the antigens to APC's have been developed and tested (in vitro and in vivo). The group is also interested in the immunotoxicity evaluation of the developed delivery systems.

We are also studying the role of Claspin in cancer. Due to its functions in monitoring DNA replication, activation of CHK1-mediated checkpoint responses and triggering of DNA repair, we believe Claspin may act as a (and may be an important) tumour suppressor. We have found several genetic changes in CLSPN in cancer patients and we are now investigating if these changes may contribute to tumour development.

MAIN ACHIEVEMENTS

Regarding non-viral-mediated gene delivery, an extensive screening of a variety of cell penetrating peptides and cationic polymers for their capacity to generate efficient nucleic acid delivery systems has been carried out and structure-activity relationships have been established.

A miRNA-based therapy addressing GBM cancer stem-like cells to tackle human GBM is currently being developed. In this regard, we have observed that overexpression of miR-128 and miR-302a rendered human GBM stem cells susceptible to new generation chemotherapeutic drugs, such as axitinib, as revealed by a significant decrease of cell viability as compared to non-transfected cells. Mechanistically, this effect cannot be attributed to cell cycle arrest, apoptosis or mitotic catastrophe. However, miR-128 and miR-302a upregulation led to a strong increase in the expression of astroglial differentiation markers, similarly to that resulting from stem cell exposure to BMP4 (a recognized differentiation agent), a reduction of cell proliferation capacity being observed in both conditions. Combination of axitinib or sunitinib (another MTKI) with modulation of membrane lipid composition of GBM cells, through the silencing of key enzymes of lipid metabolism, such as glucosylceramide synthase (GCS), also showed to be a highly promising therapeutic approach towards GBM. Thus, GCS downregulation in combination with axitinib synergistically promoted the apoptosis of GBM cells, the efficiency of this strategy being likely correlated with an excessive generation of reactive oxygen species (ROS). Delivery of miR-144 and miR-200c, downregulated in GBM cells and involved in bioenergetic metabolism pathways, resulted in loss of migratory ability. Combination of the miRNA modulation and treatment with the mitochondria-targeting drug dichloroacetate resulted in tumor cell death.

Furthermore, we found that oxidative stress and apoptosis may be involved in chemoresistance in acute leukemia and that influx/efflux transporters (decreased OCT1 and OCNT2 and increased GL-P and BCRP, respectively) were involved in Chronic Myeloid Leukemia (CML) resistance to imatinib. Simultaneous administration of imatinib and everolimus re-sensitized resistant cells.

Long non-protein coding RNAs (lncRNAs) are currently being studied regarding their potential as therapeutic targets for GBM. In particular, downregulation of lncRNA MVIH, overexpressed in a primary GBM cell line, as well as in human GBM tumor samples, reduced the tumor cell migratory and invasive ability in vitro. Furthermore, the combined treatment consisting of lncRNA MVIH silencing followed by GBM cell incubation with the MTKI cediranib led to tumor cell death.

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 glucan-based NPs for hepatitis B vaccination, the results of immunization revealed that NPs constitute an excellent HBsAg adjuvant. Immunotoxicological studies showed that the size of the NPs has an important influence on the results.

With regard to Claspin, we have found CLSPN genetic changes that were associated with cancer development and caused partial exon skipping, decreased Claspin expression and reduced Chk1 activation.

We are also interested on new targeted therapeutic drugs in several hematological neoplasias as well as in the mechanisms involved in resistance to conventional chemotherapy and to targeted therapies in order to identify new therapeutic approaches and markers of drug response. This line of research highlighted the therapeutic potential of cellular signaling inhibitors, namely mTOR and farnesyltransferase inhibitors in lymphoid neoplasias. Moreover, we found that influx/efflux transporters were involved on imatinib resistance, and administration of imatinib and Reversine 205 or with Everolimus re-sensitize resistant cells. In addition, in CML patients, we create a predictive model of optimal response after one year of treatment using a combined profile of miRs

STEM CELL BIOTECHNOLOGY

Head: Lino Ferreira

OBJECTIVES

The main scientific objectives of the group are: (i) to use stem cell-based therapies for the treatment of ischemic diseases, (ii) to develop innovative strategies for cell reprograming, (iii) to implement stem cell-based assays and in silico approaches for drug screening and (iv) to deliver novel therapeutic compounds identified in the previous high-throughput approaches using nanotechnology-based non-viral vectors.

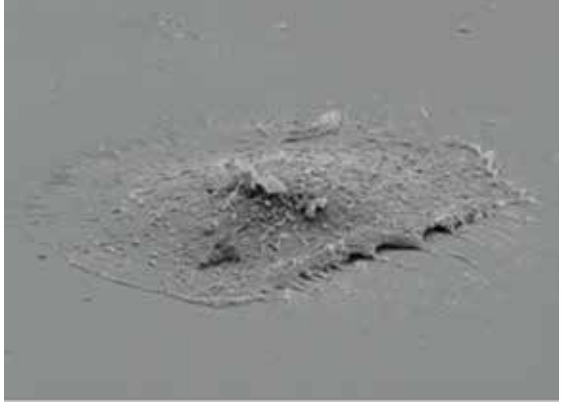
1- Stem cell-based therapies for the treatment of ischemic diseases. To evaluate the therapeutic effect of stem cells in the treatment of ischemic diseases (e.g. stroke, myocardial infarction and chronic wounds). The ongoing clinical trial (phase I/II clinical trial) with the Hospital Rovisco Pais and Centro Hospitalar e Universitário de Coimbra, with the participation of a stem cell banking company, Crioestaminal, will evaluate the therapeutic effect of CD34+ cells isolated from bone marrow of stroke patients in acute or sub-acute phases and transplanted by catheter to the brain.

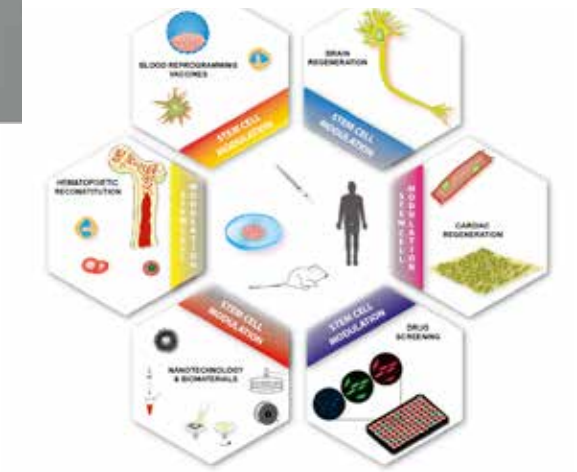
2- To develop innovative strategies for cell reprogramming. The objective is to understand the molecular determinants underlying cellular reprogramming and hematopoietic specification. Cellular reprogramming can be achieved experimentally in different ways, including nuclear transfer, cell fusion or 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 were 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.

3- 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.

4- 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 CNC.IBILI or associated institutions (IEC).





MAIN ACHIEVEMENTS

In 2019 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? (iv) what transcription factors are necessary for cell reprogramming into hematopoietic or T cells?

We have shown that fully functional arterial- and venous-like endothelial cells can be derived from induced pluripotent stem (iPSC) cells (Rosa et al, Scientific Reports 2019) and these cells can be used to generate in vitro vascular models for nanotoxicology screenings (Estronca et al, manuscript in preparation). 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 (Pitrez et al, Nature Communications 2020). We also have derived brain-like endothelial cells from human iPSC derived endothelial progenitor cells and successfully developed a BBB in vitro model (Praça et al, 2019) that can be used for drug screenings.

We have shown how cellular stemness is intimately related with mechanical properties of the cell by inducing low cellular contractility and stiffness we are able to increase the reprogramming efficiency of mesenchymal stem/stromal cells into induced pluripotent stem cells (Gerardo et al, Scientific Reports 2019).

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.

Our research in small extracellular vesicles (SEVs) have confirmed that SEVs are promising strategies for tissue regeneration and we have revealed that the kinetics of SEVs delivery has a significant impact in tissue regeneration at tissue, cellular, and molecular levels (Antunes et al, ACS Nano 2019). We also have developed a positron-emission tomography (PET)/magnetic resonance imaging (MRI) platform that are able to track SEVs in vivo (Banerjee et al, Nanoscale 2019)

We have shown that 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). 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.

We have 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. 5 papers were published in 2019 exploring these reprogramming approaches as well as a collaborative study in cancer stem cells.

COMPUTATIONAL AND SYSTEMS BIOLOGY

Head: Armindo Salvador

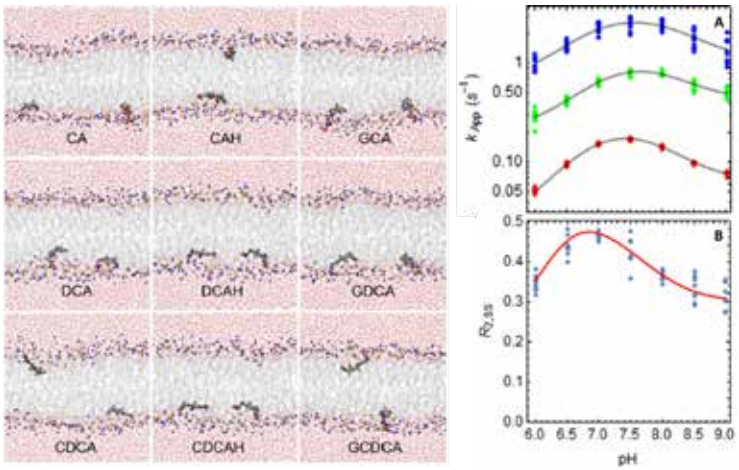
OBJECTIVES

Research at the Computational & Systems Biology Group is structured along the following three research lines:

1. 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.

2. Modeling the permeation through physiological barriers. The long-term goal of this research line is to develop quantitative structure-activity relationships (QSAR) for the permeation of physiological barriers by drugs, namely tight endothelia such as the blood-brain barrier (BBB). Failure to cross the BBB is the main factor of attrition in the development of psycho-active drugs, and is causing some of the main pharmaceutical corporations to abandon the development of such drugs altogether. The bioavailability of xenobiotics at the brain is strongly affected by their interaction with lipid bilayers and blood components (albumin, lipoproteins, erythrocytes and membranes of endothelial cells). Our work shows that the partition of drugs among the compartments strongly affects the timing and effectiveness of their permeation across the BBB. We are working towards modeling how molecular features of the xenobiotics impact on the kinetics of these critical steps and to achieve better predictions of overall permeability.

3. 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.



Left. Final snapshots of MD simulations with initial BS location in the center of the bilayer. BS molecules are depicted in licorice, while POPC and water molecules are depicted in line style. Atom colors are gray, red, brown, blue, and white, for C, O, P, N, and H, respectively. CA, CAH, GCA: cholate, in ionized, non-dissociated and glycine conjugate; CDCA, CDCAH, GCDCA, respective chenodeoxycholate forms; DCA, DCAH, CDCA, respective deoxycholate forms. Right: pH dependence of the characteristic constants for Trp fluorescence recovery and of cooperativity in condensation of Prx2. (a) pH dependence of the characteristic constants obtained from tri-exponential fits to the Trp fluorescence recovery after treatment of 1 μM Prx2 with 1 μM or 2 μM H2O2 (representative experiment). R2,SS is the ratio between the rate constant for condensation for dimers where the second site is in disulfide form and that for dimers where the second site is in sulfenic form. The dots represent best-fit estimates of the characteristic constants for replicate injections from two experiments. The solid lines represent the best-fit curves for the pH-dependence model described in [DOI: 10.1021/acs.biochem.8b00188]. (B) pH dependence of the cooperativity in condensation. Dots, based on the kApp values in panel (A); line, calculated from the best-fit parameters for the pH-dependence model.

MAIN ACHIEVEMENTS

Bile salts (BS) are biosurfactants crucial for emulsification and intestinal absorption of cholesterol and other hydrophobic compounds such as vitamins and fatty acids. The interaction of BS with lipid bilayers is relevant for passive diffusion processes through intestinal epithelium such as reabsorption of BS, as well as their degree of toxicity to intestinal flora and their potential applications in drug delivery. We used molecular dynamics simulations to address at the atomic scale the interactions of cholate, deoxycholate, and chenodeoxycholate, as well as their glycine conjugates with POPC bilayers. In this set of BS, variation of three structural aspects was addressed, namely conjugation with glycine, number and position of hydroxyl substituents, and ionization state. From atomistic simulations, the location and orientation of BS inside the bilayer, and their specific interactions with water and host lipid, such as hydrogen bonding and ion-pair formation, were studied in detail. Membrane properties were also investigated to obtain information on the degree of perturbation induced by the different BS. Differences in macroscopic membrane partition thermodynamics and translocation kinetics were rationalized in terms of the distinct structures and atomic-scale behavior of the bile salt species. In particular, the faster translocation of cholate is explained by its higher degree of local membrane perturbation. On the other hand, the relatively high partition of the polar glycine conjugates is related to the longer and more flexible side chain, which allows simultaneous efficient solvation of the ionized carboxylate and deep insertion of the ring system. [Front. Physiol. 10, 393. DOI:10.3389/fphys.2019.00393]

In higher organisms, the 2-Cys peroxiredoxin II (Prx2) is involved in the H2O2-mediated regulation of cell proliferation, apoptosis, cell migration, neuroprotection, angiogenesis and tumorigenesis. Understanding the kinetics of its reactions with H2O2 is a key step towards clarifying the mechanisms of those regulatory processes. Prx2 is a pentamer of dimers in antiparallel juxtaposition. Each monomer carries a very H2O2-reactive Cys (peroxidatic Cys, CP), proximal to a less reactive (resolving, CR) Cys in the other monomer. In the catalytic cycle, CP reduces H2O2, being oxidized to a sulfenic acid (CP-SOH), which in turn undergoes a condensation with the proximal CR, forming a disulfide. Through an iterative theoretic-experimental approach in collaboration with the labs of Dr. Christine Winterbourn (U. of Otago, NZ) and Dr. Flávia Meotti (U. of São Paulo, Brazil) we have previously demonstrated the occurrence of positive cooperativity between the two sites in a dimer in the H2O2 reduction step and negative cooperativity in the condensation step. Over 2019 we extended these studies to examine the interactions of Prx2 with glutathione (GSH) and towards clarifying the molecular underpinnings of cooperativity. We showed that GSH is able to reduce the Prx2 disulfide through a thiol-disulfide exchange reaction showing mild positive cooperativity. Furthermore, through an analysis of the pH dependence of the rate of the homocondensation reaction we showed that the redox state of one site in a dimer does not significantly influence the pKa's of the CP-SOH and of the CR-SH at the other site. Therefore, the observed cooperativity is not mediated by the modulation of these site's acidity. Instead, the redox state of one site substantially influences the rate constants for the condensation reactions between the CP-SO(H) and the CR-S(H) in the various protonation states. Together with other evidence, this observation suggests that cooperativity in condensation results from the modulation of the collisional frequency among the CP-SOH and the CR-SH groups at one site by the redox state of the other site [DOI: 10.1101/2020.05.11.087908]. Molecular dynamics studies in collaboration with the Data Driven Molecular Design group at CNC to further clarify the molecular underpinnings of this phenomenon are ongoing.

MEDICAL MICROBIOLOGY

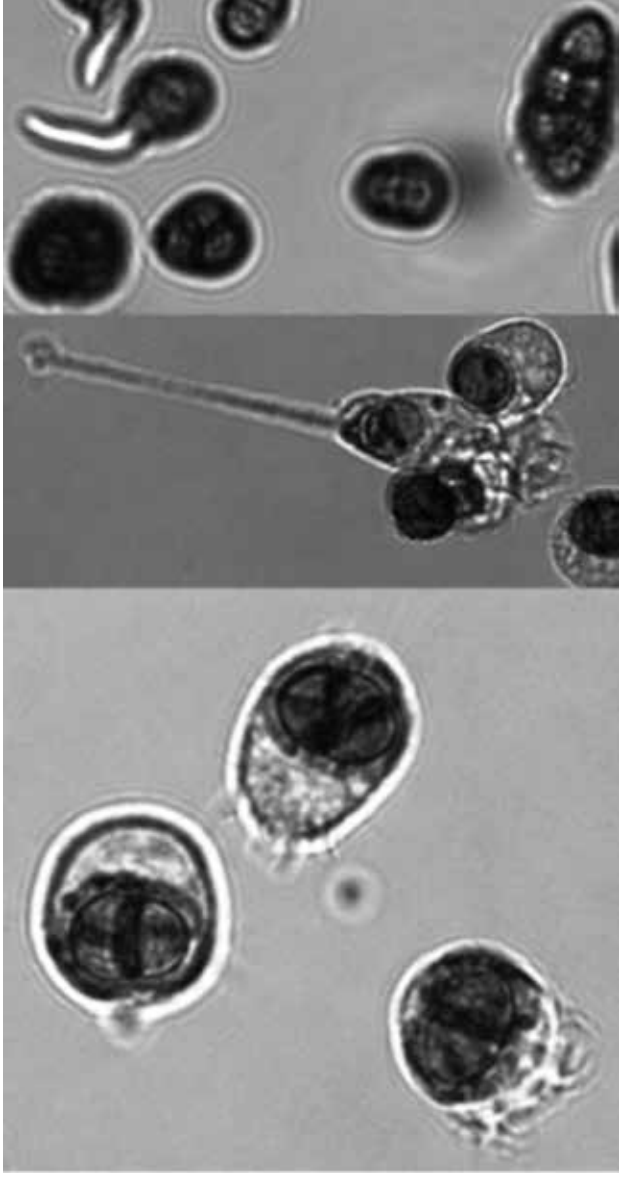
Head: Teresa Gonçalves

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. 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 (2019) our specific objectives were to seek for novel therapies to eradicate fungal infections with a focus on oral and filamentous fungi affecting the respiratory system. We continue to pursue how the purinergic metabolism and adenosine A2A receptors can be modulated to ameliorate pathological conditions of the elderly such as chronic inflammation of the gut.

Phagocytosis of A. infectoria sporesl



MAIN ACHIEVEMENTS

-Mycobiome of the upper respiratory system of allergic patients and, IgEs against fungal cell wall extracts and EVs from the fungi isolated from those patients.

- Antifungal activity of plant extracts

- Response of macrophages to Alternaria infectoria spores (11046_2019_339_MOESM2_ESM.mp4)

MOLECULAR MYCOBACTERIOLOGY AND MICROBIOME

Head: Nuno Empadinhas

OBJECTIVES

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

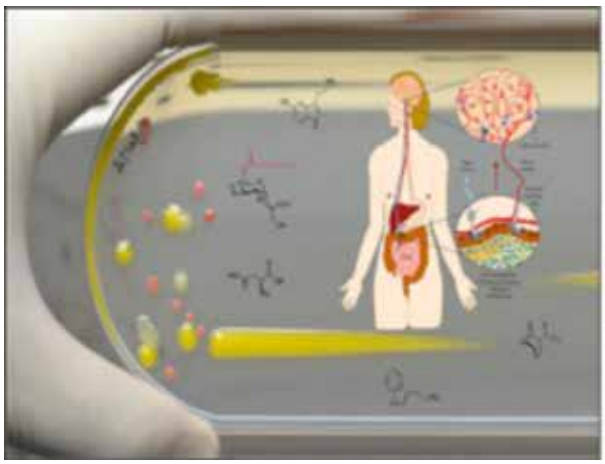
Mycobacterial Pathways and biosynthesis of antimicrobials - Mycobacteria cause serious infections beyond tuberculosis (TB), mostly in the chronically ill and in the elderly. They are "a global priority for which innovative new treatments are urgently needed" (WHO, 2017).

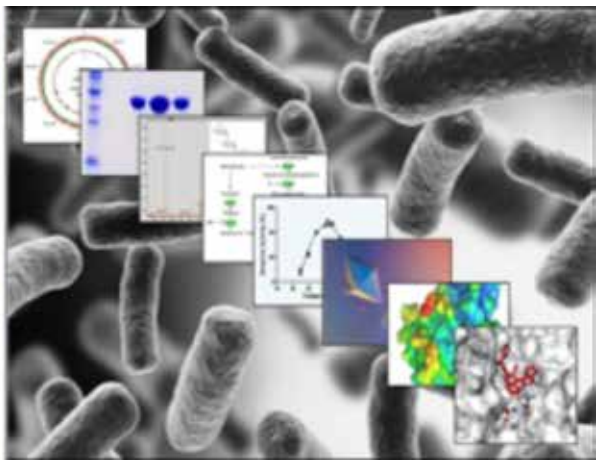
We aim at deciphering pathways for mycobacterial polymethylated polysaccharides, regulators of their cell wall assembly and potential targets for rational drug design.

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.





MAIN ACHIEVEMENTS

Molecular Mycobacteriology & biosynthesis of antimicrobials – A novel mechanism for replication and recycling of a mycobacterial intracellular polysaccharide that modulates fatty acid metabolism and assembly of the cell envelope was identified and characterized (Ripoll-Rozada et al, 2019, PNAS). These findings build on previous achievements from our group that identified the genes of two essential mycobacterial pathways and new promising enzyme targets that were the founding members of new enzyme families at the IUMB database (Cereija et al, 2019, IUCrJ). The group has also identified an Actinobacterial orphan biosynthetic cluster that hints at a completely novel class of secondary metabolites. A family of kinases was revealed (Manso et al, 2019, mBio), which is likely to represent the missing link for incorporation of environmental glucosamine into an antibiotic biosynthesis pathway.

Parkinson's Gut Microbiome - The gut microbiomes of Parkinson's Disease (PD) patients was comprehensively characterized and their profiles revealed unique microbial signatures. In vitro and in vivo results confirmed how a specific microbial neurotoxin imparts chronic neuronal mitochondrial damage and probably the onset of PD features.

Diabetic Wounds Microbiome - Sampling of over 200 diabetic patients skin and wounds and isolation of relevant microbiota allowed the creation of a DFU biobank with over 2000 strains of over 50 species. Antimicrobial susceptibility trials and interspecific competition assays revealed bacterial communication phenomena in the DFU ecosystem. Genomes of relevant DFU microbiota were sequenced. We could successfully modulate mice DFU microbiomes toward healthier profiles with topical administration of certain neuropeptides.

Public Health - We isolated multidrug resistant strains nontuberculous mycobacteria (NTM) from hospital wards (Pereira et al 2019, BMC Microbiol). NTM patients' houses and water distribution systems were sampled and numerous mycobacterial species could be isolated and identified by WGS (Tiago et al, 2019, Microbiol Resour Announc), including opportunistic pathogens members of M. abscessus-chelonae clade.

MEDICINAL CHEMISTRY & DRUG DISCOVERY

Head: Jorge A. R. Salvador

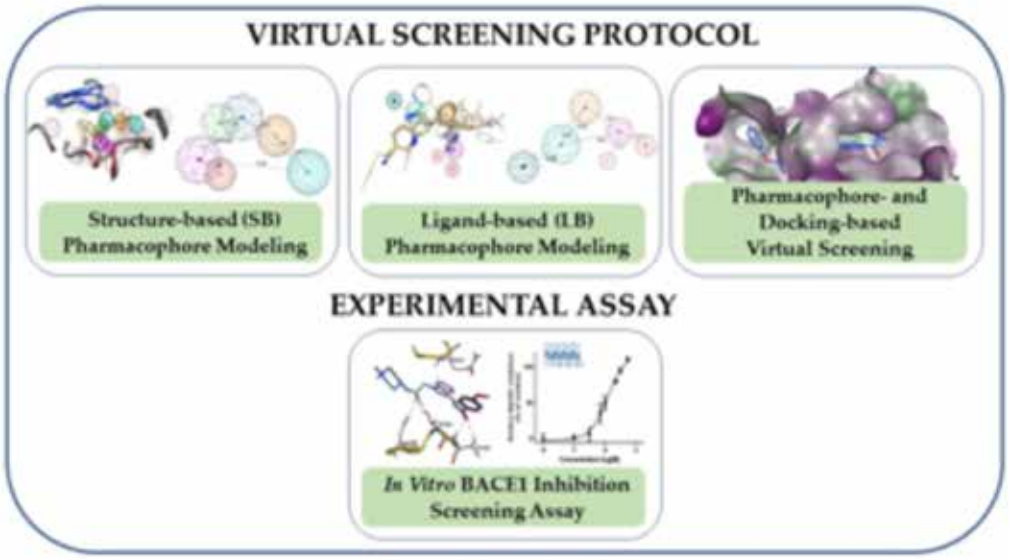
OBJECTIVES

Pentacyclic triterpenoids are a class of pharmacologically active and structurally rich natural products with privileged motifs for further modifications and SAR analyses. We focused on the anticancer activity of the semisynthetic oleanane and ursane triterpenoids derivatives of glycirrethynic and madecassic acid. We synthetized a series of novel glycirrethynic and madecassic acid (MEA) derivatives and screened them for antitumor activity against the NCI-60 cancer cell line panel.
Alzheimer's disease is a severe neurodegenerative disorder and so far there is no prevention or treatment of this disorder.

Our main goal is the identification of novel anti-Alzheimer's agents, namely molecules targeting BACE1, ang glutaminyl cyclase by combining distinct but complementary approaches.

The work plan regarding computational studies includes pharmacophore-based virtual screening and molecular docking studies with the purposed in identifying hits acting with high affinity on BACE1 and glutaminyl active sites (allowing a reduction in the number of compounds to evaluate), and prediction of in silico pharmacokinetic (e.g., blood-brain barrier (BBB) permeation) and toxicity properties to assure only the compounds with the suitable profile will be experimentally tested. The biological evaluation aims to assess the hits BACE1 and glutaminyl cyclase inhibition potency, cellular toxicity and in vivo efficacy of the best candidate using animal models of the disease.

Antimicrobial resistance (AMR) is considered one of the major Public Health threats nowadays, with very few therapeutic options for the treatment of multidrug resistant Gram-negative bacteria infections. It is crucial to characterize resistance mechanisms and to understand the epidemiology of drug resistance at molecular level, and to investigate new strategies/molecules to fight AMR. Our objectives were focused on resistance dissemination by conjugation and natural transformation in clinically relevant Gram-negative bacteria, the role of heavy metals in AMR spread that supplement animal food and to ascertain the activity of polyphenols in gut bacterial infection.



MAIN ACHIEVEMENTS

A series of novel madecassic acid (1) derivatives was synthesized, and their cytotoxicity was evaluated against the NCI-60 panel of cancer cell lines. Several analogues exhibited broad-spectrum cytotoxic activities over all nine tumor types represented in the panel, with more potent antiproliferative activities observed against selected cancer cell lines, including multidrug-resistant phenotypes. Among them, the best compound showed GI50 (50% growth inhibition) values ranging from 0.3 to 0.9 μM against 26 different tumor cell lines and selectivity for one colon (COLO 205) and two melanoma (SK-MEL-5 and UACC-257) cell lines at the TGI (total growth inhibition) level. The mode of action of this compound was predicted by CellMiner bioinformatic analysis and confirmed by biochemical and cell-based experiments to involve inhibition of the DNA replication process, particularly the initiation of replication, and disruption of mitochondrial membrane potential. The present findings suggest this novel madecassic acid derivative may have potential as an anticancer therapeutic lead for both solid and hematological tumors. DOI: 10.1021/acs.jnatprod.8b00864

The treatment options for a patient diagnosed with Alzheimer's disease (AD) are currently limited. The cerebral accumulation of amyloid-β is a critical molecular event in the pathogenesis of AD. When the amyloidogenic β-secretase (BACE1) is inhibited, the production of Aβ peptide is reduced. Henceforth, the main goal of our study is the discovery of new small bioactive molecules that potentially reach the brain and inhibit BACE1. The work was conducted by a customized molecular modelling protocol, including pharmacophore-based and molecular docking-based virtual screening (VS). Structure-based (SB) and ligand-based (LB) pharmacophore models were designed to accurately screen several drug-like compound databases. The retrieved hits were subjected to molecular docking and in silico filtered to predict their ability to cross the blood–brain barrier (BBB). Additionally, 34 high-scoring compounds structurally distinct from known BACE1 inhibitors were selected for in vitro screening assay, which resulted in 13 novel hit-compounds for this relevant therapeutic target. This study disclosed new BACE1 inhibitors, proving the utility of combining computational and in vitro approaches for effectively predicting anti-BACE1 agents in the early drug discovery process. https://doi.org/10.3390/biom10040535

We demonstrated the ability of AMR determinants to undergo natural transformation in different clinical Acinetobacter spp. isolates, which may facilitate AMR dissemination in the hospital environment, and we showed by genetic studies that heavy metals can select for AMR genes and contribute for its emergence and spread. Moreover, Portuguese red wine polyphenols prevent the pathogenicity of Escherichia coli at gut level, which deserves to be further explored as an antimicrobial strategy to fight infection.

BIOTECHNOLOGY:

MICROBIOLOGY OF EXTREME ENVIRONMENTS

Head: Milton Costa

OBJECTIVES

1. Continued studies on the mechanisms involved in stress adaptation of thermophilic, halophilic and desiccation-resistant bacteria.

2. To identify new compatible solutes and elucidate their biosynthetic pathways and their role in stress tolerance.

3. To isolate and characterize novel organisms from extreme environments for basic studies and for their biotechnological potential.

4. Metagenomics of extreme environments in Portugal, namely hot springs, salt mines and solar exposed rock surfaces to look for enzymes involved in the degradation of plastics and wood products such as cellulose, lignin and xylan.

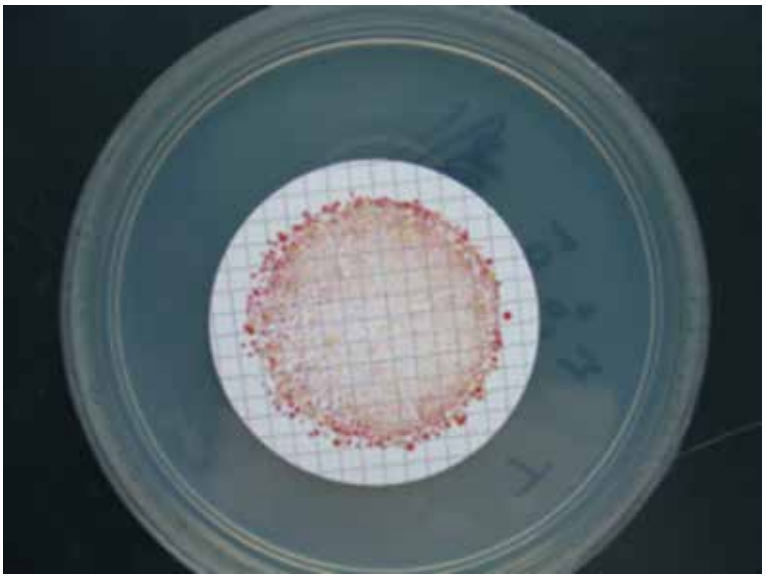


Figure legend. Growth of halophilic thermophilic bacteria and archaea from saline environments.

MAIN ACHIEVEMENTS

1. Recent research led to the description of new bacteria and archaea from extreme environments with the purpose of finding new organisms that have biotechnological potential. These organisms have different origins that also contribute to our knowledge of microbial diversity and their metabolic and biosynthetic processes. The genomes sequence analysis of over 20 genomes has been the source of genes that have biotechnological potential.

2. We embarked on an extensive study on the biodiversity of several geothermal areas in Portugal using in situ examination of 16S rRNA gene sequences as a modern assessment of biodiversity. It is well known that this methodology produces an extremely good picture of the biodiversity since the vast majority of organisms cannot be isolated in culture.

3. We also continued our studies of the identification and function of compatible solutes isolated from extremophilic organisms, namely slightly halophilic thermophiles, as well as extremely radiation resistant organisms. Several candidate genes were identified in the metagenomes of the hot springs.

BIOTECHNOLOGY:

MOLECULAR BIOTECHNOLOGY

Head: Isaura Simões

OBJECTIVES

The long-term goal of our group is to contribute to a better understanding of the molecular mechanisms of microbial pathogenicity and facilitate the identification of new factors/molecular pathways that may constitute pathogen- or host-directed targets for therapeutic intervention. Our current research interests can be summarized in the following strands:

i) Study of proteolysis and proteostasis in the context of infection, both on the relevance of these mechanisms for bacterial pathogenesis and for modulating host-pathogen interactions. Our main working model is Spotted Fever Group (SFG) Rickettsia.

ii) Understand the molecular mechanisms that define species-specific patterns of SFG Rickettsia cellular tropism and their relevance for rickettsial pathogenesis.

iii) Identification of bacterial virulence proteins (e.g. surface-exposed membrane proteins) susceptible of antibody-based targeting strategies, for both structural and functional characterization and/or ultimate therapeutic intervention.

In a parallel strand we also aim to:

iv) Continue exploring the functional and biotechnological aspects of plant proteases, namely their role and potential targetability in allergic disorders

These 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, complemented with various system-wide quantitative approaches.

MAIN ACHIEVEMENTS

1) Identification of bacterial and host factors required for the different intracellular fate of pathogenic versus non-pathogenic species of Rickettsia in macrophage-like cells

• We pursued with studies to understand in detail the role of macrophages in rickettsial pathogenesis. We evaluated early host transcriptional responses by RNAseq (at 1 hpi) (ref. a) and proteome signatures by SWATH-MS (at 24 hpi) (ref. b) of THP-1 macrophages infected with R. conorii and R. montanensis. Our results revealed that infection with pathogenic R. conorii interfered with a myriad of cellular processes (e.g., inflammatory responses, metabolic responses, survival, proteostasis network, and transcription). These results provide evidence for a substantial reprogramming and mechanistic differences between Rickettsia-macrophage-tropic vs. non-tropic phenotypes, providing multiple testable hypotheses that we are now validating.

a. Curto P., Riley S.P., Simões I., Martinez J.J. (2019). Front Cell Infect Microbiol. 9:97. doi: 10.3389/fcimb.2019.00097. eCollection 2019.

b. Curto P., Santa C., Allen P., Manadas B., Simões I., Martinez J.J. (2019) Front Cell Infect Microbiol.9:43. doi: 10.3389/fcimb.2019.00043. eCollection 2019.

2) Development of a core platform specialized on antibody-based products and services

• 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 will ultimately enable the development of novel immunotherapies and immunoresearch tools. The core of the antibody technological platform is the CNC Avian Technological Unit, a unique animal research unit also implemented by the group and fully dedicated to exploit birds as bioreactors (http://www2.biocant.pt/structuralbiotechnology/index.php/resources/). This is the only unit of its kind in Portugal, holding IP on avian experimentation systems that enable core R&D activities (PCT/IB2017/054766).

• We have contributed to a review in the field of Parasitology, that presents the most relevant applications of avian IgY antibodies in the fight and control of parasitic infections (ref. a.).

a. Diraviyam, T., Ambi, S. V., Vieira-Pires, R. S., Xiaoying, Z., Sekaran, S., Krishnan, U. (2019). International Journal of Biological Macromolecules, 136, 755-763 doi: 10.1016/j.ijbiomac.2019.06.118.

• We have launched a parallel effort with IT collaborators to understand the possibilities of blockchain-based intellectual property protection, namely of high-value antibodies (ref. b)

b. Barata, S., Vieira-Pires, R. S. and Cunha, P.R. (2019). Conference Paper, International Conference on Information Systems Development (ISD2019), 28-30th August, Toulon, France

3) Biochemistry, biology and biotechnology potential of plant proteases

• We characterized a novel atypical aspartic protease (AP) expressed in Arabidopsis roots (ASPR1). Recombinant ASPR1 produced by transient expression in Nicotiana benthamiana displayed atypical biochemical properties and unique specificity preferences resembling those of fungal APs. ASPR1 overexpression suppressed primary root growth and lateral root development, implying a previously unknown biological role for an AP (ref. a).

a. Soares A., Niedermaier S., Faro R., Loos A., Manadas B., Faro C., Huesgen P.H., Cheung A.Y., Simões I. (2019) J. Exp Bot. Apr 12;70(7):2157-2171. doi: 10.1093/jxb/erz059

• Acacia caven (Mol.) Molina pollen causes pollinosis in South America. The aim of this work was to characterize the proteolytic enzymes of A. caven pollen, and study their influence on allergy. A 75-kDa peptidase (Acaciain peptidase) was purified and classified as a serine peptidase. We showed that Acaciain peptidase can alter the integrity of the epithelium barrier, causing cell permeability, increasing the allergic sensitization and exacerbating the overall bronchoconstrictive effect detected in asthmatic lungs. This novel serine peptidase constitutes a relevant therapeutic target in the treatment of allergic disorders (ref a.).

a. Barcia C, Coelho AS, Barberis S, Veríssimo P. (2019). Biotechnol Appl Biochem. 2019;10.1002/bab.1837. doi:10.1002/bab.1837

• In this invited review, we give an overview of the current knowledge on the distinctive features and functions of both atypical and nucellin-like APs, and discuss this emerging pattern of functional complexity and specialization among plant pepsin-like proteases.

a. Soares A., Ribeiro Carlton S.R., Simões I. (2019) J. Exp Bot. Apr 12;70(7):2059-2076. doi: 10.1093/jxb/erz034.

INTERNATIONALIZATION

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

Projects in Collaboration

NEUROSCIENCE, VISION AND BRAIN DISEASES STRAND

Synapse Biology

- Martínez-Rodríguez E, Martín-Sánchez A, Coviello S, Foiani C, Kul E, Stork O, Martínez-García F, Nacher J, Lanuza E, Santos M*, Agustín-Pavón C* (2019) Lack of MeCP2 leads to region-specific increase of doublecortin in the olfactory system. Brain Struct & Function 224: 1647-1658. * joint last authors

- Supervision of Elisa Corti, PhD student of Syn2Psy (synaptic dysfunction in neuropsychiatric disorders) training network funded by Marie Sklodowska Curie Actions – European Commission H2020. (2019-2023) (Supervisors: Carlos B. Duarte, Paulo Pinheiro, Ramiro D. Almeida)

- Supervision of Orsolya Antal, PhD student in Syn2Psy – Synaptic Dysfunction in Neuropsychiatric Disorders, an ITN funded by the Marie Sklodowska Curie Actions (2019-2023) (Supervisors: Ana Luisa Carvalho, Thomas Knöpfel)

- Collaboration with Andrea Barberis from the Italian Institute of Technology (iit) in the project entitled "The K+-Cl- cotransporter (KCC2) to maintain GABAergic neurotransmission: a novel therapeutic strategy for epilepsy".

- Collaboration with Maurizio Taglialatela (University Federico II, Naples), for the study of mechanisms that regulate Kv7 channels

- Collaboration with Angela Vincent and Sarosh Irani (University of Oxford), in a project focused on anti-CASPR2 autoimmune encephalitis

- Collaboration with Inbal Israely (Columbia University, NY) in studying how metabolic hormones regulate spine dynamics in the hippocampus

- González-Durruthy M, Giri AK, Moreira IS, Concu R, Melo A, Ruso JM, Cordeiro NNDS (2020) Computational modelling of mitochondrial channel nanotoxicity – Nano Today 34, 100913.

Koukos PI, Roel-Touris J, Ambrosetti F, Geng C, Schaarschmidt J, Trellet ME, Melquiond ASJ, Xue LC, Honorato RV, Moreira IS, Kurkcuoglu Z, Vangone A, Bonvin AMJJ (2020) An overview of data-driven HADDOCK strategies in CAPRI rounds 38-45, Proteins, https://doi.org/10.1002/prot.25869

Barreto CAV, Baptista SJ, Bueschbell B, Magalhães P, Preto AJ, Lemos A, Rosario-Ferreira N, Schiedel A, Machuqueiro M, Melo R, Moreira IS (2020) Arrestin and G-protein interactions with GPCRS: a dynamical perspective, in GPCRs as Therapeutic targets, Wiley, 2020, edited by Gilchrist A - accepted for publication.

Magalhães PR, Machuqueiro M, Almeida JG, Melo A, Cordeiro MNDS, Verde SC, Gumus ZH, Moreira IS, Correia JDG, Melo R (2019) Dynamical rearrangement of human epidermal growth factor receptor 2 upon antibody binding: effects on the dimerization, Biomolecules, 9, pii, E706.

Redox Biology and Brain Sensing

Ongoing research collaboration and student mentoring is maintained active (although no collaborative paper was published during 2019) with Enrique Cadenas from University of Southern California, LA, USA on redox regulation in aging brain and neurodegeneration and with Greg Gerhardt from Center for Microelectrode Technology, University of Kentucky, USA on technological development of microbiosensors for stereotaxic insertion into the brain.

Neuroendocrinology and Aging

Collaborative publication : Gaspar LS, Álvaro AR, Carmo-Silva S, Mendes AF, Relógio A, Cavadas C. The importance of determining circadian parameters in pharmacological studies. British Journal Pharmacology 2019 Aug;176(16):2827-2847.

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 one PhD student; in vitro progeria models).

The group is integrated in a COST Action "An integrative action for multidisciplinary studies on cellular structural networks". COST Action. CA15214.

João Pedro Magalhães – Liverpool University – projecto collaborator,

Vision, Brain Imaging and Cognitive Neuroscience

Papers (international collaboration)
See European Projects and publications of the group

Book Chapter (international collaboration)

3Rui Bernardes, Lília Jorge, Ana Nunes, and Miguel Castelo-Branco Machine Learning Approaches in OCT: Application to Neurodegenerative Disorders Book Chapter in OCT in Central Nervous System Diseases The Eye as a Window to the Brain Editors: Grzybowski, Andrzej, Barboni, Piero (Eds.) Springer 2020

Scientific collaborations

Reza Farivar, McGill University, Canada
Rainer Goebel, University of Maastricht
Agneta Nordberg, Karolinska Institute
Alcino Silva, University of California at Los Angeles
Richard Edden, John Hopkins University

Post-graduation and post-docs interchange

Bruno Direito (Carnegie Mellon University)

Networking

Coordination of the National Brain Imaging Network

Participation in EuroBioimaging (European infrastructure)

Participation in PtCrin, a branch of ECRIN (European infrastructure)

Participatiion in Ageing@Coimbra, European Innovation Partnership on Active and Healthy Ageing

Member of InnoSTARS, EIT Health Knowledge Innovation Community

Participation in European Projects (H2020): STIPED, IMI-2

Neuromodulation

-Networks:
International Alliance for Healthy Ageing (with Univ. Newcastle, Groningen Medical School, Univ.Copenhagen, Mayo Clinics)
Association for Science and Information on Coffee

-Research grants:
CAPES-FCT program with Rui Prediger (Univ. Federal Santa Catarina, Brazil)
Joint project of the Association Nationale de Recherche 'ROle of Adenosine Receptors on synapse stabilization (ROAR)' with Sabine Levy (CNRS, Institur Fer à Moulin, Paris) and Christophe Bernard (INSERM, Univ.Méditerrannée, Marseille).

-Graduate training:
Co-supervision of a PhD student (Mara Yone Fernandes) with Geanne Matos (Univ. Federal Ceará, Brazil)
Co-supervison of a PhD student (Angela Patricia França) with Rui Prediger (Univ. Federal Santa Catarina, Brazil)
Co-supervison of a PhD student (Lisiane Souza) with Pablo Pandolfo (Univ. Federal Fluminense, Brazil)
Co-supervision of a PhD student (Xinli Xu) with Nelson Rebola (Univ. Bordeaux, France)

Mitochondrial Dysfunction and Signaling in Neurodegeneration

Graduate Training:
- "Neuroscience and Mental Health: a Clinical and Molecular Perspective in Neuropsychiatric and Neurodegenerative Disorders", The Doctoral Programme in Health Sciences, organized by the Faculty of Medicine, University of Coimbra.
Coordinators: Ana Cristina Rego and João O. Malva
Date: April 1-5, 2019

- "Molecular and cellular mechanisms of ageing and neurodegeneration"
EIT Health_EpiDEMPrev advanced course
Coordinators: Ana Cristina Rego and João O. Malva
Date: April 2-5, 2019
International collaborative publications:
- Pinho R, Paiva I, Jercic KG, Fonseca-Ornelas L, Gerhardt E, Fahlbusch C, Garcia-Esparcia

INTERNATIONALIZATION

NEUROSCIENCE, VISION AND BRAIN DISEASES STRAND

P, Kerimoglu C, Pavlou MAS, Villar-Piqué A, Szego É, Lopes da Fonseca T, Odoardi F, Soeroes S, Rego AC, Fischle W, Schwamborn JC, Meyer T, Kügler S, Ferrer I, Attems J, Fischer A, Becker S, Zweckstetter M, Borovecki F, Outeiro TF (2019) Nuclear localization and phosphorylation modulate pathological effects of alpha-synuclein. Hum Mol Genet. 28: 31-50. doi: 10.1093/hmg/ddy326. PMID: 30219847

Invited speaker in international meetings:
Rego A. C. (2019) Mitochondrial and Ca2+ deregulation in neurons in early stages of Alzheimer's disease pathogenesis and brain aging following immediate exposure to amyloid-beta oligomers. "Ageing: models, mechanisms and therapies" conference _ Session III: Ageing mechanisms (under the project ERAChair@UC), 28-29th June, University of Coimbra, Coimbra, Portugal.
Rego A. C. (2019) Mitochondrial deregulation in Huntington's disease - role of SIRT3. BNA 2019 Festival of Neuroscience, 14-17th April, Dublin, Ireland.

Research collaboration with the following researchers:
- 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
- Thorsten Schlaeger (PhD) Boston Children's Hospital, Boston, MA, USA
- Michael Hayden (MD, PhD), University of British Columbia, Vancouver, Canada
- Tiago Fleming Outeiro (PhD), University Medizin Goettingen, Goettingen, Germany

Aging and Brain Diserases: advanced diagnosis and biomarkers

Rosas I, Martínez C, Clarimón J, Lleó A, Illán-Gala I, Dols-Icardo O, et al. Role for ATXN1, ATXN2, and HTT intermediate repeats in frontotemporal dementia and Alzheimer's disease. Neurobiol Aging. 2020 Mar;87:139.e1-139.e7. doi: 10.1016/j.neurobiolaging.2019.10.017.

Gazzina S, Grassi M, Premi E, Cosseddu M, Alberici A, Archetti S, et al. Genetic FTD Initiative, GENFI. Education modulates brain maintenance in presymptomatic frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2019 Oct;90(10):1124-1130. doi: 10.1136/jnnp-2019-320439.

Premi E, Calhoun VD, Diano M, Gazzina S, Cosseddu M, Alberici A, et al. Genetic FTD Initiative, GENFI. The inner fluctuations of the brain in presymptomatic Frontotemporal Dementia: The chronnectome fingerprint. Neuroimage. 2019 Apr 1;189:645-654. doi: 10.1016/j.neuroimage.2019.01.080.

Baldeiras I, Santana I, Leitão MJ, Vieira D, Duro D, Mroczko B, et al. Score as a tool to predict progression from mild cognitive impairment to dementia in Alzheimer's disease. Alz Res Therapy 2019;11(1):2. doi: 10.1186/s13195-018-0456-x.

van Maurik IS, Bos I, Vos SJ, Bouwman FH, Teunissen CE, Scheltens P, et al,. Biomarker based prognosis for patients with mild cognitive impairment. Lancet Neurology 2019; doi: 10.1016/S1474-4422(19)30283-2 28.755

Zerr I, Villar-Piqué A, Schmitz VE, Poleggi A, Pocchiari M, Sánchez-Valle R, et al. Evaluation of human cerebrospinal fluid malate dehydrogenase 1 as a marker in genetic Creutzfeldt-Jakob disease patients. Biomolecules 2019; 9, 800; doi:10.3390/biom9120800.

van der Ende E, Meeter LH, Poos JM, Panman JL, Jiskoot LC, Dopper EGP, et al. Serum neurofilament light chain in genetic frontotemporal dementia: a longitudinal, multicentre cohort study. The Lancet Neurology 2019; 18 (12): 1103-1111. http://dx.doi.org/10.1016/s1474-4422(19)30354-0.

Mendes T, Cardoso S, Guerreiro M, Maroco J, Silva D, Alves L, et al. Can Subjective Memory Complaints Identify Aß Positive and Aß Negative Amnestic Mild Cognitive Impairment Patients?. Journal of Alzheimer's Disease 2019; 70 (4): 1103-1111. http://dx.doi.org/10.3233/jad-190414.

Alves C, Jorge L, Canário N, Santiago B, Santana I, Castelhano J, et al. Interplay Between Macular Retinal Changes and White Matter Integrity in Early Alzheimer's Disease. Journal of Alzheimer's Disease 2019; 70 (3): 723-732. http://dx.doi.org/10.3233/jad-190152

Guerreiro R, Escott-Price V, Hernandez DG, Kun-Rodrigues C, Ross AO, Orme T, et al. Heritability and genetic variance of dementia with Lewy bodies. Neurobiology of Disease 2019; 127: 492-501. http://dx.doi.org/10.1016/j.nbd.2019.04.004.

Nunes A, Silva G, Duque C, Januário C, Santana, I, Ambrósio AF, et al. Retinal texture biomarkers may help to discriminate between Alzheimer's, Parkinson's, and healthy controls PLOS ONE 2019; 14 (6): e0218826. http://dx.doi.org/10.1371/journal.pone.0218826.

Lleó A, Alcolea D, Martínez-Lage P, Scheltens P, Parnetti L, Poirier J, et al. Longitudinal cerebrospinal fluid biomarker trajectories along the Alzheimer's disease continuum in the BIOMARKAPD study. Alzheimer's & Dementia 2019; 15 (6): 742-753. http://dx.doi.org/10.1016/j.jalz.2019.01.015

Chincarini A, Peira E, Morbelli S, Pardini M, Bauckneht M, Arbizu J, et al. Semi-quantification and grading of amyloid PET:

A project of the European Alzheimer's Disease Consortium (EADC) NeuroImage 2019; Clinical 23: 101846. http://dx.doi.org/10.1016/j.nicl.2019.101846

Liehr T, Carreira IM, Balogh Z, Garrido ED, Verdorfer I, Coviello DA, et al. Regarding the rights and duties of Clinical Laboratory Geneticists in genetic healthcare systems; results of a survey in over 50 countries. Eur J Hum Genet. 2019 Aug;27(8):1168-1174. doi: 10.1038/s41431-019-0379-4.

New Targets and Therapeutics for Chronic Diseases

Collaborative publications
R. Boia, P.A.N. Dias, J.M. Martins, C. Galindo-Romero, I.D. Aires, M. Vidal-Sanz, M. Agudo-Barriuso, H.C. de Sousa, A.F. Ambrósio, M.E.M Braga and A.R. Santiago. Porous poly(ε-caprolactone) implants: a novel strategy for efficient intraocular drug delivery. J. Control. Release. 2019, 316:331-348. doi: 10.1016/j.jconrel.2019.09.023. PMID: 31715277.

Kumar Singh A, Cabral C, Kumar R, Ganguly R, Kumar Rana H, Gupta A, Rosaria Lauro M, Carbone C, Reis F, Pandey AK. Beneficial Effects of dietary polyphenols on gut microbiota and strategies to improve delivery efficiency. Nutrients. 2019; 11(9). pii: E2216. doi: 10.3390/nu11092216.

Gomes S, Bosco B, Loureiro JB, Ramos H, Raimundo L, Soares J, Nazareth N, Barcherini V, Domingues L, Oliveira C, Bisio A, Piazza S, Bauer MR, Brás JP, Almeida MI, Gomes C, Reis F, Fersht AR, Inga A, Santos MMM, Saraiva L. SLMP53-2 restores wild-type-like function to mutant p53 through Hsp70: promising activity in hepatocellular carcinoma. Cancers (Basel) 2019; 11(8). pii: E1151. doi: 10.3390/cancers11081151.

Reis F, Sá-Moura B, Guardado D, Couceiro P, Catarino L, Mota-Pinto A, Veríssimo MT, Teixeira A, Ferreira PL, Lima MP, Palavra F, Rama L, Santos L, van der Heijden R, Gonçalves C, Cunha A, Malva JO. Development of a healthy lifestyle assessment toolkit for the general public. Front Med (Lausanne). 2019; 6:134. doi: 10.3389/fmed.2019.00134.

Das A, Reis F, Mishra PK. mTOR signaling in cardiometabolic disease, cancer, and aging 2018. Oxid Med Cell Longev. 2019; 2019: 9692528. doi: 10.1155/2019/9692528.

Effect of Hypoproteic and High-Fat Diets on Hippocampal Blood-Brain Barrier Permeability and Oxidative Stress. de Aquino CC, Leitão RA, Oliveira Alves LA, Coelho-Santos V, Guerrant RL, Ribeiro CF, Malva JO, Silva AP, Oriá RB. Front Nutr. 2019 Jan 9;5:131. doi: 10.3389/fnut.2018.00131. eCollection 2018. PMID: 30687711

Alves CH, Wijnholds J. Microglial Cell Dysfunction in CRB1-Associated Retinopathies. Adv Exp Med Biol. 2019;1185:159-163. doi: 10.1007/978-3-030-27378-1_26. Review. PubMed PMID: 31884605.

Bousquet J, Pham-Thi N, Bedbrook A, Agache I, Annesi-Maesano I, Ansotegui I, ... Malva J.... and Zuberbier T (2019) Next-generation care pathways for allergic rhinitis and asthma multimorbidity: a model for multimorbid non-communicable diseases-Meeting Report (Part 2). J Thorac Dis 11(9):4072-4084. doi: 10.21037/jtd.2019.09.38.

Augusto-Oliveira M, Arrifano GP, Lopes-Araújo A, Santos-Sacramento L, Takeda PY, Anthony DC, Malva JO, Crespo-Lopez ME. (2019) What Do Microglia Really Do in Healthy Adult Brain? Cells 8(10). pii: E1293. doi: 10.3390/cells8101293.

Bousquet J, Pham-Thi N, Bedbrook A, Agache I, Annesi-Maesano I, Ansotegui I, ... Malva J.... and Zuberbier T (2019) Next-generation care pathways for allergic rhinitis and asthma multimorbidity: a model for multimorbid non-communicable diseases-Meeting Report (Part 1). J Thorac Dis 11(8):3633-3642. doi: 10.21037/jtd.2019.08.64

Bousquet JJ, Schünemann HJ, Togias A, Erhola M, Hellings PW, Zuberbier T, ...Malva J....and Mask Study Group (2019) Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. Clin Transl Allergy 9:44. doi: 10.1186/s13601-019-0279-2.

Bédard A, Basagaña X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, ... Malva J...., Bousquet J and Mask Study Group (2019) Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. J Allergy Clin Immunol 144(1):135-143.e6. doi: 10.1016/j.jaci.2019.01.053.

Bousquet J, Bedbrook A, Czarlewski W, Onorato GL, Arnavielhe S, Laune D, ...AND MASK Group (J Malva is member of the MASK Group) (2019) Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. Clin Transl Allergy 9:16. doi: 10.1186/s13601-019-0252-0. Erratum in: Clin Transl Allergy. 2019 Oct 9;9:52

Augusto-Oliveira M, Arrifano GPF, Malva JO, Crespo-Lopez ME. (2019) Adult Hippocampal Neurogenesis in Different Taxonomic Groups: Possible Functional Similarities and Striking Controversies. Cells 8(2). pii: E125. doi: 10.3390/cells8020125.

Menditto E, Costa E, Midão L, Bosnic-Anticevich S, Novellino E, Bialek S, ... Malva J...., Bousquet J and Mask Group (2019) Adherence to treatment in allergic rhinitis using mobile technology. The MASK Study. Clin Exp Allergy 49(4):442-460. doi: 10.1111/cea.13333.

Member of the editorial board
Raquel Santiago: Guest Editor of the Special Issue "Retinal Ganglion Cells" in International Journal of Molecular Sciences together with Dr. Marta Agudo-Barriuso (Experimental Ophthalmology Group, Instituto Murciano de Investigación Biosanitaria-Virgen de la Arrixaca & Universidad de Murcia, Murcia, Spain) and Dr. Eloisa Herrera (Instituto de Neurociencias CSIC-UMH, Alicante, Spain).

CAMPUS Training
CRISH 2 – Co-cReating Innovative Solutions for Health 2.0
EIT Health – CAMPUS Training for Executives and Professionals
Coordination: Joan Escarrabil - Hospital Clinic Barcelona and Barcelona Institute for Global Health (ISGlobal)

Graduate Training
José María Cabrera Maqueda
Doctoral Programme in Vision Sciences (University of Murcia, Spain)
January – April 2019

Rosalba Vitagliano
ERASMUS training - Student from the "Università degli Studi del Sannio di Benevento", Benevento, Italy
May – July 2019

Shelly Feygleman
Research Exchange Programme
Medical student - Faculty of Medicine of Rappaport, Israel

INTERNATIONALIZATION

METABOLISM, AGING AND DISEASE STRAND

Cell Signaling and Metabolism in Diseases

Neurodegenerative diseases, course PhD Program "Experimental Biology and Biomedicine" (PDBEB), CNC, Univ. Coimbra, Coimbra, Portugal, 08-12 april, 2019. Invited speakers: Michael Heneka (Univ. Hospital of Bonn, Bonn, Germany), Pascal Derkinderen (Univ. Nantes & Centre Hospitalier Universitaire de Nantes, France), Tiago F. Outeiro (Univ. Medical Center Goettingen, Germany)

"Impact of the action of natural products on human innate immune and tumor cells" project CAPES, (Health and Well-Being – Biological Sciences), cooperation Portugal-Brazil– Universidade Federal Paulista Júlio de Mesquita Filho (UNESP - Campus de Botucatu), UNESP AGREEMENT - NOTICE 02/2019, # 88887.194785/2018-00 (2019-2022).

Carmen García-Rodriguez from Institute of Biology and Molecular Genetic. CSIC-University of Valladolid, Spain. Collaborative research.

Maurício Sforcin, Departamento de Microbiologia e Imunologia, Instituto de Biociências, UNESP,18618-970, Botucatu, SP, Brasil. Collaborative Projects (Própolis: Modulação da apresentação antigénica e ativação diferencial de linfócitos T; Entidade Financiadora: FAPESP, Brasil, Referência: 2015/03493-3.

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

Other national publications (6000.)

Cardoso SM (2020) Avanços Na Investigação Sobre A Doença De Parkinson: Onde Estamos? Cidade Solidária.

Marinheira J, Silva S e Cruz MT. Células Estaminais Pluripotentes Induzidas no Tratamento da Doença de Alzheimer. Acta Farmacêutica Portuguesa 2019; 8(2): 3-30.

Mateus DM, Borges O, Cruz MT. Células T com Recetor de Antigénio Quimérico (CAR): Uma Nova Estratégia Imunoterapêutica. Rev Port Farmacoter, 2019;11:103-112.

Oliveira J, Madeira N, Cruz MT, Pereira CF (2019) Inflamação na doença bipolar: identificação de novos alvos terapêuticos. Rev Port Farmacoter. 11, 17-28.

Mitochondria Metabolism and Disease

Collaborations:

Albert Rizvanov, Kazan Federal University, Russia

Alessandro Valli, Centro Cardiologico Monzino, Italy

Anatoly Zhitkovich, Brown University, USA

Anika Hartz, Bjorn Bauer, University of Kentucky, USA

Bart Ghesquiere, VIB, Leuven, Belgium

Clemens Steegborn, University of Bayreuth, Germany

Daniel Dorta, University of São Paulo, Brazil

David Sinclair, Harvard Medical School, USA

Elmar Heinzle, Universität des Saarlandes, Germany

Erich Gnaiger, Oroboros, Austria

Faustino Mollinedo, CSIC, Spain

Ignacio Vega-Naredo, University of Oviedo, Spain

Jan Kopecky, Academy of Sciences, Czech Republic

Jeffrey Stuart, Brock University, Canada

Jiiri Neuzil, Griffith University, Australia

Joan Rosselo, CSIC, Spain

John Wise, University of Louisville, Louisville, USA

Laura Vergani, University of Genoa, Italy

Louise Torp Dalgaard, Department of Science, Systems and Models, Denmark

Maria Almeida, University of Arkansas, USA

Maria Felice Brizzi, Università degli Studi di Torino, Italy

Maria Portillo, University of the Basque Country, Spain

Mariusz Wieckowski, Nenski Institute, Poland

Mark Nijland, Laura Cox, University of Texas Health Science Center, USA

Nika Danial, Dana-Farber Cancer Institute, USA

Patricia Scott, Jon Holy, Kendall Wallace, University of Minnesota, USA

Peter Nathanielsz, University of Wyoming, USA

Piero Portincasa, University of Bari, Italy

Pinchas Cohen, University of Southern California, USA

Saber Hussain, Wright State University, USA

Werner Koopman, Radboud University Medical Centre, The Netherlands

Coordination of networks:
"FOIE GRAS", H2020-MSCA-ITN-2016, Ref. 722619, 2017-2020
"mtFOIE GRAS", MSCA-RISE-2016, Ref. 734719, 2017-2020

Metabolic Control

Araújo, P.M., Viegas, I., Rocha, A.D., Villegas, A., Jones, J.G., Mendonça, L., Ramos, J.A., Masero, J. And Alves, J.A. 2019. Understanding how birds rebuild fat stores during migration: insights from an experimental study. Sci. Reports. 9, Article number: 10065.
Collaborations with:
Elisabet Borsheim and Shannon Rose at the Arkansas Children Research Institute, US
Project Title: Assessment of oxidative capacity in obese children.

Louise Daalgard and Havard Jenssen at Roskilde University, Denmark
Project Title: Combination therapy synergistically accelerates diabetic wound closure

Mirela Delibegovic at the University of Aberdeen, UK
Projec Title: Effects of PTP1b modulation on Wound Healing

Jan Eriksson and Maria Joao Pereira at Uppsala University, Sweden
Projec Title: Antipsychotic drug induced metabolic dysfunction

Morten Bjerregaard-Andersen at the University of Southern Denmark, Denmark
Projec Title: COVID-19 and Type 1 Diabetes – a multicentre study

INTERNATIONALIZATION

STEM CELL-BASED AND MOLECULAR THERAPIES STRAND

Vectors and Gene Therapy Group

Projects under international Consortiums/ Networks:
- European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative; Joint Programme on Neurodegenerative Disease Research. European Consortium. 2016-2019.
- Advanced models of polyglutamine disorders (HD, SCA3, SCA7); Joint Programme on Neurodegenerative Disease Research. European Consortium. 2016-2019.
- Folate-Target Nanodevices To Activated Macrophages For Rheumatoid Arthritis (FOLSMART); NMP-06-2015 - Novel nanomatrices and nanocapsules. European Consortium, Jan2016-Dec2019.

- GoNanoBioMat with reference ProSafe/0001/2016 (abril 2017/march 2019).
- Towards a single therapy with a synergistic drug combination against triple negative breast cancer and neuroblastoma by nucleolin-mediated multicellular targeting. Funding agency: EURONANOMED II (ERANET), 2016-2020.

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

- Red Transfronteriza de Innovación en Diagnóstico Precoz de Leucemia para un envejecimiento saludable – IDIAL-NET (projecto colaborativo entre Portugal e Espanha financiado no âmbito do Interreg-POCTEP, 2019/2021).
Collaborative Publications:
- S.M.A. Pinto, M.J.F. Calvete, M.E. Ghica, S. Soler, I. Gallardo, A. Pallier, M.B. Laranjo, A.M. Cardoso, M.M.C.A. Castro, C.M.A. Brett, M.M. Pereira, É. Tóth, C.F.G.C. Geraldes.
- "A biocompatible redox MRI probe based on a Mn(ii)/Mn(iii) porphyrin" Dalton Transactions 48 (2019) 3249-3262. DOI: 10.1039/c8dt04775h.

Stem Cel Biotechnology

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).

Systems and Computational Biology

University of Otago (New Zealand):
Researchers: Christine Winterbourn, Alexander Peskin Projects:
Characterizing the operation of the Prx2/ Trx1/TrxR system in human erythrocytes. Characterizing the kinetics and molecular mechanisms of human 2-Cys peroxiredoxins. Understanding the redox responses of erythrocytes of G6PD-deficient children.
University of São Paulo (Brasil)
Researcher: Flávia Meotti
Project: Characterizing the kinetics and molecular mechanisms of human 2-Cys peroxiredoxins.
University Sains Islam Malaysia (Malaysia)
Researchers: Fook-Choe Cheah
Project: Understanding the redox responses of erythrocytes of G6PD-deficient children
University of Saarland (Germany):
Researchers: Elmar Heinzle
Project: Development and application of a method for profiling mitotic-cycle-dependent metabolism without having to synchronize cells
MouseAGE (COST Action BM1402)
Participation in Working Group 4: "Novel Technologies and Future Developments"

Molecular Mycobacteriology and Microbiome Group

Graduate Training

Mariana Hugo Silva. Tuberculosis research: Flow Cytometry and preparation of human monoclonal antibodies from B cells. Erasmus+ Program, Karolinska Institutet, Stockholm, Sweden. 04/2019 to 08/2019.

Evaluation of International Grant Proposals
Evaluation Committee "Immunology and Infection", The French National Research Agency (ANR), France (Nuno Empadinhas).

REWIRE (Reinforcing Women In Research) Programme, University of Vienna (https:// rewire.univie.ac.at/), Vienna, Austria (Nuno Empadinhas).

Editorial Board Member (Nuno Empadinhas)

Scientific Reports
Frontiers in Immunology (Guest Associate Editor in Nutritional Immunology)

Collaborations
Gunilla Kallenius and Christopher Sundling, Karolinska Institutet, Stockholm, Sweden.

Tom Blundell and Vitor Mendes, University of Cambridge, United Kingdom.

Reinaldo B. Oriá, Federal University of Ceará, Fortaleza, Brazil.

Medicinal Chemistry & Drug Discovery

S. Fulsundar, S. Domingues, K. M. Nielsen. Vesicle-mediated gene transfer in A. baumannii. Chapter 9. pp 87-94. In Acinetobacter baumannii: Methods and Protocols, Methods in Molecular Biology, vol. 1946. Indranil Biswas and Philip N. Rather (eds.). Nature Springer Science+Business Media, LLC, part of Springer Nature. https://doi.org/10.1007/978-1-4939-9118-1_9.

S. Domingues, N. Rosário, Â. Cândido, D. Neto, K. M. Nielsen, G. J. Da Silva. Competence for natural transformation is common among clinical strains of resistant Acinetobacter spp. Microorganisms. 7:30. doi:10.3390/microorganisms7020030.

Figueiredo R, Card RM, Nunez-Garcia J, Mendonça N, da Silva GJ, Anjum MF. (2019) Multidrug-Resistant Salmonella enterica Isolated from Food Animal and Foodstuff May Also Be Less Susceptible to Heavy Metals. Foodborne Pathog Dis. 16:166-172. doi: 10.1089/fpd.2017.2418

Training
PhD Thesis: Coxiella burnetii and Q Fever: an emergent zoonosis in Portugal?", Sofia Ferreira Anastácio.
Supervisor: Gabriela Jorge da Silva and Co-Supervisor: Dr. Karim Sidi-Boumedine , Co-Head of the National Reference Laboratory on Q Fever French Agency for Food, Environmental and Occupational Health Safety (ANSES), France)

Collaborative publication
Débora Botura Scariot, Hélito Volpato, Nilma Souza Fernandes, Edna Filipa Pais Soares, Tania Ueda-Nakamura, Benedito Prado Dias Filho, Zia Ud Din, Edson Rodrigues-Filho, Adley Forti Rubira, Olga Borges, Maria Do Céu Rodrigues Sousa, Celso Vataru Nakamu-ra. 2019. Activity And Cell-death Pathway On Leishmania infantum Induced By Sugiol: Vectorization Using Yeast Cell Wall Particles Obtained From Saccharomyces cerevisiae. Frontiers in Cellular and Infection Microbiology 9:208. doi: 10.3389/fcimb.2019.00208.
JCR® IF =3.52 /Q1

Claudia Carbone, Maria do Céu Teixeira, Maria do Céu Sousa, Carlos Martins-Gomes, Amelia M. Silva, Eliana Maria Barbosa Souto, and Teresa Musumeci1 2019. Clotrimazole-Loaded Mediterranean Essential Oils NLC: A Synergic Treatment of Candida Skin Infections. Pharmaceutics 11(5): 23.DOI: 10.3390/pharmaceutics11050231.
JCR® IF = 4.773 /Q1

Scariot DB, Volpato H, Fernandes NS, Lazarin-Bidóia D, Borges O, Sousa MDC, Rosa FA, Jacomini AP, Silva SO, Ueda-Nakamura T, Rubira AF, Nakamura C (2019). Oral treatment with T6-loaded yeast cell wall particles reduces the parasitemia in murine visceral leishmaniasis model. Scientific Reports 9:20080, https://doi.org/10.1038/s41598-019-56647-w.
JCR® IF = 4.122/Q1

Graduate Training Networks

Bolsa de Doutorado Sanduíche no Exterior – SWE, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), chamada específica Capes (N° 88881.190109/2018-01). Bolsa concedida à mestre Laiza Gabriela Gavioli Coelho da Universidade Federal de São Carlos, Brasil no período de Dezembro de 2018 a Outubro de 2019.

Bolsa de Doutoramento, Programa Bolsas de Estudo de Pós-graduação para Estudantes dos PALOP e Timor Leste (104/SBG/17). Bolsa concedida a mestre Amélia Amélia Nkutxi Vueba no período de 2017 a 2019.

Microbiology of Extreme Environments

Collaborative publications in Publications

Collaborative project led by Ramon Rosselló-Morá and some twenty other worldwide investigators to investigate high salt sites by metagenomic analysis and culture dependent isolation of hyperhalophilic organisms. Ongoing.

Collaboration with two Polish colleagues from the University of Lodj to isolate and to perform metagenomic analysis of hyperhalophiles in Polish salt Mines. Ongoing.

Metafluidics project: Advanced toolbox for rapid and cost-effective functional metagenomics screening: microbiology meets Microfuidics (METAFLUIDICS). HORIZON 2020 Comissão Europeia, BIOTEC-6-2015, project GA 685474. June 2016 (Milton S. da Costa, Group leader).

Molecular Biotechnology

Collaborative publications:
Curto P., Riley S.P., Simões I., Martinez J.J. (2019) Macrophages Infected by a Pathogen and a Non-pathogen Spotted Fever Group Rickettsia Reveal Differential Reprogramming Signatures Early in Infection. Front Cell Infect Microbiol. 9:97. doi: 10.3389/fcimb.2019.00097. eCollection 2019

Curto P., Santa C., Allen P., Manadas B., Simões I., Martinez J.J. (2019) A Pathogen and a Non-pathogen Spotted Fever Group Rickettsia Trigger Differential Proteome Signatures in Macrophages. Front Cell Infect Microbiol.9:43. doi: 10.3389/fcimb.2019.00043. eCollection 2019.

Soares A., Niedermaier S., Faro R., Loos A., Manadas B., Faro C., Huesgen P.H., Cheung A.Y., Simões I. (2019) An atypical aspartic protease modulates lateral root development in Arabidopsis thaliana. J. Exp Bot. Apr 12;70(7):2157-2171. doi: 10.1093/jxb/erz059.

Diraviyam, T., Ambi, S. V., Vieira-Pires, R. S., Xiaoying, Z., Sekaran, S., Krishnan, U. (2019). Chicken egg yolk antibody (IgY) as diagnostics and therapeutics in parasitic infections – A review. International Journal of Biological Macromolecules, 136, 755-763 doi: 10.1016/j.ijbiomac.2019.06.118.

Barcia C, Coelho AS, Barberis S, Veríssimo P. Acaciain peptidase: The first South American pollen peptidase potentially involved in respiratory allergy [published online ahead of print, 2019 Oct 19]. Biotechnol Appl Biochem. 2019;10.1002/bab.1837. doi:10.1002/bab.1837

Collaborative Research:
Dr. Alexander Wlodawer, Macromolecular Crystallography Laboratory, NCI-Frederick, USA,
Dr. Alice Y. Cheung, University of Massachusetts at Amherst, Amherst, USA.
Dr. Juan J. Martinez, Department of Pathobiological Sciences, LSU School of Veterinary Medicine, Baton Rouge, USA
Dr. Pitter Huesgen, Central Institute for Engineering, Electronics and Analytics (ZEA-3), ForschungszentrumJülich, Germany
Dr. Diraviyam Thirumalai, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

PARTICIPATION IN THE ORGANIZATION OF SCIENTIFIC MEETINGS

FEBRUARY 2019

Organizing of the meeting: "XIII Congress of the Portuguese Neuropediatrics Society", Coimbra
Date: February 7-8, 2019
CNC.IBILI members involved in the organization: Catarina R. Oliveira

MARCH 2019

Organizing of the meeting: "Sessão de Encerramento (Oficial) da Semana Internacional do Cérebro 2019 -Quando o Cérebro fica Dependente", FNAC – Fórum Coimbra, Portugal
Date: March 17, 2019
CNC.IBILI members involved in the organization: Ana Cristina Rego

MAY 2019

Organizing of the Meeting: "Symposium at the 53rd Annual Scientific Meeting of the European Society for Clinical Investigation, Coimbra, Portugal,
Date: May 2019
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the Meeting: "EASD-NAFLD Study group Annual Meeting", Lisbon
Date: May 8-9 2019
CNC.IBILI members involved in the organization: John Jones

Organizing of the meeting: "EASD-EGIR Study group Annual Meeting, Lisbon
Date: May 9-10 2019
CNC.IBILI members involved in the organization: John Jones

Organizing of the Meeting: "53rd Annual Meeting of the European Society for Clinical Investigation," Coimbra, Portugal
Date: May 22-24, 2019
CNC.IBILI members involved in the organization: Paulo Oliveira, Catarina R. Oliveira

Organizing of the meeting: "IV Symposium of the Portuguese Glial Network - Glia Diversity in Neuromodulation and Neurodegeneration", Lisbon
Date: May 29, 2019
CNC.IBILI members involved in the organization: Francisco Ambrósio

JUNE 2019

Co-organizer of the Symposium:, Prieto LXX XXL Lx Fest - a one-day symposium on the occasion of the academic jubilee of Manuel J. E. Prieto", Lisbon, Portugal
Date: June 2019
CNC.IBILI members involved in the organization: Luis Loura

Organizing of the Meeting: "Conference on Ageing: Models, Mechanisms and Therapies", Faculty of Medicine, University of Coimbra, Polo III,
Date: June 28- 29, 2019
CNC.IBILI members involved in the organization: Lino Ferreira, Cristina Rego, Claudia Cavadas

JULY 2019

Organizing of the Meeting: "MiP/MitoEAGLE Training School 2019. Mitochondrial respiratory physiology: Challenges on data sharing, reproducibility, and interpretation,. Coimbra, Portugal
Date: July 08-12, 2019
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the meeting: "XIV European Meeting on Glial Cells in Health and Disease - Contribution of glial extracellular vesicles to neurodegenerative diseases", Porto,
Date: July 10-13, 2019
CNC.IBILI members involved in the organization: Francisco Ambrósio

SEPTEMBER 2019

Organizing of the meeting: "Synuclein Meeting 2019:"Where we are and where we need to go", Axis Hotel Ofir, Porto, Portugal
Date: September 1-4, 2019
CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing of the Meeting: "2nd FEBS Advanced Lecture Course on Oncometabolism," Luso, Portugal.
Date: September 1-6, 2019
CNC.IBILI members involved in the organization: Paulo Oliveira

3 internatuinal scientific meetins organization

22 national scientific meetins organization

Organizing of the meeting: "2019 Summer School on Computational Biology, Coimbra (Portugal)"
Date: September 2-12, 2019
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the meeting: "4th course of Basics in Human Genetic Diagnostics – A Course for CLGs in education (in collaboration with the ESHG European Medical Board), Figueira da Foz,
Date: September 9 - 13, 2019
CNC.IBILI members involved in the organization: Aging And Brain Diseases: Advanced Diagnosis and Biomarkers group members

Organizing of the meeting: "8th European Calcium Society (ECS) Workshop "Calcium Signaling in Aging and Neurodegenerative Diseases", Hotel Tryp, Coimbra, Portugal
Data: September 18-20, 2019
CNC.IBILI members involved in the organization: Ana Cristina Rego, Claudia Pereira

OCTOBER 2019

Organizing of the conference: "16th International Conference in Molecular Systems Biology, Manila, Philippines"
Date: October 2019
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the meeting: "CRISH Course – Co-creation of innovative solutions for health", Coimbra
Date: October 3-4, 2019
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the meeting: "33th Meeting of the "Grupo de Estudos de Envelhecimento Cerebral e Demência"", Curia,
Date: 11-12 October 2019
CNC.IBILI members involved in the organization: Catarina R. Oliveira

Organizing of the conference: "WBC 2019 – Workshop on Biological Chemistry, Lipids & Proteins – Interactions for Life". Casa Aido Santo, Nespereira, Portugal.
Date: 11-13 October 2019,
CNC.IBILI members involved in the organization: Mª João Moreno

Organizing of the Meeting: "European Vision Research Association Meeting 2019", Nice, France
Date: October 17-19, 2019
CNC.IBILI members involved in the organization: Miguel Castelo-Branco

NOVEMBER 2019

Organizing of the Meeting: "23th Annual Meeting of "Sociedade Portuguesa de Genética Humana (SPGH)", Coimbra
Date: November 14-16 2019
CNC.IBILI members involved in the organization: Aging And Brain Diseases: Advanced Diagnosis and Biomarkers group members

DECEMBER 2019

Organizing of the meeting: "Encontro de Jovens Investigadores em Biologia Estrutural e Computacional (EJIBCE), Lisbon, Portugal"
Date: December, 2019
CNC.IBILI members involved in the organization: Irina Moreira

Organizing of the Meeting: "Congress of Microbiology and Biotechnology (MicroBiotec 2019)", Coimbra, University of Coimbra, Portugal
Date: 5-7 December,2019
CNC.IBILI members involved in the organization: Gabriela Silva, Teresa Gonçalves

Organizing of the meeting: "CIBB Meeting 2019", Coimbra
Date: December 19-20, 2019
CNC.IBILI members involved in the organization: Francisco Ambrósio

GRADUATE STUDIES PROGRAMME

During 2019 CNC.IBILI organized 12 Advanced Courses (inserted at the Doctoral Programme in Experimental Biology and Biomedicine - PDBEB at CNC) and hosted XX seminars. Local graduate students and researchers attended the seminars, whereas the advanced courses also met the interest of people from other Portuguese Universities. Besides the organization of courses and seminars, CNC.IBILI also supported ongoing research work for Ph.D. and M.Sc. theses. Throughout this year 14 Ph.D. and 86 M.Sc. theses were concluded.

Advanced Courses 2019

Core Technologies @ CNC
January 21 - February 1, 2019
Coordinator: Luisa Cortes

Connecting the Researchers with the society
February 18 - 22, 2019
Coordinator: Sara Amaral

Computational biology
February 25 - March 1, 2019
Coordinators: Irina S. Moreira & Alexandra P. Carvalho & Armindo Salvador

Oncometabolism: Principles and Applications
March 11 - 15, 2019
Coordinator: Paulo Oliveira & João Ramalho

Fighting infection
March 18 - 22, 2019
Coordinator: Nuno Empadinhas & Isaura Simões

Neuronal circuits & behavior
April 1 - 5, 2019
Coordinator: João Peça

Neurodegenerative disorders
April 8 - 12, 2019
Coordinators: Paula I Moreira, Cláudia Pereira, Armanda Santos, Teresa Cruz, Sandra M Cardoso

Advanced Therapies
April 22 - 26, 2019
Coordinator: Luís Almeida & Lino Ferreira

Synapse structure and function
April 29 - May 3, 2019
Coordinator: Ana Luisa Carvalho & Carlos Duarte

Proteomics Approaches in Life Sciences
May 6 - 10, 2019
Coordinator: Bruno Manadas, Isaura Simões & Sandra Anjo

Drug development
May 13 - 24, 2019
Coordinator: João Nuno Moreira & Luís Almeida

Animal experimentation
May 28 - 30, 2019
Coordinator: Paula Mota

CNC.IBILI SEMINARS

January

9.1.2019 | The mechanism of wound healing through the fibroblast switching between two states
Rui Dilão (Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal)
Host: Hugo Fernandes

10.1.2019 | Arc/Arg3.1 as a major coordinator of cognition
Sonia A. L. Correa (School of Pharmacy and Medical Sciences, Faculty of Life Sciences, University of Bradford, UK)
Host: Luis P Almeida

10.1.2019 | Funding Opportunities EIT Health
Jorge Figueira (DITS), Marta Passadouro (DITS), Jorge Pimenta (IPN)
Host: Sara Amaral

11.1.2019 | Action at a distance on object–related ventral temporal representations
Jorge Almeida (Center for Research in Neuropsychology and Cognitive and behavioral intervention (CINEICC), University of Coimbra)
Host: Claudia Cavadas

23.1.2019 | Mechanisms of nuclear positioning during cell migration and muscle development
Edgar Gomes (Institute of Molecular Medicine, University of Lisbon)
Host: Mário Grãos

30.1.2019 | Amyotrophic Lateral Sclerosis in the Lab and in the Society
Filomena Silva (CNC, University of Coimbra), Pedro Souto (President APELA), Maria Eulália Ribeiro (Vice-President APELA)
Host: Sara Amaral

February

1.2.2019 | Microbial signatures in diabetic skin: opportunities for therapeutic intervention
Ana Maranha (CNC, University of Coimbra)
Host: Sónia Pereira

6.2.2019 | Rational Protein Engineering
Alexandra Carvalho (CNC, UC-Biotech)
Host: Lino Ferreira

15.2.2019 | Deregulation of BDNF signalling in Alzheimer´s Disease: new opportunities for treatment
Maria José Diógenes (IMM, University of Lisbon)
Host: Ana Cristina Rego

19.2.2019 | Journalists and scientists: how to communicate?
Teresa Firmino (Jornal Público)
Host: Sara Amaral

CNC.IBILI SEMINARS

20.2.2019 | Blockchain. What is it? Good for?
Paulo Rupino (CISUC, Department of Informatics Engineering, University of Coimbra)
Host: Ricardo Pires

22.2.2019 | Fine Timescale Coordination of Thalamic Activity with mPFC and CA1 non-REM Oscilations
Carmen Varela (Psychology Department Florida Atlantic University)
Host: Ana Luisa Carvalho

22.2.2019 | Science Communication in Portugal - how far are we?
Joana Lobo Antunes (ITQB-UNL and Rede SciComPT)
Host: Sara Amaral

March

6.3.2019 | Computational Design of Functional Proteins for Biomedicine
Bruno Correia (EPFL - École Polytechnique Fédérale de Lausanne)
Host: Ricardo Vieira-Pires/Pedro Castanheira

15.3.2019 | The ATPase Inhibitory Factor 1: A double-edge sword?
Jose M. Cuezva (Universidad Autónoma de Madrid, Spain)
Host: Paulo Oliveira

20.3.2019 | The CRISPR revolution
Chase Beisel (Helmholtz Center for Infection Research, University of Würzburg, Germany)
Host: Isaura Simões

22.3.2019 | Cybersecurity risks and threats in the health sector
Paulo Empadinhas (ENISA - EU Cyber Security Agency, Greece)
Host: Nuno Empadinhas

27.3.2019 | Quantum GX2 MicroCT System for in vivo Imaging - from bone to heart
Sasha (Alexandre) Belenkov (Applications Scientist, PerkinElmer, Inc.)
Host: Vilma Sardão

29.3.2019 | Regulation of neuronal connectivity and synaptic plasticity by endo- and fitocannabinoids
Ana M. Sebastião (IMM and Faculty of Medicine, University of Lisbon)
Host: Carlos Duarte

April

1.4.2019 | Imaging the brain and cerebrospinal fluid at the nanoscale
Juan Varela (School of Biology,, University of St. Andrews, UK)
Host: Mariana Bexiga

3.4.2019 | Using biomarkers to define disease risk in pre-clinical Alzheimer's disease
Lefkos Middleton (Imperial College London, UK)
Host: João Malva & Ana Cristina Rego

3.4.2019 | A medicinal chemistry approach for the development of novel anti-tumor agentes by targeting p53-MDM2/X interactions
Maria M.M. Santos (Med.ULisboa, University of Lisbon)
Host: Irina Moreira

5.4.2019 | Store-operated calcium entry in stroke models
Agnese Secondo (Università degli Studi di Napoli Federico II, Napoli, Italy)
Host: Ana Cristina Rego & João Malva

5.4.2019 | Microglia-mediated synapse loss in the pathogenesis of neurodegeneration
Rosa Paolicelli (University of Lausanne, Switzerland)
Host: João Peça

10.4.2019 | Neuroinflammation in Alzheimer´s disease
Michael Heneka (University Hospital Bonn, Germany)
Host: Organizers on the BEB advanced course "Neurodegenerative Disorders

12.4.2019 | Targeting Proteases for the Treatment of Distinct Neuropathologies: Inhibiting a Protease (Calpain) vs. Enhancing a Protease (Cathepsins)
Ben Bahr (William C. Friday Laboratory, University of North Carolina – Pembroke, USA)
Host: Carlos Duarte

12.4.2019 | Is PD a Low-grade Inflammatory Bowel Disease?
Pascal Derkinderen (Nantes University, France)
Host: Organizers on the BEB advanced course "Neurodegenerative Disorders

17.4.2019 | The peculiarities of prostate cancer metabolism
Silvia Socorro (CICS-UBI-Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior)
Host: Vilma Sardão

CNC.IBILI SEMINARS

May

3.5.2019 | The role of the hippocampal CA2 area in social memory (dys)function
Torcato Meira (Life and Health Sciences Research Institute (ICVS), University of Minho, Portugal and Department of Neuroscience, Zuckerman and Kavli Institutes, Columbia University, USA.)
Host: Ângela Inácio

8.5.2019 | Deciphering signal transduction using PTMScan: An affinity proteomics method for quantitative profiling of post-translational modifications
Sriram Aravamudhan (Cell Signaling Technology, Inc)
Host: Bruno Manadas

9.5.2019 | Evolution and functional relevance of protein phosphorylation
Pedro Beltrão (European Bioinformatics Institute (EMBL-EBI))
Host: Bruno Manadas

10.5.2019 | Protease networks in skin inflammation and repair
Ulrich auf dem Keller (Technical University of Denmark (DTU))
Host: Isaura Simões

16.5.2019 | Early Life Exposure to Cadmium, Diet-Induced Liver Disease and the Role of Zinc
Jamie Young (Department of Pharmacology and Toxicology, School of Medicine,University of Louisville, USA)
Host: Carmen Alpoim

17.5.2019 | Design and optimization of potent, CNS-penetrant transthyretin stabilizers with a little help from Machine Learning
Carlos Simões (Chief Technology Officer, BSIM Therapeutics)
Host: João Nuno Moreira

22.5.2019 | CRB1-inherited retinal dystrophies Milestones towards a gene therapy treatment for Retinitis Pigmentosa
Henrique Alves (iCBR)
Host: Hugo Fernandes

24.5.2019 | Olfaction and social behavior in a Mecp2-null mouse model of Rett syndrome
Mónica Santos (CNC-Center for Neuroscience and Cell Biology)
Host: Carlos Duarte

June

5.6.2019 | Coffee, Caffeine and Health
Rodrigo Cunha (CNC-Center for Neuroscience and Cell Biology)
Host: Lino Ferreira

7.6.2019 | Evolving Brains, Health and Lifestyle
Nuno Lourenço (CISUC, Department of Informatics Engineering, University of Coimbra)
Host: Teresa Oliveira & Paulo Oliveira

14.6.2019 | Phenotypic Plasticity: a non-genetic way of tumor cells to evade therapy
Célia Gomes (iCBR - Coimbra Institute for Clinical and Biomedical Research, Faculty of Medicine of University of Coimbra)
Host: Francisco Ambrósio

19.6.2019 | Metabotropic receptors as a common dysfunction in neurodevelopmental disorders
João Peça (CNC-Center for Neuroscience and Cell Biology)
Host: Lino Ferreira

21.6.2019 | Neuronal KCNQ channelopathies: a paradigm for rare developmental disorders highlighting therapeutic targets for more common diseases
Maurizio Taglialatela (Department of Neuroscience, University of Naples Federico II, Naples, ITALY)
Host: Ana Luísa Carvalho

July

3.7.2019 | Modeling and optimizing metabolism: applications in metabolic engineering and human health
Miguel Rocha (University Minho)
Host: Irina Moreira

5.7.2019 | Multidrug resistant tumours: searching for novel biomarkers, molecular targets and therapeutic tools
M. Helena Vasconcelos (i3S/IPATIMUP, FFUP)
Host: Amália Jurado

12.7.2019 | ATP-derived adenosine controls synaptic and memory dysfunction in β-amyloid models of Alzheimer's disease
João Pedro Lopes (CNC-Center for Neuroscience and Cell Biology)
Host: Ricardo Rodrigues

CNC.IBILI SEMINARS

16.7.2019 | The lysosomal iron throne takes control of mitochondria
Nuno Raimundo (Independent Group Leader Universitätsmedizin Göttingen Institute of Cellular Biochemistry)
Host: Paulo Oliveira

16.7.2019 | Regulation of vesicle acidification at the neuronal synapse
Ira Milosevic (Ph.D. - Principal Investigator European Neuroscience Institute (ENI) University Medical Center Göttingen (UMG))
Host: Ana Cristina Carvalho

17.7.2019 | Glycosylation in cancer biology and cellular communication: molecular mechanisms and clinical implications
Celso Reis (I3S - Instituto de Investigação e Inovação em Saúde IPATIMUP - Institute of Molecular Pathology and Immunology)
Host: Hugo Fernandes

19.7.2019 | Política de Inovação na Universidade de Coimbra
Luís Simões da Silva (Vice-Reitor para a Inovação e Empreendorismo Departamento de Engenharia Civil da Universidade de Coimbra Diretor do ISISE – Institute for Sustainability and Innovation in Structural Engineering)
Host: Lino Ferreira

22.7.2019 | Your Fast and Flexible Slide Scanner
Soren Prag (PhD, Application Specialist, Carl Zeiss Microscopy, GmbH)
Host: Luísa Cortes

24.7.2019 | Development of phage-based medicines-the Portuguese reality
Clara Leandro (TechnoPhage, SA)
Host: Isaura Simões

26.7.2019 | An RNA modification on the polyA tail promotes mRNA stability
Luísa Miranda Figueiredo (Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa)
Host: Paulo Oliveira

September

11.9.2019 | FluidFM: nanotechnology for single cell experiments
Maria Milla & Paul Monnier (Life Science Application Specialist)
Host: Paulo Oliveira

12.9.2019 | O (en)canto de investigar
Ricardo Neves (CNC)
Host: Sara Amaral

13.9.2019 | The Comics of Science
André Caetano (Illustrator)
Host: Sara Amaral

18.9.2019 | Modeling and optimizing metabolism: applications in metabolica engineering and human health
Miguel Rocha (University of Minho)
Host: Irina Moreira

24.9.2019 | Principles of Quantitative Westerns in 15 mins
Jan Wolfram (Azure Byosystems, CA, USA)
Host: Vilma Sardão

25.9.2019 | Mechanical and functional plasticity of cells
Inês Pinto (INL - International Iberian Nanotechnology Laboratory)
Host: Armindo Salvador

27.9.2019 | Investigação em Síndrome de Angelman - Apresentação da ANGEL e da ASA
Manuel Costa Duarte & Catarina Costa Duarte (ANGEL President & Vice President)
Host: João Ramalho Santos

27.9.2019 | On stress, vulnerability to psychopathology and neuroscience communities
Carmen Sandi (BMI-EPFL Switzerland & Fens - Federation of European Neuroscience Societies)
Host: Ana Luísa Carvalho

October

2.10.2019 | Measuring forces at the nanoscale for cardiovascular risk evaluation
Nuno Santos (Faculty of Medicine of Lisbon University & IMM-Lisbon)
Host: Akhilesh Rai

CNC.IBILI SEMINARS

4.10.2019 | Receptor dynamics and nano-organization: new facets of NMDAR functions
Joana Ferreira (IINS, University of Bordeaux)
Host: Ana Luísa Carvalho

11.10.2019 | Basic research fueling clinical studies for new therapeutic approaches for age-related macular degeneration
Sandra Tenreiro (CEDOC, Nova Lisbon University)
Host: Francisco Ambrósio

16.10.2019 | Acetyl-CoA: a signaling metabolite at the intersection of metabolism, epigenetic and cell plasticity
Alessandro Carrer (Veneto Institute of Molecular Medicine (VIMM), Padova, Italy)
Host: Miguel Mano

25.10.2019 | Os cientistas e os outros
Ana Sanchez (ITQB, Nova Lisbon University)
Host: João Ramalho-Santos

28.10.2019 |Fifty years of neuroscience research: where are we standing right now?
Wil Smeets (VU University Medical Center, Faculty of Medicine, Amsterdam, Netherlands)
Host: Carlos Duarte

30.10.2019 | Deep learning potential to fill the gene-disease gap
Joel Arrais (Informatic Engineering Department, University of Coimbra)
Host: Isaura Simões

November

6.11.2019 | Sensitive and automated assessment of DNA strand break by AUREA gTOXXs
Paula Braun & Frank Gehring (3T Analytic, Tuttlingen, Germany)
Host: Paulo Oliveira

8.11.2019 | Synaptogenesis stimulates a proteasome-mediated ribosome reduction in axons
Rui Costa (CNC)
Host: Ramiro Almeida

15.11.2019 | Microglia: responders or inducers of neurodegenerative disorders
Adelaide Fernandes (iMED.ULisbon & Faculty of Pharmacy, University of Lisbon)
Host: Ana Luísa Cardoso

22.11.2019 | Fatty liver: The experience of an internal medicine service
Armando Carvalho & Jorge Leitão (Faculty of Medicine, UC & Coimbra University Hospital Center)
Host: Paulo Oliveira

27.11.2019 | Improvement of aging hallmarks by mitotic competence rewire
Elsa Logarinho (IBMC-i3S, University of Porto)
Host: Lino Ferreira

29.11.2019 | Mitochondrial dynamics in synapse development
Cátia Silva (Netherlands Institute for Neuroscience)
Host: Ricardo Rodrigues

December

6.12.2019 | Vascular niche remodeling in acute myeloid leukemia
Delfim Duarte (i3S, IPO Porto & Faculty of Medicine, University of Porto)
Host: Lino Ferreira

13.12.2019 | Science and Theatre
Mário Montenegro (Marionet & CEIS20, FLUC)
Host: Sara Amaral

18.12.2019 | Integrative modelling of bimolecular complexes
Alexandre Bonvin (Faculty of Science, Utrecht University)
Host: Irina Moreira

PHD THESIS CONCLUDED IN 2019

Ana Rita de Carvalho Acúrcio
Discovery and development of novel small-molecule imune system modulators
December 17, 2019
Co-Supervisor: Jorge António Ribeiro Salvador

Ana Oliveira
The role of HOXA9 as a modulator of the tumor microenvironment in glioblastoma
2019
Supervisor:

Catarina Araujo Gomes Rebelo
Nanomedicine to modulate brain activity
2019
Supervisor: Lino Ferreira

Celso Alves
Sphaerococcus coronopifolius bromoterpenes: Antitumor activity and intracellular signal pathways characterization on in vitro human cellular cancer models
November 8, 2019
Supervisor: Carmen Alpoim

Dina Pereira
The role of ageing in polyglutamine-induced neurodegeneration. A study in Machado-Joseph disease models
2019
Supervisor: Luis Almeida

João Filipe Alves Amorim
Understanding the underlying mechanisms regulating aging and longevity
December 11, 2019
Supervisor: Carlos Palmeira

Lara Franco
Long-term impact of early life stress on adult social behavior and prefrontal cortical circuits
2019
Supervisor: João Peça

Luciana Ferreira
Pathophysiology of Persistent Doxorubicin Cardiotoxicity: a Mitochondrial-epigenetics Link
June 26, 2019
Supervisor: Paulo Oliveira

Mafalda Santos Costa
Mycobacterial methylmannose polysaccharides' biosynthesis
July 22, 2019
Supervisor: Nuno Empadinhas

Michelle Vang
Peptides and their effects on wound healing
2019
Co-Supervisor: Eugenia Carvalho

Romina Paula de Aguiar Guedes
Targeting the proteasome in anticancer therapy by a computational based drug discovery approach
December 16, 2019
Co-Supervisor: Jorge António Ribeiro Salvador

Samuel Filipe Duarte Chiquita
The changing brain in Alzheimer's disease: is the retina a mirror of disease onset and progression?
September 27th, 2019
Supervisor: Francisco Ambrósio, Miguel Castelo- Branco

Sofia Alexandra Ramos Ferreira
The role of P2 receptors in the migration of medial ganglionic eminence-derived interneurons
January 29, 2019
Supervisor: Ricardo Rodrigues

Sofia Ferreira Anastácio
Coxiella burnetii and Q Fever: an emergent zoonosis in Portugal?
2019
Supervisor: Gabriela Jorge da Silva

MSC THESIS CONCLUDED IN 2019

14 PhD Thesis concluded

86 MSc Thesis concluded

Alexander Michael Ribeiro Santos
Transtirretina e Apneia Obstrutiva do Sono
2019
Supervisors: Cláudia Cavadas, Ana Rita Álvaro

Ana Carolina Silva Caetano
Identification of blood brain barrier modulators
2019
Supervisor: Lino Ferreira

Ana Carolina Silva
Allele-specific silencing of Machado-Joseph Disease
September 2019
Supervisor: Ana Luisa Carvalho, Rui Nobre

Ana Catarina da Silva Franco
Neuroendocrine peptides as therapeutic strategy to delay skin aging
2019
Supervisors: Cláudia Cavadas, Célia Aveleira

Ana Lousã Rodrigues Mendes Santos
Utilização do MLPA na identificação do perfil genético do carcinoma da cavidade oral, no follow up e na conduta médica
2019
Supervisor: Joana Barbosa Melo

Ana Luisa Bernardo
Impact of traumatic brain injury on Astrocytes: role of neuropeptide Y
September 2019
Supervisor: Francisco Ambrosio

Ana Rita Moura Fernandes
Resetting the clock on metabolic dysfunction: a new role for ataxin-2
2019
Supervisors: Cláudia Cavadas, Sara Carmo Silva

Ana Sofia Ferreira
Gender-specificities of exercise effects in a model of chronic anxiety: focus on the peripheral metabolism and glucose homeostasis
September 13, 2019
Supervisor: Francisco Ambrosio

Ana Teresa Capitão Moreira de Sá
Targeting adenosine A2A receptors to manage Angelman syndrome symptoms
July 15, 2019
Supervisor: Paula Canas, Ângelo Tomé

André Filipe Conceição
CRISPR/Cas9 as a tool for gene therapy in Machado-Joseph disease: silencing ATXN3 and CAG expansion correction
September 2019
Supervisor: Ana Luisa Carvalho, Carlos Matos

André Santos Paula
Usher syndrome: dysfunctional olfactory brain regions and statistical classification of disease status using fMRI
June 2019
Supervisor: Miguel Castelo- Branco

Andrea Cristina Rodrigues dos Santos
Pesquisa dos protozoários Giardia e Cryptosporidium em moluscos bivalves através de técnicas moleculares
2019
Supervisor: Maria do Céu Rodrigues de Sousa

Andreia Marques
Alpha-synuclein in Extracellular Vesicles - the spreading mechanism behind Parkinson's disease?
October 2019
Supervisor: Luis Almeida, Rita Perfeito

Anianna Piscosquito
rhBMP-7 effects on wound healing in diabetic mice - a pilot study
2019
Supervisor: Eugenia Carvalho, Carlos Duarte

Bárbara Vicente dos Santos
Biomarkers of aging in Obstructive Sleep Apnea
2019
Supervisors: Cláudia Cavadas, Ana Rita Álvaro

Beatriz Lapa
Metabolism as a therapeutic target in acute myeloid leukemia – glycolysis or oxidative phosphorylation
2019
Supervisor: Ana Cristina Gonçalves

Caren Jane Rodrigues
The role of neuropeptide Y in articular chondrocyte functions
2019
Supervisor: Alexandrina Mendes, Claudia Pereira

MSC THESIS CONCLUDED IN 2019

Carolina Freitas
Impacto socioeconómico nos cuidadores informais de doentes de Alzheimer
February 2019
Co-supervisor: Isabel Santana

Caroline Veloso
Role of Mitochondria-Targeted Novel Antioxidants based in Dietary Polyphenols
October 11, 2019
Supervisor: Paulo Oliveira

Catarina Coval
Pesquisa de Fatores de Patogenicidade de Escherichia coli Isoladas de Géneros Alimentícios e de Ambientes de Produção Alimentar
2019
Supervisor: Jorge Salvador

Catarina Milheiro Soares da Silva
Elucidating GATA2 Transcription Factor Role during DNA Replication and Epigenetic Inheritance.
2019
Supervisores: Filipe Pereira, Paula Veríssimo

Cinzia Miarelli
Alterations of Neural K+-Cl- Cotransporter KCC2 During Status Epilepticus: Possible Impact on GABAergic Neurotransmission
September 2019
Supervision: Miranda Mele
Co-supervision: Carlos B. Duarte

Clarissa Becher
High-Throughput screening for extracellular vesicle content modulation for cardiovascular application
2019
Supervisor: Hugo Fernandes

Cristiana Bento
Esterilização supercrítica de aerogéis de polímeros naturais para aplicações biomédicas
2019
Co-Supervisor: Nuno Empadinhas

Daniel Agostinho
Diagnóstico diferencial de doenças neurodegenerativas com base em dados multimodais de imagem (PET e Ressonância Magnética)
September 2019
Supervisor: Miguel Castelo- Branco

Daniela Catarina Gaspar Santos
Histological and morphological analysis of developing neuronal precursors derived from human iPS cells
Supervisor: Claudia Pereira

Daniela Filipa Correia de Almeida
Deteção dos protozoários Giardia lamblia e Cryptosporidium sp. em saladas embaladas prontas a consumir
July 2019
Supervisor: Maria do Céu Rodrigues de Sousa

Débora Tatiana de Sousa Mena
Effect of dual therapy with liraglutide and ghrelin on brain metabolism and intracellular stress in the Huntington's disease R6/2 mouse model
Supervisor: Ana Duarte, António Moreno

Diana Andrade
Effects of DNMT1, DNMT3 and DNMT3b gene expression on chronic lymphocytic leukemia
Supervisor: Ana Bela Sarmento Ribeiro

Diogo Rafael Mendes Pessoa
Classificação automática de vocalizações ultrassônicas de roedores: estudo do neurodesenvolvimento
November 2019
Supervisor: Miguel Castelo- Branco

Duarte Silva
Aldehyde dehydrogenase polymorphisms: its role in myelodysplastic syndromes and acute myeloid leukemia
2019.
Supervisor: Ana Cristina Gonçalves

Filipa Alexandra Silva
Skin sensitizers: moving forward new approaches for toxicity prevision and sensitization management
Supervisor: Mª Teresa Cruz Rosete

Flávia Rodrigues
Combined therapeutic strategies for hepatocellular carcinoma mediated by nanosystems
September 2019
Supervisor: Henrique Faneca, Paula Verissimo

Gabriela Oliveira
Role of the Adenine Nucleotide Translocator 2 in P19 Embryonal Carcinoma Stem Cells Mitochondrial Profile
September 18, 2019
Supervisor: António Moreno

Hugo Rafael Santos Ferreira
Characterization of the emotional fingerprint of METH intoxicated animals
2019
Supervisor: Francisco Ambrosio

Inês João Dinis Ferreira
Investigating Appetite Regulation System in an Animal Model of Progeria
2019
Supervisors: Cláudia Cavadas, Célia Aveleira

Inês Morais
Urine extracellular vesicles: a promising tool for Regenerative Medicine?
2019
Supervisor: Hugo Fernandes

Ivo Manuel Ferreira Machado
Modulation of complex I and oxidative capacity in cells under metabolic stress: the crosstalk between miR-378 and metformin
July 23, 2019
Supervisor: Anabela Pinto Rolo

Jessica De Pascale
Mitochondria-associated membranes: a platform for transferring endoplasmic reticulum stress signals to mitochondria in innate immune cells. does lithium promote an adaptive cellular response and survival?
Supervisor:

Jéssica Gonçalves Da Silva
Avaliação das propriedades imunotoxicológicas de nanopartículas de PLA
2019
Supervisor: Olga Borges, Sandra Jesus

Joana Cláudia Ferreira da Silva
Assessing the safety profile of biodegradable poly(□-caprolactone) implants – effect on microglia-mediated neuroinflammation
March 7, 2019
Supervisor: Francisco Ambrósio

Joana Sampaio
Reorganização do cérebro e plasticidade neurosensorial
July 2019
Supervisor: Miguel Castelo- Branco

João Braz
Establishment and Characterization of Human Pluripotent Stem Cells derived Brain Organoids
October 2019
Supervisor: Luis Almeida, Liliana Mendonça

João Lima
The effect of gambogic acid and silibinin in Acute Myeloblastic Leukemia
2019
Supervisor: Ana Bela Sarmento Ribeiro

João Pedro Ferreira da Costa Novo
Effect of methylphenidate on microglia: tracking direct and brain endothelial cells-mediated changes
September 9, 2019
Supervisor: Francisco Ambrosio

João Pedro Estiveira Campos Silva
Controller Implementation For A SSVEP-Based BCI With Resource To Non-Volitional Neurofeedback
September 2019
Supervisor: Miguel Castelo- Branco

João Vieira
Utilization of a Silica Nanoparticle for transport and delivery of a recombinant protein for cancer treatment
September 2019
Supervisor: Henrique Faneca, Paula Verissimo

Laura Carvalho
Impact of nucleolin downregulation on cellular features of triple negative breast cancer cells
2019
Supervisor: João Nuno Moreira

Luís Filipe Henriques Oliveira
Understanding the Genetic Program of Conventional Dendritic Cells Type 2 (cDC2) with Direct Cell Reprogramming
2019
Supervisores: Filipe Pereira, Ana Luísa Carvalho

Luis Grilo
Obesity-induced hepatic changes during pregnancy
September 12, 2019
Supervisor: António Moreno, Susana Pereira

Luis Perpetuo Silva
NMR analysis of urinary acetaminophen-glucuronide enrichments from 2H and 13C metabolic tracers in mouse models
February 2019
Supervisor: John Jones

Manuel Moura Ramos
Exploring success network in real time functional magnetic resonance imaging (rtfMRI) neurofeedback
2019
Supervisor: Miguel Castelo- Branco

Margarida Fernandes Beatriz
Mitochondrial characterization in Huntington's disease fibroblasts and iPSC-derived cells
September 2019
Supervisor: Ana Cristina Rego, Carla Lopes

Margarida Silva
P-Cadherin Role on the Mitochondrial Biology of Breast Cancer Cells
September 12, 2019
Supervisor: António Moreno

Maria da Paz Olímpio Lardosa Paz
Analysis of eyetracking data applied to autism spectrum disorder during virtual reality experiments
September 2019
Supervisor: Miguel Castelo- Branco

MSC THESIS CONCLUDED IN 2019

Maria Inês Barros
Assessing the putative role of mesenchymal stromal cells' effectors in Machado-Joseph disease
March 2019
Supervisor: Luis Almeida, Catarina Miranda

Maria Inês Alves
Effect of Sex on Brain Metabolism and Intracellular Stress in Type 2 Diabetes
2019
Supervisor: Ana Duarte, António Moreno

Mariana Biscaia
Targeted delivery of doxorubicin and c6-ceramide combinations to non-small cell lung cancer cells: key factors for C6-ceramide's cytotoxicity
2019
Supervisor:

Mariana Terra
Development of gene and drug delivery nanosystems for hepatocellular carcinoma cells
September 2019
Supervisor: Henrique Faneca, Rosemary Cordeiro

Marlene Santos Domingues
Impact of astrocytes on memory: role of astrocytic adenosine A2A receptors
January 19, 2019
Supervisor: Paula Agostinho, Ângelo Tomé

Marta Barão
Uncover the mechanism behind miRNA function on cell survival
2019
Supervisor: Hugo Fernandes

Marta Silva Lapo Pais
Diagnóstico diferencial de doenças neurodegenerativas com base em dados de PET em correlação com outras modalidades de imagem
2019
Supervisor: Miguel Castelo- Branco

Marta Sofia Pereira
Skin allergens: molecules with an improbable therapeutic application for Alzheimer's disease
Supervisor: Claudia Pereira, Mª Teresa C. Rosete

Martins IG
Cerebral small vessel disease and its neuropsychological correlates: unraveling socio-emotional impairment in a sample with sporadic CSVD
2019
Co-supervisor: Isabel Santana.

Miguel Rosado
A different perspective of circulatory biomarker in neurodegenerative diseases: focus on blood peptidome and complexome
2019
Co-supervision: Bruno Manadas

Natalia Sozza Bernardi
Avaliação das propriedades imunotoxicologicas das nanopartículas de PCL e PCL/Glucano
2019
Supervisor: Olga Borges, Sandra Jesus

Nuno Rocha de Jesus
Sirolimus and metformin on acute lymphobastic leukemia in childhood
2019
Supervisor: Ana Bela Sarmento Ribeiro

Olga Fokt
Mitochondrial respiratory chain complexes and antioxidant enzymes analysis in diabetes and chronic periodontitis-derived human blood mononuclear cells
July 2019
Supervisor: Ana Cristina Rego

Pedro Matos
A Computational Method to Predict the Combinatory Effect of Drugs in Cancer
2019
Supervisior: Irina Moreira
Co- Supervisior: Luis Pereira de Almeida

Rafaela Ferrão
Mitochondria-based screening of drug neurotoxicity in differentiated SH-SY5Y cells
September 16, 2019
Supervisor: Teresa Oliveira, António Moreno

Rodrigo Carreira
Evaluation of antioxidant effects of mitochondria-targeted polyphenolic agents in Human Skin Fibroblasts
January 15, 2019
Supervisor: António Moreno

Rosa Mafalda Amorim Figueiredo
GABA levels relate to BOLD signal in Neurofibromatosis Type 1 June 2019
Supervisor: Miguel Castelo- Branco

Rui Gomes
IREB2 gene polymorphisms in colorrectal cancer and its relation with the disease
2019
Co- Supervisor: Ana Bela Sarmento Ribeiro

Rute Pino
Finding Hidden Patterns on Cardiovascular Toxicology Problem: The case of Doxorubicin
July 18, 2019
Supervisor: Nuno Lourenço

Sara Martins Pego
Developing Real-time PCR genetics tests for fast diagnosis of LHON and Hearing Loss
2019
Co-supervision: Manuela Grazina

Sara Pereira
Application of innovative and minimally invasive methods for cancer detection in a population context
2019
Supervisor:

Sara Valente
Mitochondrial performance during osteoblast differentiation: searching new targets to counteract osteoporosis
September 10, 2019
Supervisor: Vilma Oliveira, António Moreno

Silvia Magro
Toward the identification of novel antileishmanial compounds. In vitro profile of semisynthetic compounds from Eremurus persicus and arylalkenilamines
February 20, 2019
Supervisor Maria do Céu Sousa

Silva-Spínola A
Unraveling the pathophysiological mechanisms behind white matter lesions: a study on cerebrospinal fluid and blood markers in patients with cerebral small vessel disease
2019
Supervisor: Inês Baldeiras

Sofia Alves
Comprehensive characterization of the brain proteome of a 6-OHDa animal model: new insights into Parkinson's disease
2019
Co-supervision: Bruno Manadas

Sofia dos Reis Galvão
Gender-specificities of exercise benefits in a model of chronic anxiety: focus on the neuroimune axis
September 13, 2019
Supervisor: Francisco Ambrosio

Sofia Santiago
Development of silica nanoparticles to mediate antitumor strategies
2019
Supervisor:

Susana Vieira Pinto da Cunha
Characterization of the interaction and permeation of drug-like molecules through membrane models including P-glycoprotein
September 2019
Supervisor: Ana Luisa Carvalho

Vanessa Fernandes
Patient-specific iPSC-derived NESC for Machado-Joseph disease treatment
September 2019
Supervisor: Carlos Duarte, Liliana Mendonça

Vanessa Simões Lourenço
Adenosinergic control of fear extinction: the role of adenosine A2A receptors in the basolateral amygdala
July 24, 2019
Supervisor: Ana P. Simões, Ângelo Tomé

Vera Cristina Martinho Pais
Effect of class I histone deacetylase inhibitors in 3xTg-AD mice
July 2019
Supervisor: Ana Cristina Rego

TECHNOLOGY TRANSFER

Head: Ana Catarina Cunha Santos

The biomedical and biotechnological nature of the research performed at CNC brings an additional responsibility towards society. As such, our institute has been committed in allocating the knowledge and technologies here developed to local industries and organizations 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 CNC, 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 2019, CNC gave the first steps towards the construction of a technology transfer office through the execution of a project—"LifeSciences ByCENTRO: Valorização do Conhecimento em Ciências da Vida"—and the hiring of a technician in this area. Our institute dynamized and performed the following tasks and events in technology transfer:

• scouted the intellectual assets of our institute and created a portfolio—named "Technological Portfolio CNC"—to be soon disseminated in the new institutional website (Figure 1);

• developed and implemented a "Scorecard" system to evaluate technology maturation according to the international recognized Technology Readiness Levels scale (evaluated 20 technologies);

• financed five proof-of-concept and prototypes of innovative technologies and products;

• organized the event "Innovation Day@CNC" to promote technology transfer, innovation, and entrepreneurship among researchers;

• participated in several events (forums, summits, conferences, meetings, and networking/information sessions) to advertise the technologies, patents and scientific platforms of CNC;

• submitted five provisional patent applications;

• established contacts with industry and investors towards commercial valorisation of the intellectual CNC assets.

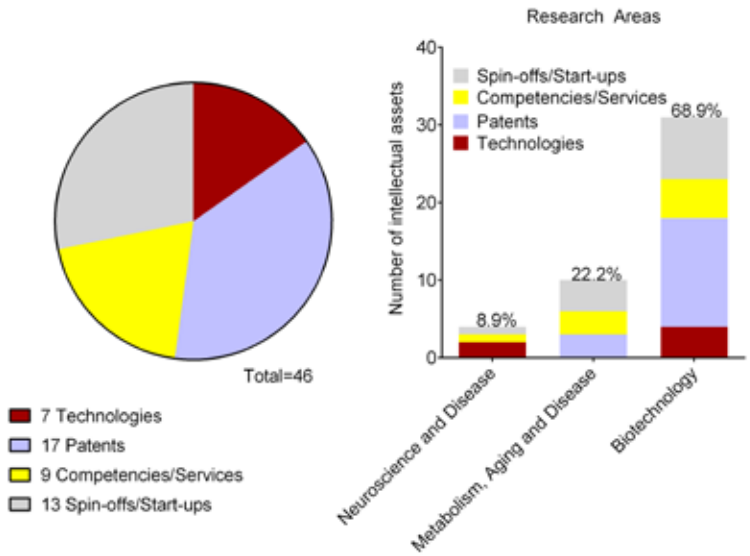


Figure 1: Intellectual assets CNC at the end of 2019. Through technology transfer, CNC assures the application of the research developed here to the greater benefit of our local community and general society.

SCIENCE COMMUNICATION @ CNC.IBILI

Head: Sara Varela Amaral, PhD.

Team: Ana Teresa Viegas, João Cardoso, Lia Lopes and Sara Varela Amaral

One of the major challenges of the contemporary research is to develop new and innovative ways to engage society in science and scientific topics. This is the main role of Science Communication Office - disseminating scientific advances to the benefit of society and to the research process itself, liaising between the different areas of the research institute, the media, and the publics.

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.

Therefore, CNC.IBILI has been strongly committed to promoting and disseminating scientific knowledge to society through the enthusiastic involvement of its researchers in science communication projects using different strategies.

Science in the Media

Social 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 2019 CNC.IBILI was in the news 629 times with an advertising value of 2.820.216 euros, reaching a total number of 33.197.77 audiences.

Social Networks

To reach a wider population we improve our presence in social networks. At the end of 2019 we have more than 12.000 followers at different social networks: Facebook, Twitter, Linkedin, Instagram and youtube.

Public Engagement in Science

CNC.IBILI 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.

Brain Awareness Week (BAW)
March 2019

The Brain Awareness Week (BAW) 2019 organized by CNC.IBILI consortium of University of Coimbra happened in Coimbra during March (1st - 31st March 2019). The project "Brain O'Clock – time to make it right!" was supported by FENS, DANA Foundation and SPN. In 2019, CIBB neuroscientists invite the citizens for several challenges during BAW. Our proposal aimed to promote a healthy lifestyle and an active aging by engaging society in neuroscience and increasing the scientific culture. This project also aimed to involve a bigger number of researchers in Science Communication compared to the previous years. In this regard, we took advantage of our "know-how" in the following fields: Neuroscience, Metabolism and Biotechnology. The project promoted several initiatives for different publics.

School time
Neuroscientists went to Elementary, Middle and High Schools, Senior Universities and Associations to deliver neuroscience information in different formats: hands-on activities, games, formal lectures, and experiments.

Lab time
During BAW researchers from CNC.IBILI opened the doors of their laboratories and received visits from different publics that can explore different themes in neuroscience as: Can we enhance our brain?; How does the sleep affects our metabolism?; Study of human behavior; How do we have energy to the brain?; How neurons die in Alzheimeŕ s disease?; Neurons, obesity and aging; Brain development; How can you address neurodegenerative disorders?

Food time
We distributed a flyer to several places with illustrations promoting a healthy diet and an active lifestyle and explaining its relevance in our metabolism.

Debate time
"When the brain becomes dependent" - 17th March, FNAC Coimbra Session for general audience about dependencies at a public café in a shopping center. The initiative counted with the participation of a psychologist, three medical doctors and neuroscientist.

Selfie time
In order to create meeting places between science and society, we produced audio-visual contents about neuroscience research and brain facts. We produced four small videos, "Selfie Science", where different neuroscientists explained in an informal way their research projects. The videos were shared at CNC youtube channel and social networks (Facebook and Twitter).

Travel time
During one week, we promoted speed datings between scientists and the public, while they traveled together the city by bus. The researchers had the opportunity to share their researcher in an informal way and citizens received scientific information in an unexpected way.

Radio time
The neuroscientists approached brain-related topics and explain their research in the podcast "Ciência aos Domingos" at RUC - Rádio Universidade de Coimbra.

Game time

Neuroscientists played a board-game with the public during a session promoted at the bar "Casa das Artes" in Coimbra. The game is called "Braindemic" and players are researchers whose mission is to treat neurodegenerative disorders. This event was frequented by adults and young adults.

Quiz time

We organized a public quiz at "Aqui Base Tango", a local coffee shop. The neuroscientists developed the questions and the public was challenged to explore brain-related themes. This type of activity is very popular in Coimbra and often frequented by young adults.

Pub time

Researchers participated in the 16th edition of PubhD Coimbra. This event challenge PhD students from different research areas to talk about their PhD projects. March edition was centered in the brain.

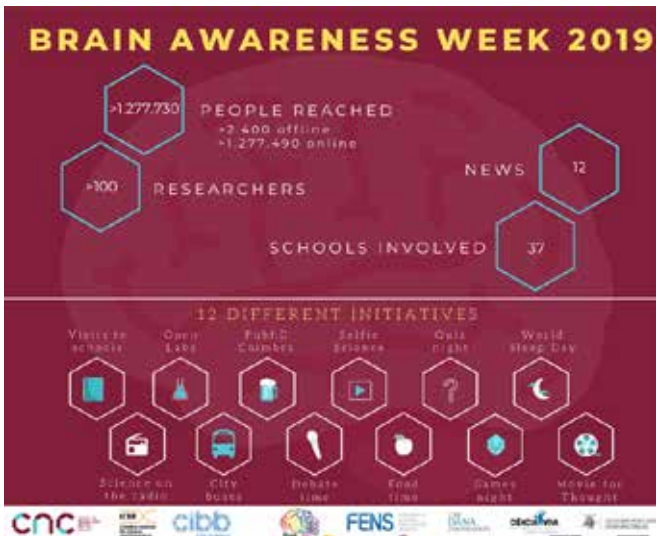
Movie time

During the 19th edition of our internal "Beer for Thought" event, the researchers saw the movie "Inside Out", in order to inspire them to address emotions and brain-related topics in a funny and simplified way.

Sleep time

In the context of the World Sleep Day on March 15th, CNC.IBILI researchers collaborated with the Portuguese Sleep Association (APS) to promote healthy sleep habits as part of a healthy lifestyle and an active aging. We organized the following initiatives: a) development of new hands-on activities for different publics; b) an animation about the brain and sleep to share online (website and social media); c) public event "Sleep Well, Aging Well", that gathered scientists, medical doctors, and the society, with a theatre performance about Sleep Apnea disorder.

Our activities involved 100 researchers and reached directly more than 2400 people from different publics in the following activities: school time and lab time (37 schools have participated), food time, debate time, travel time, game time, quiz time, pub time, and sleep time.
In digital media – Facebook, Twitter and Instagram - we made 76 posts about BAW. The radio time initiative reached 3589 people in our social media and the videos "Selfie Science" reached to 13461. Moreover, the awareness spot for the World Sleep Day reached 100.000 people on social media and 1.265.780 people on television audience.



Science in the Lab

September 2019

Science in the Lab program, supported by Ciência Viva, raises high school students' awareness of career opportunities in numerous scientific fields, namely the biomedical sciences, by promoting science education and experimental research. In 2019 we received 21 high-school for internships in different research fields (Table 1; Figure 2). This initiative was an opportunity to conduct hands-on research under the mentorship of experienced instructors at one of the national's premier biomedical research facilities.

Name of the internship	Number of students	Field	Principal Investigator
"Laboratório fora da caixa"	2	Science Communication	Sara Amaral
"Nanopartículas direcionadas para células cancerígenas"	1	Neuroscience	Ana Filipa Cruz
"Dormir será uma perda de tempo?"	2	Neuroscience	Ana Rita Álvaro
"Caracterização de modelos de doenças neurodegenerativas (Doenças de Alzheimer e Huntington)"	2	Neuroscience	Sandra Mota
"Quando as Baterias Falham: o papel das mitocôndrias nas nossas células e como a sua falha pode provocar doenças"	2	Metabolism	Paulo Oliveira
"Altos e baixos da doença Bipolar"	2	Neuroscience	Rosa Resende
"Microorganismo, eles estão no meio de nós"	3	Metabolism	Marta Mota
"Desenvolvimento de nanossistemas para mediar estratégias antitumorais"	3	Biotechnology	Henrique Faneca
"Como reparar um coração partido?"	2	Biotechnology	Mariana Bexiga
"Estudo da função neuronal in vitro"	2	Neuroscience	Filipe Duarte

Table 1 – Internships for high-school students from "Science in the Lab" programme.

Figure 2 – Students involved in the Science in the Lab project 2019.

Science in the Summer
July and September 2019

During 20 days, Science Communication Office, with Rómulo Science Center and Science Museum, developed activities to society in streets of the Coimbra´s downtown (Café Santa Cruz) in order to bring scientific knowledge close to community. 10 researchers actively participated in this initiative.

European Researchers´Night (ERN)
September 2019

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. In 2019 CNC.IBILI were at Coimbra Botanical Garden and at Science Museum. We developed a set of hands-on activities (in different fields as neuroscience, cell biology, microscopy) and CNC.IBILI researchers participated in one-to-one conversations with publics. More than 100 researchers from CNC.IBILI participated in this initiative with 24 hands-on activities and speed-dating initiatives. More than 700 people visited Botanical Garden and Science Museum during ERN 2019.

Fig. 3 – ERN 2019

Educational initiatives with IEC

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: overall 183 people participated in the activities that involved 20 CNC researchers. In 2019, CNC researchers participate in 2 conferences for a broad audience and 17 advanced courses for high-school students. This activities engaged more than 400 people.

Theatre & Science

Since 2009 CNC has participated in several activities that use the artistic language to explore scientific subjects in one attempt to create new ways of communicating with the public. Several theatre plays were staged in close collaboration with CNC.IBILI researchers, either as actors, authors or sources of inspiration. In 2019 our researchers collaborate with three different projects with Marionet theatre company:

• Sistemas corporais
CNC was an active partner in "Sistemas Corporais" project. In 2019 (January @ Convento de São Francisco, Coimbra), CNC organized a an art&science workshop targeting children about the brain and neurons, integrated in the "The Secret gland play". About 50 children participated at the workshop.

• Unknownness Lab
The 'Unknownness Lab' is a research and creation initiative to tackle scientific challenges with an interdisciplinary team of scientists and artists. The aim is to address unresolved scientific problems using artistic perspectives, tools and techniques, trying to achieve, eventually, some progress or enlightenment regarding those problems, and to evaluate the process and possible advantages of addressing scientific questions in an interdisciplinary way. In 2019, the 'Un_n__nn___Lab' promoted an event – A Máquina dos Sonhos - during N&D CIBB Retreat (May @ Casa das Artes, Miranda do Corvo). 6 CNC researchers were involved in the meetings, discussion and preparation of the theatre performance. More than 100 CIBB members were at the retreat.

• Holy CIBB
Theatre play presented in CIBB annual meeting (December @ UC) with the participation of 20 CNC.IBILI researchers.

Fig. 4 – Researchers involved in "Holly CIBB" theatre play

MICRODay

In 2019 we celebrated the 1st National Microscopy Day – MICRODay 2019.
This event, promoted by the Portuguese Platform of Bioimage (PPBI), had the main goal of allowing students to explore microscopy. The participants had the opportunity of exploring microscopy in diseases such as schizophrenia and autism, and in other themes. More than 25 high-school students participated in MICRODay 2019 at CNC.IBILI.

Fig. 5 – Organizers of MICRODay 2019 at CNC.IBILI

UniStem Day

Outreach day dedicated to Stem Cells research. This international event engaged about 30 high-school students that visited CNC.IBILI labs.

Immunology Day

We commemorated the Day of Immunology, in our UC-Biotech building, Cantanhede. 60 participants from high school had the opportunity to explore several themes in immunology field with the participation of 6 CNC.IBILI Researchers.

Science & Technology Week
November 2019

During Science & Technology Week CNC.IBILI researchers promoted several science communication initiatives in different venues. This initiative involved 40 CNC.IBILI researchers and more than 780 persons. 14 schools participated (students from kindergarten to high-school).

Fig. 6 – Summary of Science and Technology Week 2019

PubhD Coimbra

PubhD is an informal science communication initiative where PhD students share their projects, avoiding a formal presentation. The event happens monthly in a very popular pub in Coimbra. During 2019, 8 researchers from CNC.IBILI participated in PubhD during 2019. Each edition has an average audience of 40 people then about 480 people interacted with this event.

Comics

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 one comics, involving different researchers and an illustrator, about tuberculosis, launched in World Tuberculosis Day.

Audiovisual materials

In 2019, CNC.IBILI have been developing science communication videos focusing on different research topics: the video lines Selfie Science and ASK (Always Seeking Knowledge) Researchers. Selfie Science episodes aim to schematically explain scientific research projects to a non-academic public. ASK Researchers series promotes the online interaction with society - everyone can submit their questions to the featured researcher to be answered in an interview format. We launched the projects in March of 2019 and since then we explored several scientific topics, by releasing an episode of each video line on a monthly basis. In 2019 we lauched 8 ASK Researchers and 9 Selfie Science. All the videos are available at Youtube channel.

Name	Researcher	Research Field	Views
Autism: from the lab to the society	Catarina Seabra	Neuroscience	2125
Progeria: Benjamim Button backwards?	Célia Aveleira	Neuroscience	769
Male infertility: and when we don´t know why?	Sandra Amaral	Metabolism	991
Quail eggs to produce new drugs?	Ricardo Pires	Biotechnology	769
Mycobacteria: naturally resistant to antibiotics!	Susana Alarico	Microbiology	445
Alzheimer´s disease: why do we fall into oblivion?	Francisco Queiroz	Neuroscience	758
Nutrition and physical activity during pregnancy: a way to potentiate children's health?	Susana Pereira	Metabolism	882
Alzheimer's disease: An impossible cure?	Sandra Mota	Neuroscience	418

Table 2 – 2019 ASK Researchers videos

Additionally, we produced an animation about Machado-Joseph Disease, with a close collaboration of the researchers from Gene and Stem Cell Therapies for the Brain group, available at *http://www.cnbc.pt/outreach/DMJ-infografia_leg_versaofinal.mp4*.

Name	Researcher	Research Field	Views
Stress and microglia in brain development	Ana Luísa Cardoso	Neuroscience	2120
Depression and A2A receptors	Anna Pliássova	Neuroscience	2184
mTOR and paused pluripotency	Bibiana Silva	Metabolism	4793
Messengers in our brain and Alzheimer´s disease	Fábio Sousa	Neuroscience	1796
Reprogramming cells to combat tumors?	Luís Oliveira	Biotechnology	4057
Machado Joseph´s disease and the brain mail	Catarina Miranda	Biotechnology	3897
Obstructive sleep apnea: should we sleep on it?	Laetitia Gaspar	Neuroscience	2581
Stargazin and its involvement in cognitive defects	Gladys Caldeira	Neuroscience	1389
Green leaves and brain-vascular communication	João Gonçalves	Neuroscience	533

Table 3 – 2019 Selfie Science videos

Advanced Course
Connecting Researchers with the Society
February 2019

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 an advanced course, integrated in PhD Programme in Experimental Biology and Biomedicine (PDBEB), in order to help scientists to engage the public in different environments. 22 students, from PDBEB and from other PhD programs, participated in this intensive course (5-days) with the participation of 18 speakers from different fields as public engagement in science, visual communication, media, technology transfer, career development and art&science.

Fig. 7 – Summary of Science Communication Activities numbers in 2019

CORE FACILITIES AT 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 AT 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

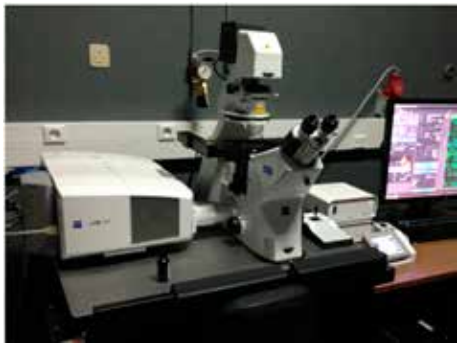
FACSAriaIIIIII (Becton Dickinson) – 12 colours

CORE FACILITIES AT CNC

MICROSCOPY IMAGING CENTER OF COIMBRA

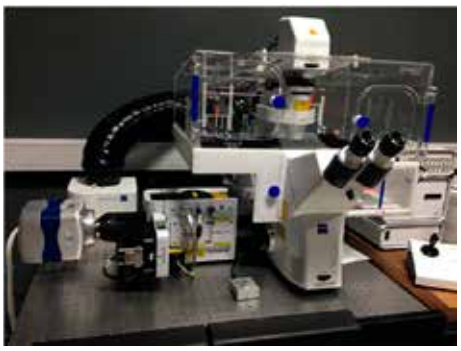
Head: Luisa Cortes, PhD.

The Microscopy Imaging Center of Coimbra at the Center for Neuroscience and Cell Biology (MICC-CNC) is an open infrastructure that provide researchers with equipment and expertise required for multi-dimensional imaging of cells and tissues at high resolution and to perform quantitative image analysis. Resources include widefield, confocal and laser capture microdissection microscopy, as well as equipment for live cell imaging and image analysis. In fact, the MICC has a highly skilled and multidisciplinary scientific staff committed in training users to operate the microscopes and helping on the implementation of advanced imaging techniques, as well as on the design of robust image analysis protocols. Training is mandatory before users can access the equipment and this has two main outputs: minimizing improper handling, extending the lifetime of each equipment, and decreasing repair costs. Additionally, MICC-CNC offers technical support from project planning to data presentation, through the choice of reagents and equipment, analysis of experimental results and image processing. Technical support is extended to external academic units interested in using the Laser Capture Microdissection (LCM) technology present in our unit (MICC). This technology consists on a P.A.L.M. Laser-Catapulting Microdissecting Microscope that employs laser microdissection and pressure catapulting to extract biological material of interest out of a tissue specimen, and is one of the few systems present in Portugal.



Point Scanning Confocal - LSM 710

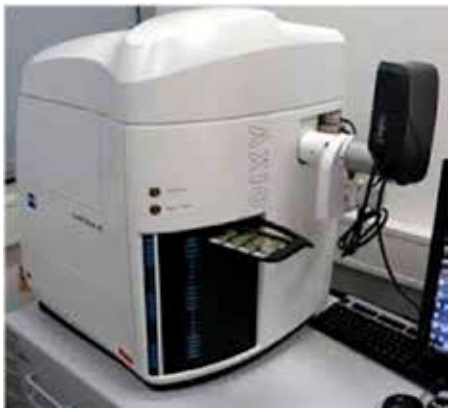
In 2019, MICC-CNC has been actively involved in the organization of advanced fluorescence microscopy courses such as the 'Basic Concepts on Imaging Tools and Data Analysis' integrated in the Syn2Psy Network School I, that provided PhD and Master students with the fundamentals of light microscopy, fluorescence microscopy, live cell imaging, and specific light microscopy imaging methodologies applied to Biomedicine. Furthermore, the team participated in the organization and coordination of the Core Technology Course of the BEB PhD program (2019/2020) that aimed to provide an overview of the technological platforms available at CNC.



Spinning Disk Cell Observer

Moreover, MICC-CNC, in collaboration with Carl Zeiss, organized the workshop 'Tissue Clearing Workshop' (20th – 22nd March 2019), a 3 days intensive workshop that covered various topics in tissue clearing by hands-on experience, from optimization and application of various clearing techniques, to light-sheet microscopy imaging, 3D visualization and quantification. This was the first course fully dedicated to Tissue Clearing organized in Portugal.

The MICC team, especially Luisa Cortes as president of the organizing committee (main organizer), was involved in the organization of 'SPAOM 2019 - Spanish and Portuguese Advanced Optical Microscopy', from 6th to 8th of November 2019. SPAOM is a joint effort from the Red Española de Microscopía Óptica Avanzada (REMOA) and the Portuguese Platform of Biomedical Imaging (PPBI), that aims to promote new insights in microscopy applications, developments and technologies, fostering interactions and collaborations between scientific community and industry. SPAOM 2019 offered a great opportunity for attendees to learn the most recent developments in the field of light microscopy, and their impact in the advance of life science research, from an impressive group of invited speakers.



Slide Scanner Axio Scan.Z1

MICC-CNC is part of the PPBI - Portuguese Platform of Bioimaging, a national research infrastructure of the National Roadmap of Research Infrastructure, and belongs to the Zeiss labs@location community providing in depth knowledge and dedicated services.

CORE FACILITIES AT CNC

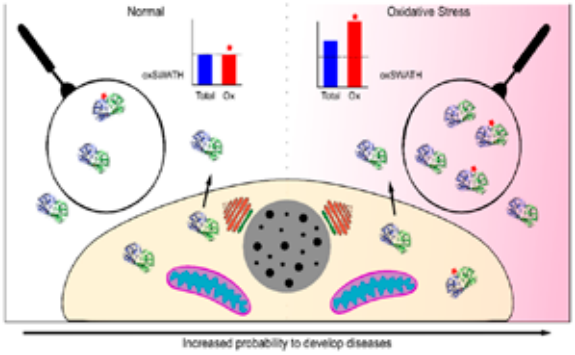
MASS SPECTOMETRY UNIT

Head: Bruno Manadas, PhD.

During 2019 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:

The impact of our research in the community has raised quite significantly as the number of publications, projects, and services provided clearly show. However, we also believe that the invitations to: i) perform collaborative projects, ii) write book chapters and tutorials, and iii) disseminate our research through advanced courses and seminars, shows the influence of the research being performed in the group. 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.



Publications *(Accumulated impact factor of 82, 11 publications in Q1 (1 in top 5%; 4 in top 10%), 5 in Q2 and 3 non indexed):*

1Willemse, E.A.J., et al, Pre-analytical stability of novel cerebrospinal fluid biomarkers. Clin Chim Acta, 2019;.

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Tsironi, T., et al, High pressure processing of European sea bass (Dicentrarchus labrax) fillets and tools for flesh quality and shelf life monitoring. Journal of Food Engineering, 2019. 262: p. 83-91, IF 4.499.

SERVICES AT CNC

LABORATORY OF MITOCHONDRIAL BIOMEDICINE AND THERANOSTICS

Head of Unit: Manuela Grazina
Staff:
Maria João Santos; Marta Simões; Márcia Teixeira

Certification NP EN ISO 9001:2015

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 Prof. Lee-Jun Wong and 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) 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

During this year, in the continuity of the previous, fibroblasts were cultured in order to complete functional studies to elucidate the pathogenicity of a novel genetic variant that was identified in the FASTKD2 gene, involved in post-transcriptional regulation of mitochondrial gene expression, in a patient presenting with cardiomyopathy and nephropathy. Two sorts of mitochondrial enriched fractions were prepared, and additional fibroblast samples of controls were included for comparative analyses.

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 14 patients suspected of mitochondrial cytopathies were studied, corresponding to the analysis of 18 samples, in 180 assays, including lymphocytes isolated of peripheral blood (12) and muscular biopsies (6). An MRC deficiency was detected in 7 patients (50%).

CoQ10 quantification

One sample of plasma was analysed to determine the CoQ10 levels in a patient with ataxia. The coenzyme content was normal. It is important to note that muscle tissue is more specific for detection, but it is not always available due to invasiveness of collection.

Functional studies

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

The studied patient had a novel genetic sequence variation (FASTKD2) and a phenotype characterized with cardiomyopathy and nephropathy. Analyses of MRC activity and assembly profile, and the encoded protein expressed levels were assessed. The expression of the FASTKD2 protein was significantly reduced to half of controls' average, which should explain the moderate reductions, both in detected enzymatic activity and in the assembly status. Considering the reporting that the effects of a FASTKD2 alteration appeared to be cell or tissue specific, the results were evaluated as regards the consequences on mitochondrial gene expression and possible association with heterogeneous clinical phenotypes.

Genetic analysis

Genetic screening is the only available tool for attainment of a definitive diagnosis in many diseases. Concerning OXPHOS disorders and given its dual genetic origin, complexity and heterogeneity, the study of nuclear genome, mitochondrial DNA (mtDNA) and bigenomic crosstalk factors, using a genetic integrative approach is mandatory, although very complex.

Thirty-eight samples (blood – 34 and muscle – 4) were received for DNA extraction. Seven DNA samples were also received for genetic analysis.

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 2019, 42 samples of 40 patients were analysed using this strategy and the findings included several polymorphisms in all samples and two point mutations (m.3460G>A and m.11778G>A) in three patients (6,9%). These pathogenic mutations were further confirmed by PCR-RFLP and automated sequencing.

The 24h testing of the Top 3 LHON primary mutations was implemented in order to give a faster response to the cases and some patients suspected of LHON were screened.

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, we investigated 4 samples of 4 patients, comprising a total of 111 real time PCR reactions.

Concerning the screening of nuclear genome (nDNA) defects causative of MRC diseases, 10 samples were screened by next generation sequencing (NGS).

Additionally, POLG2 and POLG1 genes were analysed in 1 and 9 samples, respectively, allowing the detection of sequence variations, but none was considered pathogenic.

Screening of OPA1 gene (5 samples) and OPA3 gene (2 samples) also revealed sequence variations without pathogenicity.

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 192 samples, divided in 16 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.

According to the procedure followed at the LBioMiT, around 1280 sequence variations were assigned in the mtDNA, including several polymorphisms, some reported alterations and two point mutations (m.3460G>A and m.11778G>A), both associated with LHON, in three patients.

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.

SERVICES AT CNC

LABORATORY OF NEUROGENETICS

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

During 2019, the Neurogenetics Laboratory continued to pursue the genetic analysis of patients with Neurological diseases, providing molecular diagnostic tests to the affected individuals as well as offering predictive tests to other family members, still asymptomatic, in the context of genetic counseling. 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 been also used, in particular RP-PCR and ELISA assays, to detect the C9orf72 expansion and the serum GRN level, respectively, to study the patients with Frontotemporal lobar degeneration (FTLD) and/or Amyotrophic lateral sclerosis (ALS).

The majority of the patients were followed at the different units of the Neurology Department of Centro Hospitalar e Universitário de Coimbra (CHUC), although a significant number of patients have been referred from other hospitals in the country. Variant interpretation was performed using a multistep process workflow developed in the previous year, to individually assess variants pathogenicity, based on the use of population databases and in silico prediction tools. 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, have been identified, some of which were novel, expanding the disease spectrum mutations. In addition, genetic dissection has been successful disclose the molecular profile of some complex clinical cases, and thereby explain patients clinical phenotype.

In 2019, the Neurogenetics laboratory has been focused in studying patients with the clinical diagnosis of Parkinson disease, Alzheimer disease, FTLD and ALS as in previously years. Also during this year, an increase number of patients with cerebral small vessel disease (SVD) have been also studied, in which CADASIL constituted the most representative group (>20 families).

Of note, glioblastoma and cavernous malformations patients followed at the Neurosurgery unit of CHUC, continued to be referred to the laboratory to be genetic analyzed in order to improve their diagnosis and clinical management.

SERVICES AT CNC

CELLULAR MECHANOBIOLOGY

Head of Unit: Mário Grãos

Our laboratory is composed by the Laboratory of Cellular Mechanobiology, which is dedicated to R&D, and the Laboratory of Cell Biology, focused on service providing.

In 2019, we continued the 2 main services. One service allows the simultaneous determination of several bio-molecules using the multiplex xMAP technology. The other is related to testing 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), which resulted in the processing of 4687 samples.

The research activities were mostly focused on the field of Cellular Mechanobiology, namely in the context of oligodendrocytes and MSCs. During 2019, the laboratory was focused on the project (FCT grant) 'BrEin-MS — Brain Elasticity in Multiple Sclerosis and implications in mechanomodulation of oligodendrocytes: a cellular and clinical approach'. We also developed projects focused on the mechanobiology of MSCs, resulting in one published article in 2019 (https://doi.org/10.1038/s41598-019-45352-3) and one in preparation (to be published in 2020). During this year, we integrated the MSCellProduction project (a P2020/POCI/ERDF funded project led by Crioestaminal, SA) aiming to demonstrate the ability to manufacture GMP cell therapy products from different tissues. We also participated in collaboration R&D projects, namely with the laboratory of Bruno Manadas. The laboratory's scientific output was as follows: 3 peer-reviewed research articles (two Q1 and one top 5% in Scimago Multidisciplinary Sciences), 2 invited oral presentations (international), 2 conference abstracts (international) and 3 poster presentations (1 international and 2 national).

The laboratory continued to provide advanced training, hosting 1 post-doctoral researcher and 2 PhD students, 2 undergraduate students and several lab rotation students from MSc programs from the University of Coimbra. The PI served as examiner of 1 MSc thesis and lab members were examiners of 2 undergraduate theses.

The PI taught courses in the fields of Mechanobiology, Stem Cells and Apoptosis, in several MSc and PhD programmes (MBCM, MIB, PD-BEB), and academic & career development in biomedical research for students of the degree in Biology, all at the University of Coimbra.

Several outreach activities were carried out. The PI presented a lecture for high school students and teachers (about stem cells) and taught 2 courses ('Cell cycle and apoptosis', within the Cell Signalling course) organized by IEC (Instituto de Educação e Cidadania). The PI and lab members participated in several outreach activities organized by the CNC under the scope of the Brain Awareness Week.

SERVICES AT CNC

LABORATORY OF GENOME SEQUENCING

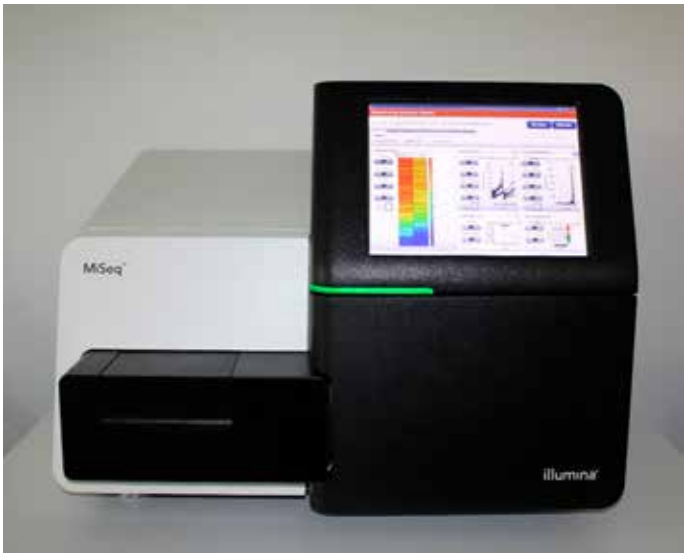
Head of Unit: Conceição Egas
Staff:
Graduate Technician | Cristina Barroso
Principal Technician | Maria José Simões
Bioinformatician | Hugo Froufe

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 2019 the Laboratory sequenced 1183 samples for external clients, in a total of 177 Gb. Biodiversity samples were the most requested application, with 32.5 Gb. Sequencing services and bioinformatics were additionally provided for CNC users, with 185 samples sequenced in a total of 112 Gb.

Genoinseq participates in the H2020 project Metafluidics: Advanced toolbox for rapid and cost-effective functional metagenomic screening - microbiology meets microfluidics (ref. 685474-2. 2016-2020) and in the P2020 project In2Genome – Integrative approach in the diagnosis of genetic diseases (ref. 17800).

Graduate students

Diogo Pinho, Ph.D. student
Raquel Varandas, Ph.D. student
Daniel Martins, Ph.D. Student

Outreach

Genoinseq presented the core facility, sequencing applications and research results in 9 external events.

Research papers:

Albuquerque, L., Egas, C., & Costa, M. S. (2019). Rubritepida. In Bergey's Manual of Systematics of Archaea and Bacteria. https://doi.org/10.1002/9781118960608.gbm01457

Albuquerque, L., Rainey, F. A., Egas, C., Froufe, H. J. C., Raposo, P., Roxo, I., & Costa, M. S. (2019). Cecembia. In Bergey's Manual of Systematics of Archaea and Bacteria. https://doi.org/10.1002/9781118960608.gbm01443

Costa, M. S., Albuquerque, L., Rainey, F. A., Froufe, H. J. C., Roxo, I., Raposo, P., & Egas, C. (2019). Elioraea. In Bergey's Manual of Systematics of Archaea and Bacteria. https://doi.org/10.1002/9781118960608.gbm01458

Paiva de Carvalho, H., Sequeira, S. O., Pinho, D., Trovão, J., da Costa, R. M. F., Egas, C., … Portugal, A. (2019). Combining an innovative non-invasive sampling method and high-throughput sequencing to characterize fungal communities on a canvas painting. International Biodeterioration and Biodegradation. https://doi.org/10.1016/j.ibiod.2019.104816

Raposo, P., Viver, T., Albuquerque, L., Froufe, H., Barroso, C., Egas, C., … da Costa, M. S. (2019). Transfer of Meiothermus chliarophilus (Tenreiro et al. 1995) Nobre et al. 1996, Meiothermus roseus (Ming et al. 2016), Meiothermus terrae (Yu et al. 2014) and Meiothermus timidus (Pires et al. 2005), to Calidithermus gen. nov., as Calidithermus chliarophilus com. International Journal of Systematic and Evolutionary Microbiology. https://doi.org/10.1099/ijsem.0.003270

Reis, A. C., Kolvenbach, B. A., Chami, M., Gales, L., Egas, C., Corvini, P. F. X., & Nunes, O. C. (2019). Comparative genomics reveals a novel genetic organization of the sad cluster in the sulfonamide-degrader "Candidatus Leucobacter sulfamidivorax" strain GP. BMC Genomics. https://doi.org/10.1186/s12864-019-6206-z

Severino, R., Froufe, H. J. C., Barroso, C., Albuquerque, L., Lobo-da-Cunha, A., da Costa, M. S., & Egas, C. (2019). High-quality draft genome sequence of Gaiella occulta isolated from a 150 meter deep mineral water borehole and comparison with the genome sequences of other deep-branching lineages of the phylum Actinobacteria. MicrobiologyOpen. https://doi.org/10.1002/mbo3.840

SERVICES AT CNC

MITOXT SERVICES LABORATORY: PREDICTIVE MOLECULAR TOXICOLOGY BASED ON MITOCHONDRIAL FUNCTION

Coordinator: Paulo Oliveira

Team: Vilma Sardão, Teresa 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 2019

2019 Annual Accounts

In 2019 funding of "Laboratório Associado – Centro de Neurociências e Biologia Celular" ascended the amount of 9.562.069,56€.

The main financing contribution was made by "Fundação para a Ciência e Tecnologia (FCT)", concerning global institution programs and national projects, namely amount of 7.915.290,36€ distribuited as follows:

Strategical Project_ UID/NEU/04539/2019	2.012.209,39€
Science Program:	1.801.519,15€
FCT Projects	4.101.561,82€

The related items supported the main part of Center for Neuroscience and Cell Biology expenses during 2019.

Besides Center for Neuroscience is financed by other national and international agencies. In 2019 Center for Neuroscience received the amount of 1.462.937,64 €, wheras other services had expenditure of amount 183.841,56€.

Main Services, not listed, is another important vector of our institution which ascends 650.236,45€ in 2019.

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 2019

Title	Financing Agency	Starting Date	Ending date	Budget €	Expenditure 2019 €
UID/NEU/04539/2019 - COORDINATOR: João Ramalho de Sousa Santos - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. UID/NEU/04539/2019	01/01/2019	31/12/2019	2 012 710,00	2 012 209,39
Sub-Total Strategical Projet					**2 012 209,39**
Norma transitória-DL 57 - COORDINATOR: João Ramalho de Sousa Santos	Fundação para Ciência e a Tecnologia - REF. Norma transitória-DL 57	04/01/2019	31/12/2025	8 811 000,00	1 089 802,29
Concurso Estímulo ao Emprego Científico Individual 2017 - Contrato - Programa - COORDINATOR: João Ramalho de Sousa Santos	Fundação para Ciência e a Tecnologia - REF. Concurso Estímulo ao Emprego Científico Individual 2017 - Contrato - Programa	15/02/2019	28/02/2025	2 872 220,66	318 292,89
Programa Investigador FCT 2014 - COORDINATOR: João Ramalho de Sousa Santos	Fundação para Ciência e a Tecnologia - REF. Programa Investigador FCT 2014	01/01/2015	25/01/2020	1 951 567,79	41 019,31
Programa Investigador FCT_4ª edição - COORDINATOR: João Ramalho de Sousa Santos	Fundação para Ciência e a Tecnologia - REF. Programa Investigador FCT_4ª e	01/11/2016	25/11/2021	2 065 304,67	352 404,66
Sub-Total Science Program					**1 801 519,15**
A reação neuroinflamatória em respostas à inflamação sistémica aguda durante delirium e o seu impacto na trajectória cognitiva e progressão para demência: estudo caso-controlo longitudinal com biomarcadores imagiológicos e moleculares - COORDINATOR: Joaquim Manuel Soares Cerejeira	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-032501	26/07/2018	25/07/2021	233 309,26	62 001,97

BaiTS-Dendrímeros biodegradáveis para o desenho de terapias neuroprotectoras direccionadas para o tratamento de acidentes vasculares cerebrais - COORDINATOR: Carlos Jorge A. M. B. Duarte - PROPONENTE: INEB-Instituto de Engenharia Biomédica - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/CTM-NAN/3547/2014	01/07/2016	31/03/2020	17 200,00	6 189,97
A interação entre cAMP e Sirtuínas como um mecanismo de controlo mitocondrial e metabólico - COORDINATOR: Carlos Manuel Marques Palmeira	Fundação para Ciência e a Tecnologia - REF. PTDC/BIM-MEC/6911/2014	31/03/2016	31/12/2019	199 260,00	102 032,77
Exossomas libertados de celulas estaminais pluripotentes induzidas - impacto na (dis)função mitocondrial na Doença de Huntington e potencial sistema p - COORDINATOR: Ildete Luísa Araújo Fereira	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-032316	06/07/2018	05/07/2021	235 334,58	30 138,02
Exossomas libertados de celulas estaminais pluripotentes induzidas - impacto na (dis)função mitocondrial na Doença de Huntington e potencial sistema para distribuição de terapêutica baseada em microRNA - COORDINATOR: Carla Nunes Lopes	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029621	06/07/2018	05/07/2021	238 749,98	40 500,38
Direcionamento multicelular mediado pela nucleolina de combinação sinergística de fármacos para o tratamento do cancro da mama triplo negativo e neuroblastoma - COORDINATOR: João Nuno Sereno de A. Moreira	Fundação para Ciência e a Tecnologia - REF. ENMed/0005/2015	01/06/2016	29/02/2020	146 200,00	58 858,55
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	01/01/2017	31/03/2021	999 999,95	181 555,53
Alterações no proteoma sináptico e excitabilidade neuronal num modelo de epilepsia do lobo temporal induzido por administração de pilpcarpina - COORDINATOR: Carlos Jorge A. M. B. Duarte	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028656	01/07/2018	30/06/2021	238 747,12	68 504,47

O transportador de K+ - CL- (KCO) como alvo para manter a neurotransmissão GABAergica: uma nova estratégia terapeutica para a epilepsia - COORDINATOR: Miranda Mele	Fundação para Ciência e a Tecnologia - REF. CENTRO-01-0145-FEDER-030659	01/06/2018	30/05/2021	237 446,83	58 898,93
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. POCI-01-0145-FEDER-029894	26/07/2018	25/07/2021	234 226,71	82 730,14
Novas abordagens em Encefalopatia hipóxicoisquémica: investigação translacional para diagnosticar e monitorizar resposta a terapia com células estaminais. - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UBI	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029311	01/06/2018	31/05/2021	203 225,04	75 512,31
Distúrbios afetivos: biomarcadores e deteção precoce - COORDINATOR: Bruno José F. O. Manadas	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-030943	26/07/2018	25/07/2021	238 743,45	53 489,90
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. POCI-01-0145-FEDER-031999	26/07/2018	25/07/2021	53 749,75	17 066,78
Impacto da agreação generalizada de proteínas ao longo da vida em mamíferos e implicações para o desenvolvimento de doenças relacionadas com o envelhecimento - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Universidade de Aveiro - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029843	01/06/2018	31/05/2021	26 250,00	5 507,96
Além do Beta-Amilóide - As Alterações Patagénicas Precoces na Doença de Alzheimer - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Universidade de Lisboa_Faculdade de Medicina - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/MED-NEU/27946/2017	01/09/2018	31/08/2021	106 997,37	2 645,21

Melhoria cognitiva no cérebro idosoe demênsia vascular em humanos através da funcionalização do acoplamento neurovascular: uma estratégia mecanística - COORDINATOR: João António Nave Laranjinha - PROPONENTE: Centro de Neurociencias e Biologia Celular - PARTICIPANTS: CHUC, UC	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029099	26/07/2018	25/07/2021	100 955,61	16 288,62
Influência das antocianinas extraídas de mirtilos cultivados em Portugal na conexão entre o intestino e o cérebro nas pertubações do espetro do autismo: utilização de modelos in vitro e in vivo - COORDINATOR: Leonor Martins de Almeida	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029089	01/06/2018	31/05/2021	238 694,84	63 127,08
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. POCI-01-0145-FEDER-028261	25/07/2018	24/07/2021	63 125,00	19 976,89
Bloqueio da neurodegenerescência por dispersão de silenciadores génicos. - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029716_ Spread Silencing	01/07/2018	30/06/2021	238 749,59	34 014,86
O papel dos grânulos de stress nas doenças de poliglutaminas: da patogénese à terapia molecular - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Universidade do Algarve	Fundação para Ciência e a Tecnologia - REF. ALG-01-0145-FEDER-029480	13/10/2018	12/10/2021	57 000,00	0,00
Papel da desregulação dos microRNAS na doença de MAchado - Joseph: Desenvolvimento de uma estratégia terapeutica baseada em microRNAS - COORDINATOR: Sonia Patricia Dias Duarte	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-032309	06/07/2018	05/07/2021	239 947,00	56 866,13
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. POCI-01-0145-FEDER-030737	15/06/2018	14/06/2021	240 550,73	43 536,74

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. POCI-01-0145-FEDER-028147	01/06/2018	31/05/2021	185 084,57	64 936,91
Recetores A2A da adenosina como desencadeadores de disfunção mnemónica na doença de Alzheimer: Mecanismos e possobilidade terapeutica - COORDINATOR: Rodrigo Pinto S.A. Cunha	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-031274	01/07/2018	30/06/2021	236 326,73	105 070,74
Estratégias de reparação e repressão génica para tratar a doença de Machado-Joseph - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-NMC/0084/2014	01/04/2016	31/12/2019	199 998,01	65 345,80
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	01/05/2016	31/03/2020	174 992,03	66 489,02
Controlo da proliferação de cardiomiócitos na doença e em medicina regenerativa - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: Faculdade de Ciencias Medicas (FCM/UNL) - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/BIM-MED/3363/2014	01/05/2016	31/10/2019	20 040,00	0,00
Modelos avançados de doenças de poliglutaminas - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. JPCOFUND/0005/2015	01/04/2016	30/09/2019	275 000,00	87 139,48
O estado pausado: um método inovador para bioengenharia de Células Estaminais - COORDINATOR: João Ramalho de Sousa Santos	Fundação para Ciência e a Tecnologia - REF. CENTRO-01-0145-FEDER-028871	01/06/2018	05/12/2021	237 976,10	57 021,78
Pesquisa de novos biomarcadores para a infertilidade masculina de origem desconhecida - COORDINATOR: Sandra Catarina Gomes Amaral	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028599	06/07/2018	05/07/2021	236 679,82	43 918,27

Valor prognóstico e protector da eixo de Clusterina-PON1 sobre as complicações da obesidade - COORDINATOR: John Griffith Jones - PROPONENTE: Associação Protetora Diabetes Portugal - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/BIM-MET/4265/2014	01/07/2016	31/12/2019	39 576,00	1 606,91
MitoBOOST: Uma Terapeutica de Nova Geração para a Doença de Fígado Gordo Não Alcoólico Baseado na Entrega Inteligente de Antioxidantes à Mitocôndria - COORDINATOR: Paulo Jorge G. S. S. Oliveira - PROPONENTE: Centro de Neurociencias e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. PTDC/DTP-FTO/2433/2014	01/04/2016	30/09/2019	134 052,00	18 744,01
FishFree: Uma contribuição para a validação de um ensaio alternativo ao teste letal com peixes - COORDINATOR: Paulo Jorge G. S. S. Oliveira - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/AAG-TEC/4966/2014	01/07/2016	30/06/2019	25 680,00	3 614,34
Desenvolvimento de novos antioxidantes dirigidos para as mitocondrias na melhoria do fenótipo da Esclerose Lateral Amiotrofica familiar SOD1 - COORDINATOR: Filomena Silva - PROPONENTE: Centro de Neurociencias e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029391	01/05/2018	30/04/2021	148 765,17	35 649,64
Ao Encontro das Regras para a Permeação Passiva através da Barreira Hemato-Encefálica - COORDINATOR: Armindo José Alves S. Salvador - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/DTP-FTO/2784/2014	01/07/2016	31/12/2019	69 072,00	15 380,43
Relação entre adenosina e instabilidade cromossomal: uma nova perspetiva para compreender o mecanismo oncogénico em glioblastoma - COORDINATOR: Armindo José Alves S. Salvador - PROPONENTE: Universidade da Beira Interior - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/BIM-ONC/7121/2014	01/04/2016	01/10/2019	5 000,00	2 481,84

Doenças ognitivas como sinaptopatias: Impacto de mutações humanasno gene CACNG2 - COORDINATOR: Ana Luisa Monteiro de Carvalho	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028541	01/07/2018	30/06/2021	236 245,47	107 594,61
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. POCI-01-0145-FEDER-031173	01/07/2018	30/06/2021	38 600,01	15 698,08
Mecanismos patogénicos da encefalite autoimune sináptica associada a anticorpos anti-CASPR2 - COORDINATOR: Sandra Manuela D. Santos	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029452	15/06/2018	14/06/2021	236 222,74	86 023,12
Os altos e baixos do stress celular:" a hipótese MAM" para a patofisiologia da doença Bipolar - COORDINATOR: Cláudia Maria Fragão Pereira	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028214	26/07/2018	25/07/2021	237 822,11	51 093,53
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. POCI-01-0145-FEDER-029560	01/07/2018	30/06/2021	20 125,00	5 497,52
Papel dos astrócitos no controlo da memória-foco nos recetores adenosina A2A - COORDINATOR: Paula Maria Garcia Agostinho	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-NMC/4154/2014	01/05/2016	31/07/2019	178 742,00	46 676,00
NiNjA - Nova estratégia Neuroendócrina para um envelhecimento saudável - COORDINATOR: Cláudia Margarida G. Cavadas	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-030167	01/06/2018	31/05/2021	238 646,90	99 715,01
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. POCI-01-0145-FEDER-029002	06/07/2018	05/07/2021	237 109,13	55 228,88

Cartilfactory - Desenvolvimento e Construção de um Sistema Automatizado de Fabricação em Larga Escala de Engenharia de Cartilagem Combinado Eletrofiação 3D de condrócitos e expansão celular 3D com estímulo mecânico em bioreator - COORDINATOR: Alexandrina M. F. S. P. Mendes - PROPONENTE: Universidade de Aveiro - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028424	01/06/2018	31/05/2021	70 234,46	12 224,91
Mecanismos sinápticos envolvidos nas acções dos canabinoides no cérebro e sua modulação por receptores de adenosina: implicações para a regulação do humor e memória - COORDINATOR: Attila Köfalvi - PROPONENTE: Instituto Medicina Molecular - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/DTP-FTO/3346/2014	01/03/2016	28/02/2019	9 900,00	305,59
Diagnóstico e prognóstico da esquizofrenia: a caminho de uma medicina personalizada? - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: - PARTICIPANTS:	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-SCC/7051/2014	01/06/2016	31/12/2019	199 986,54	48 899,48
Proteostasia da huntingtina e mitocondria: alvos para prevenir a disfunção neuronal na doençade Huntington - COORDINATOR: Paula Isabel da Silva Moreira - PROPONENTE: Instituto de Ciências e Tecnologias Agrárias - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-NMC/0412/2014	01/06/2016	01/12/2019	36 000,00	13 511,10
EXERCITANDO O FUTURO: Exercício Voluntário Durante Diabetes Gestacional com um Estratégia para Melhorar a Função Mitocondrial na Descendência - COORDINATOR: António Joaquim Matos Moreno - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. PTDC/DTP-DES/1082/2014	01/04/2016	30/09/2019	129 152,41	17 042,17
Polymeric NanoBioMaterials for drug delivery: developing and implementation of safe-by-design concept enabling safe healthcare solutions - COORDINATOR: Olga Maria Fernandes R. Borges	Fundação para Ciência e a Tecnologia - REF. ProSafe/0001/2016	01/04/2017	30/06/2019	149 977,00	36 350,80

Development of an innovative targeted-nanoparticle formulation for combined gene therapy and chemotherapy application in hepatocellular carcinoma - COORDINATOR: Henrique Manuel S. Faneca	Fundação para Ciência e a Tecnologia - REF. IF/01007/2015	01/07/2017	31/10/2021	50 000,00	3 374,44
ARCADLIKE - Desenvolvimento da Arquitetura Fisiológica do colagénio em cartilagem desenvolvida in-vitro por combinação de estímulo mecânico e scaffolds fibrosos anisotrópicos em biorreator - COORDINATOR: Alexandrina M. F. S. P. Mendes - PROPONENTE: UA - Universidade de Aveiro - PARTICIPANTS: Centro de Neurociências e Biologia Celular	Fundação para Ciência e a Tecnologia - REF. PTDC/EMS-TEC/3263/2014	01/06/2016	03/03/2019	73 368,00	5 126,25
Red2Discovery-As macroalgas vermelhas Sphoerococcus Coronopifolius e Asparagopsis armata como alvos para a descoberta de novos fármacos de origem marinha - COORDINATOR: Maria Carmen M. C. Alpoim - PROPONENTE: Instituto Politécnico de Leiria - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/MAR-BIO/6149/2014	01/06/2016	30/11/2019	27 600,00	5 617,66
SNAPs alternativas na libertação de neurotransmissores: da função molecular à disfunção neurocognitiva - COORDINATOR: Paulo César da Silva Pinheiro	Fundação para Ciência e a Tecnologia - REF. PTDC/BIA-CEL/29451/2017	01/10/2018	30/09/2021	234 410,41	70 068,56
Eficácia pré-clinica 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. POCI-01-0145-FEDER-029152	01/06/2018	31/05/2021	41 525,00	6 729,98
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	12/01/2018	31/12/2020	48 161,27	43 576,80
MitoBEN - COORDINATOR: Paulo Jorge G. S. S. Oliveira	Agência de Inovação, S.A. - REF. CENTRO-01-0145-FEDER-037892	01/01/2018	31/12/2020	47 140,37	40 585,26

Uso de fitoquímicos redox-activos para desencadear a hormesis mitocondrial: Desenvolvimento de uma nova geração de ingredientes para a cosmética - COORDINATOR: Paulo Jorge Gouveia Simões da Silva Oliveira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028607	26/07/2018	25/07/2021	159 006,95	54 884,85
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. POCI-01-0145-FEDER-029297	06/07/2018	05/07/2021	166 749,26	15 904,16
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. POCI-01-0145-FEDER-030712	15/06/2018	14/06/2021	224 839,21	60 250,41
Hierarquia social e adversidades no período juvenil: regulação neuroepigenética e modulação optogenética dos circuitos do cortex pré-frontal - COORDINATOR: João Peça Silvestre - PROPONENTE: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-SCC/3247/2014	01/04/2016	01/10/2019	198 205,00	50 881,65
Identificação e caracterização funcional de microRNAs reguladores de dano cardíaco por esquemia-reperfusão - COORDINATOR: Miguel Luís Cunha Mano	Fundação para Ciência e a Tecnologia - REF. PTDC/BIM-MEC/2968/2014	01/04/2016	31/12/2019	177 541,08	23 985,86
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	01/10/2016	30/09/2020	106 233,00	16 658,02
IF/00578/2014/CP1258/CT0002 - COORDINATOR: Irina Moreira	Fundação para Ciência e a Tecnologia - REF. IF/00578/2014/CP1258/CT0002	15/01/2015	09/11/2019	50 000,00	13 406,50

Mecanismos da indução hemogénica em fibroblastos humanos - COORDINATOR: Carlos Filipe R. L. Pereira	Fundação para Ciência e a Tecnologia - REF. PTDC/BIM-MED/0075/2014	01/03/2016	01/06/2019	198 687,00	20 600,79
Visualização da terapia génica dos sistema nervoso central - COORDINATOR: Luisa Maria O. P. L. Cortes	Fundação para Ciência e a Tecnologia - REF. PTDC/BBB-NAN/0932/2014	01/06/2016	31/12/2019	199 999,00	120 412,54
Glicerol como ingrediente alternativo para rações de peixe-potencial para aquacultura - COORDINATOR: Ivan Daniel Santos M. Viegas - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. PTDC/CVT-NUT/2851/2014	31/03/2016	15/10/2019	170 244,00	18 932,19
Co-encapsulação em transportadores lipidos nanoestruturados como uma plataforma multifuncional para o tratamento de tumores cerebrais - COORDINATOR: Carla Sofia Pinheiro Vitorino - PROPONENTE: Centro Neurociencias e Biologia celular - PARTICIPANTS: UL	Fundação para Ciência e a Tecnologia - REF. PTDC/CTM-NAN/2658/2014	01/07/2016	30/06/2019	166 492,00	31 232,73
Pequenas moléculas inibidoras do proteassoma: 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	01/07/2016	30/06/2020	60 636,00	14 251,68
Papel do Exercício Físico no tratamento da hipertensão Resistente - COORDINATOR: Maria Joana Barbosa de Melo - PROPONENTE: Universidade de Aveiro	Fundação para Ciência e a Tecnologia - REF. PTDC/DTP-DES/1725/2014	01/09/2016	31/12/2019	10 800,00	2 137,84
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. POCI-01-0145-FEDER-029592	26/07/2018	25/07/2021	236 788,94	67 013,97
IF/01182/2015 - COORDINATOR: Vilma A. Sardão	Fundação para Ciência e a Tecnologia - REF. IF/01182/2015	01/07/2017	30/06/2021	50 000,00	7 354,12

IF/01272/2015 - COORDINATOR: Alexandra Teresa Pires Carvalho	Fundação para Ciência e a Tecnologia - REF. IF/01272/2015	01/07/2017	01/07/2021	50 000,00	1 111,02
IF/01492/2015 - COORDINATOR: Paula Canas	Fundação para Ciência e a Tecnologia - REF. IF/01492/2015	01/07/2017	01/07/2021	49 950,00	4 132,40
Decoding the role of host non-coding RNAs in infection by bacterial pathogens - COORDINATOR: Ana Sofia Bregieiro Eulálio	Fundação para Ciência e a Tecnologia - REF. IF/01105/2015	01/07/2017	31/08/2019	50 000,40	42 564,76
IF/00825/2015 - COORDINATOR: Célia Alexandra F.O. Aveleira	Fundação para Ciência e a Tecnologia - REF. IF/00825/2015	01/07/2017	01/07/2021	50 000,00	7 990,49
Alergénios cutâneos: moléculas com uma aplicação terapêutica improvavel para a doença de Alzheimer - COORDINATOR: Maria Teresa T. Cruz Rosete	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029369	26/07/2018	25/07/2021	235 872,07	63 123,31
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. POCI-01-0145-FEDER-028163	26/07/2018	25/07/2021	26 015,63	1 898,10
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. POCI-01-0145-FEDER-029221	15/06/2018	14/06/2021	132 399,17	67 899,03
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. POCI-01-0145-FEDER-032625	25/07/2018	24/07/2021	29 849,56	6 771,38

Os receptores A2A para a adenosina controlam a formação de axónios durante o desenvolvimento neuronal: novas estratégias para prevenir a epileptogénes - COORDINATOR: Joana Medeiros Vieira Marques	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028160	06/07/2018	05/07/2021	238 108,56	50 219,73
Identificação e caracterização funcional de microRNAs que regulam a infecção por estirpes de Stphylococcus aureus clinicamente relevantes. - COORDINATOR: Ana Sofia Bregieiro Eulálio	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029999	26/07/2018	25/07/2021	234 226,71	53 700,86
Desenvolvimento de um nanossistema inovador para mediar um estratégia terapêutica combinada e multi-alvo para o carcinoma hepatocelular. - COORDINATOR: Henrique Manuel S. Faneca	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-030916	01/07/2018	30/06/2021	238 634,37	67 189,27
Um modelo vascular de Progeria para identificar mediadores da perda de células do musculo liso. - COORDINATOR: Lino da Silva Ferreira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UC	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029229	26/07/2018	25/07/2021	213 487,06	78 104,88
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. POCI-01-0145-FEDER-031679	01/06/2018	30/05/2021	24 375,00	835,64
BrainEdition:controlo remoto da edição genética em celulas estaminais neurais. - COORDINATOR: Sónia Luzia Claro de Pinho	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028060	22/06/2018	21/06/2021	239 947,07	37 671,19
Uma biblioteca de nanoparticulas activáveis por acção da luz para a libertação de terapias baseadas em RNA - COORDINATOR: Vitor Francisco - PROPONENTE: - PARTICIPANTS:	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029414	06/07/2018	05/07/2021	238 697,08	55 538,20

Vacina Terapêutica para a Hepatite B crónica: Desenvolvimento de nanopartículas à base de glucano com o objectivo de direccionar os antigénicos para as células imunitárias e induzir actividade antiviral - COORDINATOR: Olga Maria Fernandes R. Borges	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-030331	15/07/2018	14/07/2021	234 902,55	61 940,90
EXO-HEART: Protecção e regeneração cardíaca mediada pela administração sistémica e direccionada de exosomas. - COORDINATOR: Hugo Agostinho Machado Fernandes	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029919	01/07/2018	30/06/2021	237 289,21	62 600,94
Indução de Células Apresentadoras de Antigénio por Reprogramação Celular Direta - COORDINATOR: Carlos Filipe R. L. Pereira	Fundação para Ciência e a Tecnologia - REF. CENTRO-01-0145-FEDER-030013	01/06/2018	31/05/2021	238 471,74	69 079,01
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. POCI-01-0145-FEDER-029017	01/07/2018	30/06/2021	56 250,00	47 762,03
Translação da reprogramação celular direta em células dendrítcas na imunoterapia do cancro. - COORDINATOR: Carlos Filipe R. L. Pereira	Fundação para Ciência e a Tecnologia - REF. CENTRO-01-0145-FEDER-039473	01/04/2018	31/03/2021	48 925,50	41 428,86
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. POCI-01-0145-FEDER-030550	15/11/2018	14/11/2021	220 849,74	68 617,42
Propriedades viscoelásticas do cérebro em Esclerose Multipla e implicações em mecanomodulação de oligodendrócitos: uma abordagem celular e clínica - COORDINATOR: Mário Grãos - PROPONENTE: CNBC - PARTICIPANTS: UNIVERSIDEDE DE COIMBRA	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029516	26/07/2018	25/07/2021	192 615,36	56 214,70

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. POCI-01-0145-FEDER-031356	15/06/2018	14/06/2021	196 773,35	69 323,47
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	03/09/2018	02/09/2021	78 850,00	12 977,38
Alvejamento de transportadores de aminoácidos catiónicos para radioteranóstica do cancro: uma abordagem experimental e de quimica computacional - COORDINATOR: Irina Moreira - PROPONENTE: IST-ID - PARTICIPANTS: CNBC	Fundação para Ciência e a Tecnologia - REF. PTDC/QUI-NUC/30147/2017	01/09/2018	31/08/2021	23 449,35	8 395,79
Desenho racional de uma esterase termoestável para a produção de bioplásticos de alto valor para aplicações biomédicas - COORDINATOR: Alexandra Teresa Pires Carvalho - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: Universidade de Aveiro	Fundação para Ciência e a Tecnologia - REF. MIT-EXPL/ISF/0021/2017	03/09/2018	02/12/2019	93 157,99	76 961,49
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	17/09/2018	16/09/2021	238 721,61	51 820,13
					4 101 561,82
Alemtuzumab therapy in Multiple Sclerosis: tracking immune cell trafficking, induced molecular mechanisms and aftermath effects - COORDINATOR: Inês Baldeiras	Sanofi aventis, Lda. - REF. GZ-2017-11730	01/04/2019	31/07/2022	302 087,00	11 243,57

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	01/01/2013	31/12/2025	11 186,27	3 130,52
Exploring striatal postsynaptic SAPAP3 in Huntington's disease - COORDINATOR: Ana Cristina Carvalho Rego	The University Hospital of Ulm - REF. Exploring striatal postsynaptic SAPAP3 in Huntington's disease	01/10/2018	31/10/2019	50 000,00	36 512,83
Prémio Mantero Belard 2017 - COORDINATOR: Carlos Jorge A. M. B. Duarte - PROPONENTE: IMM - PARTICIPANTS: CNBC	SCML - REF. Prémio Mantero Belard 2017	01/01/2018	31/12/2020	5 093,25	609,38
Role of NT3/TrkC in the regulation of fear - Project 85/18 - COORDINATOR: Monica Pinto dos Santos	Bial-Portela & Companhia, S.A. - REF. Role of NT3/TrkC in the regulation of fear - Project 85/18	01/03/2019	28/02/2022	42 500,00	19 135,92
Combination therapy synergistically accelerates diabetic wound closure - COORDINATOR: Eugénia Maria L. Carvalho	EFSD-Europ. Found. S. Diabetes - REF. EFSD-Microvascular Complicatio	09/11/2015	31/12/2020	70 000,00	5 445,81
Adenosine A2A receptors as triggers of memory - COORDINATOR: Rodrigo Pinto S.A. Cunha	Fundação para Ciência e a Tecnologia - REF. Maratona da Saúde 2016	01/05/2017	30/04/2019	24 980,00	0,00
MATERA_5402 - COORDINATOR: Lino da Silva Ferreira	MATERA	01/09/2010	31/12/2019	27 820,88	865,41
Promoting endothelial progenitor cell function in diabetic would healing - COORDINATOR: Ermelindo Carreira Leal	EFSD-Europ. Found. S. Diabetes - REF. Promoting endothelial progenitor	01/01/2013	31/12/2020	50 000,00	0,00
Evaluate novel calpain inhibitors from Blade Therapeutics - COORDINATOR: Luis Pereira de Almeida	Blade Therapeutics - REF. Blade	19/07/2018	31/12/2025	140 000,00	16 284,12
Silencing Machado-Joseph Disease/ Spinocerebellar ataxia type 3 trough the systemic route - COORDINATOR: Rui Jorge Gonçalves P. Nobre	National Ataxia Foundation - REF. ATAXIA_Silencing MJD through..	31/12/2013	31/12/2019	10 823,71	934,83
Early life stress and social hieraschies: the role - COORDINATOR: João Peça Silvestre	Bial-Portela & Companhia, S.A. - REF. 266/16 Early life stress	01/01/2017	31/12/2019	48 000,00	20 064,08

"Mitochondrial Trafficking In Alzheimer Disease: Revealing the Role of Hummr." - COORDINATOR: Paula Isabel da Silva Moreira	Alzheimer´s Association - REF. NIRG-13-282387_ Mitochondrial	01/11/2013	31/12/2020	71 495,56	2 780,94
Coffee protects against NAFLD progression through preservation of intestinal permeability and inhibiton of liver fibrosis - COORDINATOR: John Griffith Jones	Institute for Scientific Information on Coffee - REF. Coffee protects against NAFLD	01/07/2019	30/06/2021	112 903,00	2 645,48
W81XWH-18-1-0532_Adenosine Receptor Antagonism Affords Integrated Benefits for Neurological Symptoms of Neurological Symptoms of Neurofibromatosis Typ - COORDINATOR: Rodrigo S. Cunha	Army Medical Research - REF. W81XWH-18-1-0532_ Adenosine Receptor	15/09/2018	14/09/2019	99 714,38	0,00
Adenosine A2A receptors as a new opportunity to manage and detail the neurobiology of emotional distress. - COORDINATOR: Rodrigo Pinto Cunha	LA CAiXA - REF. LA Caixa - HR17-00523 - adostress	18/12/2019	14/12/2022	333 516,00	0,00
Bolsa PMJMCD2017 - COORDINATOR: Rodrigo Pinto S.A. Cunha	Fundação Amélia de Mello - REF. Bolsa PMJMCD2017	01/01/2018	31/12/2019	25 000,00	7 462,71
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	01/04/2015	31/12/2020	60 853,05	0,00
Advanced Induced Pluripotent Stem Cell –based Models of Machado-Joseph disease - COORDINATOR: Magda Santana	National Ataxia Foundation - REF. Advanced Induced Pluripotent	01/01/2016	31/12/2019	31 905,49	1 238,00
Novel cerebrospinal fluid and serum biomarkers for Multiple Sclerosis_ RG-1601-075 - COORDINATOR: Carlos Jorge A. M. B. Duarte	National Multiple Sclerosis - REF. Multiple Sclerosis_ RG-1601-075	01/10/2016	30/09/2020	149 586,13	47 746,62
The toxinogenic gut microbiome in sporadic Parkinson`s Disease: a quest for "antiPDbiotics - COORDINATOR: Sandra Morais Cardoso	SCML - REF. Prémio Mantero Belard´2016	01/01/2017	30/06/2020	199 098,00	62 021,99
The influence of maternal bonding in neuroimmune synaptic sculptin - COORDINATOR: Ana Luisa Colaço Cardoso	Bial-Portela & Companhia, S.A. - REF. The influence of maternal...26	01/01/2017	31/12/2019	45 000,00	16 630,40

Calpain-mediated proteolysis in Machado-Joseph disease - COORDINATOR: Ana Teresa Antunes Simões	National Ataxia Foundation - REF. Calpain-mediated proteolysis i	01/01/2017	31/12/2019	14 210,00	0,00
Towards personalized beta-cell mass imaging in type 2 Diabetes - Consortium Agreement - ZonMw file Nº 40-41200-98-9307 - Date 01-07-2017 - COORDINATOR: Nuno Miguel Silva Empadinhas	INFARMED - REF. FIS-FIS-2015-01_DIA_20150630-1	01/02/2017	28/02/2019	100 000,00	24 443,37
Towards personalized beta-cell mass imaging in type 2 diabetes - COORDINATOR: Hugo Agostinho Machado Fernand - PROPONENTE: Stichting Katholieke Universiteit	Zon Mw - REF. Zon Mw	06/08/2017	06/06/2021	128 059,00	22 799,65
FLAD - Health Care 2020 - COORDINATOR: Paulo Jorge G. S. S. Oliveira	Fundação Luso-Americana - REF. FLAD - Health Care 2020	01/01/2018	31/03/2019	20 000,00	721,77
Optic Nerve Atrophy - Santhera - COORDINATOR: Maria Manuela Monteiro Grazina -	Santhera Netherlands - REF. Optic Nerve Atrophy_Santhera	01/07/2018	30/06/2022	63 999,98	16 885,06
Inhibition of macrophage protein tyrosine phosphatase !B (PTP1B) as a novel therapy for improved wound healing in diabetes - COORDINATOR: Eugénia Maria L. Carvalho	The University Court of the University of Aberdeen - REF. DUK grant_ PTP1B	17/09/2018	16/09/2019	17 327,45	3 169,42
SymbioReactor-Sustainable production of bioactive metabolites from microbial symbionts of marine sponges and corals - COORDINATOR:Maria da Conceição V. Egas - PROPONENTE: Instituto Superior Técnico - PARTICIPANTS: Universidade de Aveiro	IST-ID - REF. FA-05-2017-032	06/09/2019	05/09/2021	29 153,00	0,00
Silencing the SCA3-causing gene ATXN3 through CRISPR interference - COORDINATOR: Carlos Adriano A.Andrade Matos	National Ataxia Foundation - REF. ATXN3 through CRISPR interference	01/03/2019	29/02/2020	12 914,00	5 292,87
A Saúde no Saber - COORDINATOR: Sara Varela Amaral	Ciência Viva - REF. 45-2019/478	01/07/2019	01/12/2021	20 000,00	0,00
A system approach to find a blood-based biomarker for Machado-Joseph Disease - COORDINATOR: Magda Santana	National Ataxia Foundation - REF. Machado-Joseph Disease_blood-based biomarker	01/03/2019	28/02/2021	43 399,05	13 532,09

Cooperação Científica e Tecnológica FCT/HUNGRIA 2017/2018 - COORDINATOR: Anabela Marisa Azul	Fundação para Ciência e a Tecnologia - REF. Cooperação Científica e Tecnológica FCT/ HUNGRIA 2017/2018	01/01/2018	31/12/2019	4 000,00	611,80
Novas terapias para Doença de Chagas: reposicionamento de drogas com efeito sinergístico com Benzonidazol para combater infecção por Trypanosoma cruzi - COORDINATOR: Miguel L. C. Mano	Fundação para Ciência e a Tecnologia - REF. FCT/ CAPES-2018/2019	16/04/2018	30/04/2021	9 000,00	1 301,77
Paulo Cesar da Silva Pinheiro - COORDINATOR: Paulo César da Silva Pinheiro	Fundação Calouste Gulbenkian - REF. Paulo Cesar da Silva Pinheiro	01/01/2005	31/12/2019	10 000,00	64,58
Econtro CNC 2014 Programa Dout - COORDINATOR: João Ramalho de Sousa Santos	- REF. Econtro CNC 2014 Programa Doutoral	01/01/2014	31/12/2019	2 450,00	0,00
3º Simpósio International PDBE - COORDINATOR: João Ramalho de Sousa Santos	- REF. 3º Simpósio International PDBE	01/07/2016	31/12/2019	2 195,64	0,00
Paula Isabel da Silva Moreira - COORDINATOR: Paula Isabel da Silva Moreira	L`Oréal - REF. Paula Isabel da Silva Moreira	01/11/2008	31/12/2019	20 000,00	0,00
Human Chromaffin Cells and NPY - COORDINATOR: Cláudia Margarida G. Cavadas	- REF. Human Chromaffin Cells and NPY	20/11/2002	31/12/2019	5 851,58	0,00
Tecnimede - REMANESCENTE - COORDINATOR: Cláudia Margarida G. Cavadas	- REF. Tecnimede	01/10/2014	31/12/2019	7 918,01	0,00
Prémio Janssen Inovação - COORDINATOR: Cláudia Margarida G. Cavadas	Janssen-Cilag - REF. Prémio Janssen Inovação	01/10/2016	31/12/2019	20 000,00	0,00
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	01/07/2017	31/08/2019	5 000,00	28,50
Terapia Machado Josefh - COORDINATOR: Luis Pereira de Almeida	- REF. Terapia Machado Josefh	01/01/2012	31/12/2019	8 031,75	636,25

Mini-Simposyum 'Vaccines and A - COORDINATOR: Olga Maria Fernandes R. Borges	NOVARTIS FARMA S.A. - REF. Mini-Simposyum 'Vaccines and A	01/03/2011	31/12/2019	250,00	0,00
Prémio Envelhecimento SPN - COORDINATOR: Elisabete Batista Ferreiro	Sociedade Port. Neurociências - REF. Prémio Envelhecimento SPN	01/06/2011	31/12/2020	15 600,00	589,23
APU/ASTELLAS 2011 - COORDINATOR: João Nuno Sereno de A. Moreira	APU - REF.APU/ASTELLAS 2011	25/07/2012	31/12/2019	7 000,00	65,11
EFSD - European Foundation Study Di - COORDINATOR: Eugénia Maria L. Carvalho	EFSD-Europ. Found. S. Diabetes - REF. Saldos Fundos EFSD transitados	09/01/2013	31/12/2020	22 960,43	10 208,98
AsHeCe - Marta Pereira - COORDINATOR: João Nuno Sereno de A. Moreira	- REF. AsHeCe - Marta Pereira	01/01/2013	31/12/2019	8 000,00	41,10
Bolsa Cient.LPCE2014 Miranda M - COORDINATOR: Carlos Jorge A. M. B. Duarte	Liga Port. contra Epilepsia - REF. Bolsa Cient.LPCE2014 Miranda M	31/03/2014	31/12/2019	3 500,00	0,00
Fundos FBG - COORDINATOR: Maria Manuela Monteiro Grazina	- REF. Fundos LBG	10/12/2013	31/12/2019	23 138,51	2 029,50
Fundos Obesidade - COORDINATOR: Maria Manuela Monteiro Grazina	Sanofi aventis, Lda. - REF. Fundos Obesidade	01/06/2017	31/12/2025	22 600,00	2 222,03
Bial - REMANESCENTE - COORDINATOR: Inês Maria Pombinho de Araújo	BIAL - REF. Bial - REMANESCENTE	01/09/2014	31/12/2019	15 293,99	0,00
Exocord - REMANESCENTE - COORDINATOR: Lino da Silva Ferreira	- REF. Exocord	01/01/2017	31/12/2019	32 458,67	3 876,75
Livro de Neurociências - COORDINATOR: Ana Cristina Carvalho Rego	- REF. Livro de Neurociências	01/01/2016	31/12/2019	2 400,00	0,00
Brain Buskers - COORDINATOR: Sara Varela Amaral	Liga Port. contra Epilepsia - REF. Brain Buskers	29/11/2017	31/12/2020	1 664,25	74,47
EMBO - COORDINATOR: Ana Sofia Bregieiro Eulálio	EMBO - REF. EMBO	01/04/2017	31/12/2020	13 919,00	2 068,61

14º Edição do Programa Doutoral PDBEB - COORDINATOR: João Ramalho de Sousa Santos	Bluepharma - REF. 14º Edição do Programa Doutoral PDBEB	01/01/2018	31/12/2019	500,00	384,20
FENS and IBRO-PERC Support for Graduate Courses in 2018 - COORDINATOR:Ana Luisa Monteiro de Carvalho	FENS - REF. FENS IBRO-PERC	01/02/2018	30/09/2019	6 000,00	1 487,52
Prémio 2º lugar no concurso Janssen Inovação 2018 - COORDINATOR: Sara Matias Silva	Janssen-Cilag - REF. Prémio 2º lugar no concurso Janssen Inovação 2018	17/05/2018	31/12/2019	20 000,00	7 726,76
Astrazeneca - iMed Conference 10.0 - COORDINATOR: Rodrigo Filipe Nunes Ribeiro	Fundação Astrazeneca - REF. Astrazeneca - iMed Conference 10.0	01/11/2018	31/12/2020	3 000,00	0,00
Universidade Kazan_bench fees - COORDINATOR: Paulo Jorge G. S. S. Oliveira	Universidade Kazan - REF. Universidade Kazan	17/09/2018	16/09/2019	1 800,00	142,07
Prémio EIT Health_Grupo Alexandrina Mendes - COORDINATOR: Alexandrina M. F. S. P. Mendes	European Institute of Innovation Tecnology EIT - REF. Prémio EIT Health_ Grupo Professora Doutora Alexandrina Mendes	01/01/2019	31/12/2020	15 378,15	13 018,02
Bolsa SPOT João Pedro Moreira - COORDINATOR: Alexandrina M. F. S. P. Mendes	Sociedade de Ortopedia e Traumatologia - REF. Bolsa SPOT João Pedro Moreira	23/01/2018	31/12/2020	2 500,00	664,22
Bolsa de Investigação SPT-Seculo XXI - COORDINATOR: Eugénia Maria L. Carvalho	Sociedade Portuguesa de Transplantação - REF. Bolsa de Investigação SPT-Seculo XXI	01/03/2019	30/11/2020	10 000,00	1 661,00
CIBB Meeting 2019 - COORDINATOR: Ricardo Rodrigues	- REF. CIBB Meeting 2019	01/11/2019	31/12/2019	850,00	564,00
Dana-FENS Brain Awareness Week grants 2019 - COORDINATOR: Sara Varela Amaral	FENS - REF. Semana do cérebro 2019	15/02/2019	31/12/2019	1 001,00	908,41
Ocupação Cientifica de Jovens nas Férias - 2019 - COORDINATOR: Sara Varela Amaral	Ciência Viva - REF. Ocupação Cientifica de Jovens nas Férias - 2019	01/07/2019	30/10/2019	3 736,00	3 700,99
Prémio "Best Scientific Poster from the Innovative Competition-AstraZeneca Foundation" - COORDINATOR: João Miguel Esteves C.S. Cardoso	Fundação Astrazeneca - REF. Prémio_Best Scientific Poster from the Innovative Competition-AstraZeneca Foundation	01/01/2018	31/12/2021	1 000,00	0,00

Bebday2019 - COORDINATOR: Mariana Laranjo	- REF. Bebday2019	01/08/2019	31/12/2019	150,00	0,00
LifeSciences ByCENTRO: Valorização do Conhecimento em Ciências da Vida - COORDINATOR: João Ramalho de Sousa Santos	Instituto Financeiro para o Desenvolvimento Regional - REF. CENTRO-01-0246-FEDER-000011	27/03/2017	26/03/2020	169 804,60	51 380,98
Advanced toolbox for rapid and cost-effective functional metagenomic screening - microbiology meets microfluidics - COORDINATOR: Milton Simões da Costa - PROPONENTE: Universidade Madrid	Univ. Autónoma Madrid - REF. GA 685474 B I O T E C - 6 - 2 0 1 5 Metafluidics	01/06/2016	30/11/2020	407 590,00	106 071,52
TRoMBONE - 748583 - COORDINATOR: Lino da Silva Ferreira	Research Executive Agency - REF. TRoMBONE - 748583	01/04/2017	31/03/2019	160 635,60	26 635,28
Foie Gras_722619 - COORDINATOR: Paulo Jorge G.S.S.Oliveira - PARTICIPANTS: Fyziologicky Ustav, UNIBA, FFUL, NENCKI, UPORTO, INTITUT NATIONAL, CNR, HMGU, CSIC	European Commission - REF. Foie Gras - 722619	01/01/2017	31/12/2020	793 616,78	213 874,80
Rise Foie Gras_734719 - COORDINATOR: Paulo Jorge G. S. S. Oliveira - PARTICIPANTS: CNR, FFUL, HMGU, CSIC, UNIBA, UPORTO, NENCKI, KCL, MEDIAGNOST, APDP, OROBOROS, microBiolytics	European Commission - REF. Foie Gras RISE - 734719	01/06/2017	31/05/2021	102 400,00	22 506,09
InnoCore - Core Technologies for Education and Innovation in Life Sciences - COORDINATOR: Carlos Jorge A. M. B. Duarte - PROPONENTE: University of Trento	University of Trento - REF. InnoCore	01/09/2019	31/08/2022	59 649,00	1 086,88
CAFFEIN - Cancer Associated Fibroblasts (CAF) Function in Tumor Expansion and Invasion - COORDINATOR: João Nuno Sereno de A. Moreira - PROPONENTE: University of Copenhagen	European Commission - REF. Marie Curie grant 316610	01/10/2012	31/12/2020	201 432,00	172,20
Functional high-throughput analysis of the role of microRNAs in cardiac ischemia-reperfusion injury - COORDINATOR: Miguel L. C. Mano	European Commission - REF. 701096-microCardio-MSCA-IF-EF-ST	01/03/2016	31/12/2020	148 635,60	6 957,09

Training European Network: Metabolic Dysfunction associated with Pharmacological Treatment of Schizophrenia - COORDINATOR: Eugénia Maria L. Carvalho	Agencia Estatal CSIC - REF. TREATMENT-721236	01/01/2017	31/12/2020	428 904,72	109 374,35
Synaptic Dysfunction in Neuropsychiatric Disorders - COORDINATOR:Ana Luisa Monteiro de Carvalho - - 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	25/02/2019	28/02/2023	1 045 802,48	94 057,99
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	01/06/2018	31/05/2022	623 269,08	165 712,25
Improving drug delivery to the brain and glioblastoma treatment using temperature._Nano Brain - COORDINATOR: Lino da Silva Ferreira	European Commission - REF. Nano_Brain 842405	01/07/2019	30/09/2019	147 816,04	16 070,32
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	07/05/2018	06/05/2020	148 638,60	69 178,71
Projetos de Desenvolvimento e Implementação de Infraestruturas de Investigação inseridas no RNIE - COORDINATOR: Bruno José F. O. Manadas - PROPONENTE: Faculdade de Ciencias da Universidade de Lisboa - PARTICIPANTS: CNBC e Outros	Fundação para Ciência e a Tecnologia - REF. Nó da RNEM - Dr. Bruno Manadas	01/01/2017	31/12/2019	357 823,98	27 115,47
PPBI_Portuguese Platform of BioImaging - COORDINATOR: Luisa Maria O. P. L. Cortes - PROPONENTE: Instituto de Biologia Molecular e Celular	Rede PPBI - REF. PINFRA/22122/2016	01/06/2017	31/05/2021	275 180,00	157 071,00
Sub-Total Others National and International Projects					**1 462 937,64**

GENetic Frontotemporal dementia Initiative (GENFI) - COORDINATOR: Isabel Santana	- REF. GENFI	15/02/2016	31/12/2020	14 138,08	325,00
JPND BIOMARKAPD - COORDINATOR: Catarina Isabel N. R. Oliveira	- REF. JPND BIOMARKAPD	01/01/2016	31/12/2019	2 188,87	0,00
From Protein Structure to biological funtion through interactomics- an integrated view (2nd edition) - COORDINATOR: Bruno José F. O. Manadas	- REF. Cursos Bruno Manadas	01/01/2018	19/01/2019	10 350,00	780,33
Cursos de Verão Doutor Carlos Palmeira - COORDINATOR: Carlos Manuel Marques Palmeira	- REF. Cursos de Verão Doutor Carlos Palmeira	01/04/2019	29/04/2019	8 930,03	4 892,55
8º Workshop da Sociedade Europeia de Cálcio - COORDINATOR: Cláudia Pereira	- REF. 8º Workshop da Sociedade Europeia de Cálcio	01/06/2019	31/12/2019	13 607,21	8 510,27
Summer School - COORDINATOR: Armindo José Alves S. Salvador	- REF. Summer School	01/06/2015	31/12/2019	6 667,00	2 151,19
Curso Bioteria Teór/Prát_2015 - COORDINATOR: João António Nave Laranjinha	- REF. Curso Bioteria Teór/Prát_2015	01/08/2015	31/12/2019	8 298,50	0,00
Fórum Pós-docs - COORDINATOR: Ermelindo Carreira Leal	- REF. Fórum Pós-docs	01/02/2018	31/12/2019	1 505,00	0,00
Brain without borders - COORDINATOR: Luis Pereira de Almeida	- REF. Brain without borders	01/09/2016	31/12/2019	1 470,78	0,00
Formações do Gab. Comunicação - COORDINATOR: Sara Varela Amaral	- REF. Angariação fundos Gab. Comunicação da Ciência	01/01/2017	30/12/2019	140,00	10,56
Curso FOIE GRAS - COORDINATOR: Paulo Jorge G. S. S. Oliveira	- REF. Cursos de faturação Paulo Oliveira	01/09/2017	31/12/2019	2 493,40	1 746,20
Faturação Cursos Paula Mota II - COORDINATOR: Paula Cristina Cardoso R. Mota	- REF. Faturação Curso Janeiro 2019 - Paula Mota	01/11/2018	31/12/2019	23 750,00	16 849,76
Curso Faturação Paula Mota III - COORDINATOR: Paula Mota	- REF. Curso Faturação Paula Mota III	01/09/2019	30/08/2020	22 300,01	13 363,07

Stress, Resilience and Epigenetic alterations: Frontal cortex and Social dominance. - COORDINATOR: Ana Cristina Carvalho Rego	- REF. Consultancy Agreement - Sigma-Tau B.V. and UC_StREs-FSD	01/01/2018	31/12/2020	18 500,00	12 288,24
AAV-miATXN3w, AAV-GFP reporter, and new to develop transgene-containing AAVs - COORDINATOR: Luis Pereira de Almeida - PROPONENTE: UNIQURE Biopharma B.V. - PARTICIPANTS: CNBC; UC	- REF. Collaboration agreement_uniQure biopharma B.V.	17/12/2018	31/12/2025	52 187,50	191,70
Evaluation of MJD/SCA3 preclinical drug discovery model systems - COORDINATOR: Luis Pereira de Almeida	- REF. MJD/SCA3 Models	01/09/2019	31/12/2025	43 500,00	42,79
European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative - COORDINATOR: Luis Pereira de Almeida	- REF. ESMI project continuation_UniQure Biopharma B.V	26/11/2019	31/12/2025	10 000,00	0,00
Targeting mutant ATXN3 for the treatment of Spinocerebellar Ataxia 3 (SCA3) - COORDINATOR: Luis Pereira de Almeida	Wave Life Sciences USA, Inc. - REF. Wave Collaboration	01/04/2018	31/12/2025	300 000,00	40 666,48
Pharmatex In vitro Studies Program - INNOTECH 2015 - COORDINATOR: João Ramalho de Sousa Santos	Laboratoire Innotech - REF. INNOTECH 2015	31/12/2014	31/12/2020	218 086,76	13 671,18
Revascularização e angiogénese - COORDINATOR: João Ramalho de Sousa Santos	MERCK- REF. Revascularização e angiogénese, Merck	20/12/2016	31/12/2020	121 951,22	12 906,56
Nanodrug 3rd Summer School&Int - COORDINATOR: Lino da Silva Ferreira -	- REF. Nanodrug 3rd Summer School&Int	01/04/2014	31/12/2019	19 984,00	3 776,31
Study: Evaluation of Gecko polymer ability to inhibit bacterial growth by direct contact - COORDINATOR: Lino da Silva Ferreira	- REF. Evaluation of Gecko polymer	17/07/2017	31/12/2020	2 000,00	719,35
TimeUp - INESPO III - COORDINATOR: Susana Isabel Elias Alarico	Universidade de Coimbra - REF. TimeUp - INESPO III	01/03/2018	30/07/2019	3 252,03	2 912,58

Exploring the role of pridopidine on mitochondrial function and dynamics in Huntington`s disease models - COORDINATOR: Ana Cristina Carvalho Rego	TEVA Pharmaceutical Indust. - REF. Exploring the role of pridopid_TEVA	01/01/2017	31/12/2020	120 282,00	1 420,81
Supplementation of Coriolus versicolor (biomass) - a nutritional presymptomatic approach against cognitive deficits - COORDINATOR: Ana Cristina Carvalho Rego -	- REF. Micology Research Laboratories	01/09/2017	31/12/2019	8 000,00	2 998,53
NIH - 75N95020P00076 - COORDINATOR: Attila Köfalvi	- REF. 75N95020P00076 NIH	01/01/2017	24/01/2021	21 351,00	2 021,59
DDZ_FLAME_L_study - COORDINATOR: John Griffith Jones	German Diabetes Center - REF. DDZ_FLAME_L_ study	01/06/2017	31/12/2020	10 234,00	2 222,16
Project Furan toxicity in human and rat hepatocytes - COORDINATOR: Carlos Manuel Marques Palmeira	- REF. Comparison the acute effects..	01/08/2017	31/12/2020	28 200,00	1 926,60
Faturação Dr. Lino Ferreira - COORDINATOR: Lino Ferreira	Universidade de Coimbra - REF. Faturação Universidade de Coimbra	01/01/2018	31/12/2019	22 238,92	618,12
MSCellProdutction: Produção de Células Estaminais Mesenquimais em Conformidade com os requisitos de Boas Práticas de Fabrico - COORDINATOR: Mário Grãos	- REF. MSCellProduction	01/07/2019	15/08/2021	7 850,00	0,00
Microscopia - COORDINATOR: Luisa Maria O. P. L. Cortes	- REF. Microscopia	01/01/2012	31/12/2019	105 443,07	36 829,63
Sub-Total Others Services					**183 841,56**
TOTAL					**9 562 069,56**

IBILI FINANCIAL REPORT 2019

2019 Annual Accounts

Title	Financing Agency	Principal Investigator	Starting Date	Ending Date	Budget (iCBR)	Expenditure 2019
ERAatUC - 669088	European Commission H2020 - Societal Challenges	João Malva	01/05/2019	30/06/2020	2.762.404,48€	817.499,94€€
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€	29.361,00€
19313-EPIDEMPREV	European Commission EIT HEALTH	João Malva	01/01/2019	31/12/2019	65.125,00€	33.492,47€
19220 - CALMA	European Commission EIT HEALTH	01/01/2019	31/12/2019	65.125,00€	33.492,47€	13.543,55€
CRISH - ID 19226	European Commission EIT HEALTH	Flávio Nelson Reis	01/01/2019	31/12/2019	18.375,00€	13.087,10€
HeaLIQs (19142) EIT HEALTH	European Commission EIT HEALTH	01/01/2019	31/12/2019	25.250,00€	13.543,55€	115.996,61€
IDIAL_NET	European Commission	01/01/2019	31/12/2019	18.375,00€	13.087,10€	-
CARE 2.0	European Commission	01/01/2019	31/12/2019	187.500,00€	115.996,61€	2.382,75€
Unidade de I&D – CNC-IBILI	Ana Bela Sarmento	01/06/2019	31/12/2021	93.333.33€	-	273.090,16€
Crosstalk between perivascular adipose tissue and blood vessels in obesity and vascular dysfunction	FCT	01/01/2019	31/12/2019	57.000,00€	2.382,75€	67.426,24 €
Engineered Biodegradable Drug Delivery System for the Release of 2-Cl-IB-MECA for the treatment of glaucoma	FCT	01/07/2016	01/07/2019	199.512,00 €	67.426,24 €	73.876,69€

Novartis	Novartis	Francisco Ambrósio	-	-	30.000,00€	30.000,00€
PET com sistema inovador de leitura dupla para correção de DOI	FCT PTDC/BBB-IMG/4909/2014	Ana Cristina Santos	01/06/2016	31/12/2019	23.220,00€	20.915,05€
BrainHealth2020	CCDRC CENTRO-01-0145-FEDER-000008	Luis Almeida/ Francisco Ambrósio	01/01/2017	31-12-2020	1.599.829,61€	-
HealthyAging2020	CCDRC CENTRO-01-0145-FEDER-000012	João Ramalho/ Henrique Girão	01/01/2017	31/12/2020	1.795.810,88	-
GenomePT - Lab. Nacional Sequenciação	FCT POC1-01-0145-FEDER-022184	Henriqueta Coimbra Silva	01/06/2017	30/04/2021	593 489,91 €	160.881,96€
NECSUS - Neuroadaptation After Cataract and Refractive Surgery Study	European Society of Cataract and	Joaquim Murta	13/05/2016	12/05/2019	392.706,00€	3.236,03€
ONCONET SUDOE	INTERREG	Maria Filomena Botelho	01/06/2016	30/06/2019	235.382,90€	29.361,66€ €
Regulação farmacológica das proteínas da família p53: a caminho de novas terapias anticancerígenas	FCT PTDC/DTP-FTO/1981/2014	Flávio Nelson Reis	01/04/2016	01/04/2019	20.004,00€	6.188,84€
PPBI – Plataforma Portuguesa de Bioimagem	Agência Desenvolvimeto e Coesão	Henrique Girão	01/06/2017	30/05/2020	218.906,00€	63.930.36€
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€	90.456,70 €
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€	-
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€	90.469,00 €

Speed, crash and run: exersomes boost neuroenergetics and mood in mice on speed	FCT MOOD EXERSOMES - 030786	Frederico G.S.C. Pereira	26/07/2018	25/07/2021	239.413,80€	97.527,34 €
Modeling Angiogenesis in Type 2 Diabetes Mellitus - integrating experimental and theoretical approaches	FCT ANGIODIA -031743	Raquel Seiça	26/07/2018	25/07/2021	33.125,00€	7.312,63€
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	33.952,78 €
Environmental enrichment protects adult hippocampal neurogenesis and memory decline induced by systemic inflammation	FCT MercuMemory - 031699	Carlos Fontes Ribeiro	26/07/2018	25/07/2021	239.475,67€	21.628,22
Contribution of olive polyphenols and olive oil for the prevention of cardiovascular diseases	FCT PHENOLIVA - 032492	Flávio Reis	07/072018	06/07/2021	238.115,29	-
Dialysis membranes by design: targeting neutrophil elastase to reduce inflammation/oxidative stress in end-stage renal disease	FCT DIAL4LIFE - 031322	Flávio Reis	10/08/2019	09/08/2019	23.643,50€	5.617,64€
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€	-€
Mediterranean Enriched Diet for tackling Youth Obesity	FCT MED4YOUTH - PRIMA/0004/2018	Maria Filomena Botelho	01/12/2019	30/11/2021	93.815,00€	17,88€
Nova Terapêutica de RNA de Interferência para o Glaucoma	FCT siRNAGlau - 039743	António Francisco Ambrósio	01/10/2019	30/09/2021	215.064,98€	8.943.05€
3D DENTOFACIAL SURGERY F ULL P LANNIN G	FCT ARTHUR - 039690	Francisco Caramelo	01/10/2019	30/09/2021	131.322,65€	17 ,88€
iPET - Sistema PET inteligente para imagiologia pré-clínica	FCT iPET - 039880	Ana Cristina Santos	11/09/2019	10/03/2022	161.898,78€	-

PUCLICATIONS

Synapse Biology Group

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Neuroendocrinology and Aging Group

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Gaspar LS, Álvaro AR, Carmo-Silva S, Mendes AF, Relógio A, Cavadas C. The importance of determining circadian parameters in pharmacological studies. British Journal Pharmacology 2019 Aug;176(16):2827-2847.

Vision, Brain Imaging and Cognitive Neuroscience

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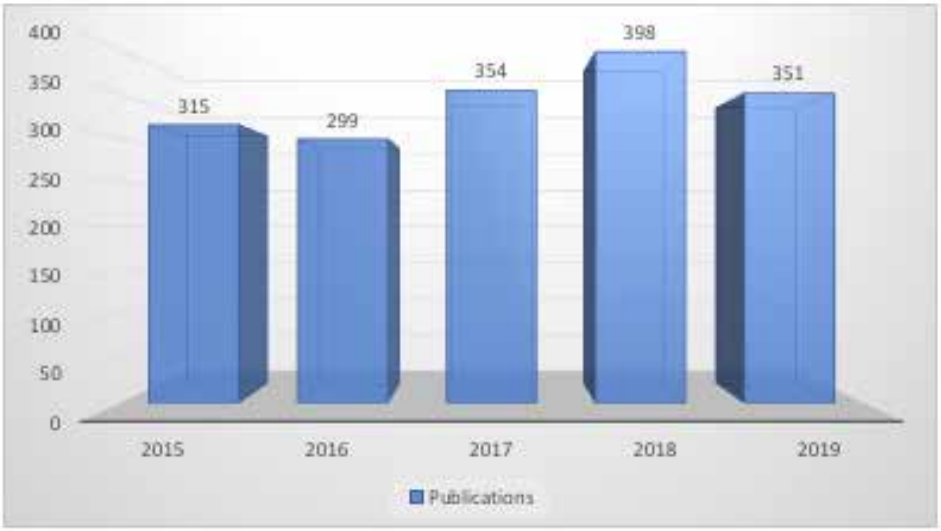

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