ANUAL REPORT 2018

CNC.IBILI

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INDEX

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INTRODUCTION

CNC.IBILI is a multidisciplinary research consortium created at the University of Coimbra in 2015, resulting from the fusion of two biomedical research institutes of excellence, CNC, recognized by FCT as a Laboratório Associado in 1990 and IBILI, a research institute of Biomedical Sciences at the Faculty of Medicine, University of Coimbra. CNC.IBILI brings together researchers from the Faculties of Medicine, Pharmacy, Science and Technology, and the Institute for Interdisciplinary Research, committed to foster fundamental, translational and biotechnology research and advanced training in biomedical sciences, whose scientific skills were evaluated of the highest standard by an international scientific advisory board. The CNC.IBILI research strategic plan for 2015-2020 was approved as excellent by FCT. The core scientific activity of the CNC.IBILI research Consortium is organized in 3 thematic strands, "Neuroscience, Vision and Brain Diseases", "Metabolism, Aging and Disease" and "Stem-Cell based and Molecular Therapies". Research is performed under an overarching, from molecule to man approach, focused on the understanding of brain function and disease mechanisms and therapeutic strategies. For this purpose, research is performed using cellular and animal models of disease and human subjects, in a close connection with the Coimbra University Hospital Center (CHUC). Simultaneously, this core activity is complemented by a molecular biotechnology approach, opening the scope of biomedical research being carried out at CNC.IBILI. The collaboration with industry, namely in the biotechnology entrepreneurship campus created in Biocant Park, promotes a more competitive knowledge-based economy in the region. The 2018 Annual Report of activities of the CNC.IBILI Research Consortium highlights the main achievements resulting from the development of its research strategic plan. In 2018, CNC.IBILI pursued its main goal, the understanding of brain function and disease mechanisms leading to the development of target- oriented therapeutic strategies, supported by novel molecular biotechnology approaches and by a tight interaction with health institutions, namely the Coimbra University Hospital Center (CHUC). This period was successful in attracting competitive funding either at national and international level. The scientific productivity of CNC.IBILI in 2018 is demonstrated by a rate of publication of 398 scientific papers in peer reviewed journals, an effort supported by grant projects achieved in competitive calls. CNC.IBILI is strongly committed to post-graduate education and training, being involved in the coordination of masters and Ph.D. Programs at the University of Coimbra and also in international training networks. Through the Outreach program, innovative actions aiming to improve society scientific education and perception of the importance of science for human health have been developed in schools and in collaboration with "Ciência Viva" and "Instituto de Educação e Cidadania" (IEC). The 2018 Annual Report highlights the CNC.IBILI accomplishments and the contribution of its dedicated researchers, students, support teams and administrative staff to achieve the main scientific goals of this research Consortium.

2018

Facts & Figures (2018)

RESEARCH STAFF

Integrated Members holding Ph.D.	173 + (85 Post Doctoral Fellowships)
Ph.D.Students	162
MSc Students	84

PUBLICATIONS

Scientific papers published	398
Scientific papers In Press	25

THESIS CONCLUDED

Ph.D. thesis	30
MSc thesis	93

Organization of CNC.IBILI

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)

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 2017, the research groups for Thematic Strand can be identified, according to the following organization:

Neuroscience, Vision and Brain Diseases | 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 | 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 | 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)
Pharmacometrics Group (Head: Amílcar Falcão)

Biotechnology

Microbiology of Extreme Environments Group (Head: Milton Costa)
Molecular Biotechnology Group (Head: Isaura Simões)

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

Research groups in the NVBD research line are interested in understanding synaptic transmission and plasticity in the central nervous system. We have contributed to the characterization of the nanoscale synaptic topography of glutamate receptors of the NMDA type (Kellermayer et al., 2018), and characterized mechanisms of synaptic scaling in excitatory synapses (Louros et al, 2018). In addition, computational approaches have been used for prediction and targeting of interaction interfaces in G-protein coupled receptor oligomers (Schiedel et al., 2018). Neuromodulation by the purinergic receptors, namely the A2A receptor, was found to control glutamatergic synaptic plasticity in fast spiking interneurons of the prefrontal cortex (Kerkhofs et al., 2018), to be a critical mediator of neurodegeneration triggered by convulsions (Canas et al., 2018), and to control microglia in a brain region-specific manner (Mendes et al., 2018). Moreover, elevated pressure changed the purinergic system of microglia cells (Rodrigues-Neves et al., 2018). Blockade of adenosine A2A receptor recovered early deficits of memory and plasticity in a mouse model of Alzheimer's disease (Silva et al., 2018). One focus of the NVBD area is on neurodegeneration and aging. In vivo simultaneous measurements of •NO, O2 and cerebral blood flow (CBF) in the rat hippocampus along chronological age in response to glutamatergic activation and in correlation with cognitive performance demonstrated an age-dependent impairment of neurovascular and neurometabolic coupling (Lourenço et al., 2018). In a mouse model of Huntington's disease, the subventricular zone-derived progenitor cells were characterized (Silva et al., 2018), and a whole brain longitudinal study showed distinct trajectories of neurochemical, structural connectivity and volumetric changes (Petrella et al., 2018). Repeated mesenchymal stromal cell treatment was found to sustainably alleviate Machado-Joseph disease (Miranda et al., 2018), another polyglutamine disorder. In Alzheimer's disease animal models, diminished O-GlcNAcylation was shown to be correlated with mitochondrial anomalies (Pinho et al., 2018). Addition of the β42/40 ratio to the cerebrospinal fluid biomarker profile increased the predictive value for underlying Alzheimer's disease dementia in mild cognitive impairment (Baldeiras et al., 2018). Another study found that mtDNA copy number may be associated with age of onset in familial amyloid polyneuropathy (Santos et al., 2018). Brain imaging studies have shown that the retinal ganglion cell layer predicts normal-appearing white matter tract integrity in multiple sclerosis (Alves et al., 2018). Understanding the effects of the drugs of abuse is also the focus of research at NVBD. We have found that chronic methylphenidate treatment affects hippocampal neurovasculature, memory performance and the brain's immune privilege (Coelho-Santos et al., 2018a, b). In addition, aquaporin-4 could be targeted against methamphetamine-induced brain alterations (Leitão et al., 2018). 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 resulting in > 130 publications during 2018.

FUTURE PLANS

The NVBD researchers will continue to develop studies to further understand brain function and brain diseases. In the near future, ongoing research will result in very relevant contributions from junior NVBD group leaders, e.g. in the fields purines in brain development and brain diseases, in understanding presynaptic mechanisms of neurotransmission, and in the study of synaptic and postsynaptic density proteins implicated in autism and schizophrenia in specific cell-types and neuronal circuits. Our studies of age-related neurodegeneration are paralleled by the investigation of aging as a risk factor for chronic diseases, and of strategies to rescue hypothalamus functionality to delay the aging phenotype, a research line that is gaining momentum in the NVBD area. The contribution of clinicians to the NVBD line of research has increased in 2017, with important publications coming out [e.g. Sargento-Freitas et al., 2017; Batista et al., 2017]; it is expected that the link between fundamental researchers and clinicians is tightened in the future. NVBD groups are developing novel tools and methodologies, including web-servers for computational methods, the generation of novel animal models, brain-region specific approaches and newly designed biosensors. An innovative multimodal approach, encompassing metabolic, electric and hemodynamic measurement, tailored to study spread depolarization (SD) events in rat brain has been developed (Lourenço et al., 2017), and provides simultaneous neurometabolic and electrophysiological information. The introduction of opto- and chemo-genetic methods by several groups will further enhance research in the NVBD line. Several collaborative projects among NVBD groups have been initiated, enabling multidisciplinary efforts. Multiple strong collaborative publications have come out in 2017 [e.g. Gonçalves et al, 2017; Caetano et al., 2017], and several researchers have been successful in joint applications for funding, planting the seeds for new successful collaborative efforts in the future, that add to the extensive network of international collaborations of the neuroscience groups at CNC.IBILI.

Synapse Biology Group

Carlos B Duarte	PhD (Head of Group)
Ana Luísa Carvalho	PhD
Ana Luísa Colaço Cardoso	PhD
Emília Duarte	PhD
João Miguel Peça-Silvestre	PhD
Mónica Santos	PhD
Paulo Pinheiro	PhD
Ramiro Almeida	PhD
Sandra Santos	PhD
Angela Inácio	Post Doctoral Fellow
Catarina Morais Seabra	Post Doctoral Fellow
Dominique Fernandes	Post Doctoral Fellow
Gladys Caldeira	Post Doctoral Fellow
Ivan Salazar	Post Doctoral Fellow
Joana Guedes	Post Doctoral Fellow
Lara Oliveira Franco	Post Doctoral Fellow
Mariline Silva	Post Doctoral Fellow
Miranda Mele	Post Doctoral Fellow
Mohamed Hussein	Post Doctoral Fellow
Rui Costa	Post Doctoral Fellow
Ana Rafaela Oliveira	PhD Student
Beatriz Rodrigues	PhD Student
Debora Serrenho	PhD Student
Diana Sequeira	PhD Student
Diogo Tomé	PhD Student
Filipe Duarte	PhD Student
Jeannette Schmidt	PhD Student
Jessica Costa	PhD Student
Luís Martins	PhD Student
Marcos Gomes	PhD Student
Mariana Laranjo	PhD Student
Marina Rodrigues	PhD Student
Mário Carvalho	PhD Student
Marta Pereira	PhD Student
PASQUALINO DE LUCA	PhD Student
Rafael Carvalho	PhD Student
Cinzia Miarelli	MSc Student
Nuno Beltrão Marques	MSc Student

Redox Biology and Brain Sensing Group

João António Laranjinha	PhD (Head of Group)
Ana Margarida da Cruz 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

Neuroendocrinology and Aging Group

Cláudia Cavadas	PhD(Head of Group)PhD (Head of Group)
Alexandrina Ferreira Mendes	PhD
Ana dos Santos Carvalho	PhD
Ana Teresa Rufino	PhD
Caetana Carvalho	PhD
Célia Aveleira	PhD
Fernando Judas	PhD
Ana Rita Álvaro	Post Doctoral Fellow
Sara Silva	Post Doctoral Fellow
António Pedro Gomes	Post Doctoral Fellow
André Carvalho	PhD Student
Helena Leal	PhD Student
Inês Ferreira	PhD Student
Inês Ferreira	PhD Student
Leaticia Gaspar	PhD Student
Marisa Marques	PhD Student
João Pedro Oliveira	MD
Joaquim Moita	MD
Alexander Santos	MSc Student
Ana Catarina Franco	MSc Student
Ana Rita Fernandes	MSc Student
Caren Rodrigues	MSc Student
João Cardoso	MSc Student
Cátia Sousa	Collaborator

Vision, Brain Imaging and Cognitive Neuroscience Group

Miguel Castelo-Branco	PhD (Head of Group)
Aldina Conceição Pires Reis	PhD
Andreia Rosa	PhD
Antero Afonso de Abrunhosa	PhD
Barbara dos Santos Oliveiros	PhD
Francisco Caramelo	PhD
Francisco Cerqueira Alves	PhD
Gabriel Ferreira da Costa	PhD
Guiomar Gonçalves Oliveira	PhD
Inês Ribeiro Violante	PhD
João Santos Pereira	PhD
Joaquim Carlos Neto Murta	PhD
Jorge de Andrade Saraiva	PhD
José Paulo Domingues	PhD
José Vítor Oliveira Sereno	PhD
Luís Filipe Caseiro Alves	PhD
Mª Conceição da Fonseca	PhD
Mª Cristina Januário Santos	PhD
Mª Fátima Silva	PhD
Mª João Vidigal	PhD
Nuno David Ferreira	PhD
Otilia D´Almeida	PhD
Pedro Miguel Serrenho	PhD
Rufino Martins da Silva	PhD

Vision, Brain Imaging and Cognitive Neuroscience Group

Rui Manuel Bernardes	PhD
Sérgio José do Carmo	PhD
Bruno Miguel Leitão	Post Doctoral Fellow
Helena Catarina Pereira	Post Doctoral Fellow
Inês Bernardino	Post Doctoral Fellow
Inês Teixeira de Almeida	Post Doctoral Fellow
Joana Crisóstomo da Silva	Post Doctoral Fellow
Joana Teresa Gonçalves	Post Doctoral Fellow
João Filipe Martins	Post Doctoral Fellow
João Miguel Castelhano	Post Doctoral Fellow
Joao Pereira Figueira	Post Doctoral Fellow
Joao Valente Duarte	Post Doctoral Fellow
José Miguel Teles	Post Doctoral Fellow
Mª José Braga Ribeiro	Post Doctoral Fellow
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Ana Isabel Rodrigues	PhD Student
Ana Maria Baptista	PhD Student
Andreia Sofia Pereira	PhD Student
Carlos Manuel Amaral	PhD Student
Carolina Oliveira Alves	PhD Student
Filipa Lima Júlio	PhD Student
Hélio Jorge Gonçalves	PhD Student
Hugo Alexandre Quental	PhD Student
Marco António Simões	PhD Student
Marta Cristina Teixeira	PhD Student
Nádia Canário	PhD Student
Susana Figueiredo e Silva	PhD Student
Susana Isabel Mouga	PhD Student
Tarcícsio Guimarães	PhD Student
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Margarida Gonçalves Marques	MD
Maria Luísa Ribeiro	MD
Pedro Luís Fonseca	MD
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João André Pereira	Grant Technician
Vitor Hugo Alves	Grant Technician
Isabel Catarina Duarte	Technician
Maria de Fátima Machado	Technician

Purines in brain diseases Group

Rodrigo Cunha	PhD (Head of Group)
Aderbal Junior	PhD
Ãngela França	PhD
Angelo Tomé	PhD
Attila Kofalvi	PhD
Geanne Andrade	PhD
Henrique Silva	PhD
Joana Medeiros Vieira Marques	PhD
Paula Agostinho	PhD
Ricardo Jorge Rodrigues	PhD
Rui Prediger	PhD
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Purines in brain diseases Group

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Paula Canas	Post Doctoral Fellow
Samira Ferreira	Post Doctoral Fellow
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Anna Pliássova	PhD Student
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Cátia Lopes	PhD Student
Daniela Madeira	PhD Student
Inês Amaral	PhD Student
Liliana Dias	PhD Student
Lisiane Souza	PhD Student
Mara Fernandes	PhD Student
Marlene Pereira	PhD Student
Pedro Valada	PhD Student
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Xinli Xu	PhD Student
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João Miguel Rocha	MSc Student
Marlene Domingues	MSc Student
Vanessa Lourenço	MSc Student
Sara Reis	Grant Technician

Mitochondria and Neurodegenerative Disorders Group

Ana Cristina Rego	PhD (Head of Group)
Ildete Luísa Araujo Ferreira	PhD
Carla Nunes Lopes	PostDoctoral Fellow
Elisabete Ferreiro	PostDoctoral Fellow
Luana Naia	Post Doctoral Fellow
Sandra Mota	Post Doctoral Fellow
Lígia Fão	PhD Student
Rodolfo Águas	PhD Student
Bruno José Moraes	MSc Student
Daniela Marinho Lopes	MSc Student
Margarida Beatriz	MSc Student
Olga Fokt	MSc Student
Vera Martinho Pais	MSc Student

Aging and Brain Diseases: Advanced Diagnosis and Biomarkers Group

Catarina Resende Oliveira	PhD (Head of Group)
Bruno José Fernandes O. Manadas	PhD
Inês Esteves Baldeiras	PhD
Isabel Maria Marques Carreira	PhD
Joaquim Manuel Soares Cerejeira	PhD
Maria do Rosario Almeida	PhD

Aging and Brain Diseases: Advanced Diagnosis and Biomarkers Group

Maria Joana Lima Barbosa de Melo	PhD
Maria Manuela Monteiro Grazina	PhD
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Diana Filipa Dias Duro	PhD Student
Inês Isabel Nunes Caramelo	PhD Student
Inês Martins Malva Correia	PhD Student
Joana Catarina Amaral Pinto	PhD Student
Mafalda Rita Avó Bacalhau	PhD Student
Maria João Fe Canas dos Santos	PhD Student
Maria João N. Vicente Mexia Leitão	PhD Student
Maria Margarida Serra Coelho	PhD Student
Rafael Ribeiro Santos Silva	PhD Student
Rémy Cardoso	PhD Student
Sandra Isabel dos Santos Anjo	PhD Student
Anabela Peixinho Valente de Matos	MD
Gustavo António P. R. Cordeiro Santo	MD
Helena Beatriz M. Costa Santiago	MD
Livia Maria de Abreu F. Diogo Sousa	MD
Luis Jorge Mendonça Peres Negrão	MD
Maria do Carmo R. R. Maio Macario	MD
Maria Isabel Jacinto Santana	MD
Maria Olinda Rodrigues Rebelo	MD
Miguel António Tábuas Cunha Pereira	MD
Ricardo Manuel F. M. Félix de Morais	MD
Sónia Raquel Marques Batista	MD
Vera Mónica Milheirão Mendes	MD
Antonio Freire Goncalves	Collaborator
Antonio Joao F. de Macedo e Santos	Collaborator
Celia Margarida Alcobia Gomes	Collaborator
Francisco Jose Sales Almeida Inacio	Collaborator
Gil de Castro Nunes Vicente e Cunha	Collaborator
Mário Manuel Rodrigues Simões	Collaborator
Marta Sofia Marques Simões	Collaborator
Sandra Cristina Lopes Freitas	Collaborator
Ana Cristina Franco Santos	Technician

New Targets and Therapeutics for Chronic Diseases Group

António Francisco Ambrósio	PhD (Head of Group)
Maria Filomena Botelho	PhD
Ana Filipa Marques Brito	PhD
Ana Paula Martins	PhD
Ana Raquel Santiago	PhD
Ana Salomé Pires	PhD
Barbara Gomes	PhD
Belmiro Parada	PhD
Carlos Alberto F Ribeiro	PhD
Catarina Vale Gomes	PhD
Célia Cabral	PhD
Célia Maria Freitas Gomes	PhD
Celso Alves	PhD

New Targets and Therapeutics for Chronic Diseases Group

Elisa de Campos	PhD
Eunice Carrilho	PhD
Fernando Mendes	PhD
Filipa Isabel Cabaço Baptista	PhD
Flavio Reis	PhD
Frederico Pereira	PhD
João Malva	PhD
José Guilherme Tralhão	PhD
Mafalda Cândido	PhD
Manuel Marques Ferreira	PhD
Manuel Veríssimo	PhD
Marcos Barbosa	PhD
Margarida Abrantes	PhD
Maria Helena Madeira	PhD
Maria João Carvalho	PhD
Natália António	PhD
Paulo Fernando Santos	PhD
Rosa Cristina Fernandes	PhD
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Sofia Viana	Post Doctoral Fellow
Sónia Santos	Post Doctoral Fellow
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Ana Sofia Pais	PhD Student
António Campos	PhD Student
Carlos Marto	PhD Student
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Diogo Fonseca	PhD Student
Edgar Silva	PhD Student
Esmeralda Costa	PhD Student
Eurico Ribeiro	PhD Student
Filipe Palavra	PhD Student
Inês Aires	PhD Student
Inês Pita	PhD Student
João Casalta lopes	PhD Student
José Luis Alves	PhD Student
Leonor Barroso	PhD Student
Raquel Boia	PhD Student
Ricardo Martins	PhD Student
Ricardo Teixo	PhD Student
Rui Martins	PhD Student
Rui Pedro Oliveira	PhD Student
Samuel Chiquita	PhD Student
Sandra Ribeiro	PhD Student
Sara Nunes	PhD Student
Vania Leal	PhD Student
Beatriz Martins	MSc Student
Luciana Fernandes	MSc Student
Miguel Maria Pinheiro	MSc Student
André Alves	Grant Technician
Carlota Nóbrega	Grant Technician
Inês Preguiça	Grant Technician
Joana Serra Martins	Grant Technician

SYNAPSE BIOLOGY | (*Head: Carlos B. Duarte*)

OBJECTIVES

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

Dopamine receptors play a key role in the modulation of synaptic activity, and alterations in dopaminergic neurotransmission have also been associated with neuropsychiatric disorders. One additional goal of the group is to understand the molecular mechanisms controlling the activity of dopamine receptors.

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. 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.

This group uses in vitro (OGD - oxygen and glucose deprivation and neuronal cultures) and in vivo models (MCAO - middle cerebral artery occlusion) of brain ischemia to elucidate alterations in neuronal proteostasis following brain ischemia, and their impact in neuronal demise.

In particular, the studies address the alterations in the interplay between the ubiquitin-proteasome system and calpains.

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.

Alterations in proteostasis and neuronal death in brain ischemia

Previous studies by this group, as well as from other laboratories, have shown that the excessive activation of glutamate receptors is coupled to a dysregulation of the proteostasis in brain ischemia. However, the detailed molecular mechanisms involved, and their relative role in neuronal death, have not been fully elucidated.

ii) Structural characterization of protein-based interactions

During the reporting period, the goal has been:

During the reporting period, the goal has been:

1. the establishment of protocols and methods to study Protein-Protein Interfaces (PPIs) involving membrane proteins;

2. the understanding of ligand coupling specificity of G-protein Coupled Receptors (GPCRs) complexes, particularly dopamine receptors.

MAIN ACHIEVEMENTS

i) Glutamatergic synapse function and dysfunction in brain disorders

PI: Carlos B. Duarte

1. BDNF was found to upregulate synaptic expression and activity of GluN2B-containing NMDA receptors by enhancing local translation of the Pyk2 kinase in cultured hippocampal neurons. Under the same conditions the Pyk2 mRNA was released from hnRNP K, and this RNA binding protein was also necessary for the upregulation in the synaptic expression of GluN2B-containing NMDA receptors (Afonso et al. in press). These alterations may account, at least in part, for the effects of BDNF in long-term synaptic potentiation (LTP) in the hippocampus.
2. The upregulation in glutamatergic activity in hippocampal neurons transiently incubated in a salt solution lacking Mg2+, an in vitro model of epileptogesis, was found to decrease the synaptic stability of GABAA receptors in cultured hippocampal neurons.
3. The excessive activity of glutamatergic synapses in brain ischemia is coupled to neuronal death. Cultured cortical neurons subjected to oxygen and glucose deprivation (OGD), an in vitro model of brain ischemia, showed a disassembly of the proteasome followed by neuronal death. In contrast with the effects on the proteasome, OGD induces the activation of calpains, a group of Ca2+-dependent proteases, and our work showed a cross-talk between the two proteolytic systems (Salazar et al., in preparation).

PI: Ana Luísa Carvalho

4. We have identified multiple molecular regulators of homeostatic forms of synaptic plasticity, such as miRNA-186-5p (Silva et al., 2019) and stargazin dephosphorylation (Louros et al., 2018). miRNA-186-5p regulates the subunit composition of AMPA receptors, by targeting the GluA2 AMPA receptor subunit. Stargazin dephosphorylation mediates changes in stargazin cell surface mobility and in synaptic scaling.
5. We have characterized a newly described 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.
6. Together with the group of Laurent Groc at the IINS, University of Bordeaux, we have used super-resolution microscopy methods todescribe the topographic organization of nanodomains formed by NMDA receptors at synapses in hippocampal neurons, and to identify differential determinants for GluN2A- and GluN2B-containing NMDA receptors nanostructure (Kellermayer et al., 2018).

PI: João Peça

7. We have found that parvalbumin (PV)-positive interneurons contribute to the circuit and behavioral dysfunction in GPRASP2 conditional knockout mice (Edfawi and Guedes, et al in preparation) and we are also dissecting the contribution of GPRASP2 in hypothalamic dysfunction and obesity via the region specific deletion of this gene (Gomes et al, in preparation).
8. Our group focuses on microglia activation in disease states (Cardoso and Costa, in preparation) and how microglia is necessary for the remodeling of cerebellar circuits. We discovered that if physiological M1-like activation state is perturbed, animals may display electrophysiological and behavioral alterations (Guedes and Ferreira et al, in preparation).
9. We concluded the behavioral and electrophysiological characterization in the medial prefrontal cortex (mPFC) of adult mice following early life stress. (Franco, Carvalho et al, submitted).
10. After establishing a partnership with Dr. Guiomar Oliveira at the Autism and Neurodevelopmental Disorders Unit of the CHC Pediatrics Hospital, we have created a dental stem cell biobank of control and patient sample to develop organoid model of neurodevelopmental disorders (Seabra and Oliveira, in preparation and Sequeira et al, 2018).

ii) Structural characterization of protein-based interactions (PI: Irina Moreira)

1. PPIs/Dimers database and new predictors

The dataset constructed took as starting point the “mpstruc” online repository: http://blanco.biomol.uci.edu/mpstruc, that lists all the currently known membrane associated proteins, subdivided in the alpha-helical or beta-barrel basic types.
We employed several criteria to select the final structures:
i) both monomers should be transmembrane proteins;
ii) the existence of a clear and well visible protein-protein interaction;
and iii) all residues at the 3D structure should be clearly explicit (excluding alpha-carbon only or unknown residues).
Around 3000 features were calculated and subject to machine-learning algorithms to produce new interface predictors (Filipe P, 2019, In preparation; Preto A, 2019, In preparation). metoclopramide, N-dimethyldopamine, N-propylapomorphine, Nemonapride, Quetiapine, Quinpirole, Raclopride, Risperidone, Remoxipride, SCH23388, SCH23390, SKF38393, Spiperdone, Sulpiride and Zisprasidone (Bueschbell B, 2018, Molecules, 19; 11(9). Pii: E1779).

2. GPCRs - Dopamine receptors sub-type specificity

In this study we utilized structure-based and ligand-based computer aided design to investigate the coupling of various ligands to the dopamine family of receptors.
For the structure-based we applied homology modelling by using the resolved X-ray crystallography structures of the dopamine receptors D3R and D4R, while for ligand-based approached we assembled a new protocol using Chemmine written in R and machine-learning algorithms for a better prediction of the binding affinity.
The following ligands were taken into account: Dopamine, (+)-Butaclamol, beta-Phenylethylamine (PEA), (+/-)-2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6,7-ADTN), 7-Hydroxy-N,N-dipropyl-2-aminotetralin (7-OH-DPAT), Apomorphine, Bromocriptine, Chlorpromazine, Clozapine, Domperidone, Haloperidole, metoclopramide, N-dimethyldopamine, N-propylapomorphine, Nemonapride, Quetiapine, Quinpirole, Raclopride, Risperidone, Remoxipride, SCH23388, SCH23390, SKF38393, Spiperdone, Sulpiride and Zisprasidone (Bueschbell B, 2018, Molecules, 19; 11(9). Pii: E1779).

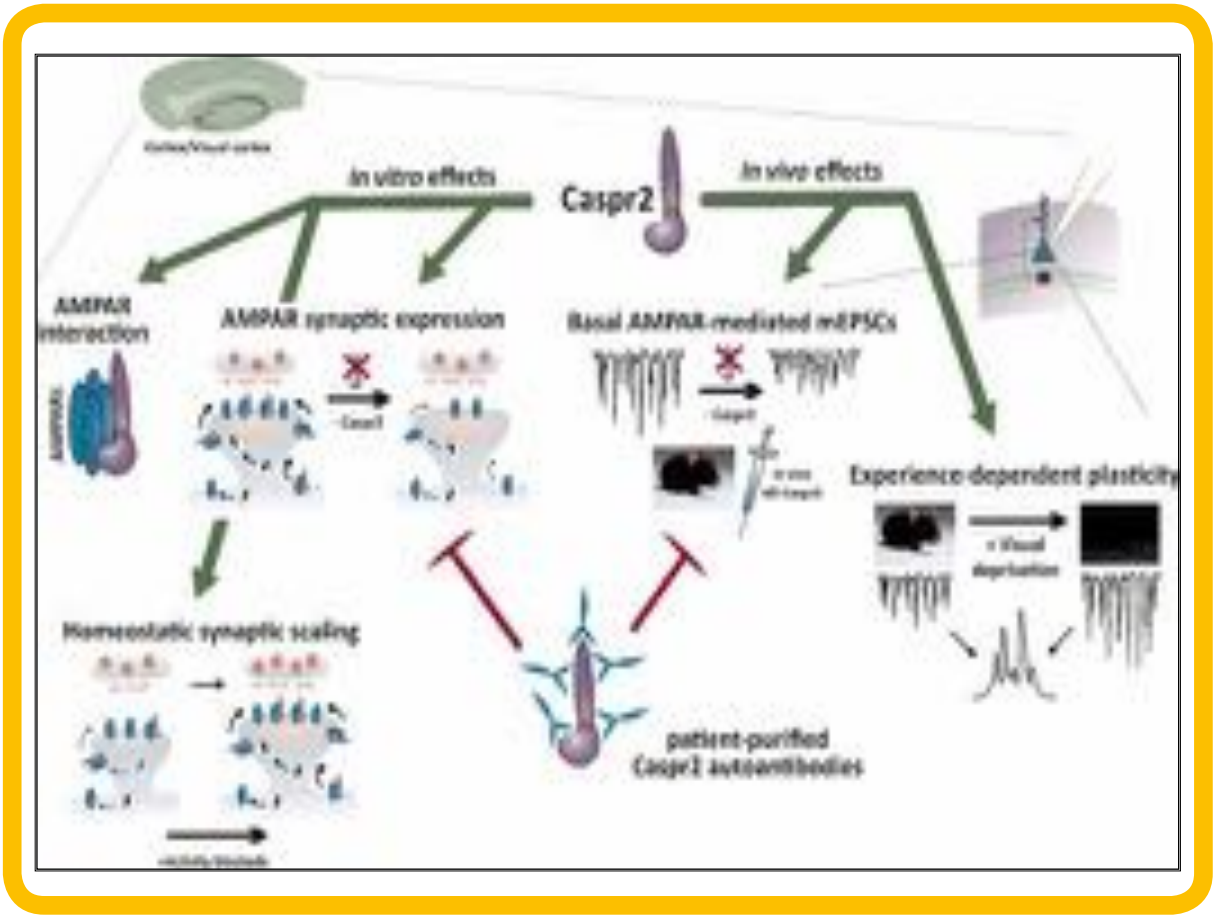


Figure 1 – *Graphical representation of the molecular and synaptic functions mediated by Caspr2 and the pathogenic effects of CASPR2 autoantibodies. Herein, we identified Caspr2 as a novel AMPAR-interacting protein necessary for the regulation of AMPAR synaptic expression and AMPAR-mediated currents in vivo. Furthermore, we uncovered a requirement of Caspr2 for the regulation of homeostatic synaptic scaling, and for the expression of visually-driven experience-dependent plasticity in the visual cortex. Finally, we explored the pathogenic effects of CASPR2 autoantibodies in Caspr2 functions and revealed that CASPR2 autoantibodies perturb the synaptic expression of AMPARs and impair excitatory synaptic transmission in the visual cortex. [This work has been published in: Fernandes, D., et al. (2019). Disrupted AMPA Receptor Function upon Genetic- or Antibody-mediated Loss of Autism-associated CASPR2. Cereb Cortex. pii: bhz032 (epub ahead of print). doi: 10.1093/cercor/bhz032.]*

REDOX BIOLOGY AND BRAIN SENSING | (*Head: João Laranjinha*)

OBJECTIVES

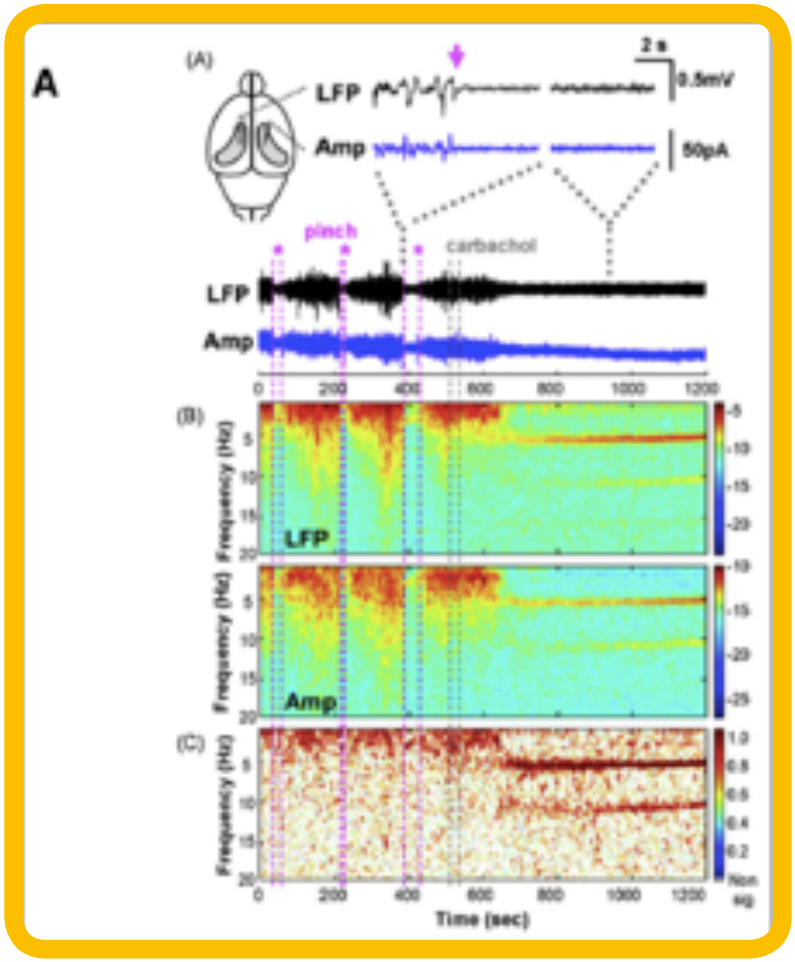
The group´s research programs address:

(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).



*The amperometric current obtained with fast sampling amperometry captures the endogenous electrical signal of the brain, such as LFP. The high coherence between the simultaneously recorded amperometric current and extracellular potential was demonstrated using a choline-oxidase Pt MEA, shown in A (adapted with permission from [48**]). A more recent application has extended the recorded frequency to 100 Hz (B), allowing simultaneous recording of pO2 and the LFP signal during chemically-induced seizures in awake behaving rodents (adapted with permission from [25**])*

MAIN ACHIEVEMENTS

The main achievements incorporate both, technological and scientific components.

Technological developments:

Updating previous work, we have established a novel strategy for concurrent recording of both local field potentials and neurochemical events from a single signal obtained at a single microelectrode.
Combined with multi-site electrode arrays that are nowadays mass-fabricated using photolithographic techniques, this seamless strategy allows concurrent in vivo recordings of chemical release and electrical activity from multiple neuronal populations with high spatiotemporal resolution, reproducibility and reliability.
Considering that neurons communicate by complex patterns of electrical and chemical signals, the ability to capture the emergent properties of neuronal networks by measuring the neurochemical and electrical activity of large populations of cells with high temporal resolution using a single sensor and recording is of obvious interest.

We designed, developed and implemented nanocomposite sensors consisting of carbon fiber microelectrodes modified with Nafion®and carbon nanotubes, and ceramic-based microelectrode biosensor arrays to measure ascorbate and glutamate in the brain with high spatial, temporal and chemical resolution.
Considering the recognized interplay between glutamate signaling and fluctuations in extracellular ascorbate levels and their putative role in brain pathophysiology, namely in age-related neurodegenerative diseases, the development of sensors which allow simultaneous in vivo measurements with high spatiotemporal resolution is highly relevant.

Scientific achievements:

We have analyzed brain bioenergetics in hippocampus of mouse and rat by using high-resolution respirometer in brain tissue - a step forward the use of isolated mitochondria or cells to study brain mitochondrial respiration - and have established:

a) The relative differences in terms of O2 consumption rates, respiratory coupling, maximal respiratory capacity, among others;
b) The interacting profiles of nitric oxide and oxygen with implications for brain bioenergetics.

Investigating the functionality of neurovascular and neurometabolic coupling in connection to nitric oxide signaling and in association to cognitive performance during aging in rat model of disease (Fisher 344) in vivo, we established that the impairment in the neurovascular coupling (and associated cognitive decline) observed in aged rats can be mimicked in young rats by promoting an unbalance in redox status towards oxidation via intracellular production of oxygen free radicals. The compromised nitric oxide signaling from neurons to local microvessels due to oxidative environment represents a novel mechanism underlying cognition decline in aging.

Using a rat model of intestinal inflammation, we have confirmed the higher anti-inflammatory action of an anthocyanin fraction extracted from blueberries as compared with 5-ASA, a first line drug in inflammatory bowel disease. Taking into account the high concentrations of dietary anthocyanins potentially reached in the gastrointestinal tract, these compounds might be envisaged as promising nutraceuticals, giving complementary benefits in the context of inflammatory bowel disease.

NEUROENDOCRINOLOGY AND AGING | (*Head: Cláudia Cavadas*)

OBJECTIVES

In our group we investigate the hypothalamus and hypothalamic related systems/mechanisms as underlying mediators and targets for interventional strategies in counteracting aging and aging related diseases.

Our research aimd to answer to the following questions:

- How aging and aging related disease change hypothalamus?
- Can we delay premature aging of Hutchinson Gilford progeria syndrome (HGPS) rodent models, normal aging or aging related diseases, by targeting the hypothalamus or using hypothalamic related mechanisms?
- Which targets in the hypothalamus should we manipulate to reduce obesity and insulin resistance?

IDoes caloric restriction (CR) and related mechanisms delay aging and aging-related diseases?

- Which are the mechanisms underlying the link between aging, obesity and circadian rhythm deregulation?
- Is sirtuin 2 a player in metabolism?
- Is ataxin-2 a player in metabolism?

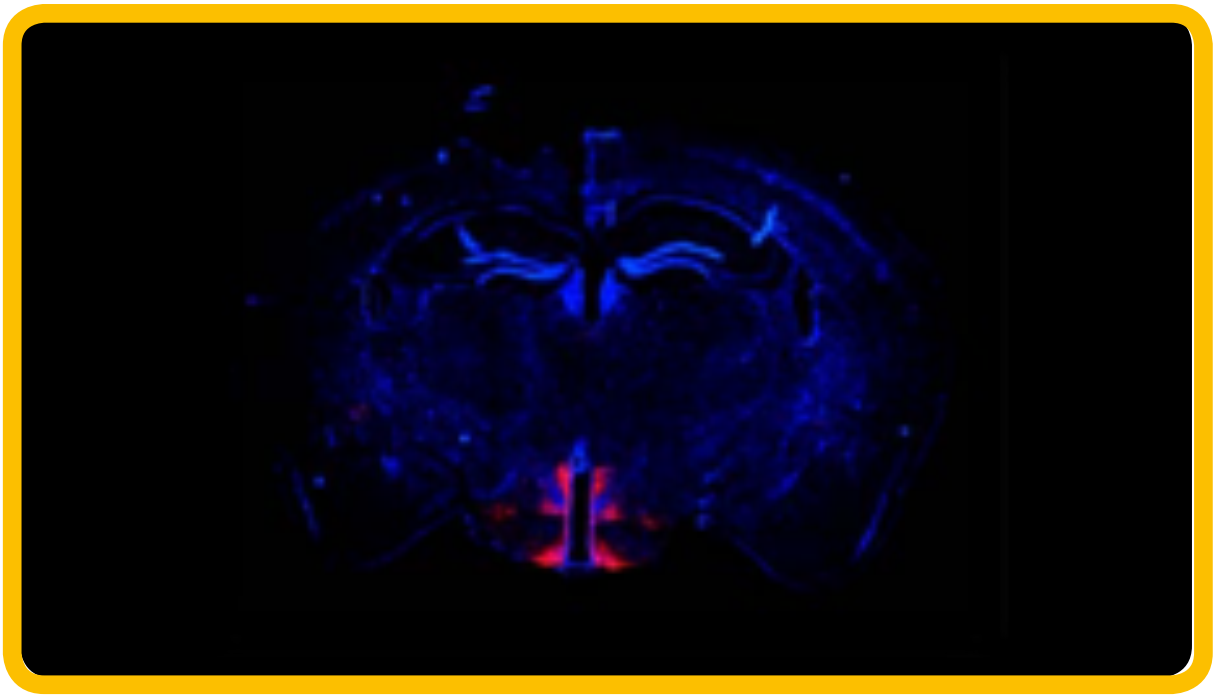


Fig. 1. Neuropeptide Y immunoreactivity (red) in the hypothalamus of mouse brain. Nuclei (blue)

MAIN ACHIEVEMENTS

a) We investigated the role of NPY and ghrelin in rescuing the aging phenotype in human dermal fibroblasts of Hutchinson-Gilford Progeria Syndrome (HSPS).
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.
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, white and brown adipose tissue, and response to insulin.

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.

VISION, BRAIN AND COGNITIVE NEUROSCIENCE | (*Head: Miguel Castelo-Branco*)

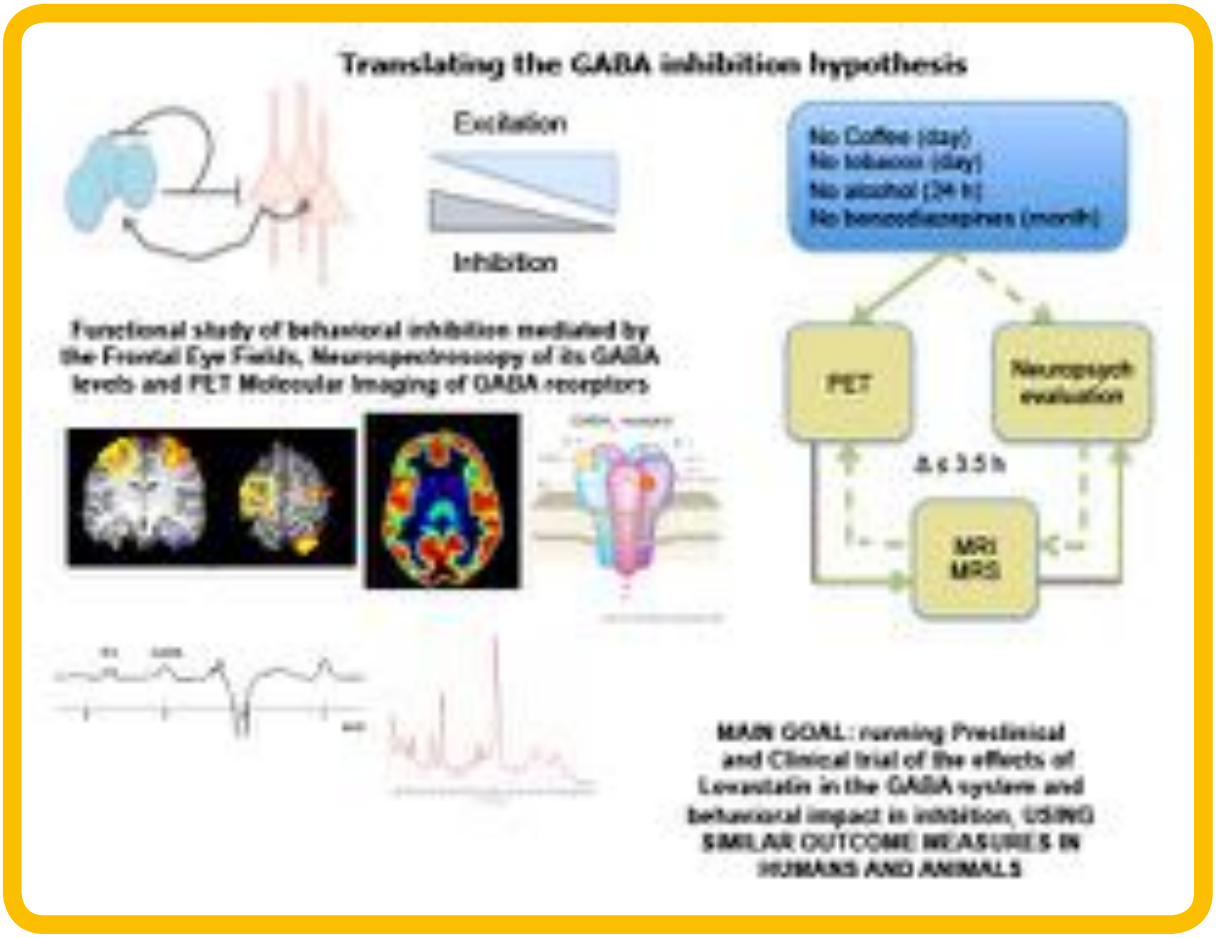
OBJECTIVES

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 I. 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 partners such as Harvard Medical School, Karolinska Institute, the Universities of Maastricht, Cardiff, Tuebingen, University College London, John Hopkins University, US as well as the Department for Neurophysiology of the Max-Planck Institute for Brain Research.

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. We have finished the first two clinical trials in Portugal concerning Medical Devices (a new BCI interface for autism rehabilitation and a neurofeedback approach). 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 Research Achievements are highlighted by demonstration that the impaired inhibition phenotype encountered in the animal model of the most common neurogenetic cause of cognitive dysfunction, neurofibromatosis type 1, also holds true for the human disease, and several publications are still being pursued in this area. Our translational work on integrating human and animal

neurodevelopmental phenotypes has also progressed. Collaborative work in international genomics consortia (such as the Autism Genome Consortium, to which we largely contributed, and Vision Genetics Consortia) is also continuing and 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 use of statistical classification methods to separate disease states or to online brain signals to control brain computer interfaces. 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 F FP7 and H2020 projects, such as BRAINTRAIN/ STIPED/IMI2/Marie Curie. After achieving a worldwide patent together with IBA, our technology transfer approaches are also evolving steadily within the newly created clinical trial unit.



PURINES | (*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-P2Y1 (ATP) receptors critically control glutamate-induced excitotoxicity.

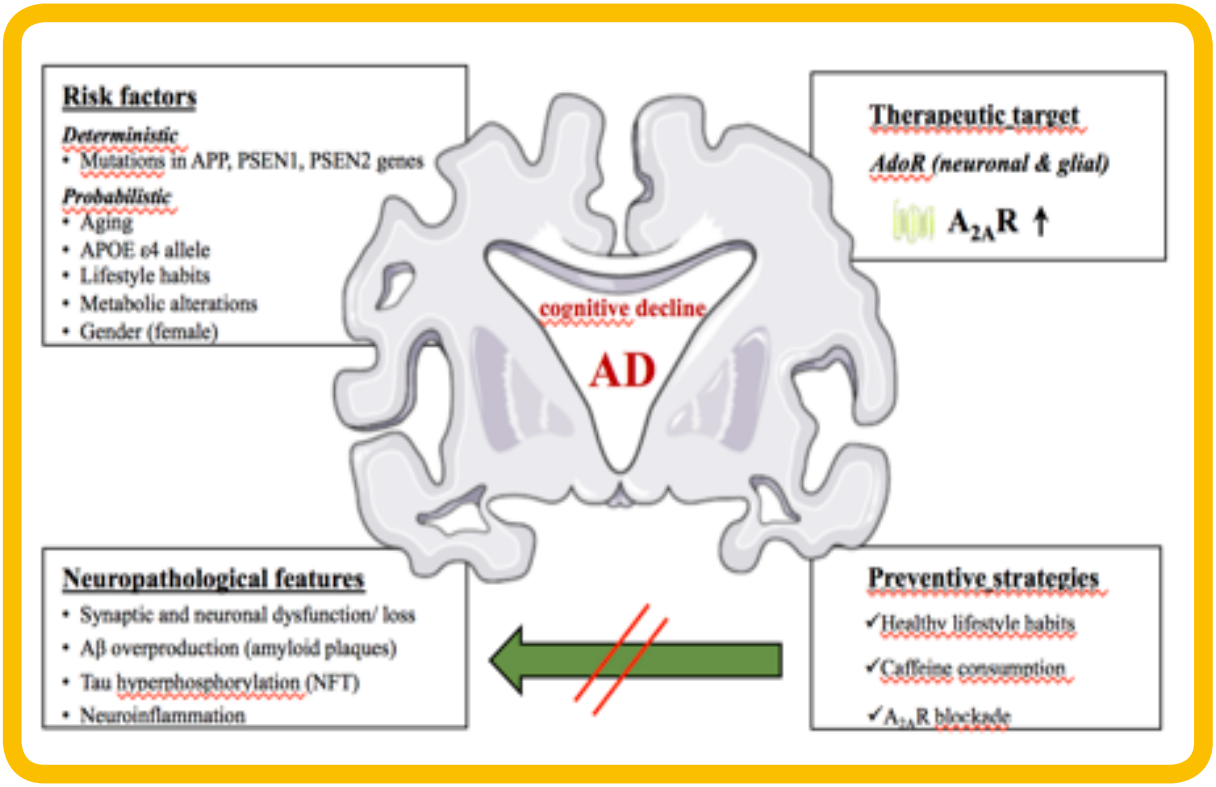
2-The over-functioning of adenosine A2A receptors (A2AR) is critical for the expression of neurodegeneration after convulsions.

3-Blockade of A2AR can revert memory deficits in an animal model of Alzheimer's disease.

4-Caffeine consumption attenuates the burden of ADHD - attention deficit and hyperactivity disorders.

5-Caffeine-induced insomnia is age-dependent.

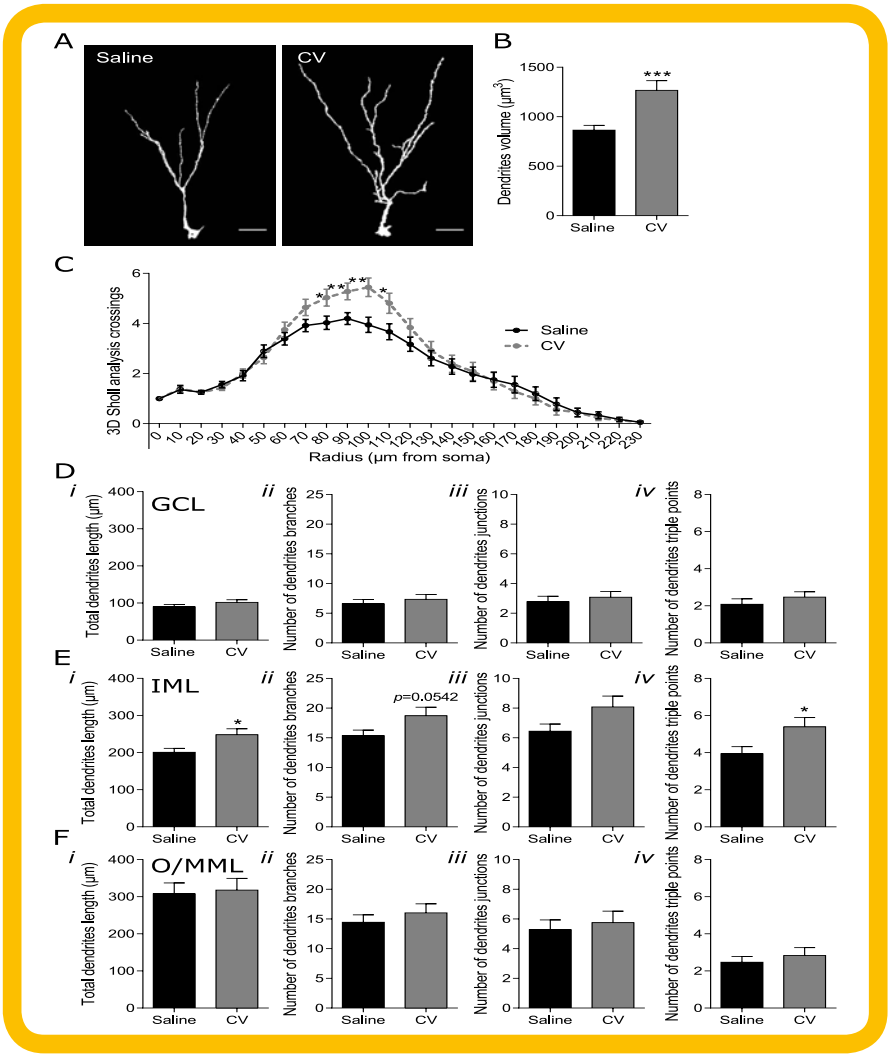
6-Identification of an electrophysiological signature of ageing-associated deterioration in brain networks.



MITOCHONDRIA AND NEURODEGENERATIVE DISORDERS | (*Head: Ana Cristina Carvalho Rego)*

OBJECTIVES

The research group "Mitochondria and Neurodegenerative Disorders" is focused on understanding cellular and molecular mechanisms associated to mitochondria in early stages of brain neurodegenerative disorders, namely in Huntington's (HD), and Alzheimer's (AD) diseases. These are chronic, debilitating and age-related brain disorders, characterized by selective cerebral neurodegeneration and cognitive decline. Modified, misfolded and/or mutant proteins affected in these diseases interfere with neuronal function, potentially causing deregulated mitochondrial function and bioenergetics, and altered intracellular redox signaling, namely after activation of glutamate synapses, or lead to defective neurogenesis, impacting on brain cognitive reserve. Although there are several mechanisms by which neurons degenerate, the initial pathways of neuronal dysfunction, occurring before main disease-related symptoms, are largely unknown for each disorder. In this perspective, by using molecular, cellular, ex-vivo and in vivo approaches, we aim to investigate early modifications affecting mitochondrial function and related signaling linked to redox regulation, 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 the local hospital, particularly in HD and AD. Identification of early disease mechanisms are envisaged to uncover relevant molecular targets for therapeutic intervention, as reviewed by us (Naia et al., 2017, Biochem. Biophys. Res. Commun). Therefore, the group aligns basic and translational research with interest in early disease stages, as well as investigation on neuroprotective therapies based on modifiers of mitochondrial function, glutamate synapse and neurogenesis, using pharmacological compounds, modulation of protein expression and/or gene correction strategies.



(Ferreiro and Pita et al., Oncotarget. 2018 Aug 31;9(68):32929-32942. doi: 10.18632/oncotarget.25978)

MAIN ACHIEVEMENTS:

By studying adult hippocampal neurogenesis, in the study published in Oncotarget (2018) we analysed the influence of the Coriolus versicolor (CV) mushroom biomass on dendritic arborization of newly-generated neurons.

Hippocampal adult neurogenesis has been considered to be a relevant contributor for brain cognitive reserve and brain plasticity.

No differences were observed in the volume of hippocampal dentate gyrus (DG) granular cell layer (GCL) and subgranular zone (SGZ) layers, in proliferation and in the number of newly-generated neurons of controls and CV-administered mice.

However, CV administration promoted a significant increase in dendritic length and branching and total dendritic volume of immature neurons, suggesting a positive effect of oral CV administration in the hippocampal neurogenic reserve.

We also observed that β-catenin levels are increased both in the nucleus and cytoplasm of DG immature neurons, suggesting that Wnt/β-catenin signalling may play an important role in the CV positive effect on the differentiation of these cells.

These data unveil a so far unexplored neurogenic potential of CV supplementation, which emerges as a possible preventive strategy for different neurological conditions.

In the context of Huntington's disease (HD), a neurodegenerative disorder causing cognitive and motor impairments, in the paper published in Hum Mol Genet. (2018) we designed a longitudinal structural imaging (MRI and DTI) and spectroscopy (1H-MRS) study in YAC128 transgenic mice, at 3, 6, 9 and 12 months of age. Structural analysis confirmed that the striatum is the earliest affected brain region. Importantly, we found for the first time, a negative correlation between striatal and hippocampal changes only in YAC128 mice. In fact, the striatum showed accelerated volumetric decay in HD, as opposed to the hippocampus. Neurochemical analysis of the HD striatum suggested early neurometabolic alterations in neurotransmission and metabolism, with a significant increase in striatal GABA levels, and specifically anticorrelated levels of N-acetyl aspartate and taurine, suggesting that the later is homeostatically adjusted for neuroprotection, as neural loss, indicated by the former, is progressing. These results provided novel insights into the natural history of HD and proved a valuable role for longitudinal multi-modal panels of structural and metabolite/neurotransmission in the YAC128 mouse model.

till in HD YAC128 mice, in the paper published in BBA – Mol. Bas. Dis. (2018), we analyzed proliferation, S migration and differentiation of adult subventricular zone (SVZ)-derived neural stem/progenitor cells (NSPC) from mild (6 month-old (mo)) and late (10 mo) symptomatic HD YAC128 mice vs age-matched wild-type (WT) mice. SVZ cells derived from 6mo YAC128 mice exhibited higher migratory capacity and a higher number of MAP2+ and synaptophysin+cells, compared to WT cells; MAP2 labeling was enhanced after exposure to BDNF.

However, BDNF-evoked neuronal differentiation was not observed in 10mo YAC128 SVZ-derived cells. Interestingly, 6mo YAC128 SVZ-derived cells showed increased intracellular Ca2+ levels in response to KCl, which was potentiated by BDNF, evidencing the presence of differentiated neurons. In contrast, KCl depolarization-induced intracellular Ca2+ increase in 10mo YAC128 SVZ-derived cells increased only in BDNF-treated YAC128 SVZ-derived cells, suggestive of decreased differentiation capacity. In addition, BDNF-untreated NSPC from 10mo YAC128 mice exhibited lower mitochondrial membrane potential and increased mitochondrial Ca2+ accumulation, in relation with NSPC from 6mo YAC128 mice.

Data evidenced age-dependent reduced migration and decreased acquisition of a neuronal phenotype, accompanied by decreased mitochondrial membrane potential in SVZ-derived cells from YAC128 mice through HD symptomatic phases.

AGING AND BRAIN DISEASES: ADVANCED DIAGNOSIS AND BIOMARKERS | (*Head: Catarina Resende Oliveira*)

OBJECTIVES:

In 2018, the group pursued in achieving its main objective focused in the identification of new biomarkers of aging and brain disorders, promoting the translation of knowledge generated in basic research to the clinic. Accordingly, the 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, neurodevelopment and bigenomic disorders and cancer. The integration in international research consortia contributed to the development of standard methodologies for sample storage and analysis, fulfilling the international criteria of quality control.

The involvement in international and national research networks has led to the implementation of collaborative research projects and to the development of novel genomic and cytogenetic methodological approaches.

Regarding biomarker-based diagnosis and prognosis of neurodegenerative diseases, we have participated in several collaborative efforts in order to: i) assess the accuracy of a previously proposed algorithm - the Erlangen Score - in predicting hazards of progression from the mild cognitive impairment (MCI) stage of Alzheimer's Disease (AD) to the dementia stage of the disease in our cohort of patients; ii) further clarify the association of specific genetic variants with AD cerebrospinal fluid (CSF) biomarkers iii) provide complete CSF total Prion Protein (tPrP) signatures across the broad spectrum of prion diseases, and iv) increase knowledge of the genetic etiology of several inherited forms of neurodegenerative diseases.

In the field of vascular neurological disorders, we have conducted a study aimed at assessing the diagnostic accuracy of plasma Adenosine deaminase 2 (ADA2) activity in differentiating patients with the recently described genetic disorder ADA2 deficiency (DADA2) from other adult patients within the Sneddon´s Syndrome (SnS).

In order to pursue bigenomic investigation of disorders, 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 to support functional genomics, allowing the implementation of functional studies for pathogenicity investigation of novel mutations. Regarding the pharmacogenomics studies, the research developed aims to identify 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. These approaches are a step forward in the clinical practice, taking advantage of the most recent techniques in Molecular Biochemistry and Genetics.

MAIN ACHIEVEMENTS:

1.1.Neurodegenerative and neuropsychiatric diseases

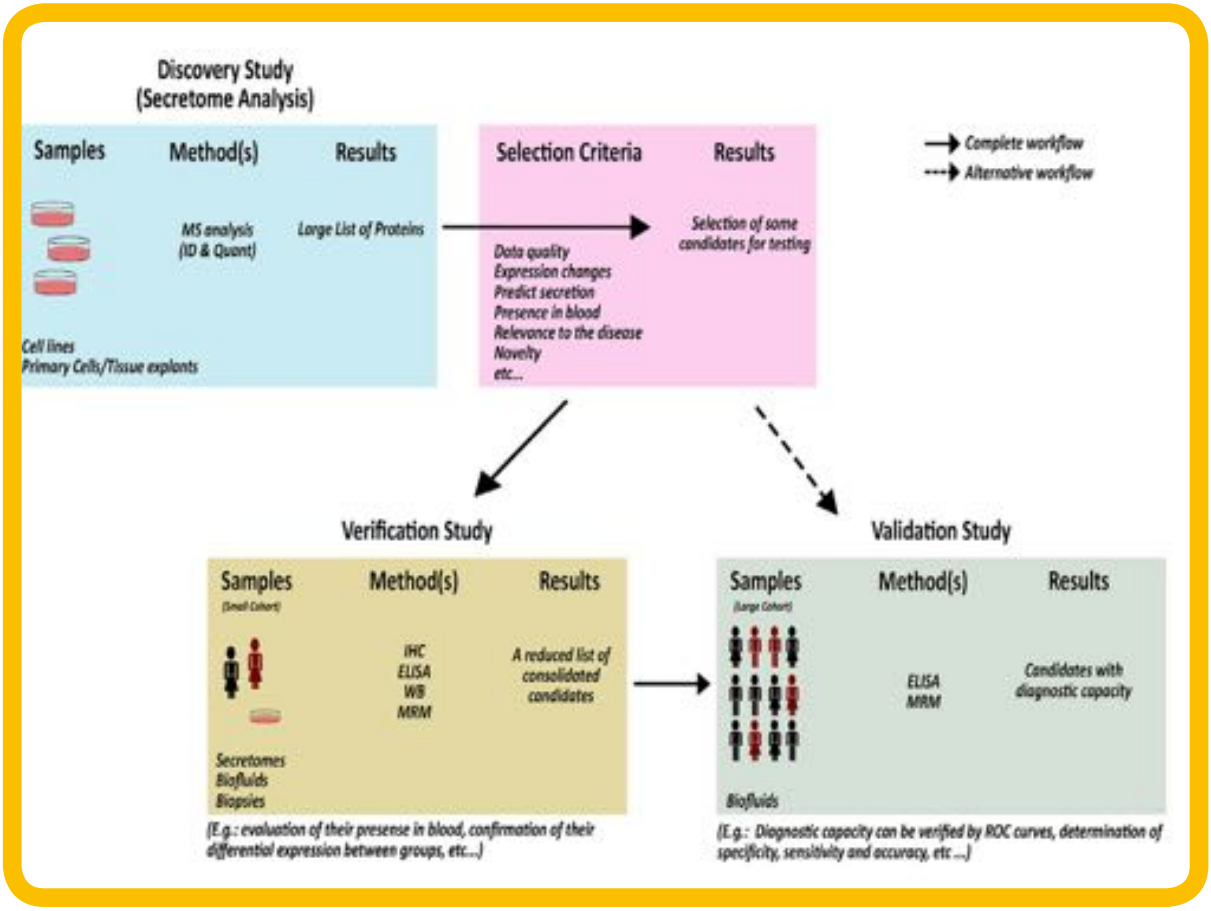
The results obtained in neurodegenerative disorders, confirmed and extended the conclusions of a previously published report that the Erlangen Score (ES) is a useful tool facilitating interpretation of a complex pattern of the CSF AD biomarkers. In fact, MCI patients with ES = 2/3 had 6–8 times higher hazards to progress to ADD compared to patients with ES = 0/1 in the first 3 follow-up years, while patients with ES = 4 had hazards 8–12 times higher compared to the ES = 0/1 group. The European multicenter genetic study, in which we are involved, reinforced the role of the five genes, APOE, LOC100129500, PVRL2, SNAR-I, and TOMM40, in AD pathogenesis. Three new AD susceptibility loci, INPP5D, CD2AP, and CASS4, showed neuropsychiatric diseases specific association with CSF tau that may point out new mechanisms and pathways. Neurodegenerative and independent of amyloid processing. The main findings of the multi-cohort study on prion diseases, showed that CSF t-PrP was decreased in all types of prion diseases regardless of their aetiology (sporadic, iatrogenic and genetic) albeit with mutation-specific exceptions in a minority of genetic cases. In some genetic prion disease, decreased levels were detected at pre-clinical stages and diminish with disease progression, suggesting that CSF t-PrP may have a role as a pre-clinical or early symptomatic diagnostic biomarker and in the evaluation of therapeutic interventions. The study on SnS showed that plasma ADA2 activity differentiated primary SnS from DADA2 with a sensitivity and specificity of 100.0%. Plasma ADA2 activity could also distinguish healthy heterozygous mutation carriers from healthy controls with a sensitivity of 97.1% and specificity of 85.7%. Therefore, plasma ADA2 activity seems a first-line diagnostic test for DADA2, suitable for implementation in clinical practice.

By applying different mass spectrometry approaches and secretome analysis, we pursued on the identification of biomarkers for Parkinson´s (PD), and Alzheimer's (AD) diseases. From the ongoing projects, a considerable increase in the number of biological samples collected from patients with first episode of psychosis (FEP) was achieved and preliminary data indicate a significant change in patients PBMC's profile. A new method "oxSWATH", was developed, which allows to monitor residue specific oxidative state in neurogenerative disorders.

2. Biomarkers of neurodevelopment and other diseases

We described the role of genomic Copy Number Variants (CNVs) in neurodevelopmental disorders that lead to cognitive impairment, improving patients' diagnosis.
We also contributed to the generation and characterization of a human iPS cell line from a patient-related control to study disease mechanisms associated with DAND5 gene mutation.
Several genomic tools were used for the assessment of new biomarkers in different pathologies, namely in cancer.

3. Biomedical Research in Bigenomic Disorders and Personalized Medicine.
The functional impact of novel mtDNA genetic sequence variation was evaluated and bioinformatics prediction analysis was performed.
The screening for genetic variants in whole-exome sequencing data of a Leber's Hereditary Optic Neuropathy (LHON) patient with m.14484T>C mutation, showed the c.280C>T and c.170delA/c.172_176delGGCAC variants in MIPEP and TOMM20L.
MIP protein levels in patient's lymphocytes were reduced, suggesting a possible decrease of substrate processing leading to an increase of unprocessed and unstable mitochondrial proteins.
The mtDNA copy number (CN) of 262 samples of Transthyretin-related familial amyloid Polyneuropathy patients (TTR-FAP Val30Met) and controls was analyzed, showing that patients and early-onset offspring have a significantly higher mean mtDNA CN.
A prospective observational study analyzed CYP2D6 pharmacogenetics in 55 Portuguese adult women undergoing elective cesarean section and revealed a positive association between alleles *4, *10 and pain and also between predicted reduced or null activity of CYP2D6 and increased pain.
So, CYP2D6 genotyping is recommended to anticipate the needs for analgesia and to adjust opioid dose and maximize clinical efficacy while reducing side effects.
Under the scope of the RIBEF-CEIBA Network Consortium interindividual and interpopulational variations in CYP2D6, CYP2C9 and CYP2C19 drug metabolizing enzyme genotypes in Latin Americans, supported the need for population-specific personalized and precision medicine programs.
A functional study was performed in 30 drug addicts' cells, confirmed that drugs of abuse have a negative effect on mitochondrial bioenergetics.



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

OBJECTIVES:

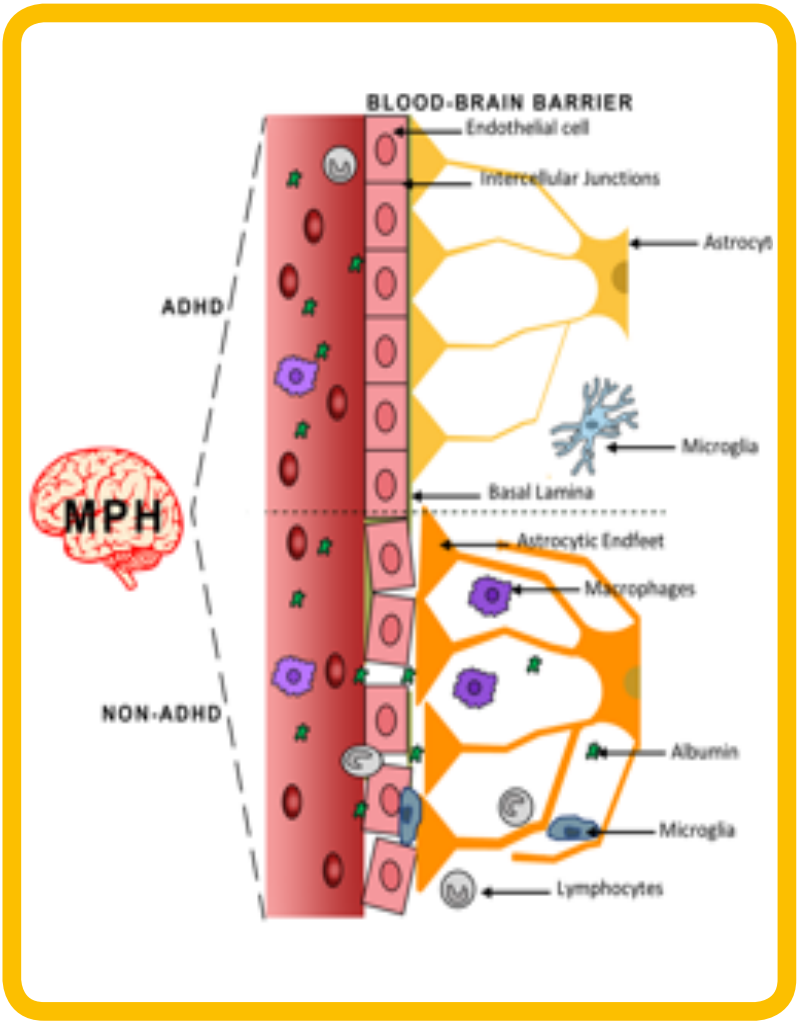
The Group has been mainly focused in chronic disorders that affect the brain and retina, but also other organs such as the heart, kidney and bone.
In general, our goals are:
- to elucidate the molecular and cellular mechanisms underlying the pathophysiology of chronic disorders affecting the brain, retina and other organs;
- to identify new potential drug targets and develop more efficient therapies and therapeutic options for the treatment of chronic disorders affecting those organs as well as evaluate the response to therapy.
Particular objectives have been defined in different sub-areas, as follows:

Vision Sciences
We have a major interest in 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 to retinal neural and vascular dysfunction and degeneration, and we have been exploring strategies that modulate adenosine receptors, the contribution of exosomes for the outer blood-retinal barrier breakdown and choroidal neovascularization, dissecting the protective mechanisms of incretin-based therapies in retinal endothelial cells function and evaluating the role of α-adducin in the structure and function the retina.
We are also developing animal models of ocular melanoma and retinoblastoma and new therapeutic approaches including photodynamic therapy, cold atmospheric plasma, ocular implants and nanoparticles activated by light.
Also in a translational perspective, we are trying to find new biomarkers for the diagnosis of these pathologies in tear fluids.
Finally, since the retina can be used as a window/mirror of the brain, we have also been investigating 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) and the Role of neuropeptide Y on traumatic brain injury outcomes.

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), considering sex-specific differences, and giving a particular attention to microglial cells, the immune cells of the central nervous system.

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 as chronic renal failure.
We also aim to develop potential therapeutic strategies for targeting Cancer Stem Cells in osteosarcoma.



MAIN ACHIEVEMENTS:

- Sitagliptin, a peptidase-4 (DPP-4) inhibitor used in the treatment of type-2 diabetes, ameliorates retinal endothelial cell dysfunction triggered by inflammation.

- The blockade of A2AR prevents the upregulation of pro-inflammatory mediators and the alterations in the complement system in human microglial cells and increases the clearance of apoptotic photoreceptors.

- In a model of prediabetes, there is subtle thinning of retinal layers without overt inflammations and vascular alterations.

- Methamphetamine interferes with AQP4, a water channel, causing brain edema and blood-brain barrier breakdown in mice striatum and hippocampus, as well as locomotor and motivational impairment.

- High dose of methylphenidate (MPH) promotes blood-brain barrier (BBB) permeability and elicits anxiety-like behavior in control and ADHD animals. In control rats, MPH also induces robust neuroinflammation.
However, in the ADHD model, a lower dose of MPH has behavioral beneficial effects.

- Coriolus Versicolor administration to mice promotes a significant increase in dendritic length and branching and total dendritic volume of immature neurons.

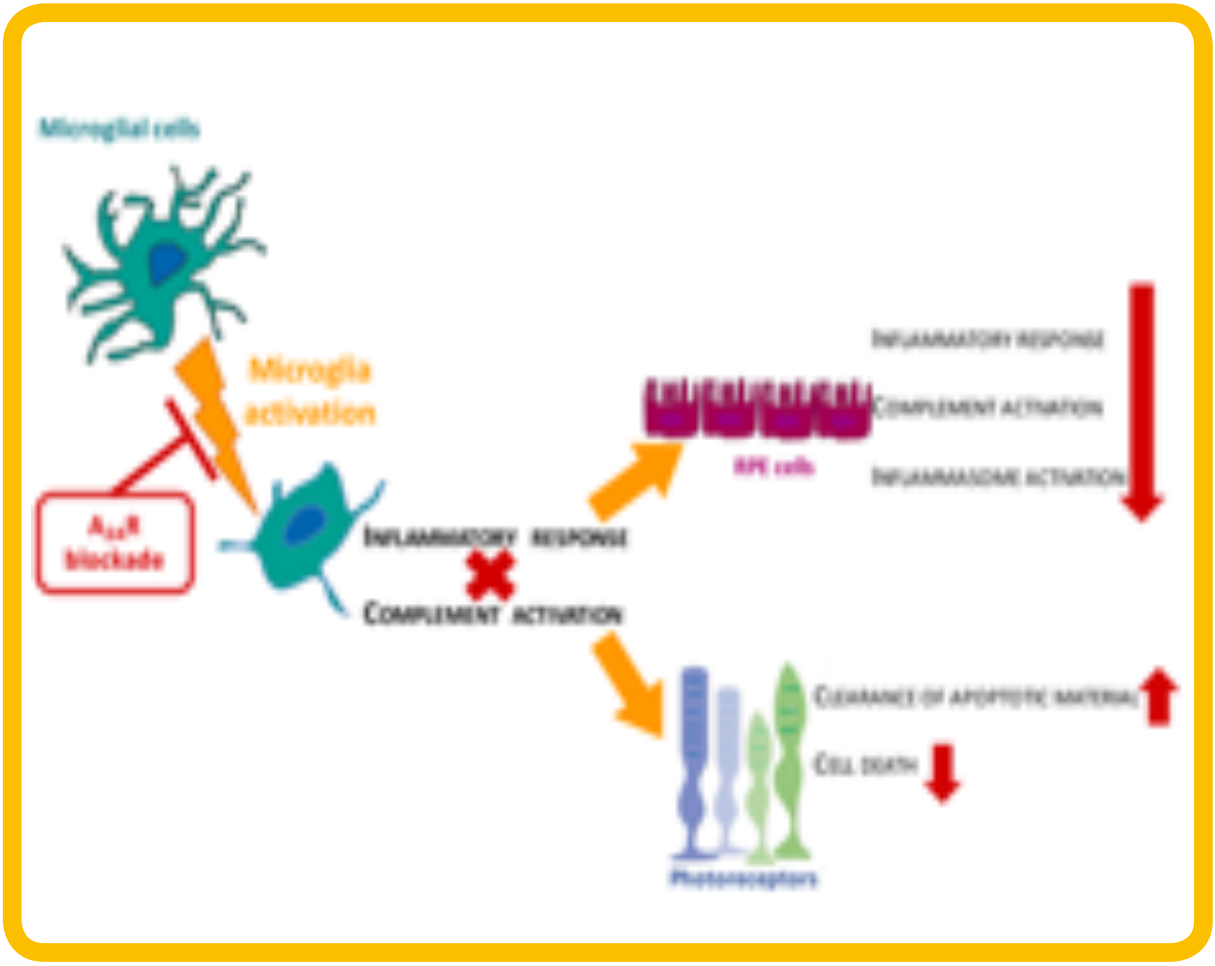
- Exercise-based interventions alone or as a conjoint therapy may be a useful tool for managing METH addiction.

- Chronic diet unbalance (high-fat or hypoproteic diet) triggers peripheral inflammation and leads to blood-brain barrier disruption and chronic neuroinflammation.

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

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

- We identified the Wnt/β-catenin signaling as a potential therapeutic target against osteosarcoma stem-like cells, for combination with established conventional therapies.
Moreover, this stem-like subset relies on oxidative phosphorylation for energy supply and is highly susceptible to the anti-diabetic Metformin either as mono- or combination therapies.



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. Finallu 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 Signaling and Metabolism in Disease Group

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Metabolic Control Group

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Alexandra Carvalho	Technician

CELL SIGNALING AND METABOLISM IN DISEASES | (*Head: Cláudia Pereira*)

OBJECTIVES

The work developed in this research Group had the following objectives:

1) To understand how mitochondrial signaling mediates pathology in patients with neurodegenerative disorders. During this period we investigated the role of mitochondrial dysfunction in the modulation of protein acetylation/deacetylation and its implications on autophagy. 2) To clarify whether O-GlcNAcylation, the posttranslational modification of intracellular proteins by β-N-acetylglucosamine (O-GlcNAc), contributes to "mitochondrial pathology" in Alzheimer's disease and its potential as a therapeutic target. 3) To elucidate how the disturbance of the Endoplasmic Reticulum (ER) stress response and of the ER-mitochondria axis can trigger pathological events associated with neuropsychiatric disorders, namely Alzheimer's and Bipolar diseases, leading to cell damage. We also intended to obtain experimental evidences supporting the therapeutic potential of compounds obtained from Portuguese natural resources.

4) To develop a disease-modifying treatment for Alzheimer's disease based on BACE1 inhibition.

5) To evaluated the responses of neuronal cells to different glycemic exposures and the role of uncoupling protein 2 (UCP2) in regulating such responses. In addition, we explored the effects of chronic, continuous, subcutaneous exposure to Exendin 4 in brain cortical glucagon-like peptide-1 (GLP-1)/insulin/insulin-like growth factor-1 (IGF-1) signaling, and in autophagic and cell death mechanisms in middle-aged male type 2 diabetic rats.

6) To elucidate the molecular mechanisms involved in peripheral and neuroinflammation and changes in the cells of the immune system associated with the inflammatory response. Additionally, we aimed at developing 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 approach may contribute to the development of efficient laboratory tests in screening for possible new drugs or potentially immunotoxic chemicals.

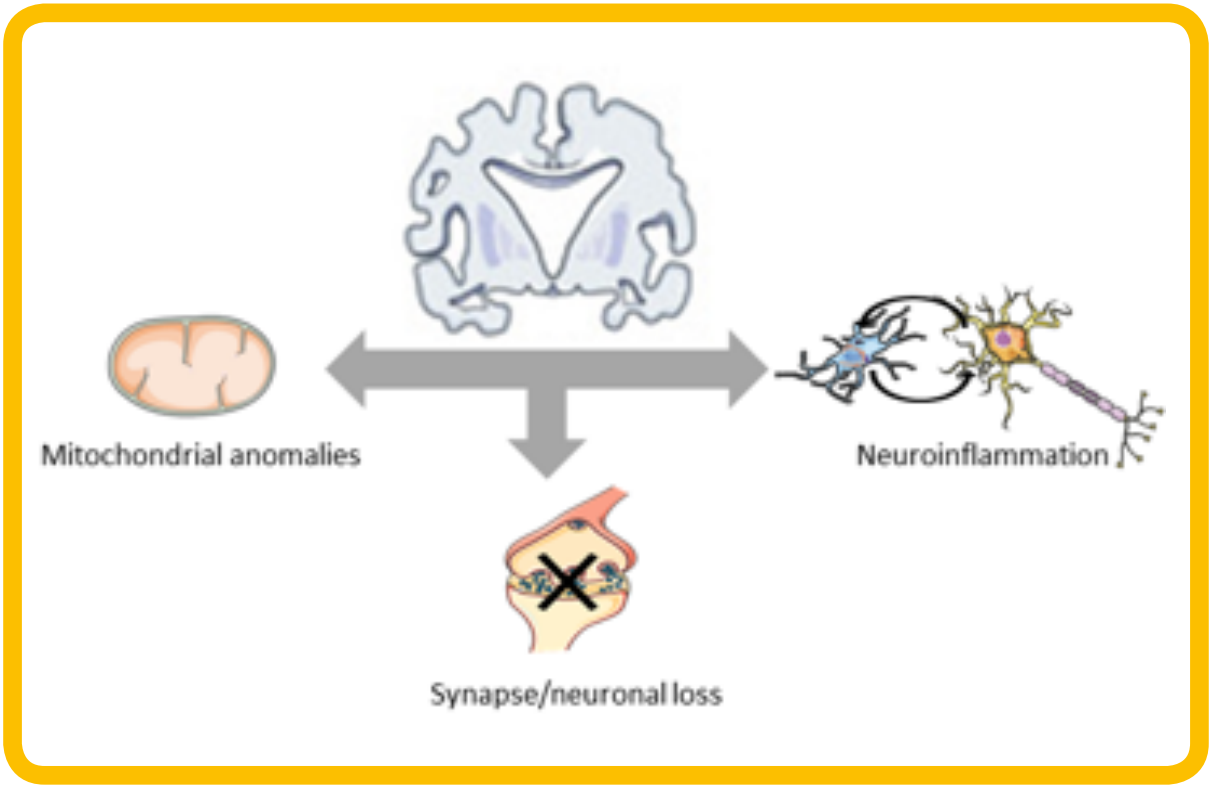


Figure 1 – Mitochondrial anomalies, neuroinflammation and synapse and neuronal loss are typical hallmarks of age-related neurodegenerative diseases.

MAIN ACHIEVEMENTS

- Protein acetylation is a key regulatory post translational modification that can be targeted to rescue the autophagic pathway with relevant implications in neurodegenerative disorders.

- O-GlcNAcylation, the posttranslational modification of intracellular proteins by O-GlcNAc is involved in Alzheimer's disease pathology functioning as a potential link between mitochondrial energetic crisis and synaptic and neuronal degeneration.

- The chronic treatment of 3xTg-AD mice with the new BACE1 inhibitors we are developing leads to a decrease in insoluble Aβ40/42 brain levels suggesting these compounds have the potential to be a disease-modifying therapy. Moreover, these compounds inhibit selectively the APP-β cleavage without interfering with the cleavage of some other BACE1 substrates.

- Diabetic brain protection exerted by Exendin-4 is mediated by GLP-1/IGF-1 signaling and autophagy.

- The mitochondrial uncoupling protein 2 (UCP2) is in the core of neuronal cell protection and/or adaptation against glucose levels variation-mediated effects and that other isoforms of neuronal UCPs can be upregulated to compensate the inhibition of UCP2 activity.

- The thiol-reactive sensitizer 1-fluoro-2,4-dinitrobenzene (DNFB) directly reacts with cytoplasmic glutathione (GSH) causing its rapid and marked depletion, which results in a general increase in ROS accumulation. In turn, trimellitic anhydride chloride (TMAC), which preferentially reacts with amine groups, induces a delayed GSH depletion as a consequence of increased mitochondrial ROS production. These divergences in ROS production seem to be correlated with the different extension of intracellular signaling pathways activation. Ultimately, our observations may help explain the distinct dendritic cells phenotype and T-cell polarizing profile triggered by skin and respiratory sensitizers.

- T. carnosus and T. camphoratus has anti-inflammatory properties.

MITOCHONDRIA, METABOLISM AND DISEASE GROUP | (*Head: Paulo Oliveira*)

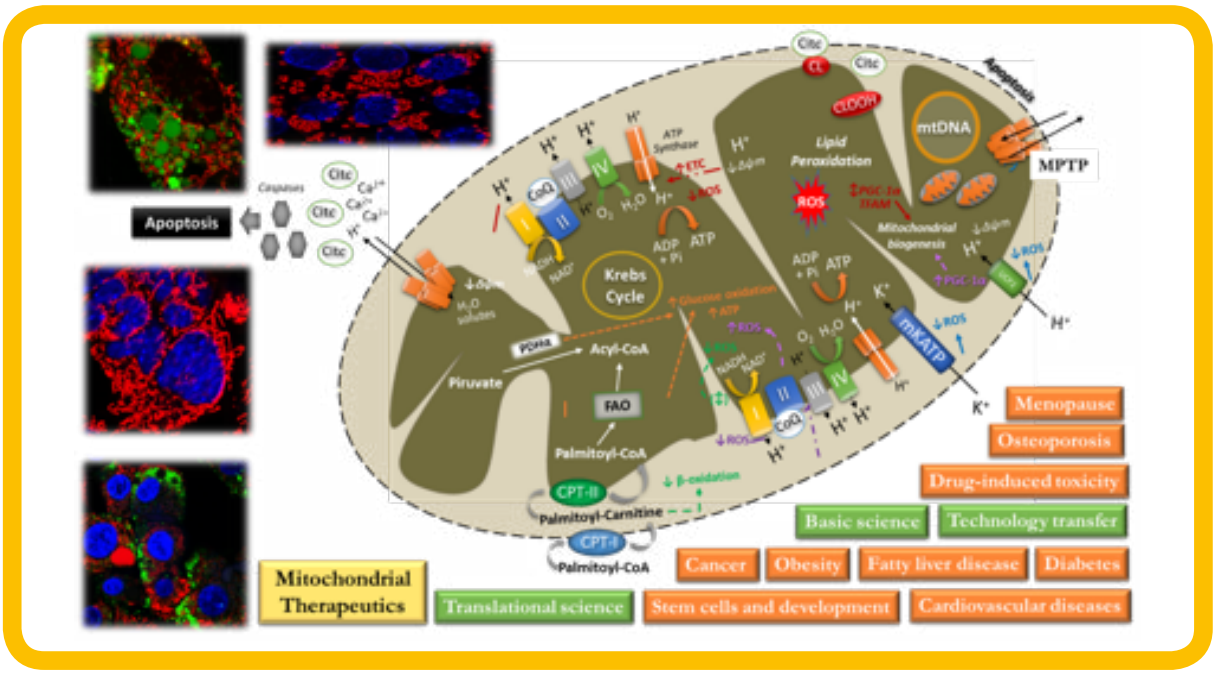
OBJECTIVES

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.

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: Metformin and Berberine modulate miRNA-378 levels, which results in an improvement of mitochondrial function through a mitohormetic program activation. We highlighted a role for miRNA-378 in the induction of a futile cycle and the improvement of mitochondrial function upon a hyperglycemic stress. The bile acid CDCA was competent to ameliorate adipocytical metabolic function even in the absence of the bile acid receptor TGR5. This is extremely relevant to the study of human effects of bile acids in metabolic improvement, since that, until now, bile acids effects were attributed to a thermogenic effect caused by the activation of TGR5, relevant for rodents but possibly inconsequential for humans. We further demonstrated activation of mitophagy, and the repopulation of the cell with more resilient, more functional mitochondria, more suited to handle the excess nutrients being supplied. CDCA could also lead to mild mitochondrial uncoupling, not harmful to the survival of the cell, but leading to a consumption of nutrients, leading to an overall reduction in energy stores and thus causing a normalization of metabolic function. Related with cancer, 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. We also showed that the HSP90 family chaperone TRAP1 provides cytoprotection of lung cancer cells by up-regulating autophagy. Our studies revealed that senescence mediates the acquisition of cancer cells chemoresistance. Additionally, we showed that exosomes and exomers are major players on the horizontal transfer of information leading to the acquisition of cancer cells chemoresistance.

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 mouse stem cell-derived cardiomyocytes, we demonstrated that suggest higher DOX concentrations mainly induces p53-dependent apoptosis, whereas for lower DOX concentrations, the cardiotoxic effects involve bioenergetic failure, unveiling PDH as a possible therapeutic target to decrease DOX cardiotoxicity. We also investigated the toxicity of new synthetic lupane derivatives, which caused perturbations in the organization of synthetic lipid bilayers, leading to changes in membrane fluidity, and loss of mitochondrial oxidative phosphorylation showing that positively charged triterpenoids target mitochondria and disrupt bioenergetics. We collected, isolated and structurally characterized active compounds from different algae, including Sphaerococcus coronopifolius and Asparagopsis armat, and evaluated their toxicity against in vitro human cellular cancer models including cancer stem cells.

3. Mitochondria-targeted therapeutics: Following previous work, and in collaboration with the University of Porto, we developed novel hydroxybenzoic acid derivatives which act as dual-target ligands, affording mitochondrial antioxidant protection and acting as cholinesterase inhibitors. Furthermore, we discovered that one of such novel compounds, AntiOXBen3, act as a potent inhibitor of the mitochondrial permeability transition pore. In the same setting, we also developed a mitochondria-targeted vitamin K derivative (MitoK) which we showed to selectively act against lung cancer cells, while protecting normal lung fibroblasts from the toxicity of doxorubicin, a conventional anti-cancer agent.

METABOLIC CONTROL GROUP | (*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, visceral fat and intestinal microbiota using 13C-enriched fructose and glucose. These methods are being 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. We are also interested in characterizing the microbial metabolism of fructose and glucose in the intestinal lumen to determine if they contribute more to beneficial products (for example butyrate) or detrimental products (for example ethanol or acetate).

b) **Evaluate insulin resistance and the oxidative capacity of human adipose tissue either drug-induced or caused by heart failure in the clinical setting**.

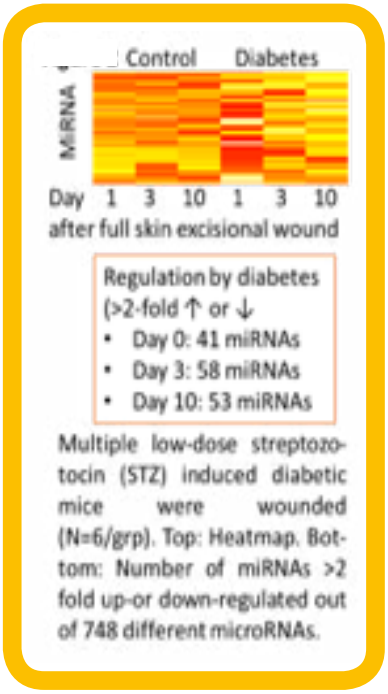
c) **Assess the effects of neuro- and antimicrobial peptides as well as specific microRNAs in skin cells in culture in an in vitro setting or in vivo in our pre-clinical models of wound healing under diabetes conditions.**

MAIN ACHIEVEMENTS

Novel 13C NMR analysis of fatty acid enrichment in the livers and adipose tissues of naturally-feeding mice that were provided with [U-13C]glucose and [U-13C]fructose in combination with deuterated water (2H2O) in the drinking water. This allowed the contribution of acetyl-CoA from exogenous fructose and glucose to hepatic de novo lipogenesis to be estimated and revealed that fructose contributed about 3 times more acetyl-CoA than glucose for de novo lipogenesis (~30% versus 10%). Both sugars together accounted for about 40% of lipogenic acetyl CoA and ~70% of glycerol-3-phosphate synthesis. The 13C NMR analysis also provided a detailed lipidomic profile of the triglyceride fatty acids including information on their position in the triglyceride molecule – which to date has not revealed by any mass-spectrometry-based method. This analysis revealed that saturated, monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) are not randomly distributed among the three glycerol esterification sites.
Instead, the sn2 site is almost entirely occupied by MUFA and PUFA while saturated fatty acids are confined to the sn1,3 sites.

As part of a long-standing and ongoing research project we established that calcineurin is an important factor involved in modulating glucose uptake in human fat cells. In addition, our studies indicate that epicardial adipose tissue from heart failure patients is clearly different from the adjacent subcutaneous adipose tissue from the same subjects in regard to proteostasis, including the biogenesis, folding, trafficking and degradation of proteins present within and outside the cell. This is very important particularly in the setting of heart failure.

We were able to specifically choose from a large discovery screening a number of microRNAs that are clearly over-expression in the setting of diabetes and our pilot studies demonstrated that when these microRNAs were inhibited either in cell cultures or in our pre-clinical wound healing model, the wound healing kinetics resumed much like in normal healthy wounds.



Multiple low-dose streptozotocin (STZ) induced diabetic mice were wounded (N=6/grp). Top: Heatmap. Bottom: Number of miRNAs >2 fold up-or down-regulated out of 748 different microRNAs.

Stem Cell-Based and Molecular Therapies

Coordinator: Luís Pereira de Almeida

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 applications of microbiology, proteolytic enzymes and siRNA/miRNA. 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

During 2018, the groups in this strand were particularly successful in attracting competitive funding, in excess of 5.6 million EURO, of which 82% from FCT/ESIF funds. Additional funding sources include the H2020 framework programme – for the MSCA-ITN NANOSTEM, an advanced training network involving research organizations, hospitals and biotech/pharma companies from 7 European countries – and private contractors like Wave Life Sciences USA, Inc., UNIQURE Biopharma B.V. and Blade Therapeutics. Overall, research efforts originated ca. 130 publications in peer-reviewed international journals and book series (not counting meeting abstracts), half of them including fruitful collaborations with institutions (academic and otherwise) from nearly 30 different foreign countries. Ca. 27% of the publications involved hospital and healthcare units/entities (notably the Coimbra University Hospitals (CHUC)) and nearly 50% 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, followed by Spain, Germany, France, Italy and the Netherlands. The majority of the publications (71%) are Q1, with nearly 40 in Top 10% journals, including Cell, Nature Cell Biology, ACS Nano, Nature Communications, EMBO Journal, Science Immunology, PNAS, Neurology 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. Indeed the areas of research of the publications range from Pharmacology & Pharmacy to Biotechnology & Applied Microbiology, to Genetics & Heredity, from Neuroscience to Haematology. Overall, the 2018 publications feature a Category Normalized Citation Impact of 1.73, one article co-authored by Prof Milton S. Costa (Int J Syst Evol Microbiol, 2018) being both a Highly Cited and Hot Paper in its field (top 1% and 0.1% citation threshold respectively). Other performance indicators include several requests for and/or concessions of IPR protection: one patent application features a vector for the use in the treatment of a polyglutamine repeat spinocerebellar ataxia (PCT/EP2018/052199), another being for cell induction/ or reprogramming to the dendritic cell state or antigen presenting cell state (PCT/IB2018/052378). A third one proposes an Anti-nucleolin antibody for oncologic use (PCT/IB2018/055471). 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 of the new core facility ViraVector for on-demand viral vector engineering and production is almost concluded.

FUTURE PLANS

As CNC.IBILI enters its next 5-year Strategic Programme rebranded as the Center for Innovative Biomedicine and Biotechnology (CIBB), the Stem Cell-based and Molecular Therapies Thematic strand will be restructured to accommodate 11 groups, changing the name 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). 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

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Maria Celeste Lopes	PhD
Nuno Fonseca	PhD
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Ana Rita Ribeiro	PhD Student
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Daniela Santo	PhD Student
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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.

MAIN ACHIEVEMENTS

Regarding non-viral-mediated gene delivery, an extensive screening of a variety of cell penetrating peptides 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 is currently being developed. In this regard, miR-128, a microRNA involved in the regulation of stemness features, showed to be detrimental to GBM cancer stem-like cells (G144 cells), and its combination with the multitargeted tyrosine kinase inhibitor (MTKI) axitinib was identified as a potential therapeutic strategy to tackle GBM. 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, also showed to be a highly promising therapeutic approach towards GBM. Overexpression 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. Moreover, we have demonstrated that regulation of microRNA expression levels combined with low amounts of chemotherapeutic agents results in a significant and synergistic cell death effect in pancreatic cancer cell lines and primary culture models. 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 increase of GL-P and BCRP, respectively) were involved on Chronic Myeloid Leukemia (CML) resistance to imatinib, and that simultaneous administration of imatinib and everolimus re-sensitize 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. Nucleolin arises as a relevant target for cancer therapy, as it is overexpressed at the surface of cancer and angiogenic endothelial cells thus enabling a dual cellular targeting strategy. In this respect, anti-nucleolin VHHs have been generated upon grafting F3 peptide-derived nucleolin-binding sequences onto a VHH CDR1 or CDR3. One of these nucleolin-binding CDR3-grafted VHH was subsequently fused to a human IgG1 Fc region, enabling a significant antibody-dependent cell-mediated cytotoxicity (ADCC). 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.

Stem Cell Biotechnology | (*Head: Lino Ferreira*)

OBJECTIVES

The main scientific objectives of the group between 2013 and 2018 were: (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. These objectives are in line with the objectives that have been proposed for the research group in the previous application of the Research Center.

1 - Stem cell-based therapies for the treatment of ischemic diseases. The objective here was to evaluate the therapeutic effect of stem cells in the treatment of ischemic diseases (e.g. stroke, myocardial infarction and chronic wounds). A clinical trial has been initiated with the Hospital Rovisco Pais and Centro Hospitalar e Universitário de Coimbra, having the participation of a stem cell banking company, Crioestaminal. The phase I/II clinical trial is running and it 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 here was to generate and functionally characterize hematopoietic stem cell-like cells from somatic cells (murine and human). his is a recent research line (February 2015) interested to study the mechanism of hematopoietic stem cell specification. To accomplish this goal, a combination of cell biology tools, gene expression and systems biology analyses are being used.

3 - To implement stem cell-based assays and in silico approaches for drug screening. The objective here was to develop several tissue models from stem cells that may be an important platform for drug discovery programs related to ischemic diseases. A particular interest of the group was to 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. The research group used many tools to accomplish this goal, including the design of new biomaterials with relevant biological information, molecular and cell biology, microfluidic systems, high content analysis, and animal experimentation.

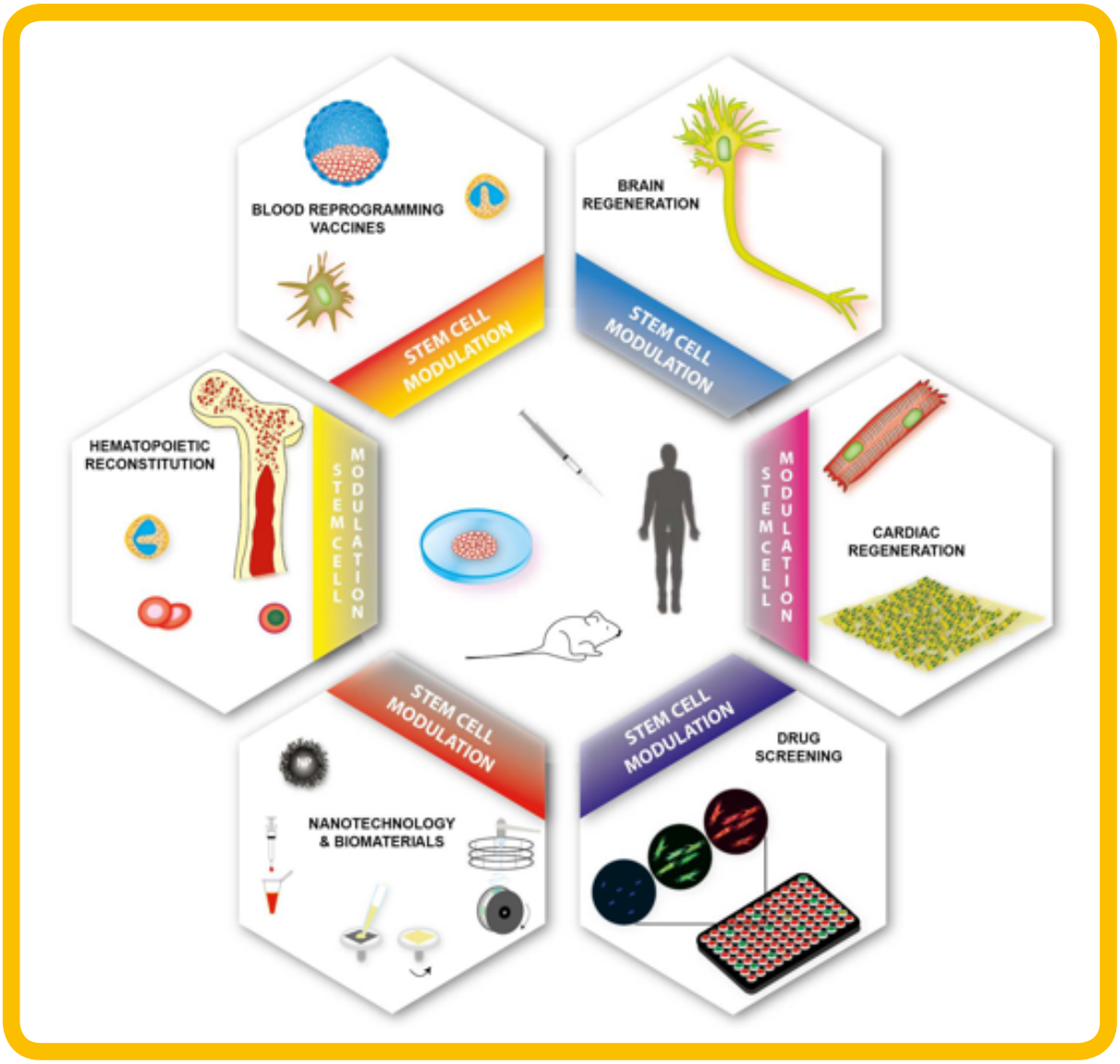
4 - To deliver novel therapeutic compounds identified in the previous high-throughput approaches using nanotechnology-based non-viral vectors. The objective includes the development of nanotechnology tools to control in vivo stem cell activity based on biomolecules identified previously (see objective 3) by high-throughput approaches. This requires contributions at different levels such as the development of formulations with high technical value to be remotely activated and the use of animal models. The main translational objectives of the group between 2013 and 2018 were: (i) to translate stem cell-based therapies into clinical trials and (ii) to launch new spin offs based in therapeutic/regenerative platforms developed in the group. These objectives were aligned with the objectives defined in the CNC.IBILI application. At that time, it was defined as objectives the creation of at least 2 spin offs and the licensing of 5-10 technologies until 2020. Regarding the first objective, the group has initiated a clinical trial with two Hospitals in the Center Region of Portugal: Centro Hospitalar e Universitário de Coimbra (Coimbra) and Hospital Rovisco Pais (Tocha). Regarding the second objective the group has launched three spin offs called CureMat, Exogenus Therapeutics and BRT. The group has also licensed 4 patents to companies.

The main training/outreach activities objectives of the group between 2013 and 2018 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

During the last 6 years, the group has done progresses to address the following scientific questions: (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?

To tackle the first question, we have generated a human in vitro model of ageing based on induced pluripotent stem cells (iPSCs) derived from patients with Progeria. SMCs are the most affected cells in Progeria patients, although the reason for such sensitivity remains poorly understood. Therefore, we have studied the reasons of Progeria-SMCs vulnerability using iPSCs obtained from Progeria fibroblast patients (Manuscript submitted). In a separate work, we have developed a in vitro heart tissue from iPSCs. For that purpose, we have developed a scaffold that reproduces key aspects of cardiac extracellular matrix while preserving the contractility of cardiomyocytes (Gouveia et al., Biomaterials 2017). In an independent work, we have identified,



using high-throughput screening, small molecules that interfere with human embryonic vascular development (Vazão et al., PNAS 2017).

To tackle the second question, we have synthesized new advanced nanomaterials to release small molecules (Boto et al., Nature Communications 2017), proteins (Lino et al., Nanoscale 2017) and miRNAs (Lino et al., ACS Nano 2018) within cells. Intracellular delivery of biomolecules is extremely useful for the manipulation of cellular processes and cell reprogramming. In the past decade, different nanoformulations have been developed for the delivery of bimolecules to cells. However most of these strategies are based on the passive diffusion of the biomolecule from the nanocarrier or on the enzymatic degradation of the nanoformulation. So far, no formulation has the capacity to orchestrate the intracellular delivery of multiple biomolecules with remote control. Recently, we have developed a formulation able to orchestrate the release of 2 or more proteins/miRNAs within the cell from the same nanocarrier using a single trigger (Lino et al., Nanoscale and ACS Nano).

To tackle the third question, we have identified recently a miRNA involved in the prosurvival effect of vascular endothelial growth factor immobilized to extracellular matrixes (Aday et al., Nature Communications 2017). In a parallel study, we have performed several screenings that led to the identification of 15 miRNAs – from a total of 2080 - capable of enhancing stem cell survival. The mechanism of action of two of the top 15 miRNAs is currently under analysis but we have made significant progress in that respect. Firstly, we have identified one mechanism involved in the miRNA-mediated survival. To that end, we used genetic and molecular tools to show how the selected miRNAs modulate an important survival pathway. Secondly, we have performed RNA-Seq experiments to further narrow our search and fully disclose the mechanism of action of both miRNAs. Thirdly, we have demonstrated their effect in vivo, in two different settings: wound healing and myocardial infarction (Manuscript in preparation).

COMPUTATIONAL AND SYSTEMS BIOLOGY | (*Head: Armindo Salvador*)

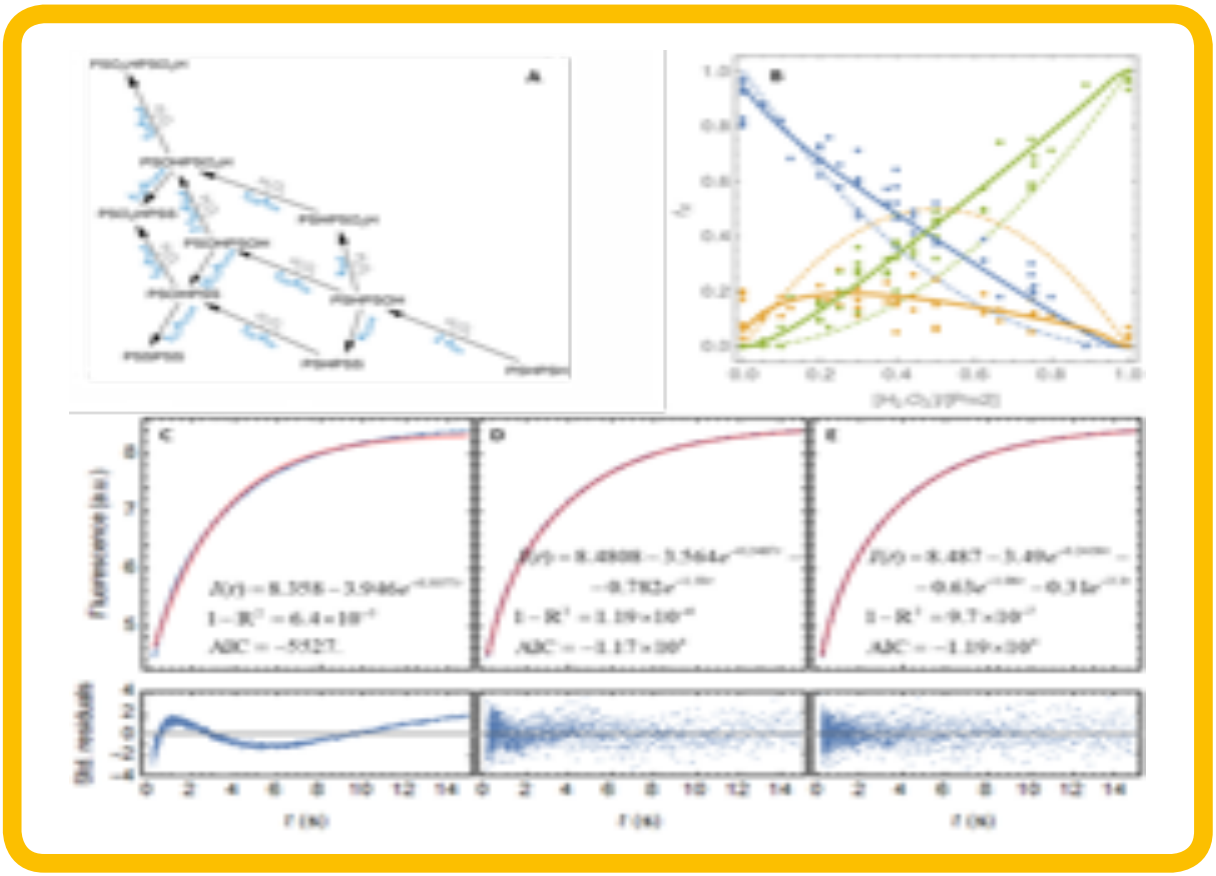
OBJECTIVES

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 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.



MAIN ACHIEVEMENTS

Peroxiredoxins are among the oldest, most widespread and most abundant proteins in cells. They control H_2O_2 concentrations in most cells. In higher organisms, the 2-Cys peroxiredoxin II (Prx2) is also involved in the H_2O_2 mediated regulation of cell proliferation, apoptosis, cell migration, neuroprotection, angiogenesis and tumorigenesis. Understanding the kinetics of its reactions with H_2O_2 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 H_2O_2 reactive Cys (peroxidatic Cys, CP), proximal to a less reactive (resolving, CR) Cys in the other monomer. In the catalytic cycle, CP reduces H_2O_2, being oxidized to a sulfenic acid (CP SOH), which in turn undergoes a condensation with the proximal CR, forming a disulfide. The disulfide is reduced by thioredoxin 1, closing the cycle. The CP SOH can also react with a second H_2O_2, forming a catalytically inactive sulfinic acid (CP SO_2H). Hitherto, it had been assumed that the two active sites in each dimer of this and other 2 Cys Prx operate independently. However, as a diagram of the interconversions among the redox states of each CP in a Prx2 dimer (panel A) shows, there are multiple possibilities for cooperativity. lation rate constants at the second site (fCS=fCO, fSS=fSO). Altogether, these studies reveal Prx2 as the first known enzyme combining positive and negative cooperativity in its catalytic cycle. 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, Brasil) we achieved a near-comprehensive characterization of the effects of the redox state of a site on the reactivity of the other. The main findings were as follows. (i) The formation of the first sulfenic acid facilitates sulfenylation of the second site (fOO≈5). This was revealed by the relative fractions of 0 (B, blue dots), 1 (yellow dots) and 2 disulfide dimers (green dots) formed upon treatment of Prx2 with various sub stoichiometric H_2O_2 amounts (B, dashed lines, prediction in absence of cooperativity; solid lines, best fit of a kinetic model allowing for cooperativity). (ii) The formation of the first disulfide delays the formation of the second one (fCC≈fOC/2). This was revealed by the hitherto unappreciated multi-exponentiality of the Trp fluorescence recovery when Prx2 is oxidized by H_2O_2 in stopped flow experiments (C E, 1 to 3 exponential best fit curves with 0.5 µM Prx2 + 0.5 µM H_2O_2, in red). (iii) The formation of the first disulfide influences neither the sulfenylation nor the sulfinylation rate constants at the second site (fOC=1, fSC=fSO). (iv) The formation of the first sulfenic acid influences neither the condensation nor the sulfinylation rate constants at the second site (fCS=fCO, fSS=fSO). Altogether, these studies reveal Prx2 as the first known enzyme combining positive and negative cooperativity in its catalytic cycle. Nitrobenzoxadiazole (NBD) labeled lipids are popular fluorescent probes of membrane structure and dynamics, and have been widely used in both model systems and living cells. Irrespective of attachment to the lipid head group or hydrocarbon chains, the NBD fluorophore generally adopts a transverse bilayer location near the host lipid carbonyl/glycerol moieties. Still, considerable variability is observed in the measured fluorescence lifetimes, indicating that overall fluorophore location is not the determinant of NBD fluorescence properties. Combining fluorescence experiments and molecular dynamics simulations, we show that for two almost identical NBD probes, significant differences in fluorophore orientation and fluorescence lifetime are observed. Integrating these findings with literature data, we demonstrate a correlation between NBD orientation and fluorescence lifetime. The latter is longer when the NBD nitro group is predominantly oriented towards the bilayer interior, compared to probes for which it points to the water medium. [Filipe et al. (2019) Phys. Chem. Chem. Phys., (2018 PCCP HOT Article)]

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. Immunosenescence, rendering the elderly more susceptible to infection, is one of our major focus, including is one of our major focus, including modulation of gut inflammation and chronic respiratory diseases. During the period of this report (2018) our specific objectives were to seek for novel therapies to eradicate fungal infections with a focus on oral and bone biofilms 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.

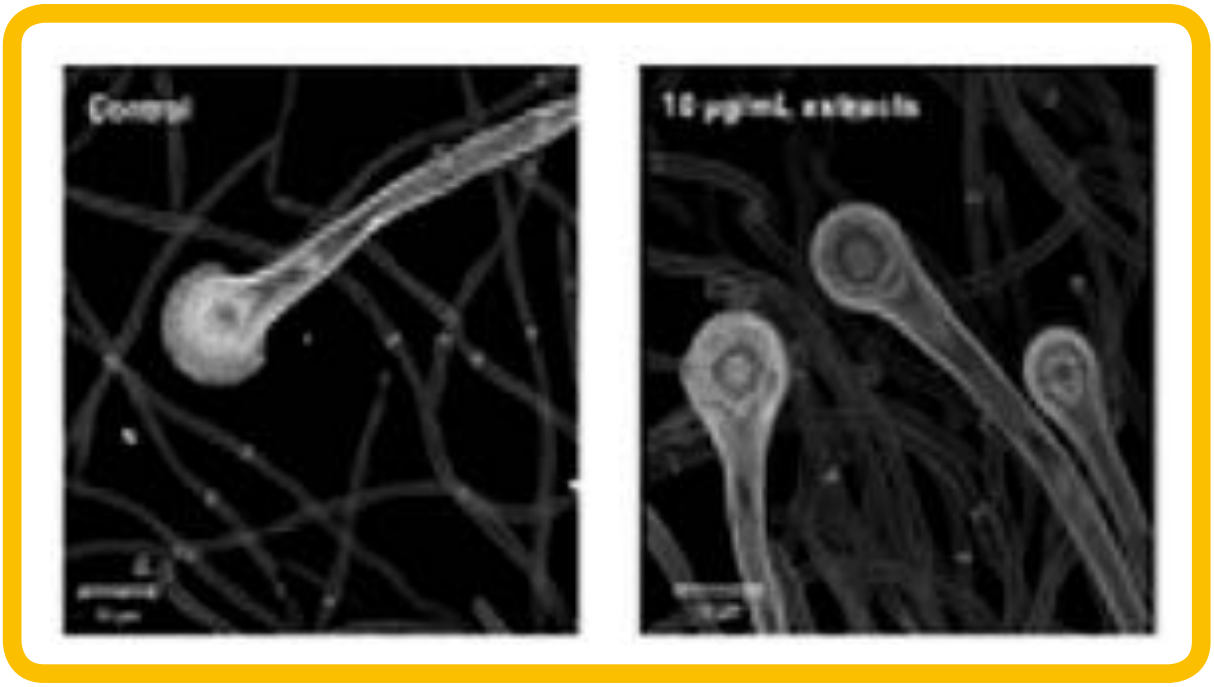


Figure 1 – Exposure of Aspergillus Fumigatus to Osmundea pinnatifida extracts: modification of sporulation pattern

MAIN ACHIEVEMENTS

Following our collaboration with an expert in algae it was identified one more, from the portuguese coast, that has a high potential of providing safe (it is edible) and highly efficient antifungals. Also, according to previous our in vitro findings, we proved, ex vixo, that Antimicrobial Photodynamic Therapy using an algal derived chlorophyll as photosensitizer, is able to eradicate complex dental biofilms. Together with a group of clinicians, including an imunoallergologist and an otorhinolaryngologist, we studied the mycobiome of the upper respiratory system of allergic patients and, in sera of those patients, we performed a screening of IgEs against fungal cell wall extracts from the fungi isolated from those patients. Moreover, an in vitro study is being initiated in order to understand if one algal extract is able to prevent fungal sensitization in allergic patients.

MOLECULAR MYCOBACTERIOLOGY AND MICROBIOME | (*Head: Nuno Empadinhas*)

OBJECTIVES

The Group's objectives are centered on 3 research lines (Microbial Pathways, Microbiome in Chronic Diseases, Public Health Microbiology) and are summarized below: Mycobacterial Pathways - Mycobacteria are "a globally established priority for which innovative new treatments are urgently needed" (WHO, 2017) that can cause an array of infections beyond tuberculosis (TB), mostly in the chronically ill and in the elderly. We aim at deciphering gene functions and characterize enzymes for biosynthesis of polymethylated polysaccharides, modulators of fatty acids metabolism and assembly of the mycobacterial cell wall, and also potential targets for rational design of innovative antimycobacterials. Biosynthesis of novel antimicrobials - Actinobacterial secondary metabolites are known for their great chemical diversity and unique biological activities (antibacterial, antifungal, antiparasitic, antiviral, anticancer or immunosuppressive agents). Sugar-modifying enzymes encoded in rare gene cluster of Actinobacteria containing a glucosamine kinase we recently identified will be characterized to elucidate the biosynthesis and unique chemistry behind a putative antibiotic while also paving the way to medical and industrial applicability. Microbiome in Chronic Diseases - Parkinson's Disease: We sought to profile the dysbiotic gut microbiome of patients with special focus on neurotoxin-producing microbes and to evaluate the effects of such neurotoxin on neuronal mitochondrial metabolism. Diabetes: Our objective in this line of research was to profile diabetic foot ulcers (DFU) microbiome in a quest for unique microbial signatures for future bacteriotherapeutic intervention. We also aimed at the construction of a unique DFU microbial biobank essential for future research. Public Health - We aim at a comprehensive screening of domestic water distribution systems to assess prevalence of opportunistic mycobacteria causing pulmonary infections in susceptible individuals. Genomic fingerprinting will allow understanding of the epidemiology and antimicrobial resistance determinants associated to this rapidly growing health threat.

MAIN ACHIEVEMENTS

Funding available to the Molecular Mycobacteriology and Microbiome Group

2018-2021	POLYREP - An intriguing mycobacterial polysaccharide: recycling, replication and beyond. POCI-01-0145-FEDER-029221, FCT/FEDER, Portugal (PI: Nuno Empadinhas).	236.321€
2018-2021	STERILAEROGEL - Green method to prepare sterilized biopolymers-based aerogels. POCI-01-0145-FEDER-032625, FCT/FEDER, Portugal (PI: Mara Braga, DEQUC; PI at CNC: Nuno Empadinhas).	29.000€
2018-2019	PROTOTRANSFER "TimeUp". Projeto INESPO III, Programa Operacional de Colaboração Transfronteiriça 2014-2020 POCTEP/FEDER (Susana Alarico).	4.000€
2018-2019	Prevalência e variabilidade genética de micobactérias não-tuberculosas em ambiente doméstico. Prémio Thomé-Villar/Boehringer Ingelheim 2017, Sociedade Portuguesa Pneumologia (PI: Raquel Duarte; Co-PI: Nuno Empadinhas). Promotor: ISPUP, University of Porto.	4.300€
2017-2020	The toxinogenic gut microbiome in sporadic Parkinson's Disease: a quest for "antiPDbiotics". Prémio Santa Casa Neurociências Mantero Belard, Santa Casa da Misericórdia de Lisboa (PI: Sandra M. Cardoso; Co-PI: Nuno Empadinhas).	199.000€
2017-2020	HealthyAging2020 - Deciphering microbiome signatures in chronic diseases for early diagnosis and modulation therapies. CENTRO-01-0145-FEDER-000012-N2323 (PI: João Ramalho Santos) (HR budget to the Molecular Mycobacteriology & Microbiome Group).	45.700€
2017-2019	MICROCARE - Microbiome of diabetic ulcers: early diagnosis, prognosis and therapy. INFARMED, Fundo para a Investigação em Saúde, FIS-FIS-2015-01_DIA_20150630-144 (PI: Sónia Pereira; Co-PI: Nuno Empadinhas).	100.000€

Relevant research achievements in the three research lines (see above) targeted by the Molecular Mycobacteriology and Microbiome Group in 2018 are summarized below:

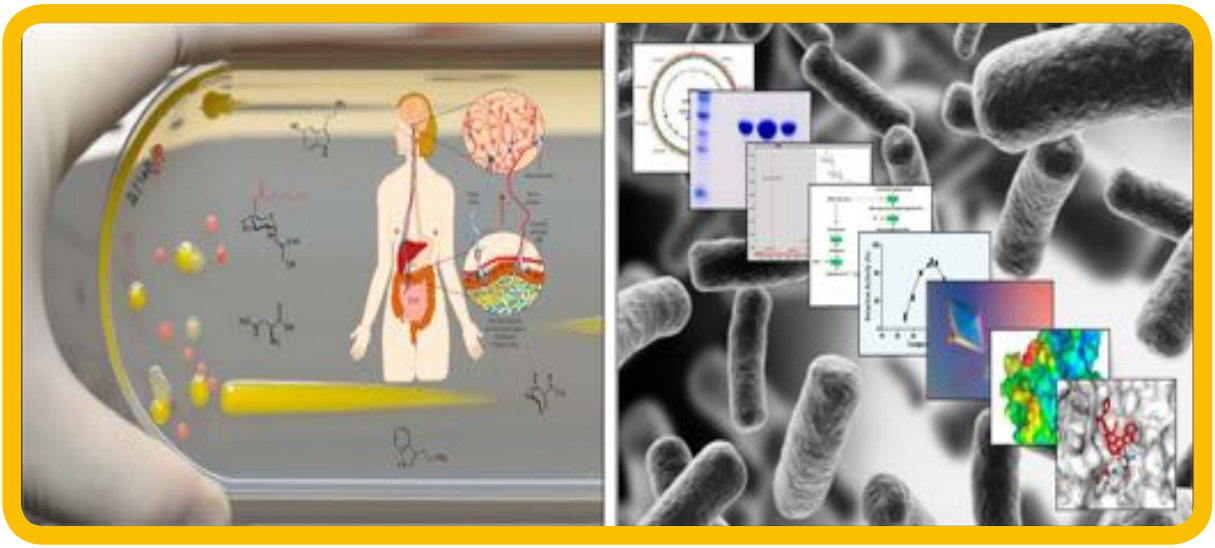
Molecular Mycobacteriology - We have deciphered an unprecedented mechanism for replication and recycling of a mycobacterial polysaccharide required for modulation of fatty acid metabolism and assembly of the cell envelope. These findings build on previous achievements in our group (Mendes et al, Nat Prod Rep) that comprehensively defined two essential mycobacterial pathways and new promising targets. We have now deciphered the first step of one of these novel mycobacterial pathways (Ripoll-Rozada et al, PNAS).

Biosynthesis of novel antimicrobials - We identified an Actinobacterial glucosamine kinase whose gene is part of an orphan biosynthetic cluster together with other sugar modifying enzymes in a unique organization that hints at a completely novel class of secondary metabolites. This family of kinases is likely to represent the missing link for incorporation of environmental glucosamine into antibiotic biosynthesis pathways (Manso et al, mBio).

Parkinson's Gut Microbiome - We investigated the gut microbiome of Parkinson's Disease (PD) patients as well as the impact of gut dysbiosis in the pathology. Microbiome profiles of PD patients revealed microbial signatures prone for bacteriotherapeutic intervention. Our vitro and in vivo results confirmed how a specific microbial neurotoxin impacts neuronal mitochondrial metabolism and some PD features (Cardoso & Empadinhas, Front Physiol).

Diabetic Wounds Microbiome - Sampling diabetic patients skin and wounds and isolation of relevant microbiota allowed creation of a DFU biobank with over 1100 strains of 50 different species, instrumental for future research (Pereira et al, Front Microbiol). Antimicrobial susceptibility trials and interspecific competition assays revealed bacterial communication phenomena in the DFU ecosystem. Genomes of relevant DFU microbiota were sequenced.

Public Health - We have isolated nontuberculous mycobacteria (NTM) from different wards in a hospital. Susceptibility assays identified multidrug resistant phenotypes, posing health risks to inpatients (Pereira et al, BMC Microbiol). We sampled water distribution systems of NTM patients' houses. Multiple mycobacterial species were identified by whole genome sequencing, including members of M. abscessus-chelonae clade isolated from most houses.



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 ursane triterpenoids derivatives of madecassic acid. We synthetized a series of novel 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, 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 active site (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 inhibition potency, cellular toxicity and in vivo efficacy of the best candidate using animal models of the disease. Additionaly we also focused on the anti-Leishmania activity of the synthetic compound, the 4-[(2E)-N´-(2,2´-bithienyl-5-methylene)hydrazinecarbonyl]-6,7-dihydro-1-phenyl-1H-pyrazolo[3,4-d]pyridazin-7-one (T6). Effects on the cell cycle, apoptosis/necrosis events, morphology and DNA integrity were also planned. Antimicrobial resistance is considered one of the major Public Health threats nowadays, with very few therapeutic options for the treatment of multidrug resistant Gram-negative bacteria. Therefore, it is crucial to understand the molecular epidemiology and mechanistic dissemination of drug resistance to delineate further fighting approaches. We have focused on the beta-lactam resistance dissemination in Acinetobacter spp.

MAIN ACHIEVEMENTS

We synthetized a series of novel madecassic acid (MEA) derivatives and screened them for antitumor activity against the NCI-60 cancer cell line panel. Some of the tested compounds, showed high similarity in their selectivity patterns with significant growth inhibitory activity at nanomolar concentrations for 80% of the tumor cells lines harboring the B-RafV600E mutation.

Structure-activity analysis revealed that a 5-membered A ring containing an a,b-unsaturated aldehyde substituted at C-23 with a 2-furoyl group seems to be crucial to produce this particular growth inhibition signature.

Follow-up analysis revealed that these compounds can effectively inhibit ERK cascade signaling in B-RafV600Emutation bearing cell lines by reducing Raf protein levels and, consequently, MEK and ERK phosphorylation without any effect on their total protein levels. DOI: 10.3389/fchem.2018.00434

Concerning Alzheimer's disease, molecular modeling studies allowed to gain new insights into the structural features of BACE1 and the generation and validation of structure-based and ligand-based pharmacophore models followed two rational strategies – one represents the essential interactions of BACE1-ligand complexes and the other was based on structurally diverse chemicals of known potent BACE1 inhibitors.

These pharmacophore hypotheses were validated through statistical parameters and then used to accurately screen large druglike compound databases.

The retrieved hits were filtered to predict their ability to cross the BBB and molecular docking enabled the selection of the best candidates for in vitro screening assay. Lastly, cell-free assays identified a collection of new and desirable hits that modulate BACE1 activity at the micromolar level. doi: 10.3389/fchem.2018.00178 and results under publication.

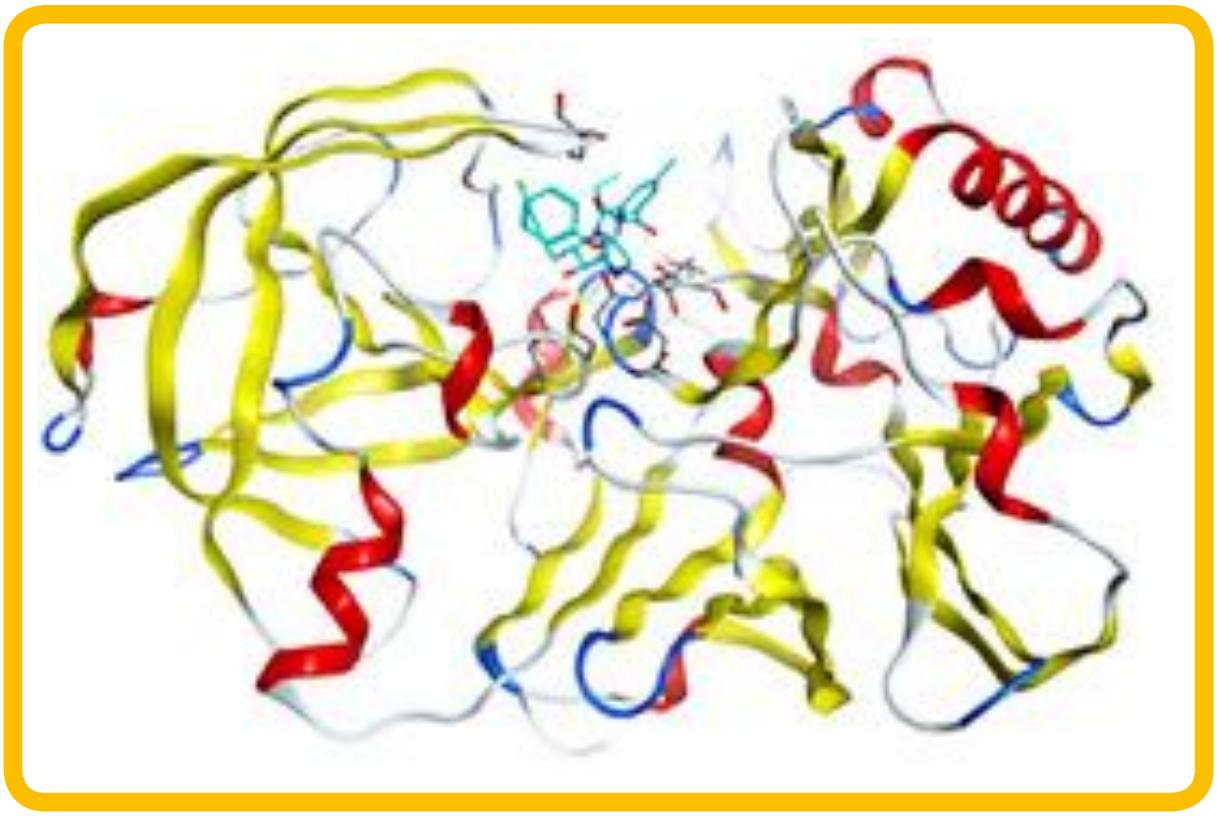
The synthetic compound, the 4-[(2E)-N`-(2,2`-bithienyl-5-methylene) hydrazinecarbonyl]-6,7-dihydro-1-phenyl-1H-pyrazolo[3,4-d]pyridazin-7-one (T6) and T6 encapsulated in glucan-rich particles, mainly composed by the cell wall of Saccharomyces cerevisiae (GPs), showed anti-parasitic activity on Leishmania infantum.

The activity of T6 was characterized by events of cell death by apoptosis like increased ROS production, cell shrinkage, phosphatidylserine exposure and DNA fragmentation.

We conclude that T6 can be considered a promising anti-Leishmania compound, and that the use of GPs for drug encapsulation is an interesting approach to the development of new effective and less toxic formulations.

effective and less toxic formulations (International Journal of Biological Macromolecules. 119: 1264-1275. https://doi.org/10.1016/j.ijbiomac.2018.08.019). We also showed that of glycoalkaloids (Brazilian Journal of Pharmacognosy 28, 673-677 https://doi.org/10.1016/j.bjp.2018.07.008) and Lavandula extracts had activity against Leishmania (Applied Sciences 9(15):3056. doi: 10.3390/app9153056). In A. baumannii, we have detected the blaNDM-1 gene, encoding an emerging carbapenemase, for the first time in the Tunisian territory, as well as a high prevalence of the blaOXA-23 gene; rendering beta-lactams ineffective against these strains.

In Portugal, it was found another carbapenamase, KPC-3, in a strain resistant to the last therapeutic options colistin and tigecycline (pan-resistant). All these genes have the potential to spread as demonstrated in vitro. Moreover, we found thatnatural transformation, an unexplored horizontal gene transfer mechanism, play a role in the dissemination of non-resistance coding genetic elements (insertion sequences) by chromosomal recombination that lead to changes in the susceptibility profile to third-generation cephalosporins in A. baumannii.



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 and also in members of the Planctomycetes, an unusual deep-rooted lineage of 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, wood products such as cellulase, lignin and xylan. 5) To unravel the microbial diversity and community structure of a deep mineral water aquifer and the bottled water produced from said water using massively parallel 454 pyrosequencing of the 16S rRNA gene, DGGE, FISH and cultivation.

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. These studies led to the identification of a new compatible solute, (2R)-2-(1-O-α-D-mannopyranosyl)-3-(1-O-α-D-glucopyranosyl)-D-glycerate (MGlyG. Genes with high identity to those leading to the synthesis of glucosylglycerate and glucosylgycerol.

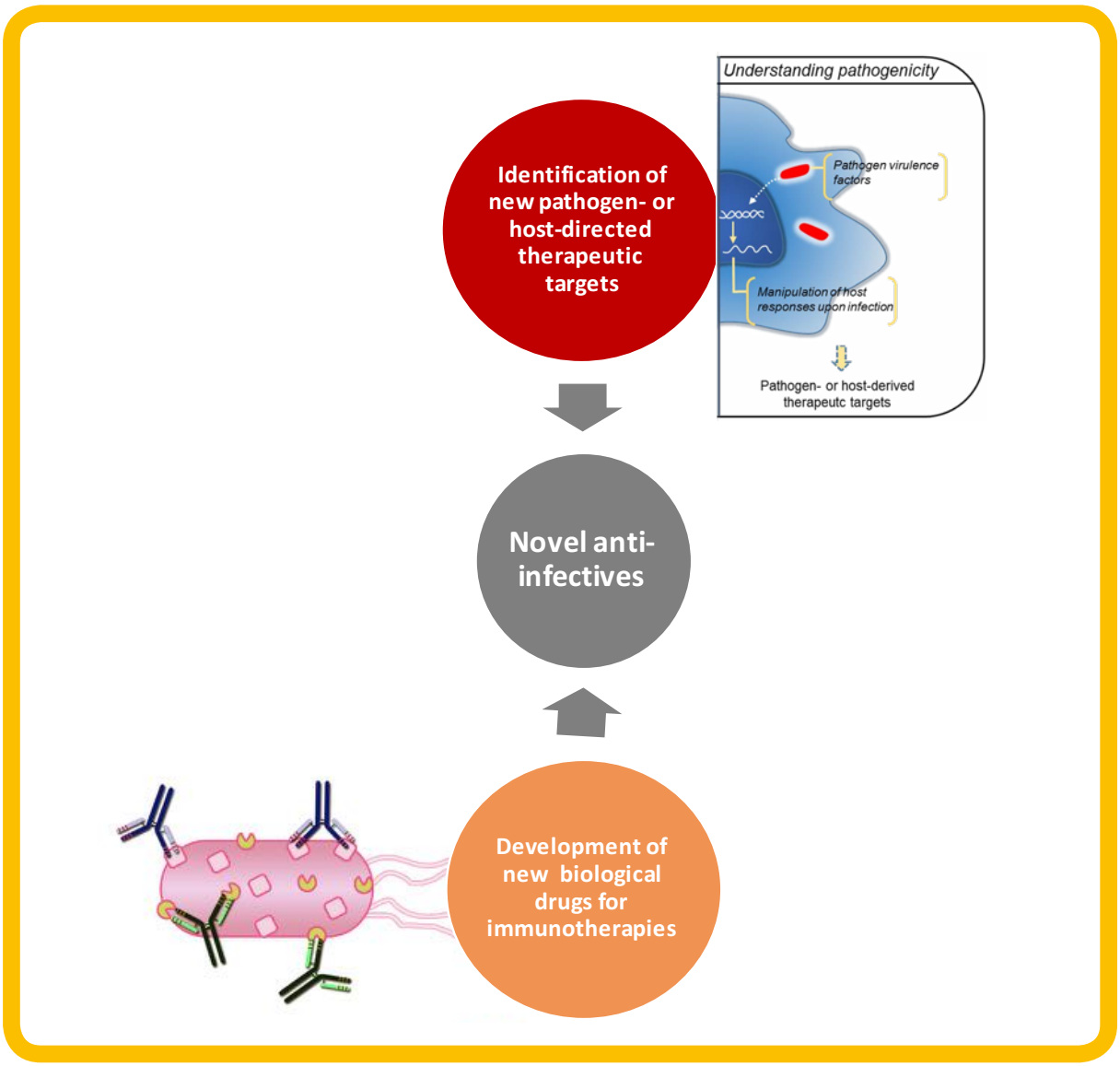
BIOTECHNOLOGY

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 aim to:
iv) Continue exploring the functional and biotechnological aspects of plant (aspartic) proteases.

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. Under the collaborative project with Dr. Juan Martinez (LSU, USA), we have evaluated early host transcriptomic responses by RNAseq (at one hpi) and proteome signatures by SWATH-MS (at 24 hpi) of THP-1 macrophages infected with R. conorii and R. montanensis. These results provide the first evidence for a substantial reprogramming and mechanistic differences between Rickettsia-macrophage-tropic vs. non-tropic phenotypes (two manuscripts submitted).

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. The avian unit is also the only one of its kind in Portugal.
  Of note is the development of proprietary housing systems for egg-laying Coturnix japonica model hosts (International Patent Application submitted), that enable core R&D activities.

3) Biochemistry, biology and biotechnology potential of plant APs

• To aim at developing more effective solutions with potential for scalability of production and commercial application, several strategies have been undertaken in more recent years to establish new cardoon-based rennets.
  This review provides an overview on these developments and on the currently available solutions, which range from producing standardized formulations of native cardoon enzymes, to the optimization of the heterologous production of cardosins and cyprosins to generate synthetic versions of these milk-clotting enzymes. Almeida C.M. & Simões I. (2018) Cardoon-based rennets for cheese production. Appl Microbiol Biotechnol. https://doi.org/10.1007/s00253-018-9032-3

- Binary blends of S. marianum–flower extract and chymosin, as coagulant preparations, enabled the manufacture of miniature cheeses with distinctive characteristics compared to those of chymosin-renneted cheeses.
  The physicochemical parameters, sensory attributes of the cheeses, and in-vitro water-soluble antioxidant activity were analyzed and compared to those properties obtained from control chymosin-renneted cheeses. S. marianum–flower extract, as a source of peptidase with distinctive characteristics, is a suitable substitute for chymosin in miniature-cheese production. The addition of vegetable rennet contributed to the development of an intense aroma and conferred antioxidant activity to the cheeses and wheys. Colombo M.L., et al. (2018) Miniature cheeses made with blends of chymosin and a vegetable rennet from flowers of Silybum marianum: Enzymatic characterization of the flower-coagulant peptidase. Food Chemistry Nov 15;266:223-231.

- Six individual cardoon genotypes(1M–6M) were selected based on a wide and consistent diversity of total and specific cardosin concentrations in flowers. During three growing seasons, the stability of 12 biochemical characteristics of flower extracts and 26 plant morphological descriptors was confirmed.
  The cardosin profiles of each genotype, based on four main groups A0, A1, A and B, were stable during the annual flower harvesting period and over all three years. This knowledge will allow an improvement in the quality and standardization of cardosin profiles from cardoon flowers used for cheese production and other innovative applications. Barracosa P., et al. (2018) Selected Cardoon (Cynara cardunculus L.) Genotypes Suitable for PDO Cheeses in Mediterranean Regions. Chem. Biodivers. Jul;15(7):e1800110.

- We pursued with the functional characterization of the atypical aspartic protease (AP) from Arabidopsis named ASPR1, for Atypical Aspartic Protease in Roots 1). ASPR1 overexpression suppressed primary root growth and lateral root development, implying a previously unknown biological role for an AP (manuscript submitted).

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 Group

Cardoso AL, Fernandes A, Aguilar-Pimentel JA, de Angelis MH, Guedes JR, Brito MA, Ortolano S et al. (2018) Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases. Ageing Res Rev 47: 214-277.

Guedes JR, Lao T, Cardoso A L, El Khoury J (2018) Roles of microglial and monocyte chemokines and their receptors in regulating alzheimer's disease-associated amyloid-ß and Tau pathologies. Frontiers in Neurology 9:549.

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Melo R, Lemos A, Preto AJ, Almeida JG, Correia JDG, Sensoy O, Moreira IS, Computational Approaches in Antibody-Drug Conjugate Optimization for Targeted Cancer Therapy, Curr Top Med Chem. 2018; 18, 1091-1109.

Schiedel AC, Kose M, Barreto C, Bueschbell B, Morra G, Sensoy O, Moreira IS, Prediction and targeting of interaction interfaces in G-protein coupled receptor oligomers, Curr Topics Med Chem, 2018; 18, 714-746.

Moreira IS & Sensoy O, Modulation of protein-protein interactions for the development of effective therapeutics – from a joint perspective of experimental and computations, Curr Topics Med Chem, 2018; 18, 645-646.

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Preto AP, Almeida JG, Schaarschmidt, J Xue LC, Moreira IS, Bonvin AMJJ, Computational tools for the structural characterization of proteins and their complexes from sequence-evolutionary data. Encyclopedia of Analytical Chemistry, 2018 - In press.

Redox Biology and Brain Sensing

Egea J. et al (2018) Corrigendum to "European contribution to the study of ROS: a summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS)". Redox Biology 14, 694-696.

Ferreira NR, Ledo A, Laranjinha J, Gerhardt GA, and Barbosa RM. (2018) Simultaneous measurements of ascorbate and glutamate in vivo in the rat brain using carbon fiber nanocomposite sensors and microbiosensor arrays. Bioelectrochemistry 121:142-150. DOI: 10.1016/j.bioelechem.2018.01.009.

Neuroendocrinology and Aging

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).

Eric Grouzmann - Division of Pharmacology and Toxicology, University of Lausanne, Switzerland (Collaborative Research; NPY and NPY fragments assessment)

Ruben Nogueiras - CIMUS, University of Santiago de Compostela, Spain (Collaborative Research; host of one Master student and one PhD student;, hypothalamus and liver crosstalk);

Xavier Nissan - I-Stem, Paris, France (Collaborative Research & Co-supervisor of PhD student; host of one PhD student; in vitro progeria models).

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)

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

Vision, Brain Imaging and Cognitive Neuroscience

Papers (international collaboration)
See European Projects above.

Gurel SC, Castelo-Branco M, Sack AT, Duecker F. Assessing the Functional Role of Frontal Eye Fields in Voluntary and Reflexive Saccades Using Continuous Theta Burst Stimulation. Front Neurosci. 2018 Dec 14;12:944.

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Scientific collaborations

Serge Picaud, Institut de La Vision, Paris, France
Reza Farivar, Harvard University, US and McGill University, Canada
Rainer Goebel, University of Maastricht
Agneta Nordberg, Karolinska Institute
Michael Wibral, University of Frankfurt
Eugenio Rodriguez, University of Chile
Alcino Silva, University of California at Los Angeles
Fred Ullen, Karolinska Institute
Valerie Voon, University of Cambridge
Richard Edden, John Hopkins University
Post-graduation and post-docs interchange

Post-graduation and post-docs interchange

Felix Duecker (postdoctoral fellow from the University of Maastricht and recently awarded a Marie Curie Fellowship)

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 (FP7 and H2020): BrainTrain, INfradev, Marie Curie Actions, STIPED

Purines and Brain Diseases

-Networks:
Member of the Steering Committee of the European Neuroscience Campus (with Univ. Amsterdam, The Netherlands; Univ. Bordeaux, France; Univ. Zurich, Switzerland; Univ. Gottingen, Germany)
Member of the European Network of Neurosciences Institutes (ENI-Net)
Member of the 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 (Marina Aparecida Magnini Portes) 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 (Amber Kerkhofs) with Huibert Manvelder (Univ.Amsterdam, The Netherlands)
Co-supervision of a PhD student (Xinli Xu) with Nelson Rebola (Univ. Bordeaux, France)

Mitochondrial Dysfunction and Signaling in Neurodegeneration

Graduate Training:

- "Neurodegenerative disorders", PhD Programme in Experimental Biology and Biomedicine, organized by the CNC-Center for Neuroscience and Cell Biology, University of Coimbra.
Coordinators: Ana Cristina Rego and Cláudia Pereira
Date: 23 – 27 April, 2018
Local: CNC (anfiteatro Ed. Faculdade de Medicina, 2º andar, Universidade Coimbra-pólo I)

- "Neuroscience and Mental Health: a Clinical and Molecular Perspective", The Doctoral Programme in Health Sciences, organized by the Faculty of Medicine, University of Coimbra.
Coordinators: Ana Cristina Rego and António Freire.
Date: February 26 – March 2, 2018
Local: iCBR Auditorium (Pólo III – Pólo das Ciências da Saúde, Azinhaga de Santa Comba, Celas)

Collaborative publications:
- Ferreiro and Pita (2018) Oncotarget 9, 32929-32942.
- Petrella et al. (2018) Hum. Mol. Genet. 27, 2125-2137.
- Silva et al. (2018) BBA - Molecular Basis of Disease 1864, 34-44.

Aging and Brain Diserases: advanced diagnosis and biomarkers

Collaborative Publications:

Willemijn J. Jansen, Rik Ossenkoppele, Betty M. Tijms, Anne M. Fagan, Oskar Hansson, William E. Klunk, Wiesje M. van der Flier, Victor L. Villemagne, Giovanni B. Frisoni, Adam S. Fleisher, Alberto Lleó, Mark A. Mintun, Anders Wallin, Sebastiaan Engelborghs, Duk L. Na, Gäel Chételat, José Luis Molinuevo, Susan M. Landau, Niklas Mattsson, Johannes Kornhuber, Osama Sabri, Christopher C. Rowe, Lucilla Parnetti, Julius Popp, Tormod Fladby, William J. Jagust, Pauline Aalten, Dong Young Lee, Rik Vandenberghe, Catarina Resende de Oliveira, Elisabeth Kapaki, Lutz Froelich, Adrian Ivanoiu, Tomasz Gabryelewicz, Marcel M. Verbeek, Páscual Sanchez-Juan, Helmut Hildebrandt, Vincent Camus, Marzena Zboch, David J. Brooks, Alexander Drzezga, Juha O. Rinne, Andrew Newberg, Alexandre de Mendonça, Marie Sarazin, Gil D. Rabinovici, Karine Madsen, Milica G. Kramberger, Agneta Nordberg, Vincent Mok, Barbara Mroczko, David A. Wolk, Philipp T. Meyer, Magda Tsolaki, Amyloid Biomarker study group*; Philip Scheltens, Frans RJ Verhey, Pieter Jelle Visser. Association of cerebral amyloid-β aggregation with cognitive functioning in persons without dementia. JAMA Psychiatry. 2018 Jan 1;75(1):84-95.

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Sánchez-Valle R, Santana I, Baldeiras I, Llorens F. Cerebrospinal fluid Neurofilament Light in neurodegenerative dementia: evaluation of diagnostic accuracy in the differential diagnosis of prion diseases. Alzheimers Dementia. 2018 Jun;14(6):751-763.

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Villar-Piqué A, Schmitz M, Lachmann I, Karch A, Calero O, Stehmann C, Sarros S, Ladogana A, Poleggi A, Santana I, Ferrer I, Mitrova E, Pocchiari M, Baldeiras I, Calero M, Collins SJ, Geschwind MD, Sánchez-Valle R, Zerr I, Llorens F. Cerebrospinal fluid total Prion protein in the spectrum of prion diseases. Mol Neurobiol. 2018 Jul 30. doi: 10.1007/s12035-018-1251-1.

Matos MR, Ferreira C, Herukka SK, Soininen H, Janeiro A, Santana I, Baldeiras I, Almeida MR, Lleó A, Dols-Icardo O, Benussi L, Binetti G, Paterlini A, Ghidoni R, Nacmias B, Meulenbroek O, van Waalwijk van Doorn LJC, Kuiperij HB, Hausner L, Waldemar G, Simonsen AH, Tsolaki M, Gkatzima O, Oliveira CR, Verbeek MM, Clarimon J, Hiltunen M, de Mendonça A, Martins M. Quantitative genetics validates previous genetic variants and identifies novel genetic players influencing Alzheimer's disease cerebrospinal fluid biomarkers. J Alz Dis 2018; 66(2):639-652.

Verheijen J, van der Zee J, Gijselinck I, Van den Bossche T, Dillen L, Heeman B, Gómez-Tortosa E, Lladó A, Sanchez-Valle R, Graff C, Pastor P, Pastor MA, Benussi L, Ghidoni R, Binetti G, Clarimon J, de Mendonça A, Gelpi E, Tsolaki M,Diehl-Schmid J, Nacmias B, Almeida MR, Borroni B, Matej R, Ruiz A, Engelborghs S,Vandenberghe R, De Deyn PP, Cruts M, Van Broeckhoven C, Sleegers K; BELNEU Consortium; EU EOD Consortium. Common and rare TBK1 variants in early-onset Alzheimer disease in a European cohort. Neurobiol Aging. 2018 Feb; 62:245.e1-245.e7. doi: 10.1016/j.neurobiolaging.2017.10.012.

Philtjens S, Van Mossevelde S, van der Zee J, Wauters E, Dillen L, Vandenbulcke M, Vandenberghe R, Ivanoiu A, Sieben A, Willems C, Benussi L, Ghidoni R, Binetti G, Borroni B, Padovani A, Pastor P, Diez-Fairen M, Aguilar M, de Mendonça A, Miltenberger-Miltényi G, Hernández I, Boada M, Ruiz A, Nacmias B, Sorbi S, Almeida MR, Santana I, Clarimón J, Lleó A, Frisoni GB, Sanchez-Valle R, Lladó A, Gómez-Tortosa E, Gelpi E, Van den Broeck M, Peeters K, Cras P, De Deyn PP, Engelborghs S, Cruts M, Van Broeckhoven C; BELNEU Consortium; EU EOD Consortium. Rare nonsynonymous variants in SORT1 are associated with increased risk for frontotemporal dementia. Neurobiol Aging. 2018 Jun;66:181.e3-181.e10. doi: 10.1016/j.neurobiolaging.2018.02.011.

González-Tablas M, Crespo I, Vital AL, Otero Á, Nieto AB, Sousa P, Patino-Alonso MC, Corchete LA, Tão H, Rebelo O, Barbosa M, Almeida MR, Guedes AF, Lopes MC, French PJ, Orfao A, Tabernero MD. Prognostic stratification of adult primary glioblastoma multiforme patients based on their tumor gene amplification profiles. Oncotarget. 2018 Jun 15;9(46):28083-28102. doi:10.18632/oncotarget.25562.

Baradaran-Heravi Y, Dillen L, Nguyen HP, Van Mossevelde S, Baets J, De Jonghe P, Engelborghs S, De Deyn PP, Vandenbulcke M, Vandenberghe R, Van Damme P, Cras P, Salmon E, Synofzik M, Heutink P, Wilke C, Simon-Sanchez J, Rojas-Garcia R, Turon-Sans J, Lleó A, Illán-Gala I, Clarimón J, Borroni B, Padovani A, Pastor P, Diez-Fairen M, Aguilar M, Gelpi E, Sanchez-Valle R, Borrego-Ecija S, Matej R, Parobkova E, Nacmias B, Sorbi S, Bagnoli S, de Mendonça A, Ferreira C, Fraidakis MJ, Diehl-Schmid J, Alexopoulos P, Almeida MR, Santana I, Van Broeckhoven C, van der Zee J; BELNEU Consortium; EU EOD Consortium. No supportive evidence for TIA1 gene mutations in a European cohort of ALS-FTD spectrum patients. Neurobiol Aging. 2018 Sep;69:293.e9-293.e11. doi: 10.1016/j.neurobiolaging.2018.05.005.

Ceroni JRM, Dutra RL, Honjo RS, Llerena JC Jr, Acosta AX, Medeiros PFV, Galera MF, Zanardo EA, Piazzon FB, Dias AT, Novo-Filho GM, Montenegro MM, Madia FAR, Bertola DR, de Melo JB, Kulikowski LD, Kim CA (2018) A Multicentric Brazilian Investigative Study of Copy Number Variations in Patients with Congenital Anomalies and Intellectual Disability. Scientific Reports 8(1):13382. doi: 10.1038/s41598-018-

Othman MAK, Grygalewicz B, Kołkowska-Leśniak A, Melo JB, Carreira IM, Liehr T (2018) Cryptic NUP214-ABL1 fusion with complex karyotype, episomes and intra-tumor genetic heterogeneity in a T-cell lymphoblastic lymphoma. J Cancer Metastasis Treat 4:50. DOI: 10.20517/2394-4722.2018.41

Capela de Matos RR, Othman MAK, Ferreira GM, Costa ES, Melo JB, Carreira IM, de Souza MT, Lopes BA, Emerenciano M, Land MGP, Liehr T, Ribeiro RC, Silva MLM (2018) Molecular approaches identify a cryptic MECOM rearrangement in a child with a rapidly progressive myeloid neoplasm. Cancer Genet; 221:25-30

Naranjo MG, Rodrigues-Soares F, Peñas-Lledó EM, Tarazona-Santos E, Fariñas H, Rodeiro I, Terán E, Grazina M, Moya GE, López-López M, Sarmiento AP, Calzadilla LR, Ramírez-Roa R, Ortiz-López R, Estévez-Carrizo FE, Sosa-Macías M, Barrantes R, LLerena A, CEIBA-Consortium of the Ibero-American Network of Pharmacogenetics and Pharmacogenomics RIBEF (2018). Interethnic Variability in CYP2D6, CYP2C9, and CYP2C19 Genes and Predicted Drug Metabolism Phenotypes among 6060 Ibero- and Native Americans: RIBEF-CEIBA Consortium Report on Population Pharmacogenomics. OMICS; 22(9):575-588. doi: 10.1089/omi.2018.0114.

International Networks

Several international collaborations aiming to bring new developments to the research performed in the group have been established:
Joint Programing in Neurodegenerative disorders (JPND) and Early Alzheimer's Disease Consortium (EADC)

Baylor College of Medicine (Houston, USA) – Lee-Jun Wong; Fernando Scaglia, University of Newcastle upon Type (UK); Robert Taylor, Mitochondrial Biology Unit - Medical Research Council (Cambridge, UK); Massimo Zeviani, Hospital Saint Joan de Déu (Barcelona, Spain); Rafael Artuch (Coenzyme Q(10) deficiency study group) and Adrián LLerena CICAB Clinical Research Centre Extremadura University Hospital and Medical School, (Badajoz, Spain).

New Targets and Therapeutics for Chronic Diseases

Participation in the EIT Health project "Healthy Lifestyle Innovation Quarters for Cities and Citizens (HeaLIQs 4 Cities)" 2018. Focus Group coordinator.

Campos EJ, Martins J, Brudzewsky D, Correia S, Santiago AR, Woldbye DP, Ambrósio AF. Impact of type 1 diabetes mellitus and sitagliptin treatment on the neuropeptide Y system of rat retina. Clin Exp Ophthalmol. 2018 Feb 14. DOI: 10.1111/ceo.13176.

Madeira MH, Rashid K, Ambrósio AF, Santiago AR, Langmann T. Blockade of microglial adenosine A2A receptor impacts inflammatory mechanisms, reduces ARPE-19 cell dysfunction and prevents photoreceptor loss in vitro. Sci Rep. 2018 Feb 2;8(1):2272. DOI: 10.1038/s41598-018-20733-2.

Sampaio TB, de Oliveira LF, Constantino LC, Costa AP, Poluceno GG, Martins WC, Dal-Cim T, de Oliveira KA, Ludka FK, Prediger RD, Tasca CI, Pereira FC. Long-Term Neurobehavioral Consequences of a Single Ketamine Neonatal Exposure in Rats: Effects on Cellular Viability and Glutamate Transport in Frontal Cortex and Hippocampus. Neurotox Res. 2018 Oct; 34(3):649-659.

Research exchange programme with international institutions:
Doroteja Jukic – "Can DPP-IV inhibitors prevent retinal neurodegeneration and blood-retinal barrier breakdown in multiple sclerosis? " - Faculty of Medicine, Croatia.
Graduate Training Networks: Standing Committee on Research Exchange (SCORE) of the International Federation of Medical Students Associations (IFMSA)

Tuition of medical students:
Ellen Brigitta Keil, medical student from Belgium, July 2018;
Magdaléna Vavříková, medical student from Czech Republic, July 2018.

Collaborative EIT Health project (HeaLIQs4Cities) with Instituto Pedro Nunes and University Medical Center Groningen to support healthy living and active ageing. Organization of Praça Vida+, a public event in Coimbra, Juy 20-22.

Development of a MOOC "End of Life Care" for EIT Health CARE Consortium.

Coordination of the University of Coimbra ERA Chair (ERA@UC) H2020 Widening project.

Preparation and submission of Phase 2 H2020 Widening Teaming project "Multidisciplinary Institute of Ageing: MIA-Portugal".

International collaborations:
Universidade de Utrecht. Holanda
Universidade de S. Francisco. Bragança Paulista. Brasil
Universidade de Rio Preto. Rio Preto. Brasil
Universidade de Campinas. Brasil

Metabolism, Aging and Disease Strand

Cell Metabolism and Quality Control

IOS Press Ebook
Alzheimer's Disease: New Beginnings; Series Advances in Alzheimer's Disease; Volume 6; 2018; Editors: George Perry, Jesús Avila, Paula I. Moreira, Aaron A. Sorensen, Massimo Tabaton
ISBN978-1-61499-875-4 (print) | 978-1-61499-876-1 (online)

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

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

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.

George Perry from College of Sciences, University of Texas at San Antonio, TX, USA – collaborative research

Mitochondria Metabolism and Disease Group

Collaborations:
Albert Rizvanov, Kazan Federal University, Russia
Anatoly Zhitkovich, Brown University, USA
Anika Hartz, Bjorn Bauer, University of Kentucky, USA
Clemens Steegborn, University of Bayreuth, Germany
Daniel Dorta, University of São Paulo, Brazil
David Sinclair, Harvard Medical School, USA
Erich Gnaiger, Oroboros, Austria
Faustino Mollinedo, CSIC, Spain
Ignacio Vega-Naredo, University of Oviedo, Spain
Jan Kopecky, Academy of Sciences, Czech Republic
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

Network
Graduate training network: "FOIE GRAS", H2020-MSCA-ITN-2016, Ref. 722619, 2017-2020
Research staff exchange network: "mtFOIE GRAS", MSCA-RISE-2016, Ref. 734719, 2017-2020

Visiting researchers
Almaz Akhunzianov (2018), Kazan Federal University, Russia
Patrycja Niewodowska (2018), Medical University of Białystok, Poland
Karolina Siewiera (2018), Medical University of Lodz, Poland John Wise (2018), Department of Pharmacology and Toxicology, School of Medicine, University of Louisville, USA

Other:
Members of the MMD are consistently involved in peer-reviewing for scientific journals, and as evaluators for funding agencies (e.g. FCT, EC-REA, and others)

Metabolic Control Group

Collaborative publication with Prof Kim´s Group from Harvard, USA Huang, H., Seung-Hwan L., Lima, I.S., Kim, S.S., Dagon, Y, Kang, M-C., Seo, J.A., Ryu, M.J., Shong, M., Hwang, D.H., Li, P., Meng, H., Chung, B-H., Kim, M.S., Park, K.S., Macedo, M.P., White, M., Belew, G.D., Jones, J.G. and Kim, Y-B. 2018. Rho-kinase regulates obesity-induced fatty liver disease by driving de novo lipogenesis. J. Clin. Invest. 128, 5335-5350.

Collaboration with Prof Matthew Merritt at the University of Florida: National Science Foundation (P17827) "High-sensitivity 13C NMR isotopomer analysis of triglyceride fatty acid enrichment from [U-13C]fructose" $15,000, Nov 1, 2018-Oct 31, 2021. Long standing and ongoing collaboration with colleagues in Sweden, Jan Eriksson and Maria Joao Pereira. Co-authors and exchange students between laboratories.

Long-standing and ongoing collaboration with colleagues in Denmark, Louise T Dalgaard, with whom we have been publishing and co-founded and exchanged students, including PhD students.

Stem Cell-Based and Molecular Therapies Brand

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.
- SynSpread: Role and mechanism of alpha-synuclein and ataxin-3 spreading in Parkinson and Machado-Joseph diseases. 2013 JPND Transnational call for "European research projects for Cross-Disease Analysis of Pathways related to Neurodegenerative Diseases. Ref. JPND-CD/0001/2013. European Consortium. 2015-2018.
- A lipidomic and miRNA-based strategy for glioblastoma treatment, (A03/2016)
Projeto ao abrigo do Programa de Ações Integradas Luso-Alemãs. 2016-2018
- 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).

Stem Cel Biotechnology

Ongoing Collaborations with:
- The University of Munster (Germany)
- The University of Groningen (the Netherlands)
- Northwestern University (USA)

INVITED SEMINARS

1. "Identification of pro survival microRNAs" - IBILI, Faculty of Medicine, University Coimbra, Portugal (2018)

2. "Stem Cells and Regenerative Medicine", University Aveiro, Portugal (2018)

POSTERS

J Crispim, H Fernandes, P Jonkheijm and D Saris: Purification of platelet-rich plasma with peptide-functionalized microspheres: ORS 2018 Annual Meeting, USA, 2018.

Antunes, HH*, Cardoso, R*, Zonari, A, Correia, J, Leal, E, Kostic, I, Jiménez-Balsa, A, Barradas, A, Pinto, V, Carvalho, E, Ferreira, L. "Controlled delivery of exosomes for chronic wound healing".

XII Spanish-Portuguese Conference on Controlled Drug Delivery, Coimbra, January 14-16, 2018.

Akhilesh Rai*, Catarina Praça*, Tiago Santos, Ana Cristovão, Romeo Cecchelli, Marie-Pierre Dehouck, Liliana Bernardinho and Lino S. Ferreira. "Targeting the neurogenic niches of adult brain by peptide-conjugated nanoparticles". XII Spanish-Portuguese Conference on Controlled Drug Delivery, Coimbra, January 14-16, 2018.

Rai, A, Comune, M, Chereddy, KK, Pinto, S, Aday, S, Ferreira, AF, Cunha, R, Rodrigues, R, Lerma, J, Simões, PN, Préat, V, Ferreira, L. "LL37 peptide conjugated gold nanoparticles with superior skin regeneration property". XII Spanish-Portuguese Conference on Controlled Drug Delivery, Coimbra, January 14-16, 2018.

Lino, MM, Simões, S, Vilaça, A, Antunes, H, Zonari, A, Ferreira, L. "Near-infrared triggered release of miRNAs for modulation of cell activity". XII Spanish-Portuguese Conference on Controlled Drug Delivery, Coimbra, January 14-16, 2018.

Pinho, S*, Rebelo, C*, Santos, T, Guedes, J, Bernardino, L, Peça, J, Ferreira, L. "Modulating neural stem cells activity by nanoparticle light-activation". XII Spanish-Portuguese Conference on Controlled Drug Delivery, Coimbra, January 14-16, 2018.

Lino, M*, Simões, S*, Pinho, S, Ferreira, L. "Intracellular delivery of multiple proteins withg spatio-temporal control". XII Spanish-Portuguese Conference on Controlled Drug Delivery, Coimbra, January 14-16, 2018.

Francisco, V, Ferreira, L. "Near-infrared light triggered release of bioactive molecules from supramolecular modified gold nanorods". XII Spanish-Portuguese Conference on Controlled Drug Delivery, Coimbra, January 14-16, 2018.

Jesus, C, Abreu, R, Fernandes, H, Ferreira, L. "Isolation and characterization of urinary extracellular vesicles for Regenerative Medicine". 1st Meeting on Vesicular Biology, Coimbra, February 16-17, 2018.

Santinha, A, Zonari, A, Pinto, V, Fernandes, D, Santos, T, Benardino, L, Carvalho, AL, Ferreira, L. "Exosomes-based therapy for stroke". 1st Meeting on Vesicular Biology, Coimbra, February 16-17, 2018.

Constantinides, C, Rai, A, Srinivas, M, Ferreira, L, Carr, C. "Comparison of Labeling Capacity for Protamine-sulphate-conjugated and FuGENE-labeled Progenitor Cardiac Stem Cells using Perfluorocarbon Nanoparticle Labels for In Vivo Murine Cardiac 19F MRI/MRS". Annual Meeting ISMRM-ESMRMB in Paris, France, June 16-21, 2018.

Antunes, HH, Cardoso, R, Correia, J, Kostic, I, Leal, E, Zonari, A, Barradas, A, Carvalho, E, Ferreira, L. "Desenvolvimento de um hidrogel para libertação controlada de exossomas - uma nova esperança para tratamento de ulceras diabéticas". 14º Congresso Português de Diabetes, Hotel Tivoli Marina Vilamoura, March 9-11, 2018.

Abreu, RC, da Costa Martins, PA, Fernandes, H, Ferreira, L. "Extracellular Vesicle Engineering: Modulation of Non-coding RNA Content". EMBO Practical Course: Extracellular Vesicles: From Biology to Biomedical Applications, EMBL Heidelberg, Germany, April 8-14, 2018.

Fernandes, H, Zonari, A, Aday, S, Seabra, C, Barata, T, Abreu, R, Leal, E, Carvalho, E, Ferreira, L. "High-content screening identifies pro-survival microRNAs". ESB 2018, 29th European Conference on Biomaterials, Maastricht, Netherlands, Sep 9-13, 2018.

Systems and Computational Biology Group

Tampere University of Technology (Finland)
Researchers: Ilpo Vattulainen, Matti Javanainen
Project: Quantitative assessment of rate constants from molecular dynamics simulations

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

VIT University (India)
Cooperation in research training of B. Tech. and M. Sc. students

MouseAGE (COST Action BM1402)
Participation in Working Group 4: "Novel Technologies and Future Developments"

Molecular Mycobacteriology and Microbiome Group

Editorial Board Member
Scientific Reports
Frontiers in Immunology (Guest Editor)

Invited Lectures
Communicable Diseases: Molecular Mycobacteriology and the Microbiome
9th EDCTP Forum: Clinical research and sustainable development in sub-Saharan Africa, 19-21 Sep 2018, Lisboa/Coimbra, Portugal (Nuno Empadinhas)

The hidden microbiome in Parkinson's Disease
9th Annual World Congress NeuroTalk-2018, 16-18 May 2018, Bangkok, Thailand (Sandra Cardoso and Nuno Empadinhas)

Pathways to stem the tide of TB drug resistance in the midst of a TB-Diabetes storm
World Health Summit Regional Meeting 2018, 19 Apr 2018, Coimbra, Portugal (Nuno Empadinhas)

Workshop: Tuberculose – conhecer para combater. IV BIENAL STEM+L. 21-23 August 2018, Maputo, Mozambique (Susana Alarico)

Collaborations
Anthony J. Clarke, university of Guelph, Canada (Nuno Empadinhas)
Tom L. Blundell, University of Cambridge, United Kingdom (Nuno Empadinhas)
Gunilla Kallenius, Karolinska Institutet, Stockholm, Sweden (Nuno Empadinhas)

Medicinal Chemistry & Drug Discovery Group

Collaborative publication

- Leandro da Costa Clementino, Angela Maria Arenas Velásquez, Thais Gaban Passalacqua, Leticia de Almeida, Marcia A.S. Graminha, Gilmarcio Z. Martins, Lígia Salgueiro, Carlos Cavaleiro, Maria do Céu Sousa, Raquel R.D. Moreira. 2018. "In vitro activities of glycoalkaloids from the Solanum lycocarpum against Leishmania infantum", Brazilian Journal of Pharmacognosy 28, 673-677 https://doi.org/10.1016/j.bjp.2018.07.008

- Volpato H, Scariot DB, Soares EFP, Jacomini AP, Rosa FA, Sarragiotto MH, Ueda-Nakamura T, Rubira AF, Pereira GM, Manadas R, Leitão AJ, Borges O, Nakamura CV, Sousa MDC. 2018. "In vitro anti-Leishmania activity of T6 synthetic compound encapsulated in yeast-derived β-(1,3)-d-glucan particles", International Journal of Biological Macromolecules. 119: 1264-1275. https://doi.org/10.1016/j.ijbiomac.2018.08.019.

H. Ben Cheikh, S. Domingues, E. Silveira, Y. Kadri, N. Rosário, M. Mastouri, G. J. Da Silva. Molecular characterization of carbapenemases of clinical Acinetobacter baumannii isolates from a University Hospital in Tunisia. 3 Biotech. 8:297. https://doi.org/10.1007/s13205-018-1310-3.

S. Domingues, N. Rosário, H. Ben Cheikh, G. J. Da Silva. ISAba1 and Tn6168 acquisition by natural transformation leads to third-generation cephalosporins resistance in Acinetobacter baumannii. Infection, Genetics and Evolution. 63:13-16. https://doi.org/10.1016/j.meegid.2018.05.007.

Graduate Training Networks

-Cooperation: Erasmus Exchange Programme of Master in Pharmacy, Dip.to Scienze del Farmaco, Univ. degli Studi di Pavia (2018); Silvia Magro; "Toward the identification of novel antileishmanial compounds. In vitro profile of semisynthetic compounds from Eremurus persicus and arylalkenilamines"
Supervisors: Maria do Céu Sousa and Simona Collina.

-Grant: PROJETOS MEC/MCTI/CAPES/CNPQ/FAPS. Programa de Doutorado Sanduíche no Exterior -88881.190109/2018-01.
Bolsa Doutorado do Programa de Pós- graduação em Biotecnologia, Centro de Ciências Exatas e Tecnologia Ciências Exatas e Tecnologia, Universidade Federal de São Carlos (UFSCAR) – Brasil.
Name: Laiza Gabriela Gavioli Coelho
Project: "Atividade leishmanicida de complexos de bases de Schiff in vivo, avaliando carga parasitária e perfil de citocinas""
Local: FFUC
Supervisors: Maria do Céu Sousa, Fernanda de Freitas Anibal e Clóvis Wesley O. de Souza.

-Cooperation: Erasmus Exchange Programme, for the acquisition of the Bachelor Degree in Medical Laboratory Sciences
Students: Anne Clementine Linde e Ida Nøkling Østebø
Home institution: Department of Life Sciences and Health, Oslo Metropolitan University, Norway
Host institution: Lab. Microbiology, Faculty of Pharmacy, University of Coimbra
Project: "Dissemination of plasmid-mediated colistin resistance, by natural transformation in Acinetobacter baumannii - An experimental study"
Time period: April to June 2018
Supervisors: Gabriela Jorge da Silva and Sara Domingues.

Participation of the Research Group at the international level

- Cooperation: Projecto financiado pelo Instituto Nacional de Ciência, Tecnologia para a Inovação Farmacêutica INCT_if , chamada INCT-MCTI/CNPq/Capes/Faps nº 16/2014.
Title: "Composição química e actividade de plantas aromáticas da reserva florestal Adolpho Ducke-manaus-Amazonas contra protozoários flagelados dos genêros Leishmania e Trypanosoma "
Coordinators: Ivan da Rocha Pitta, Universidade Federal de Pernambuco (UFPE) and Norberto Peporine Lopes, Faculdade de Ciências Farmacêuticas de Ribeirão Preto (USP), Brasil.

Name: Maria do Céu Rodrigues de Sousa
Duration: 2016-2020

- Program: 3º Termo Aditivo ao Convénio Geral de Cooperação entre a Universidade de Coimbra (Portugal) e a Fundação Oswaldo Cruz- FIOCRUZ (Brasil)

- Cooperation: Cooperação Acadêmico-Científico no âmbito dos Estudos em Saúde Urbana, entre o Grupo de Investigação da Geografia da Sáude, Faculdade de Farmácia da Universidade de Coimbra e da Fundação Oswaldo Cruz FIOCRUZ.
Coordinators: Paula Santana (GIGS/FLUC/Portugal); Maria do Céu Rodrigues de Sousa (FFUC, Portugal); Marcelo Bessa de Freitas (ENSP/Fiocruz/Brasil);Graziela Zanini (INI/Fiocruz/Brasil).
Duration: 2015-2019

Microbiology of Extreme Environments Group

Collaborative publications Above in Publications

Collaborate project led by Ramon Rossello-Moro 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.

1. 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 Group

Collaborative publications

Colombo M.L., Fernández A., Cimino C.V., Liggieri C., Bruno M., Faro C., Veríssimo P.C., Vairo-Cavalli S. (2018) Miniature cheeses made with blends of chymosin and a vegetable rennet from flowers of Silybum marianum: Enzymatic characterization of the flower-coagulant peptidase. Food Chemistry Nov 15;266:223-231. doi: 10.1016/j.foodchem.2018.06.007. (Impact factor 2017: 4.946, Quartile in Food Science & Technology: Q1)

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. Lissa Herron, Roslin Institute, University of Edinburgh, Scotland
Dr. Sandra Vairo-Cavalli, CIPROVE-Centro Asociado CICPBA, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, La Plata, Argentina

Courses & Conferences

INSTRUCT Supported Training Course: From protein structure to biological function through interactomics – an integrated view, 2nd Edition. Co-organizers and members of the Scientific Committee.

Invited talk: What can we (still) learn from plant aspartic proteases? Isaura Simões, 4th Plant Protease and Programmed Cell Death Symposium. 11-13 September, Ghent, Belgium.

Participation in the organization of scientific meetings

JANUARY 2018

Organizing of the conference: " XII Spanish-Portuguese Conference of the Controlled Release Society"
Date: 14-16 January 2018,
CNC.IBILI members involved in the organization: Conceição Pedroso Lima

Organizing of the seminar "Introduction to Pharmacogenomics – clinical applications", about the basic concepts and clinical applications of Pharmacogenomics, PhD Programme in Health Sciences and MSc in Biomedical Research, Faculty of Medicine, University of Coimbra.
Date: 25 January 2018
CNC.IBILI members involved in the organization: Manuela Grazina and Catarina Resende Oliveira

Organizing of the Seminar: Micronutrient sensing and early-life immune defense, Manuela Ferreira, Champalimaud Foundation, Center for the Unknow, Lisbon, Portugal
Date: 31 January 2018,
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the Workshop "Integrating Glial and Neuronal Function", CNC-Center for Neuroscience and Cell Biology (http://www.cnbc.pt/newsevents/news_show.asp?idnew=1926)
Date: January 2018
CNC.IBILI members involved in the organization: Carlos Duarte

FEBRUARY 2018

Organizing of the meeting: From Protein Structure to Biological Function Through Interactomics: an integrated View – 2nd edition, Cantanhede
Date: 5 -9 February 2018
CNC.IBILI members involved in the organization: Bruno Mandas

Organizing of the meeting: "1º Curso teórico-prático de citogenética e genómica laboratorial". Laboratório de Citogenética e Genómica, CIMAGO, Faculdade de Medicina, Universidade de Coimbra,
Date:19-23 February 2018
CNC.IBILI members involved in the organization: Joana Barbosa de Melo, Isabel Marques Carreira e Catarina Resende Oliviera

Organizing of the Seminar: "Basal ganglia pathophysiology: from movement to behavior and emoticons"
Speaker: José A. Obeso (Hospital Universitario HM Puerta del Sur, Universidad CEU San Pablo, Madrid, Spain), Faculdade de Medicina, Universidade de Coimbra (pólo III)
Date: 28 February 2018
CNC.IBILI members involved in the organization: Cristina Rego

MARCH 2018

Organizing of the Seminar: "Thinking beyond the nigra: alpha-synuclein-mediated synaptic dysfunction in the hippocampus"
Speaker: Tiago F. Outeiro (Univ. Medical Center Goettingen, Goettingen, Germany), Faculdade de Medicina, Universidade de Coimbra (pólo III)
Date: 1 March 2018
CNC.IBILI members involved in the organization: Cristina Rego

Organizing of the Course: PDBEB “Fighting Infection” Course, PhD Programme in Experimental Biology and Biomedicine
Date: 5-9 March 2018
CNC.IBILI members involved in the organization: Nuno Empadinhas

Organizing of the Meeting: EIT Health CARE Consortium meeting, Coimbra
Date: 8-9 March 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Workshop: “Reimagining dementia prevention and care”, Coimbra
Date: 9 March 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Course: Advanced Course “Ageing: from cellular processes to the organism” of BEB (Experimental Biology and Biomedicine) PhD program, at Center for Neurosciences and Cell Biology of University of Coimbra, Coimbra, Portugal
Date: 14 March 2018
CNC.IBILI members involved in the organization: Cláudia Cavadas

Organizing of the Seminar: Mood disorders: controversies on nosologic and nosographic aspects, Carlos Saraiva, Faculty of Medicine, University of Coimbra, Portugal
Date: March 15, 2018
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the Meeting: Sessão de Encerramento Oficial da Semana Internacional do Cérebro 2018- Theme: “Dementia and Stress” - Local: FNAC – Fórum Coimbra
Date: 18 March 2018
CNC.IBILI members involved in the organization: Cristina Rego

Organizing of the Course: In Utero Programming of Adult Metabolism and Disease – BEB Doctoral Program Course.
Date: 26-30 March 2018
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the Meeting: Portuguese Diabetes Society Translational Research Study Group Meeting
Date: March 2018
CNC.IBILI members involved in the organization: John Jones

APRIL 2018

Organizing of the Meeting: 1st Meeting on Vesicular Biology, University of Coimbra, Portugal
Date: 16–17 April 2018
CNC.IBILI members involved in the organization: Cláudia Pereira

Organizing of the Meeting: Seminar: “Targeting the kynurenine pathway in neurodegenerative diseases: from mechanisms to therapeutics” Speaker: Flaviano Giorgini (Department of Genetics, University of Leicester, United Kingdom)
Date: 23 April 2018
CNC.IBILI members involved in the organization: ANA Cristina Rego

Organizing of the Meeting: Seminar: “ER-mitochondria cross-talk in neurodegeneration: focus on Familial Alzheimer’s disease” Speaker: Paola Pizzo (Department of Biomedical Sciences, University of Padova, Padova, Italy)
Date: 27 April 2018
CNC.IBILI members involved in the organization: Ana Cristina Rego

MAY 2018

Organizing of the Meeting: Transmembrane calcium exchange in polarized and depolarized mitochondria in smooth muscle cells, Natalia Naumova-Kandaurova, Institute of Complex Systems, Bioelectronics, Forschungszentrum Jülich, Germany
Date: 4 May 2018
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the Meeting: Advanced course on Principles and Practices in Drug Development, within the PhD program on Biomedicine and Experimental Biology, CNC, Coimbra - Fundação Calouste Gulbenkian, Lisbon
Date: 10-11 May 2018
CNC.IBILI members involved in the organization: Conceição Pedroso Lima

Organizing of the Meeting: Seminar: "Biomarkers and targets in non-alcoholic fatty liver disease", Centro de Neurociências e Biologia Celular, Universidade de Coimbra (pólo I), Cecília Rodrigues (iMed.ULisboa, University of Lisbon)
Date: 18 May 2018
CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing of the Meeting: "III Symposium of the Portuguese Glial Network", Porto
Date: 18 May 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Meeting: Mitochondrial Biology and Medicine workshop at the 52nd Meeting of the European Society of Clinical Investigation (ESCI), Barcelona, Spain
Date: May 30 – June 1, 2018
CNC.IBILI members involved in the organization: Paulo Oliveira

JUNE 2018

Organizing of the Meeting: Charing the 19th Biennial Meeting of the International Society for Free Radical Research (SFRRI), Lisbon
Date: 4-7 June 2018
CNC.IBILI members involved in the organization: João Laranjinha

Organizing of the Meeting: 19th SFRRI Biennial Meeting, Lisbon, Portugal
Date: 4-7 june 2018
CNC.IBILI members involved in the organization: Catarina Resende Oliveira

Organizing of the Meeting: 19th Biennial Meeting of the Society for Free Radical Research International, Lisboa
Date: 4-7 June 2018
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the Meeting: La-Feng Dong, School of Medical Science, Griffith University, Australia
Date: 8 June 2018
CNC.IBILI members involved in the organization: Paulo J. Oliveira

Organizing of the Meeting: 1º Simpósio de Investigação em Tuberculose e Micobactérias não Tuberculosas em Portugal, Coimbra
Date: 18 June 2018
CNC.IBILI members involved in the organization: Nuno Empadinhas

Organizing of the Meeting: Adenosine control of synaptic activity & neuropsychiatric diseases' integrado na reunião científica PURINES 2018 International - Basic and Translational Science on Purinergic Signaling and its Components for a Healthy and Better World - Foz de Iguaçu, Brasil
Date: 19-22 June 2018
CNC.IBILI members involved in the organization: Rodrigo Cunha

Organizing of the Meeting: Simposium "Adenosine signaling in the retina", at "Purines 2018 International", Foz do Iguaçu, Brazil,
Date: 19-22 June 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Meeting: 6th International Iberian Biophysics Congress, Castellón (Spain)
Date: 20-22 June 2018
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the Meeting: “Onco Emergence Forum” Barcelona
Date: 21 - 22 June 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Meeting: Workshop on “Ageing: models and therapies”, Faculty of Medicine, University of Coimbra, Polo III
Date: 27 June 2018
CNC.IBILI members involved in the organization: Lino Ferreira (The meeting had the contribution of Alessandro Ori (Leibniz Institute of Ageing, Germany), Thomas von Zglinicki (University of Newcastle, UK), Bruno Jesus (IMM and University of Aveiro), Manuel Santos (University of Aveiro), Claudia Cavadas (University of Coimbra), Rodrigo Cunha (University of Coimbra) and João Malva (University of Coimbra). Approximately 75 individuals from academia and research institutions attended this meeting).

JULY 2018

Organizing of the Meeting: “VI Cell Culture and Tissue Training Course - Beyond the Microscope, Culturing Life!”, Coimbra
Date: 9 - 13 July 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Meeting: MitoPorto 2018: Mitochondrial evolution, metabolism and disease. International Symposium, University of Porto, Portugal
Date: 13 July 2018
CNC.IBILI members involved in the organization: Paula Moreira

Organizing of the Meeting: Organization of 2 events on “EIT Health Strengthen Education in Healthy Living and Active Ageing”, Grande Hotel do Luso
Date: 17-18 July 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

SEPTEMBER 2018

Organizing of the Meeting: Summer School on Computational Biology, Coimbra
Date: 5 – 14 September
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the Meeting: Symposium “The emerging roles of extracellular vesicles in health and diseases of the eye”- XXIII Biennial Meeting of the International Society for Eye Research (ISER), Belfast
Date: 9-13 September 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Meeting: “1º Curso teórico-prático de citogenética e genómica laboratorial”, Laboratório de Citogenética e Genómica, CIMAGO, Faculdade de Medicina, Universidade de Coimbra
Date: 19-23 September 2018
CNC.IBILI members involved in the organization: Joana B Melo, Isabel Marques Carreira

OCTOBER 2018

Organizing of the Meeting: Integration of the Co-evolved Mitonuclear Genomes, David Lee, University of Southern California, USA
Date: 22 October 2018
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the Meeting: Mitochondrial DNA and Derived Peptides in Health and Disease, University of Coimbra, Portugal
Date: 23 October 2018
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the Meeting: “EIT Health Strengthen Education in Healthy Living and Active Ageing”, University of Lisbon
Date: 25-26 October 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

NOVEMBER 2018

Organizing of the Meeting: “ONCOTHON”, Granada
Date: 12 - 13 November 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Meeting: “III Simpósio Nacional de ORBEAs – 3Rs in action”, Coimbra
Date: 15 November 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

DECEMBER 2018

Organizing of the Meeting: 1st Microbiome-Gut-Brain Axis joint meeting, Coimbra
Date: 7 December 2018
CNC.IBILI members involved in the organization: Nuno Empadinhas & Sandra M. Cardoso

Organizing of the Meeting: “I Simpósio Luso-Brasileiro de Neurociências”, Fortaleza
Date: 17-20 December 2018
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the Meeting: Encontro de Jovens Investigadores em Biologia Estrutural e Computacional (EJIBCE), Porto
Date: December 2018
CNC.IBILI members involved in the organization: Carlos Duarte

Graduate Studies Programme

During 2018 CNC.IBILI organized 8 Advanced Courses (inserted at the Doctoral Programme in Experimental Biology and Biomedicine - PDBEB at CNC) and hosted 69 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 36 Ph.D. and 90 M.Sc. theses were concluded.

Advanced Courses 2018

CNC PhD programme (PDBEB) course
January 21-February 1 2018
Luisa Cortes, CNC (lcortes@cnc.uc.pt)

Fighting Infection
March 5-9 2018
Nuno Empadinhas, CNC (numenius@cnc.uc.pt)

Ageing: from cellular processes to the organism
March 12-18 2018
Cláudia Cavadas, CNC (ccavadas@ci.uc.pt)

In Utero Programming of adult metabolism and disease
March 26 – 30 2018
Paulo Oliveira & João Ramalho-Santos, CNC (pauloliv@ci.uc.pt / jramalho@ci.uc.pt)

Synapses, Neuronal Circuits and Behavior
April 9 – 20 2018
Ana Luísa Carvalho, Carlos B. Duarte, João Peça, CNC (alc@cnc.uc.pt, cbduarte@ci.uc.pt, jpeca@cnc.uc.pt)

Workshop "Ageing: models and therapies"
June 27 – 20 2018
Luís Estronca, FMUC (luis.estronca@uc.pt)

IV Quantitative Fluorescence Microscopy Course
September 24 – 28 2018
Luísa Cortes, Margarida Caldeira, Tatiana Catarino, CNC (micc@cnc.uc.pt))

CNC.IBILI Seminars

January

Mesoscopic imaging for the life-sciences: trends and challenges
5.1.2018
Gabriel Martins
Instituto Gulbenkian Ciência (IGC)

Proliferation and Movement - Modeling Angiogenesis
10.1.2018
Rui Travasso
Center for Physics of the University of Coimbra

Mesenchymal stromal cells for the treatment of spinocerebellar ataxias: can they make the difference?
12.1.2018
Catarina Miranda
CNC, Coimbra

Rebuilding brain circuitries: Is the inflammatory milieu determinant?
22.1.2018
Sofia Grade
Ludwing-Maximilians-University of Munich

Translation starts with Pathology
24.1.2018
Tânia Mendes Carvalho
Histology and Comparative Pathology Lab, IMM

Science and ethics between the lab and the political decision making sphere
26.1.2018
Marisa Matias
European Parliament

Noncoding RNAs as triggers of cardiac microvascular remodeling in Heart Failure
30.1.2018
Paula Martins
CARIM Institute - University Maastricht

Micronutrient sensing and early-life immune defence
31.1.2018
Manuela Ferreira
Champalimaud Foundation, Center for the Unknow, Lisbon

February

Understanding Rickettsia-host interactions: the protease, the Trojan Horse and other stories
2.2.2018
Isaura Simões
CNC, UC-Biotech

Cross-linking/mass spectrometry strategies for applications in integrative structural biology
7.2.2018
Alexander Leitner
Institute of Molecular Systems Biology, ETH Zurich

Protein flexibility and selective promiscuity in rational drug design
8.2.2018
Carlos Camacho
University of Pittsburg, USA

The involvement of astrocytes in cognitive processing
9.2.2018
João Filipe Oliveira
ICVS, University of Minho

Targeting a neurodegenerative disease: from benchtop to biotech
9.2.2018
Rui Brito
University of Coimbra and BSIM therapeutics

Phospholipid matters in the regulation of neuron and glial function
16.2.2018
Pedro Brites
IBMC, i3S, University of Porto

Tau therapeutics in brain pathology: Exploring the link between depression and Alzheimer´s disease
23.2.2018
Ioannis Sotiropoulos
ICVS, University of Minho

Basal ganglia pathophysiology: From movement to behavior and emotions
28.2.2018
José A. Obeso
University Hospital HM Puerta del Sur, CEU-San Pablo University, Madrid, Spain

Bacterial lipid rafts disassembly inhibits MRSA antibiotic resistance
28.2.2018
Daniel Lopez
National Centre for Biotechnology (CNB) & Spanish National Research Council (CSIC), Madrid, Spain

March

Thinking beyond the nigra: alpha-synuclein-mediated synapticc dysfunction in the hippocampus
1.3.2018
Tiago Fleming Outeiro
Department of NeuroDegeneration and Restorative Research, Center for Brain,
University Medical Center Goettingen, Goettingen, Germany

AGEing in obesity and type 2 diabetes: glycotoxins and imaging biomarkers in metabolic disorders
2.3.2018
Paulo Matafome
IBILI/ICBR and ESTeSC, Coimbra

Enteropathogens shape microbiota biofilms: New insights into the causes of post-infectious inflammation
5.3.2018
Andre Buret
University of Calgary, Canada

Use of the cytoskeleton to control Shigella Infection
7.3.2018
Serge Mostowy
Imperial College London, UK

Consequences of short telomeres to the organism
13.3.2018
Miguel Godinho Ferreira
Institute for Research on Cancer and Aging of Nice, France; Instituto Gulbenkian de Ciência, Oeiras, Portugal

Mood disorders: controversies on nosologic and nosographic aspects
15.3.2018
Carlos Saraiva
Faculty of Medicine, University of Coimbra

Intrinsic and extrinsic regulation of circadian brain oscillators
16.3.2018
Hugh Piggins
University of Manchester, UK

Environmental microbiology: from basic ecology to biotechnology
21.3.2018
Newton Gomes
CESAM and University of Aveiro

Role of hippocampal neurogenic reserve in aging and Alzheimer´s Disease
23.3.2018
Elisabete Ferreiro
CNC, Coimbra

Non-genomic sperm contributions towards embryo development
28.3.2018
David Miller
University of Leeds, UK

The role of redox sensitive ion channels in the pathogenesis of acute pancreatitis
29.3.2018
Júlia Fanczal
University of Szeged, Szeged, Hungary

April

Impaired neural development restricts organism recovery upon reversible loss cohesion and consequent aneuploidy
4.4.2018
Leonardo Gaston Guilgur
IGC, Oeiras

Visual binding: how brain oscillations shape perception
6.4.2018
Gabriel Costa
IBILI/ICBR and CIBIT, Coimbra

Streptomyces skills for the production of natural products
11.4.2018
Marta Mendes
IBMC/I3S

DNA methylation players in memory formation
13.4.2018
Ana M.M. Oliveira
Interdisciplinary Center for Neurosciences,
University of Heidelberg, Germany

Principled views on synapse and circuits: Statistical and deep learning
13.4.2018
Rui Ponte Costa
Department of Physiology, Anatomy and Genetics, University of Oxford, UK and
Department of Physiology, University of Bern, Switzerland

Toward a circuit level understanding of cognition
18.4.2018
Joe Paton
Champalimaud Foundation, Lisbon, Portugal

Linking obesity and cancer through angiogenesis
18.4.2018
Raquel Soares
Faculty of Medicine of the University of Porto and i3S

The double-burden of tuberculosis and diabetes in Guinea-Bissau and the link to the CNC
19.4.2018
Plácido Cardoso
INASA - National Public Health Institute, Guinea-Bissau

Lessons from synaptic dysfunction in aging to model neurodegeneration
19.4.2018
Luisa Lopes
IMM, University of Lisbon, Portugal

Neurobiology of social behavior in zebrafish
20.4.2018
Rui Oliveira
ISPA, Lisboa, Portugal
Instituto Gulbenkian de Ciência, Oeiras, Portugal Champalimaud Center, Lisboa, Portugal

Targeting the kynurenine pathway in neurodegenerative diseases
23.4.2018
Flaviano Giorgini
Department of Genetics, University of Leicaster, UK

The mitochondrial negative regulator MCJ as a new therapeutic target for liver disease
23.4.2018
Malu Martínez-Chantar
Liver Disease Laboratory, CIC bioGuNE, Bizkaia, Spain

ER-mitochondria cross-talk in neurodegeneration: focus on Familial Alzheimer s disease
27.4.2018
Paola Pizzo
Department of Biomedical Sciences
University of Padova, Padova, Italy

May

DOs and DON Ts on Microscopy Imaging
2.5.2018
Luisa Cortes
CNC, Coimbra

Transmembrane calcium exchange in polarized and depolarized mitochondria in smooth muscle cells
4.5.2018
Natalia Naumova-Kandaurova
Institute of Complex Systems, Bioelectronics, Forschungszentrum
Jülich, Germany

Building the preclinical package towards clinical investigation of human neural stem cells in age related macular degeneration
11.5.2018
Alexandra Capela
Biotechnology Consultant; Former Senior Director of Research - StemCells inc, Palo Alto, USA

Novel approaches for the treatment of heart failure: when nanotechnology meets medicine
16.5.2018
Daniele Catalucci
National Research Council (CNR), Institute of Genetic and Biomedical Research (IRGB)

Tau a dyshomeostatic protein in Alzheimer s disease: impact for cognition and metabolism
16.5.2018
David Blum
Inserm UMR-S1172
Université Lille, France

Biomarkers and targets in non-alcoholic fatty liver disease
18.5.2018
Cecília Rodrigues
iMed, University of Lisbon

"Meet the Industry": Photodynamic Therapy in Oncology
25.5.2018
Cláudia Silva
Head of Research and Innovation at Bluepharma, COO/Deputy CEO@Luzitin

Multidrug resistant tumors: novel diagnostic and therapeutic tools
30.5.2018
M. Helena Vasconcelos
IPATIMUP/i3S - Cancer Drug Resistance Group

June

From bedside to bench: the role of cholesterol hemiesters in coronary artery disease
6.7.2018
Otília Vieira
CEDOC, NOVA University, Lisbon

Physical cues to guide vascular differentiation and assembly
7.6.2018
Sharon Gerecht
Johns Hopkins for NanoBioTechnology, Baltimore, USA

Mammalian sperm motility: fertility, metabolism and selfish genes
8.6.2018
Alexandra Amaral
Max Planck Institute for Molecular Genetics, Berlin, Germany

Horizontal transfer of whole mitochondrial restores tumorigenic potential in mtDNA-deficient cancer
8.6.2018
La-Feng Dong
School of Medical Science, Griffith University, Australia

Oxidation of uric acid in inflammatory conditions: the underlying cause of uric-related pathologies
11.6.2018
Flávia Meotti
Universiddae de São Paulo, Brasil

Suppression of proteotoxicity by serotonergic signaling: impact on neurodegenerative diseases
15.6.2018
Andreia Teixeira-Castro
ICVS, University of Minho

What drives cytokinesis in bacterial cells?
20.6.2018
Mariana Gomes Pinto
Instituto de Tecnologia Química e Biológica António Xavier (ITQB)
Universidade Nova de Lisboa

Neuroinflammation in Mutiple Sclerosis: from target discovery to development of a therapeutic strategy
22.6.2018
Adelaide Fernandes
iMed. ULisboa, University of Lisbon

Molecular Imaging with PET: from bench to bedside… and back
26.6.2018
Antero Abrunhosa
Institute of Nuclear Sciences Applied to Health

Mesenchymal stromal cells for the treatment of spinocerebellar ataxias: can they make the difference?
29.6.2018
Catarina Miranda
CNC, Coimbra

July

Edited Magnetic Resonance Spectroscopy-Faster
31.7.2018
Richard Edden
John Hopkins University

Quantitative Biology of hydrogen peroxide signaling
20.7.2018
Fernando Antunes
Center of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon

Targeting solid tumors with lipid-based nanoparticles
13.7.2018
Nuno Fonseca
CNC, Coimbra

Peroxiredoxins, the thioredoxin system and redox signalling
12.7.2018
Christine Winterbourn
University of Otago, New Zealand

Artificial Intelligence in Structural Biology
11.7.2018
Irina Moreira
CNC/ UC-Biotech, Cantanhede

September

In vitro modeling of Rett Syndrome: a road to high content imaging drug screening
17.9.2018
Gabriele Baj
B.R.A.I.N. Centre for Neuroscience
University of Trieste, Italy

Addressing the mechanism of protein import into peroxisomes using in vitro approaches
26.9.2018
Jorge Azevedo
i3S, University of Porto

Alzheimer's Disease: The amyloid hypothesis and the inverse Warburg effect
28.9.2018
Lloyd Demetrius
MCZ Associate of Population Genetics, Harvard University, USA

October

Targeting sirtuin 2 to improve metabolic functions
26.10.2018
Pedro Gomes
CNC, University of Coimbra

Engineering Biomaterials and Processes for Bone and Cartilage Biofabrication
24.10.2018
Pedro Morouço
Polytechnic Institute of Leiria, Leiria, Portugal

Integration of the Co-evolved Mitonuclear Genomes
22.10.2018
David Lee
University of Southern California, Los Angeles, USA

How vaccines train the immune system in ways no one expected
18.10.2018
Christine Stabell Benn
Statens Serum Institut, Copenhagen, Denmark

Role of hippocampal adenosine A2A receptors in psychiatric disorders
12.10.2018
Paula Canas
CNC, University of Coimbra

Mechanisms of nuclear positioning during cell Migration and muscle development
10.10.2018
Edgar Gomes
IMM, University of Lisbon

November

Exploring respiratory chains
7.11.2018
Manuela Pereira
ITQB, NOVA, Lisbon, Portugal

Olfactory bulbectomy in mice as a model of depression
16.11.2018
Roberto F Almeida
Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

Opportunities in Polysaccharides towards healthier gut microbiota
16.11.2018
Manuela Pintado
Catholic University of Portugal, Porto

Role of Adenosine A2A receptors in immunotherapy
19.11.2018
Stephen Hatfield
New England Inflammation and Tissue Protection Institute
Northeastern University, Boston, USA

Blockchain. What is it? Good for?
21.11.2018
Paulo Rupino da Cunha
CISUC, University of Coimbra

Chromatin modulators of cellular reprogramming and cancer
28.11.2018
Alexandre Gaspar Maia
Mayo Clinic, USA

The neural correlates of bistable motion perception
30.11.2018
João Duarte
CIBIT-ICNAS, University of Coimbra

December

Genetic regulation of susceptibility to infection in stem-cell transplantation
5.12.2018
Agostinho Carvalho
ICVS, University of Minho

Optical approaches to study striatal dopamine neurotransmission and corticostriatal plasticity
7.12.2018
Daniela Pereira
Champalimaud Foundation, Lisbon

Effects of lifelong training on T lymphocytes senescence
12.12.2018
Ana Teixeira
FCDEF, University of Coimbra

Developing the next-generation inducible GDNF Gene Therapy
17.12.2018
Luís Quintino
CNS Gene Therapy, Lund University, Sweden

Large scale production of Recombinant Proteins using a Poultry Transgenic System
19.12.2018
Iain Shaw
OVAGEN Group Limited, Ireland

The Setting up of an SPF Flock of Chickens for Research: Establishing The World´s first Germ-Free Chicken Flock producing Germ-Free eggs
19.12.2018
Leonard Moran
OVAGEN Group Limited, Ireland

The imaging of neuroinflammation and oxidative stress in psychotic pathology
21.12.2018
Tiago Reis Marques
Institute of Clinical Sciences, Imperial College London, UK

PhD Thesis concluded in 2018

Amber Kerkhofs
Caffeine, adenosine and acetylcholine and neuronal function in the cortex
June 2018.
Supervisor: Rodrigo Cunha

Ana Isabel Pina Rodrigues
The neural basis of dyslexia Faculty of Medicine
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Ana Maria de Figueiredo Valado
Biological markers in Multiple Sclerosis: Relevance for prognosis and therapeutics
May 2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Ana Sofia Estima da Cunha Coelho
Caracterização das alterações no biofilme e na saliva de diabéticos do tipo 1 com bomba de insulina: estudos in vivo e in vitro em fibroblastos
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Anabela Baptista Pereira Paula
Estudo dos efeitos citotóxicos e na dentinogénese reparadora induzidos por um novo material em proteções pulpares diretas
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Beatriz Maria Pinto Cruz Costa
Avaliação dos efeitos celulares, humorais e moleculares da administração do teduglutide num modelo animal de anastomose intestinal
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Bernardo Martins da Cunha Abecasis
Engineering human in vitro cardiac tissue models for preclinical research
October 2018
Supervisor: Lino Ferreira

Blanka Kellermayer
Super-resolution imaging reveals differential organization and regulation of NMDA receptor subtypes
2018
Supervisor: Carlos Bandeira Duarte

Dominique Fernandes
Role of Caspr1 and Caspr2 in the regulation of glutamatergic transmission and synaptic plasticity - implication for disease pathogenesis
2018
Supervisor: Carlos Bandeira Duarte

Edna Filipa Pais Soares
Beta-glucan-based adjuvants for hepatitis B vaccination: particulate design for prophylatic and therapeutic needs
March 2018
Supervisor: Olga Borges

Emanuel Nery de Oliveira Quartin Costa
Modulation of the hematopoietic stem cell niche by photo-triggerable nanoparticles
2018
Supervisors: Lino Ferreira and Ricardo Neves

Ericka Francislaine Dias Costa
Avaliação do polimorfismo MSH3 c.3133 G>A em carcinoma de células escamosas de orofaringe
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Francisco Manuel Queiroz Gonçalves
Physio-patological role of ecto-5'-nucleotidase – a new target for neuroprotection
May 2018.
Supervisor: Rodrigo Cunha

Inês Miranda Santos
Analysis of metabolic heterogeneity over cell division cycle in non synchronized yeast. A 13C-based experimental-computational approach
2018
Supervisor: Armindo Salvador

Inês Maria de Carvalho Laíns
Metabolómica, genética e ambiente: uma nova abordagem integradora na degenerescência macular relacionada com a idade
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Joana Balça Silva
Molecular Mechanisms of Glioblastoma Resistance: Glioma Stem-Like And Non-Stem Like Cells Specific Targets
2018
Supervisor: Ana Bela Sarmento

João André Sargento Araujo de Freitas
Endothelial progenitor cells in neoangionesis of acute ischemic stroke
2018
Supervisor: Lino Ferreira

Leisa Lopes Aguiar
Avaliação do polimorfismo XPC c.2815A>C em carcinoma de células escamosas de orofaringe
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Mafalda Rita Avó Bacalhau
Establishing the pathogenicity of novel mitochondrial DNA mutations: a cell and molecular biology approach
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Maria de la Salete de Jesus Baptista
Rational design, synthesis and evaluation of novel anticancer chemopotentiators acting on DNA-repair pathways
2018
Supervisors: Jorge Salvador e Maria Manuel Cruz Silva

Mariline Silva
Unveiling the role of microRNAs in synaptic plasticity
2018
Supervisor: Carlos Bandeira Duarte

Patricia Diogo Nunes
Photodynamic therapy applied to asepsis of root canals" PhD in Health Sciences, in Dentistry
2018
Supervisor: Teresa Gonçalves

Patrícia Sofia Alçada Tomás de Morais
The role of adenosine A2A receptor in the migration of cortical principal neurons
November 2018.
Supervisor: Rodrigo Cunha

Pedro Tiago Cardoso Curto
Rickettsia-Macrophage tropism: a link to rickettsial pathogenicity?
2018
Supervisor: Isaura Simões

Rui Miguel Rua Filipe Martins
Transplantação hepática: novos fatores de prognóstico da regulação da função mitocondrial na isquemia/reperfusão
July 2018
Supervisor: João Laranjinha

Samuel Filipe Duarte Chiquita
The changing brain in Alzheimer's disease: is the retina a mirror of disease onset and progression?
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Sónia Margarida Neto Rosa Pereira
Protective role of anthocyanins on intestinal inflammation in comparison with 5-aminosalicylic acid: in vitro and in vivo approaches.
February 2018
Supervisor: João Laranjinha

Sofia Pereira Constantino Romano
Tumor targeting of nanobody-based platforms
2018
Supervisor: Ana Bela Sarmento

Tiago Manuel Pombo Alfaro
Adenosine receptors in inflammatory lung diseases
January 2018.
Supervisor: Rodrigo Cunha

Vanessa Filipa Coelho Santos
Effect of methylphenidate on blood-brain barrier function in health and attention deficit hyperactivity disorder
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Master Thesis

Adriana Jesus Martins Duarte
Papel dos Marcadores EpCAM e OCT4 na resposta às diferentes abordagens terapêuticas de cancro na cabeça e pescoço
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Alana Gabriely Reis Duarte;
Immunocytotoxicity of chitosan nanoparticles: effect of chitosan deacetylation degree
July 2018
Supervisor: Olga Borges

Alexandra Maria J Couto Oliveira
Cytogenomic Characterization of Monoclonal Gammopathy Patients
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Alexandre Loureiro
CRISPR-Cas: Converting a Bacterial Defence Mechanism into a State-of-the-art Genetic Manipulation Tool
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Ana Catarina de Jesus Pais Pereira
Deregulated inflammasome in Bipolar Disorder (BD): a matter of stress?
2018
Supervisors: Cláudia Maria Fragão Pereira & Carlos Bandeira-Duarte

Ana Carvalho
Development of nanosystems for drug delivery into cancer cells
September 2018
Supervisor: Henrique Faneca

Ana Catarina Oliveira Castela
Efeitos do sumo de mirtilo na evolução da disfunção hepática num modelo animal de pré-diabetes
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Ana Filipa Teixeira Salvador
Preparation of semisynthetic derivatives of abietane type diterpenes
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Ana Filipa Teles
A influência do microambiente da cavidade oral na diferenciação de células tipo estaminal
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Ana Lúcia Marques
Resistance to colistin: a public health issue?
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Ana Rita Neto Mestre
Ectonucleotidases influence in Candida spp. Infections
2018
Supervisor: Teresa Gonçalves

Ana Rita Oliveira Coelho
Pinning Down TRPV1: Acupuncture Analgesia
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Ana Rita Pinheiro
Resistência Bacteriana a Carbapenemos
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Ana Teresa Martins
A resposta imunológica inata na doença de Alzheimer
2018
Supervisor: Armanda Santos

André Santos Paula
Dysfunctional Olfactory Brain Regions And Statistical Classification Of Disease Status: An fMRI Study
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

André Alexandre Ferreira Salvada
Sub-regulação de XPC em células HeLa expostas a cisplatina e suas implicações na terapêutica do cancro do colo do útero
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Antonella DiCaro
Antimicrobial susceptibility and competition of diabetic skin microbiota.
2018
Supervisors: Ana Maranha & Nuno Empadinhas

Bárbara Filipa Fernandes de Castro Morais Ramalho
Perturbação de Hiperatividade e Défice de Atenção (PHDA) e Abordagens Terapêuticas Emergentes
2018
Supervisor: Armanda Santos

Beatriz de Oliveira Martins
Effect of incretin-based therapy on gastrointestinal motility in an animal model of Multiple Sclerosis
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Beatriz Dias Ferreira
A influência do alelo epsilon 4 do gene da apolipoproteína E no risco de desenvolvimento da doença de Alzheimer
2018
Supervisor: Armanda Santos

Beatriz Filipa Varela Estremores
The role of autophagy activation mediated by Let-7 in a transgenic mice model of Machado-Joseph Disease
2018
Supervisor: Luis Pereira de Almeida

Beatriz Oliveira
The role of α-adducin in the function and structure of retina
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Beatriz Pinheiro Lopes
Plasma Atmosférico Frio no tratamento do Retinoblastoma
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Beatriz Santos Lapa
ROLE OF GLUCOSE METABOLISM IN MYELODYSPLASTIC SYNDROMES - FOCUS ON SLC2A (GLUT) FAMILY
2018
Supervisor: Conceição Pedroso Lima

Bibiana Correia Silva
Quiet! They May Be at Rest: Metabolic Regulation of Paused Pluripotency
2018
Supervisor: João Ramalho Santos

Carina Santo Henriques
Modified-Exosomes as Gene Delivery Vectors for the Treatment of Machado-Joseph Disease
2018
Supervisor: Luis Pereira de Almeida

Carlos Alberto Gaspar de Jesus
Urine extracellular vesicles: waste or a powerful tool?
September 2018
Supervisor: Lino Ferreira

Carlos Andre Viegas Barreto
Applying computational tools to the study of GPCRs structure and dynamics
2018
Supervisor: Carlos bandeira Duarte

Catarina Alexandra Simões Henriques Rolo
A Utilização de Helmintas na Terapêutica da Asma
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Catarina Isabel Moreira Leitão
Impact of an astrocytic pathology on hippocampal memory
September 2018
Supervisor: Rodrigo Cunha

Cátia Sofia Resende Lopes
Role of astrocytes in synaptic plasticity and memory in animal models of Alzheimer's disease
September 2018
Supervisor: Rodrigo Cunha

Cláudia de Jesus Azenha
Defining Transcriptional Networks Underlying Dendritic Cell Heterogeneity Using Direct Cellular Reprogramming
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Cláudia Sofia Barreto Cantadeiro
Caracterização molecular de isolados clínicos de Klebsiella pneumoniae produtores de carbapenemases e/ou resistentes à colistina
July 2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Cláudio Figueiredo Costa
Experimental Enhancement of Cellular OXPHOS Reliance for Mitochondrial Health Assessment: Development and characterization of a rapid and efficient method to induce OXPHOS in skin fibroblasts, for the assessment of mitochondrial toxicity and protection
September 2018
Supervisores: Maria Teresa Oliveira and António Moreno

Cristiana Daniela Neves José
Demência após Acidente Vascular Cerebral
2018
Supervisor: Armanda Santos

Cristiana Videira Ramos
Modelling Machado-Joseph Disease: from induced Pluripotent Stem Cells to mature neuronal subtypes
2018
Supervisor: Luis Pereira de Almeida

Daniel Agostinho
Diagnóstico diferencial de doenças neurodegenerativas com base em dados multimodais de imagem (PET e Ressonância Magnética)
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Daniel Alexandre Sousa Henriques
PSCs-derived NESCs for neuroregeneration in MJD
2018
Supervisor: Luis Pereira de Almeida

Diana Santos
Epicardial adipose tissue biology
September 2018
Supervisor: Eugénia Carvalho

Diogo André Malheiro Passos
Characterization of the postsynaptic density in a transgenic mouse model of Huntington's disease
July 2018
Supervisor: Ana Cristina Rego

Diogo Rafael Mendes Pessoa
Classificação automática de vocalizações ultrassônicas de roedores: estudo do neurodesenvolvimento
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Diogo Santos
Avaliação do potencial terapêutico dos inibidores das proteínas de shock térmico em Neoplasias hematológicas
2018
Supervisor: Ana Bela sarmento

Diogo Santos
O potencial efeito terapêutico da inibição da proteína de choque térmico 90 na leucemia mieloide crónica
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Emanuela Soares
Terapêutica da Malária: Novas Abordagens Nanotecnológicas
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Frederico Mendes e Pena
CRISPR-mediated pre-transcriptional silencing of ATXN3, the gene involved in Machado-Joseph disease
2018
Supervisor: Luis Pereira de Almeida

Gonçalo Jorge dos Santos Balteiro
Rádio-223 no tratamento do carcinoma da próstata metastático: estudo dos efeitos em linhas celulares normais
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Helena Isabel Reis Aires
Anti-senescence drugs
September 2018
Supervisor: Lino Ferreira

Inês Alexandra Figueiredo de Almeida
Efeito da exposição a betametasona e a dexametasona na morfologia e fisiologia da microglia - relação estrutura-atividade
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Inês Gonçalves
Análise do transcriptoma de tumores da Cavidade Oral: Novos Biomarcadores
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Inês Maria Nogueira Cardoso
Fetal Liver Mitochondria Alterations in an Ovine Model of Maternal Obesity
September 2018
Supervisores: Paulo J. Oliveira and António Moreno

Inês Oliveira Ferreira
Avaliação da citotoxicidade do GuttaFlow® bioseal: estudo in vitro
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Ines Tomé Ribeiro
Breaking the barriers of HFpEF: a new blood vessel on a chip model
September 2018
Supervisor: Lino Ferreira

Isabel Patrícia Dias Meireles
Efeitos de fármacos para o controlo da dor no cancro da próstata metastático
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Joana Ramos
Preparation and functionalization of mesoporous silica nanoparticles to mediate antitumor strategies
September 2018
Supervisor: Henrique Faneca

Joana Rita Pinto Velho
Study of the regioselective acylation reactions of polydatin under enzymatic catalysis
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Joana Sampaio
Reorganização do cérebro e plasticidade neurosensorial
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

João Cardoso
Exploring the role of Sirtuin 2 in lipid homeostasis
July 2018
Supervisor: Cláudia Cavadas

João Pedro Estiveira Campos Silva
Non-Volitional Sensory Neuro-Feedback
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

João Rui Correia de Carvalho e Cruz
Nutrition´s influence on aging - pathophysiological mechanisms
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Juliana Gonçalves Araújo
Complexos de Cobre derivados do imidazole: síntese e avaliação da atividade antitumoral
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Lia Marques e Costa
Estudo dos efeitos protetores dos agonistas do recetor do GLP-1 na retinopatia diabética
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Liliana Rodrigues Dias
Effect of amyloid-beta peptides on astrocytic Ca2+ signaling and gliotransmission: modulation by adenosine A2A receptors
September 2018
Supervisor: Rodrigo Cunha

Luís Cabanas
Development and evaluation of polymeric-based nanosystems for application in gene
April de 2018
Supervisor: Henrique Faneca

Manuel Moura Ramos
Exploring success network in real time functional magnetic resonance imaging (rtfMRI) neurofeedback
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Márcia Alexandra Campos Aguiar
Synthesis, photophysical characterization, and biological evaluation of promising theranostic agents for cancer
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Márcia Joana Nascimento Teixeira
Investigation of genes associated to mitochondrial import and post-translational processing in Leber's Hereditary Optic Neuropathy (LHON)
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Maria Carolina Pereira Reis
Angiogenic stimulation of the cryopreserved ovarian tissue
2018
Supervisor: João Ramalho Santos

Maria da Paz Olímpio Lardosa Paz
Analysis of eyetracking data applied to autism spectrum disorder during virtual reality experiments
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Mariana Amaral Gouveia
Preparation of new semi-synthetic steroids
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Mariana Filipa Gonçalves Madeira Rodrigues
The impact of physical exercise on circulating extracellular vesicles on methamphetamine-intoxicated mice
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Mariana Amaral Gouveia
Preparation of new semi-synthetic steroids
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Mariana Raquel Antunes Colaço
Development of nanosized glucan particles with immunostimulatory function as a delivery system for curcumin
July 2018
Supervisor: Olga Borges

Mariana Sendão Lisboa Meneses
The use of helminth parasites to treat allergic and autoimmune inflammatory diseases
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Marie Babková
The impact of the circadian rhythm regulation on hypothalamic metabolic pathways
July 2018
Supervisor: Cláudia Cavadas

Marina Passos
Factores de risco genético para perdas fetais de repetição em grávidas com complicações obstétricas
2018
Supervisor: Ana Bela Sarmento

Marta Silva Lapo Pais
Diagnóstico diferencial de doenças neurodegenerativas com base em dados de PET em correlação com outras modalidades de imagem
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Miguel Navarro
13C NMR analysis of triglyceride fatty acid enrichment from 13C-enriched lipogenic substrates
September 2018
Supervisor: John Jones

Natasha de Fátima Oliveira Esteves Rosário
Natural Transformation in Acinetobacter spp
2018
Supervisor: Medicinal Chemistry & Drug Discovery Group

Nuno Beltrão
Stargazin mutations and psychiatric disorders: the case of intellectual disability
2018
Supervisor: Carlos bandeira Duarte

Kátia Ribeiro de Jesus
Immunology and genetics in nonhuman primates: Study of KIR3DL02 interaction with MHC-class-I ligands of rhesus macaques
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Patrícia Santos de Oliveira
A interação entre a SIRT1 e o mTOR como um emergente alvo terapêutico para o cancro da bexiga
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Pedro Valada
Estudo do perfil molecular de resistência antimicrobiana de Helicobacter pylori
2018
Supervisor: Teresa Gonçalves

Rafael Silva
Biomarker Discovery in Alzheimer and Parkinson ’s disease: a Proteomics approach to PBMCs
2018
Supervisor: Aging and Brain diseases: advanced diagnosis and biomarkers

Rafael Silva Carvalho
Regulation of NMDA receptor dynamics by BDNF in cultured neurons
2018
Supervisor: Carlos bandeira Duarte

Raquel Direito Fernandes
Comparison of mitochondrial parameters between young and aged oocytes
2018
Supervisor: João Ramalho Santos

Ricardo Costa
O desafio clínico iminente da neutropenia febril - uma análise retrospetiva
2018
Supervisor: Ana Bela Sarmento

Ricardo Moreira
Investigation of Mutant Ataxin-3 Spreading in Machado-Joseph Disease
2018
Supervisor: Luis Pereira de Almeida

Rodolfo Águas
2B or not 2B that is the question about the synaptic proteasome in glutamatergic synapses
2018
Supervisor: Carlos bandeira Duarte

Rosa Mafalda Amorim Figueiredo
GABA levels relate to BOLD signal in Neurofibromatosis Type 1
2018
Supervisor: Vision, Brain Imaging and Cognitive Neuroscience

Rute Tavares
Validation of a siRNA targeting PI3KCA gene towards colorectal cancer therapy
2018
Supervisors: Cláudia Maria Fragão Pereira & Lígia Rodrigues

Tânia Alves
A via de sinalização do WNT/β-catenina e o seu papel nas leucemias mieloides
2018
Supervisor: Ana Bela sarmento

Tânia Isabel Santos Coelho
Nutrition role in inflammation and aging." Master in Medicine, University of Coimbra
2018
Supervisor: New Targets and Therapeutics for Chronic Diseases

Tiago Ochôa Pires
Exploring Japanese quail immune repertoires for antibody discovery
2018
Supervisor: Isaura Simões

Technology Transfer

Translational research and technology transfer have been progressively developed in CNC leading to a promising interaction with Industry and local authorities.
The main contribution of CNC for that goal was the creation of a technology transfer unit, Biocant, in collaboration with Cantanhede Municipal Council. This unit became the anchor of Biocant Park, a Biotechnology Park that is rapidly growing by atracting new Biotechnology companies.

BIOCANT

Biocant is a private, non-profit, innovation centre created by CNCB together with the municipality of Cantanhede for technology transfer in biotechnology. Founded 8 years ago, Biocant provides services and R&D activities based on post-genomic platforms such as whole-genome sequencing, DNA chips, proteomics, interactomics and metabolomics. Several research projects are currently in progress involving research institutions, hospitals and companies.

COMPANIES OPERATING IN BIOCANT PARK

At the present 20 companies operate in Biocant Park: AP-Bio, Biocant Ventures, Biotrend, Converde/CEV, Crioestaminal, Equigerminal, Hittag Biotecnology, Interactome, GenePrediT, Genebox, GeneLab, Matera, Vetdiagnos, 4Health, Cell2B, Klon, NutriAdd, Treat U, Reg4Life and Coimbra Genomics. Along with Biocant they form a biotech cluster of excellence that attracted altogether over 70M€ euros investment (50% is private) and generated 400 highly qualified jobs.

Science Communication and Outreach

Coordinator: Cláudia Cavadas, PhD
Team: Adalberto Fernandes, Ana Teresa Viegas & 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: i) dissemination through the media; ii) through digital communication (websites and social networks); iii) through public engagement projects.

SCIENCE IN THE MEDIA

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. Figure 1 shows the media appearance during 2018.

Figure 1 – CNC.IBILI at the Media during 2018.

DIGITAL COMMUNICATION

EXTERNAL: SOCIAL NETWORKS

To reach a wider population we improve our presence in social networks. At the moment we have a total of 9.246 followers at different social networks: facebook, twitter, linkedin and instagram, as shown at Figure 2.

Figure 2 – Followers of CNC social networks.

INTERNAL: NEWSLETTER "SYNERGIES"

CNC has its own internal monthly newsletter called "Synergies". The main goal of this newsletter is to promote the interaction among the members, leading to a greater cooperation. In order to achieve this goal, "Synergies" disseminates several relevant information about the center, related to the scientific research, science communication, funding and events, through the following sections:

- What Happened?
- Publications
- Awards / Honors
- Events at CNC
- Scientific Meetings and Events
- Public Engagement in Science
- CNC on the News
- Opportunities
- New faces | New roles
- Don't miss out
- PhD Defenses
- What Will Happen?
- PDBEB Advanced Courses
- CNC.IBILI Seminars
- Timeline (future events)

The newsletter is distributed through a specific mailing list, reaching more than 400 contacts, including researchers and non-research staff.
Moreover, the newsletter is posted on our website and also on our social media networks, in order to get the public aware of our news and activity. In 2018 we launched 12 editions of Synergies.

PUBLIC ENGAGEMENT IN SCIENCE

CNC.IBILI is strongly involved in Public Engagement in Science projects. Figure 3 shows the general data from 2018 related to this kind of initiatives.

Figure 3 – Data of Public Engagement Projects during 2018.

BRAIN AWARENESS WEEK (BAW)

March 2018

The Brain Awareness Week (BAW) 2018 organized by CNC.IBILI, supported by FENS, DANA Foundation and Sociedade Portuguesa de Neurociências, happened in Coimbra (1st-30th March 2019).
Our project – Neuro adventures - aimed to increase the scientific culture in neuroscience as well as engage society in scientific research (Figure 3).

Figure 3 – Programme of CNC.IBILI BAW 2018.

The BAW 2018 promoted several activities:

1. NEURO-ADVENTURES AT THE SCHOOLS

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 (Figure 4).

Figure 4 – Photos of the activities at schools and community centers.

2. NEURO-ADVENTURES AT THE LAB

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?; Eye as a window for brain; Study of human behavior; How do we have energy to the brain?;How neurons die in Alzheimer´s disease?; Neurons, obesity and aging; Brain development.

3. NEURO-ADVENTURES AT THE PUB

During BAW we promoted the 6th edition of PubhD Coimbra and 3 PhD students share their projects with the audience in a very popular pub in Coimbra. The students are from different areas: neuroscience, psychology and astrophysics. The central theme was the brain.

4. MICROSCIENCE PHOTO GALLERY

We launched the exhibition "The beauty of our cells" with more than 70 microscopy images obtained during research projects at CNC and IBILI. The exhibition resulted from a partnership between CNC.IBILI and Coimbra´s science center Exploratório and will be available for visits during 1 year. After this period, the exhibition will be exposed in science and cultural centers different Portuguese cities (Figure 5).

Figure 5 – "The beauty of our cells" exhibition.

5. SELFIE SCIENCE

In order to create meeting places between science and society, we developed audio- visual contents about neuroscience research and brain facts. We developed five small movies, "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).

6. SPN EVENT - BRAIN AND DEMENTIA

18th March, FNAC Coimbra

Session for general audience about dementia at a public café in a shopping center. The initiative counted with the participation of a psychologist, two medical doctors, a neuroscientist and the president of Alzheimer association (Figure 6).

Figure 6 – "Brain and Dementia" public event.

Our BAW activities involved more than 70 researchers and reached directly more than 1000 people from different publics in the following activities: Neuro-adventures at the schools, Neuro-adventures at the labs, Neuro-adventures at the pub, launch of exhibition "The beauty of our cells, public events. There were 26 news published about our BAW project in national and regional newspapers. In digital media – facebook, linkedin, twitter and instagram - we made 32 posts about BAW (with 4 849 likes, shares and comments) and reached 43 900 people.

WORLD SLEEP DAY
16TH MARCH 2019

CNC joint the Portuguese Sleep Association (APS) to celebrate World Sleep Day 2018 (16th March) and developed an extensive campaign on the weeks before and after the World Sleep Day (WSD). It was directed to all ages of professional and non-professional people. One of the aims of the campaign was that every portuguese live being who, on the 16th March, went to school, to work, to internet or social network, read the newspaper, listened to the radio or watched TV, would hear about the importance of sleep, how to respect it, to have a good life. This campaign promoted several initiatives:

1. 1. Comics: We produced the comic strip "Voyages without insomnia" (Figure 7) about sleep to celebrate World Sleep Day (16th March) in a national newspaper - Público. Público is one of the most prestigious daily newspaper in Portugal. The comics explored the importance of sleep for brain function and the research that have been made in this field. The comic strip reached 33 353 people (daily circulation number).

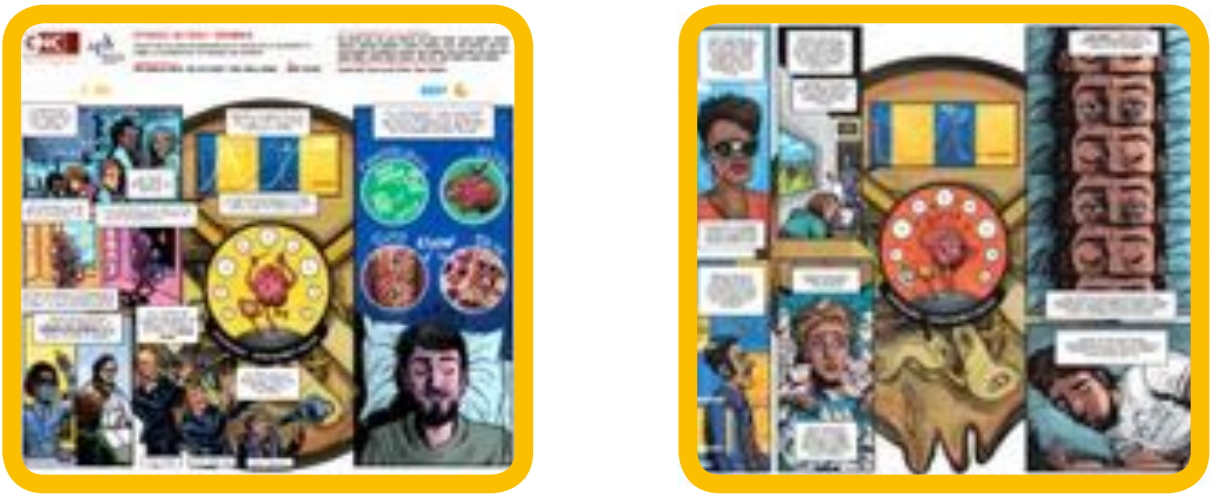


Figure 7 – "Voyages without insomnia".

1. 2. A WSD leaflet: A leaflet was done with the strip cartoon and it was spread to all the social and cultural events that were taking place on the WSD on Coimbra;
2. 3. Event: We promoted the public event "Is sleep a waste of time?" in Exploratório science center. This informal session target children from elementary school and explored the importance of sleep. The event occurred at Hemisferium and counted with the participation of one medical doctor and one neuroscientist. About 30 children participated.
3. 4. Video: a video was elaborated to alert for the importance of attending to sleep rhythms to achieve a healthy life. It was spread out to main TV channels, many hospitals and health centres, homecare providers, pharmacies, site, social networks (more than 330 000 views all);
4. 5. Many interviews on the main TV channels, radio, magazines and newpapers.

SCIENCE IN THE LAB
SEPTEMBER 2018

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 2018 we received 23 high-school for internships in different research fields (Table 1; Figure 8). 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. The 12 scientific internships offered in 2018 were the following:

Name of the internship	Number of students	Field	Principal Investigator
"Laboratório fora da caixa"	1	Science Communication	Sara Amaral
"Células estaminais como modelos para doenças neurodegenerativas"	2	Neuroscience	Carla Lopes
"Biologia da Reprodução e Células Estaminais"	2	Metabolism	João Ramalho-Santos
"Um tratamento para a doença de Alzheimer poderá estar próximo?"	1	Neuroscience	Armanda Santos
"Eles, micróbios, no meio de nós"	3	Metabolism	Daniela Antunes
"Enzimas que comem plásticos: análise computacional da estrutura"	1	Biotechnology	Alexandra Carvalho
"Respiração celular – alimentos para a mente (FOOD for Thought"	3	Neuroscience	Ana Ledo
"Mitocôndria: de ex-bactéria ao motor das nossas células: metabolismo, terapêutica e toxicologia"	3	Metabolism	Paulo Oliveira
"A procura do elixir da juventude – hormonas e neurónios em ação"	3	Neuroscience	Célia Aveleira
"Andam as nossas células também stressadas?"	1	Metabolism	Cláudia Pereira
"Viagem ao mundo das avarias na fábrica de energia"	1	Neuroscience	Manuela Grazina
"Utilização de mini-cérebros para perceber o autismo"	2	Neuroscience	Catarina Seabra

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

Figure 8 – Students involved in the Science in the Lab project 2018.

SCIENCE IN THE SUMMER
JULY AND SEPTEMBER 2018

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 2018

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 2018 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 19 hands-on activities, speed-dating and an art&science performance (collaboration with Marionet). More than 1100 people visited Botanical Garden and Science Museum during ERN.

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 35 CNC researchers. In 2018, CNC researchers participate in several initiatives:

- 3 Conferences (99 participants):

1. "Células estaminais: o que são? Onde estão?"
2. "Análise de circuitos neuronais em doenças psiquiátricas"
3. "A doença de Parkinson: diferentes mecanismos, a mesma (dis)função"

- 7 Advanced courses for high-school students and teachers (70 participants):

1. "Biologia molecular: do gene à proteina"
2. "Desafios na saúde: doenças do séc.XXI"
3. "Diabetes gestacional"
4. "Neurociências I"

5. “Neurociências II”
6. “Regulação celular”
7. “Metabolismo e envelhecimento: à procura do elixir da juventude”

- 3 internship programes for high-school students (14 participants)

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 researchers, either as actors, authors or sources of inspiration. In 2018 our researchers collaborate with two different projects with Marionet theatre company:

- **Sistemas corporais**
  CNC was an active partner in “Sistemas Corporais” project. In 2018, CNC participated in the following initiatives:
  - The Empatic Limbo play: CNC researchers were at the theatre foyer before and after the play talking about neuroscience issues;
  - The Secret gland play: CNC participated in the construction of an art&science workshop targeting children about the brain and neurons. We organized a pilot session with 20 primary school students to test the workshop. The workshop will accompany a theatre play about body systems.

- **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 2018, the ‘Un_n__nn___Lab’ had a 3 event where the problem at stake is discussed and the results of the research are presented. The first public session took place in September 2018, during European Researchers´Night and count with an audience of 28 people. A theatre performance about OSA (Obstructive Sleep Apnea) was staged. 6 CNC researchers were involved in the meetings, discussion and preparation of the theatre performance.

BRAIN BUSKERS

The Brain Buskers project aims to promote public engagement in science, joining science with the daily and cultural life of the city, and have an impact on local communities.
Its informal nature promotes the understanding of daily-life biochemical phenomena, demystifying the image of scientists, and increasing the scientific literacy.
This project also revealed to be important to scientists to inspire new generations with scientific knowledge to communicate science with the society. Inspired by buskers’ street performances, the project “Brain Buskers” was born aiming to capture the attention of the public to unveil and explore biochemical phenomena in an informal environment, taking advantage of the scientific expertise of the researchers our center.
The researchers left their laboratories and embraced the challenge to take science to the city’s daily life and communicate with the society in public spaces, such as streets, parks, beaches and pubs, among others. With this project, we aimed to bring science close to the society by creating meeting places between scientists and citizens, building informal and unexpected conversations about scientific contents, with main focus on CNC.IBILI target research fields: neuroscience, metabolism and biotechnology. In total, we had around 764 people participating in our activities throughout the 16 events with the participation of 24 researchers (Figure 9; Table 2).
This project was sponsored by Biochemical Society.

Figure 9 – Some of Brain Buskers events.

	schedule				engaged
28th April (Saturday)	10 am to 4 pm	Downtown	Streets of Coimbra's downtown and central café	Children, teenagers, young adults & adults	45
10th May (Thursday)	11 pm to 3 am	Queima das Fitas – Coimbra 2018	Annual academic party with music concerts. Around 15.000 daily spectators	Young adults	250
11th May (Friday)	2 pm to 5 pm	Jardim Botânico da Universidade de Coimbra	Botanical Garden of the University of Coimbra	Children & young adults	25
29th May (Tuesday)	9.30 pm to 10.30 pm	Teatro Académico Gil Vicente	Academic theatre – after a play of Marionet company	Young adults & adults	30
1st June (Friday)	3 pm to 5 pm	Academia Futebol Londrelão	Football academy	Children	15
15th June (Friday)	6 pm to 8 pm	Casa das Artes Bissaya Barreto	During the matinée event inserted in the program of the venue	Children & young adults	15
29th June (Friday)	10 am to 1 pm	Figueira da Foz beach	Scientific activities at the beach	Children, teenagers, young adults & adults	4
26th July (Thursday)	8 pm to 10 pm	Expofacic	The largest activity fair in the central region and one of the largest in the country. More than 25.000 daily spectators	Children, teenagers, young adults & adults	20
31st August (Friday)	3 pm to 6 pm	Barra beach, Aveiro city	Scientific activities at the beach	Children, teenagers, young adults & adults	75
15th September (Saturday)	10 am to 2 pm	Jardim Botânico da Universidade de Coimbra	During the weekly sustainable agriculture market	Children, teenagers, young adults & adults	50
21st September (Friday)	6 pm to 8 pm	Casa das Artes Bissaya Barreto	During the matinée event inserted in the program of the venue	Children & young adults	35
19th to 23rd November	10 am to 12 pm (every morning during one week)	City buses	Researchers travelled in the city's buses to chat with the public	Young adults & adults	200

Table 2 – Details of the Brain Buskers events.

3RD SCIENCE FESTIVAL – OLIVEIRA DO BAIRRO (FECIOB)
OCTOBER 2018

FeCiOB is a science festival that happened every year in Oliveira do Bairro during 3 days, promoted by Câmara Municipal de Oliveira do Bairro and Instituto de Educação e Cidadania. 21 CNC.IBILI researchers participated with hands-on activities, games and talks. Numbers from FeCiOB 2018 showed that more than 5500 people visited the initiative.

Figure 10 – Researchers in FeCiOB 2018.

SCIENCE & TECHNOLOGY WEEK
NOVEMBER 2018

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 820 persons. Science & Technology Week 2018 promoted the following activities:

- Visits to schools (13 visits to schools, more than 430 students from kindergarten to secondary schools with the participation of 27 researchers);
- Open Labs (5 open labs, 78 students from kindergarten to secondary schools with the participation of 12 researchers)
- Scientists on the Bus (5 initiatives, more than 180 people reached with the participation of 11 researchers)
- PubhD Coimbra (1 initiative, , more than 50 people on the audience with the participation of 1 CNC.IBILI researcher)
- Science Day at Vila Nova do Tazem (1 initiative, more than 90 persons reached with the participation of 2 CNC.IBILI researchers)

Figure 11 – Some photos of Science & Technology Week 2018.

SCIENCE AT EUG
JULY 2018

The European University Games (EUG) and some CNC researchers, namely from European project FOIE GRAS (coordinated by CNC), partnered to communicate the biological underpinnings of exercise practice on our body in order to promote a healthy lifestyle for body and mind. For this purpose, 52 researchers were involved in writing 14 illustrated chronicles published biweekly in Diário de Coimbra, recording short radio rubrics at Radio Universidade de Coimbra (RUC) and participating in speed-dating at an interactive outreach booth (The Paddle Bar) at the EUG2018 precinct during the games period. In the domain of Art+Science, besides the illustrations for the chronicles, an illustrator worked together with some researchers for the production of a short comic launched in Público online. EUG-CNC project intended to reach a broader and more diverse public as possible by creating content to be displayed through multiple formats and via different mediums, engaging the audience on their most preferred communication channel.
Then several initiatives took place:

1. Illustrated Chronicles:

We produced 14 illustrated chronicles that were published in Diário de Coimbra (regional newspaper – daily circulation number: 7239 readers/day), EUG newsletter (3612 subscribers) and websites – CNC (3081 visualization between Jul-Sep 2018), EUG (1349 visualizations between Jul-Sep 2018) and FOIE GRAS (57 visualizations between Jul-Sep 2018). The themes explored were:

- Physical exercise, health and fat-free livers: An introduction
- Pumping metabolism: The role of exercise
- How my fat liver became very slim
- Good food and exercise a day keeps the doctor away
- A tale of a (too much) sugar and how to fight it
- The (good) residents from within and how to keep them happy
- Exercise and the Cardiovascular system: Inseparable in health and disease
- The Tic-Tac of Exercise Practice
- Exercise Practice and (In)fertility
- Exercise practice as a natural beneficial therapy for menopause
- Not to move because it hurts, or moving not to hurt?
- Exercise Practice and Brain Development
- Sports and Neurodegenerative Diseases
- Memory Run - About the cognitive benefits of exercise

Figure 12 – Some illustrated chronicles (illustrations: Rui Tavares).

2. Radio pieces:

We produced with RUC 13 small radio pieces that explore relationships between sports and science. The radio pieces went air every day during EUG (at 107.9 FM - RUC) and were shared in CNC social networks. RUC dedicated a 2 hour radio programme to this project. See here the first part and the second part.

3. Leaflets “Healthy living with exercise”

We produced 2000 leaflets containing the illustrations and the main scientific messages of the chronicles and distributed through the city during EUG.

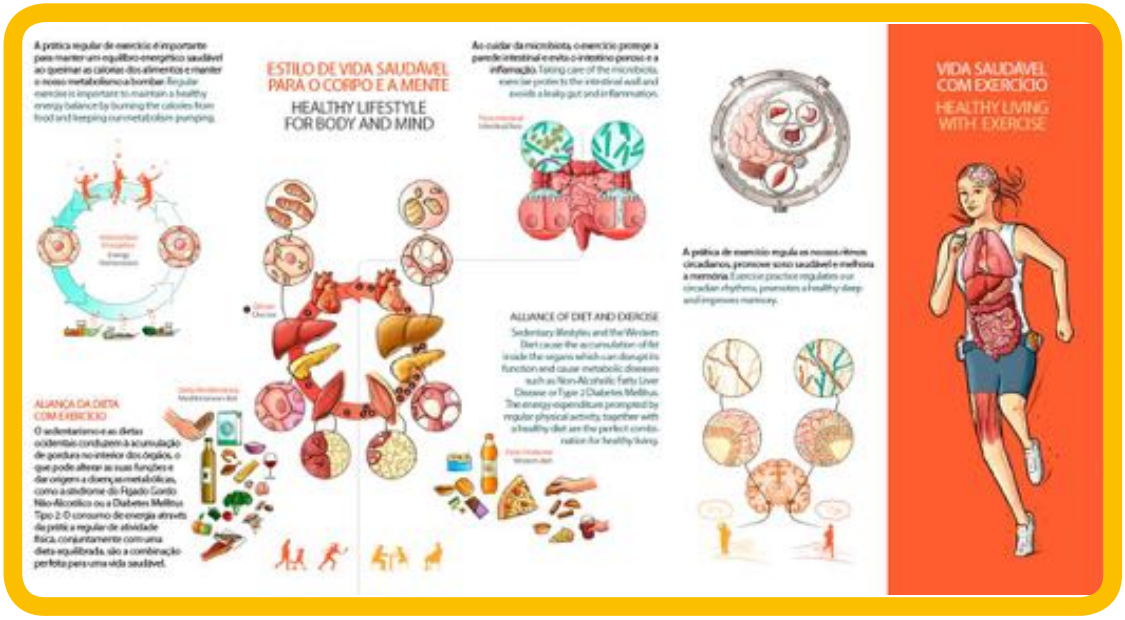


Figure 13 – Leaflet (illustrations: Rui Tavares).

4. Short comic

A short comic “Exercise, mitochondria…& Us” were launched in Público online during the first day of EUG 2018. The comic explored some biomedical content as energy homeostasis, energy expenditure, actin-myosin system, mitochondrial biogenesis and physical activity recommendations. The number of the pageviews is 6814.

Figure 14 – Comic “Exercise, mitochondria...& Us” (illustrations: Rui Tavares).

5. Speed-dating with scientists in Pedal Bar

During EUG (14th-28th July) we promote speed-dating with scientists at the games arena (every-day). 1112 people interact with researchers in Pedal Bar – people from 33 nationalities, mainly young adults and 36% are foreigner.

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 2018, 12 researchers from CNC.IBILI participated in PubhD. Each edition has an average audience of 40 people then about 480 people interacted with this event.

Figure 15 – Participants of PubhD Coimbra during 2018 (some of them are from CNC.IBILI)

COMICS
MARCH, MAY AND JULY 2018

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 three comics, involving different researchers and an illustrator: one about sleep (launched at WSD), one Reproduction and one about Science and Sport (launched during EUG 2018, only online).

Figure 16 – "Voyages in (in)fertility" - one of the comics produced during 2018 (illustrations: Rui Tavares).

TRAINNING AND COMMUNICATION WITH PEERS

ADVANCED COURSE – CONNECTING RESEARCHERS WITH THE SOCIETY
JANUARY 2018

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. 20 students, from PDBEB and from other PhD programs, participated in this intensive course (5-days) with the participation of 25 speakers from different fields as public engagement in science, media, technology transfer, career development and art&science.

BEB DAY
JANUARY 2018

Students from PDBEB programme organized a meeting with actual and old PDBEB students to share ideas and experiences. During the event the participants explored themes as career development, science communications, industry and research in different fields. The BEB day launched an award sponsored by Bluepharma – 2nd BEB/Bluepharma award – targeting PhD students. The awarded student went to an European biomedical conference by free. 47 people participated in BEB day 2018.

Figure 17 – BEB day programme.

BEER FOR THOUGHT
JANUARY - DECEMBER 2018

Science Communication Office and other CNC members hosted the initiative "Beer for Thought", an event to promote networking between CNC members. In 2018 we hosted 7 editions of "Beer for Thought" with Craft Beer kindly provided by our researcher John Jones. .

Core Facilities at CNC

ANIMAL HOUSE

Head of Unit: Prof. João Laranjinha

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.

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 (type1)

Laminar flow chamber

FLOW CITOMETRY 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.

FACSAriaTMIII (Becton Dickinson) – 12 colours

FACSCalibur (Becton Dickinson) - 4 colours

MICROSCOPY IMAGING CENTER OF COIMBRA - CNC

Head of Unit: Luísa Cortes

The Microscopy Imaging Center of Coimbra, at the Center for Neuroscience and Cell Biology (MICC-CNC), is an open infrastructure for conventional and advanced imaging techniques, based on Light Microscopy.

The MICC-CNC has highly skilled and multidisciplinary scientific staff deeply committed to the training of new users and the planning of microscopy based experiments, by choosing equipment and acquisition protocol, and performing imaging processing and analysis. In 2018, the MICC facility supported around 240 users from 58 research groups, with more than 25000 hours of equipment usage.

MICC-CNC is a well-established and renowned facility at the Portuguese scientific community which can be attested by the increase number of external services performed at the facility. External users are from different Portuguese research institutions: University of Coimbra, University of Algarve, University of Minho, University of Beira Interior, CEBAL, University of Évora. The most requested services are: widefield microscopy, confocal microscopy and laser microdissection.

The facility organizes regular advanced courses to all the scientific community providing the fundamentals, as well as the advanced techniques on fluorescence microscopy, live cell imaging and image analysis. Catarino T., Caldeira M.V. and Cortes L. organized the "IV Quantitative Fluorescence Microscopy Course" (CNC, Sept 24th- 28th) and coordinated the "Pratical Course on Calcium Imaging", at the University of Beira Interior, as a collaboration with CICS-UBI - Health Sciences Research Center (22nd-23rd November 2018); Cortes L lectured at several post-graduation courses (the BEB and Health Science Doctoral Programmes. Master Programme at the Valladolid University)

MICC-CNC is a Zeiss Labs@location Partner of the community of ZEISS customers, sharing and providing in depth knowledge and dedicated services, and with expertise in specific applications of imaging technologies. In accordance with the protocol agreement Lab@location, MICC-CNC has performed external services for Carl Zeiss Microscopy and was contacted to provide specialized technical service in the area of Laser Microdissection to the Philip Morris company. This service was fully supported by the Philip Morris company and, given the specification of the samples, the service was provided at the company's premises in Neuchatel, Switzerland.

Moreover, MICC-CNC is a node of the Portuguese Platform for BioImaging (PPBI), a research infrastructure of the RNIE roadmap, Cortes L being the Coordinator for the Mondego & Beiras Pole. MICC-CNC also participates in the EuroBioImaging network, which is an ESFRI initiative.

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

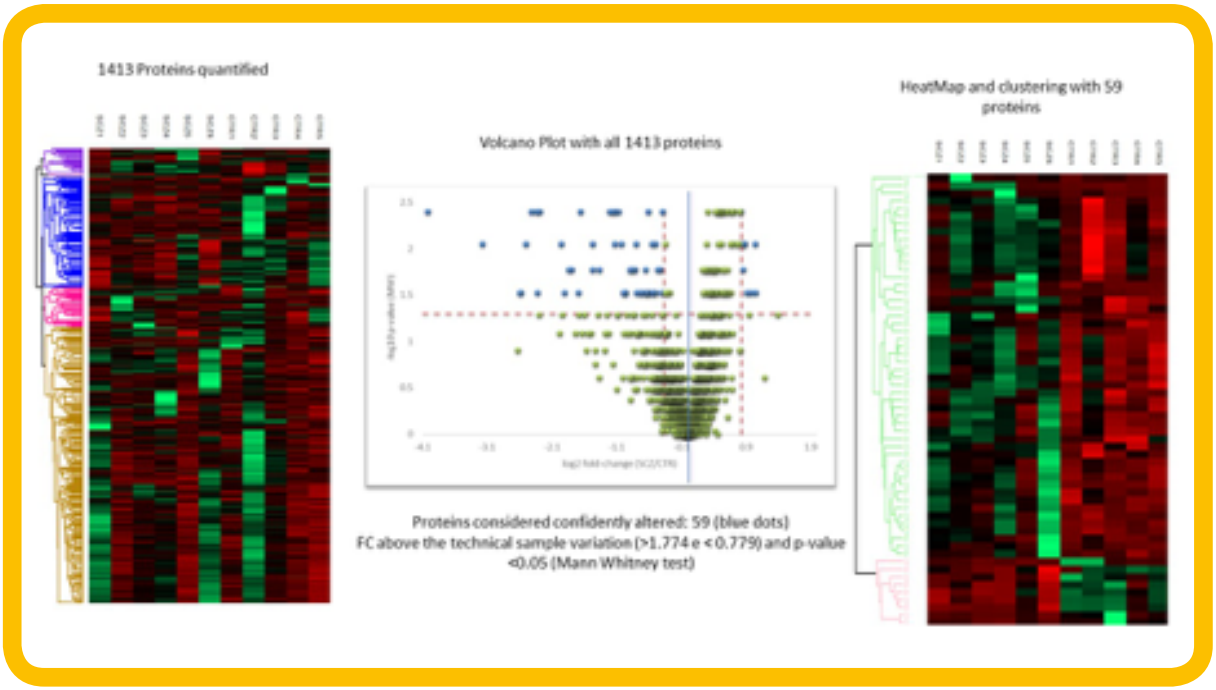
LIFE SCIENCES MASS SPECTROMETRY - LSMS

Head of Unit: Bruno Manadas

During 2018 the LSMS developed several research projects coordinated by CNC, but also national and international collaborations.
The research performed over the last years resulted in four publications with an average IF above four.
Besides the continuation of an FCT project started in 2016 and a PAC project started in 2017, both with a strong proteomics and metabolomics component, the lab also increased the number of funded projects.
One project headed by the lab, two projects co-headed and five more projects with collaborations.
The certified services under the ISO 9001 compliance have been extended and new plans to cover the remaining laboratory research methods under this compliance are being implemented (becoming, therefore, the only ISO 9001 certified research mass spectrometry lab in Portugal).

MAIN ACHIEVEMENTS

The impact of our research in the community has raised quite significantly as the number of projects 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 increasing 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.



Example of a proteomics screening performed on PBMCs from First Episode of Psychosis (SCZ) and matched controls (Ctr) where 1413 proteins were quantified between all samples (left panel); 59 proteins show statistically meaningful differences (center panel), and they allow a pattern recognition between the two groups (right panel).

Services at CNC

Laboratory of Mitochondrial BioMedicine and Theranostics

Head of Unit: Manuela Grazina

Staff:
Superior Technicians | Marta Simões and Maria João Santos.

Certification NP EN ISO 9001:2015.

The director of the Laboratory of Mitochondrial BioMedicine and Theranostics (LBioMiT) (Manuela Grazina) 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 (MRC Mitochondrial Biology Unit, Cambridge, UK), Prof. Robert Taylor (Mitochondrial Pathology, University of Newcastle upon Tyne, UK) and 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 Diagnosis

During this year, in the continuity of the previous, the culture of fibroblasts was performed for the accomplishment of functional studies to elucidate the pathogenicity of novel genetic variants identified in patients. It included samples of one patient presenting encephalopathy with epilepsy and another patient with cardiomyopathy and nephropathy, both with different novel variants identified in a gene (FASTKD2) involved in post-transcriptional regulation of mitochondrial gene expression.
Additional fibroblast samples of controls were seeded 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 8 patients suspected of mitochondrial cytopathies were studied, corresponding to the analysis of 9 samples, in 90 assays, including lymphocytes isolated of peripheral blood (6), muscular biopsies (2) and fibroblasts (1). An MRC deficiency was detected in three patients (37.5 %).

A total of 8 patients suspected of mitochondrial cytopathies were studied, corresponding to the analysis of 9 samples, in 90 assays, including lymphocytes isolated of peripheral blood (6), muscular biopsies (2) and fibroblasts (1). An MRC deficiency was detected in three patients (37.5 %).

CoQ10 quantification

Two samples of muscle were analyzed to determine the CoQ10 levels in two patients with ataxia. The coenzyme content was normal in both samples.

Functional Studies

Following the research developed in the scope of a PhD thesis, a set of functional genomics' assays was implemented, highlighting the reverse translational research nature of the work developed at the LBioMiT, reinforcing the bridges between services for diagnostic screening and applied biomedical research. In one patient presenting encephalopathy with epilepsy, a mutation has been found affecting the protein Fas-activated serine-threonine kinase domain 2, the mutation impact for the phenotype was analysed by a f unctional genomics approach.
Major alterations were evident among the results of different assays, namely that mitochondrial assembly was significantly altered for complex I (Figure 1, patient P3), evaluated by Blue Native–PAGE with

in whom Native–PAGE with mitochondrial-enriched fractions (MEFs) of fibroblasts. This study was presented in 15th Symposium of the Portuguese Society for Metabolic Disorders, showing that inherent OXPHOS-assembly profiles provide further relevant information about consequences of identified disease-causing mutations and/or phenotypes representing an important tool in the scope of diagnostic studies.

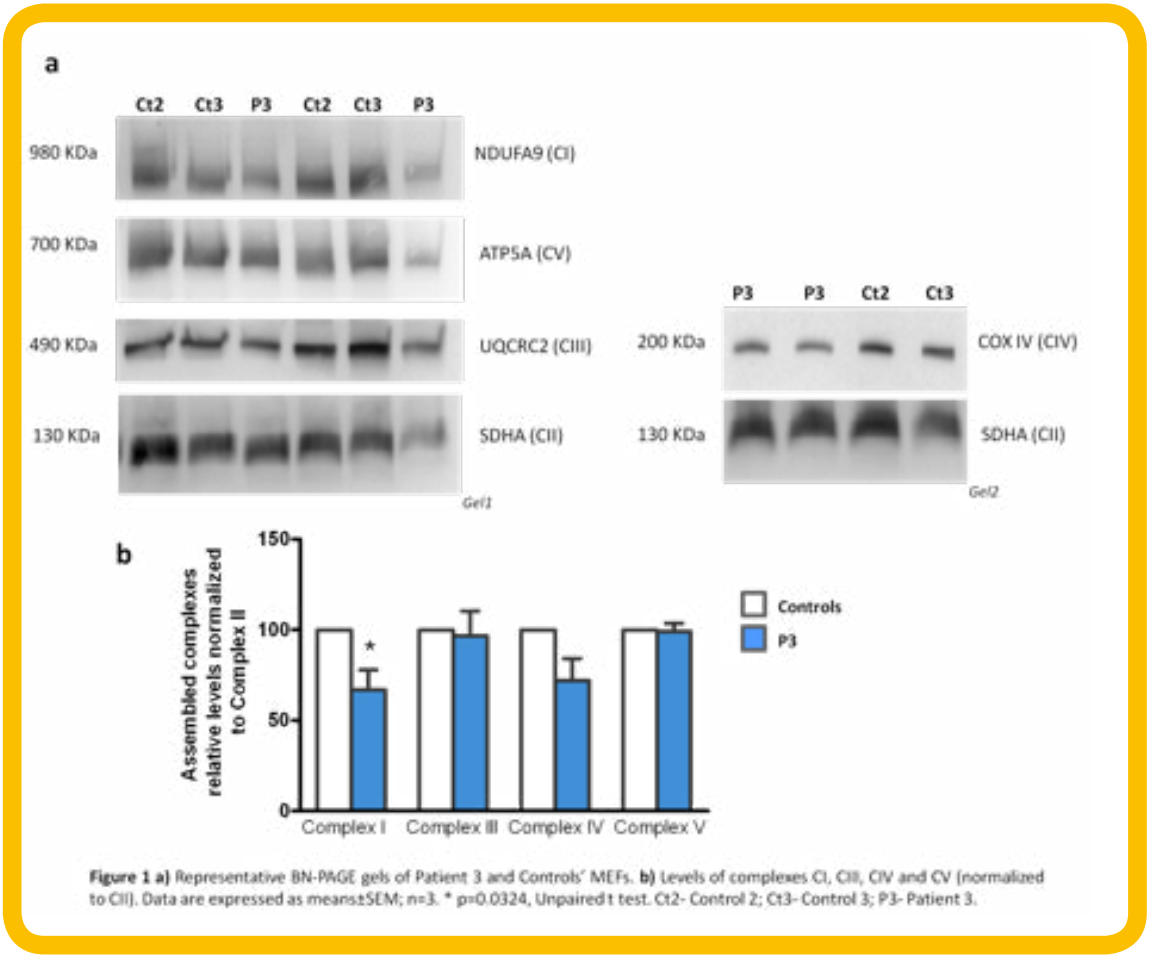


Figure 1 a) Representative BN-PAGE gels of Patient 3 and Controls' MEFs. **b)** Levels of complexes CI, CIII, CIV and CV (normalized to CII). Data are expressed as means±SEM; n=3. * p=0.0324, Unpaired t test. Ct2- Control 2; Ct3- Control 3; P3- Patient 3.

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 and bigenomic crosstalk factors, using a genetic integrative approach is mandatory, although very complex.

Mitochondrial DNA (mtDNA) genomes studies: 32 samples (blood – 30 and muscle – 2) were received for DNA extraction. A sample of DNA was also received for genetic analysis.

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 2018, 24 samples of 23 patients were analysed using this strategy and the findings included several polymorphisms in all samples and two point mutations (m.11778G>A and m.13513G>A) in two patients (8.3%). These pathogenic mutations were further confirmed by PCR-RFLP and automated sequencing, respectively.

A pathogenic mutation (m.14487T>C) was screened in blood and amniocytes samples of a family member of one index case, previously diagnosed at LBioMiT, but the mutation was absent in these samples. Gene panel analysis was also performed in selected samples, according to clinic manifestations.

The Top 3 LHON primary mutations were analysed in three patients with LHON suspicion, to give a faster response to the cases.

In addition, the screening of a single mutation (m.1555A>G) in three patients with Deafness was also performed.

The sequencing of the MT-RNR1 gene was also accomplished in one of these patients.

The screening of deletions using flanking PCR of 6 hot-spot regions was continued.

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 the screening of nuclear genome (nDNA) defects causative of MRC diseases, 30 samples were screened by next generation sequencing (NGS). Additionally, POLG1 gene was analysed in 6 samples, allowing the detection of some sequence variations, but no pathogenic mutations were identified.
Screening of OPA1 gene (1 sample) revealed a pathogenic mutation associated with Dominant hereditary optic atrophy. One case (family relative) was also analysed to confirm a mutation in SURF1 gene detected in index case. The relative was heterozygous for the mutation.

Bioinformatics´ Analysis

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 pathogenicity.
According to the procedure followed at the LBioMiT, around 800 sequence variations were assigned in the mtDNA, including several polymorphisms, some reported alterations and two point mutations (m.11778G>A and m.13513G>A), associated with LHON and Leigh Syndrome respectively, in two 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 bioinformatics filtering 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 three cases.

Laboratory of Neurogenetics

Head of Unit: Maria Rosário Almeida and Ana Cristina Santos

During 2018, the Neurogenetics Laboratory continued to pursue the genetic characterization of patients with Parkinson disease (PD), Alzheimer disease (AD), Frontotemporal lobar degeneration (FTLD) and Amyotrophic lateral sclerosis (ALS) providing an early and accurate diagnosis to patients referred from different hospitals in the country. Also, this year the genetic tests have been expanded to other brain diseases such: as cavernous malformations and cerebral small vessel disease (SVD), in collaboration with Neurologists from the Centro Hospitalar e Universitário de Coimbra (CHUC). The genetic tests encompassed both diagnostic tests and predictive tests referred from the Neurology department and Genetic counseling unit, respectively, in order to identify asymptomatic relatives at high-risk to develop the disease. The methodology used involved mainly sequencing of genes which could occurred individually, gene-by-gene, using Sanger sequencing or by gene Panels using Next Generation Sequencing technology (NGS), recently developed in the laboratory. For the targeted NGS, a panel of 37 known causative-genes associated with AD, ALS, PD, FTLD and SVD has been selected.
Thus, with this approach, some of the still genetically unexplained cases have been solved, and the diseases mutation spectrum and the clinical associated phenotypes have been increased. However, the use of this new technology has brought new problems and challenges, both at the technical level and in terms of data analysis, as well as for the interpretation of the results. Therefore, during 2018 we have been focused in developing and acquiring experience in the genetic variation interpretation process before reporting the genetic result. The variants interpretation was based on criteria published by the American College of Medical Genetics and Genomics (ACMG) which recommended that the variants have to be allocated to one of the five categories: i) clearly pathogenic (class V), ii) likely to be pathogenic (class IV), iii) unknown clinical significance (class III), iv) unlikely to be pathogenic (class II) and v) clearly not pathogenic (class I). Hence, supplementary studies focused on literature reported, population requencies, clinical presentations, f mutation databases and possibly case-specific research data have been performed to achieve an accurate classification of the identified variants. In 2018, the variants of unknown significance (VUS) represented a problem for the interpretative process and today their prioritization remains a primary challenge since its identification could not be used for the clinical management of patients and families. Hence, different pipelines strategies using bioinformatics' analysis have been developed to perform the reading, alignment and the variant calling. In addition, the yielded variants were evaluated for coverage and visually inspected using the Integrative Genomics Viewer and a multistep process workflow, including mapping, variant calling and annotation, which was developed and optimized to individually assess variants pathogenecity, according to the currently ACGS guidelines. Also, several in silico prediction algorithms have been used as well as the allelic frequency available in different populations databases (eg. 1000 Genome project and ExAC).

Cellular Mechanobiology

Head of Unit: Mário Grãos

The group's main research interest is in the field of Cellular Mechanobiology, developing projects that extend within the broader areas of Cellular and Molecular Biology, Biochemistry and Neurosciences. We have been focusing on understanding the molecular details and intracellular signaling pathways responsible for integrating biophysical and biochemical stimuli (through mechanotransduction) involved in cellular differentiation, cellular potency (maintenance of undifferentiated state and reprogramming) and regulation of the cellular proteome.

Our current models include adult and pluripotent stem cells, neural progenitors and other cell types relevant for neurodegenerative diseases (namely multiple sclerosis), regenerative and precision medicine.

Specifically, in 2018 we aimed to:

1. Unravel the molecular mechanisms involved in the mechanoregulation of oligodendrocyte differentiation (as a follow up study of Lourenço et al., Scientific Reports, 2016).

The BrEin-MS project (which started in 2018) has a particular focus in the context of Multiple Sclerosis (MS) and the mechanical changes reporteIn the future we also aim to provide data regarding brain elasticity of MS patients undergoing distinct treatment regimens, providing future directions for new treatments tackling such biophysical issues.

2. Test the influence of distinct laminin isoforms during the in vitro differentiation of oligodendrocytes under defined mechanical conditions.

Although laminin-211 is undoubtfully a major extracellular matrix (ECM) element reported to be involved in the differentiation of oligodendrocytes, there are hints in the literature suggesting that other laminin isoforms may also play an important and yet rather unexplored role in this context.

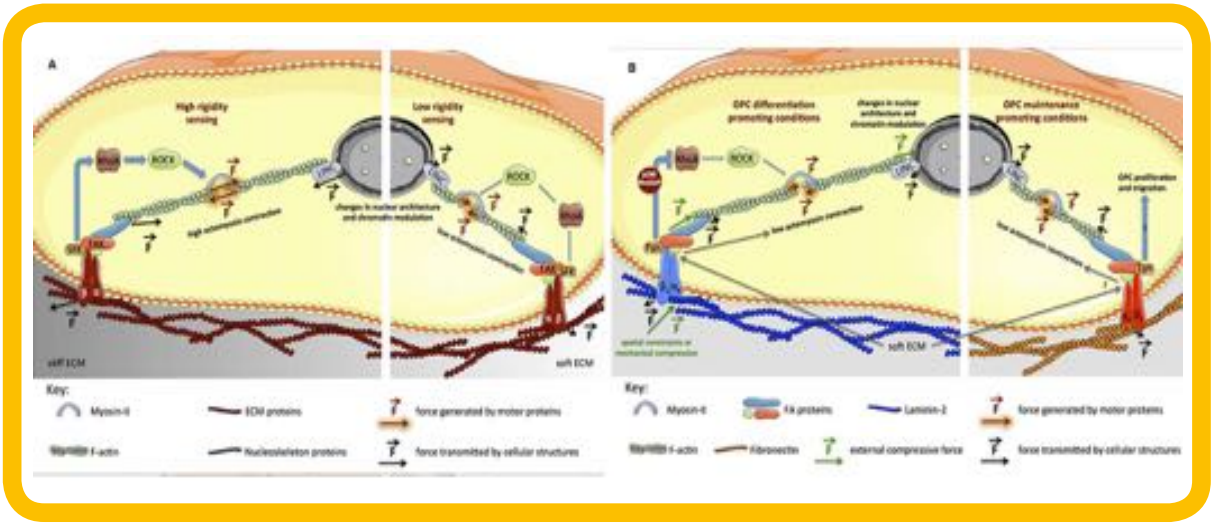
3. Address the effect of mechanical cues and understand the underlying mechanisms involved in cellular reprogramming to pluripotency.

Cellular reprogramming was a major breakthrough in the stem cell biology field.

Nevertheless, much remains to be understood regarding the underlying mechanisms and how the extracellular environment influences cell reprogramming.

4. Evaluate the effect of biophysical stimuli in the extracellular and intracellular proteome of mechanosensitive cells.

The specific objective of the former is the production of enhanced secretome for the rescue of neuronal cells, and of the latter is to further understand the mechanisms involved in cellular mechanotransduction.



The main achievements obtained during 2018 regarding the aforementioned objectives were the following:

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

2. We took advantage of distinct human recombinant laminin isoforms to setup several in vitro studies in order to understand the capacity of such ECM proteins to support the adhesion and differentiation of oligodendrocyte progenitor cells (using the rat CG4 cell line as a model).
Comparing with recombinant laminin-211 (as well as its purified counterpart), the main laminin described in oligodendrocyte biology, we found another laminin isoform (reported to be present in the CNS) that excels the capacity of the former in providing adhesion (number of cells/area) and differentiation (more MBP+ cells/area and higher morphological differentiation) of oligodendrocytes when cultured in rat brain-compliant substrates (Young's modulus of 6.5 kPa, as shown in Lourenço et al., Scientific Reports 2016 and discussed in Lourenço and Grãos, Frontiers in Cellular Neuroscience, 2016).
As future work, it remains to dissect the mechanistic details and to understand the significance of these findings, not only for the setup of in vitro oligodendrocyte differentiation platforms, but in vivo as well as. This work resulted in a MSc thesis (under embargo).

3. As part of our unpublished work, we identified two sets of proteins (by performing quantitative and unbiased proteomics analyses in collaboration with the group of Bruno Manadas, CNC) whose levels change significantly in the extracellular medium or in the intracellular milieu of MSCs (mesenchymal stem/stromal cells) cultured on substrates with distinct degrees of stiffness.
For the first part, we have used the conditioned medium (CM) of these cells and compared its ability to rescue neurons challenged with oxidative stress agents. We found an enhanced rescuing capacity of the CM obtained from cells cultured on substrates with specific mechanical conditions in comparison with that obtained from cells cultured in standard conditions (polystyrene tissue culture plates).
This suggests that the distinct mechanical properties of cell culture substrates, which resulted in changes in the composition of the conditioned media, in fact has a significant functional impact on the neuronal recuing ability of the CM.
We are currently exploiting these observations and studying the role of distinct differentially expressed proteins.
For the second part, we have focused on one of the proteins identified, which we have shown for the first time to respond to mechanical stimuli both in terms of expression level and subcellular localization.
This protein plays several important roles in the cell (both in physiology and disease), which we are currently dissecting in a context of mechanotransduction.

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.

This year the unit added the NextSeq platform (Illumina) to the other two sequencers available, MiSeq (Illumina) and Ion Proton (ThermoFisher) and validated the exome sequencing, and the genome and metagenome sequencing applications with the new sequencer. Bioinformatics analyses were also validated for these applications.

In exome sequencing, the laboratory continued the development of ExomeLoupe, a user-friendly variant interpretation software. This software was presented at ESHG18 (Milan, Italy) and ASHG18 (San Diego, USA).

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).

In 2018 the Laboratory sequenced 677 samples for external clients, in a total of 39.8 Gb. Biodiversity samples were the most requested application, with a total of 20.31 Gb sequenced. Sequencing services and bioinformatics were additionally provided for CNC users, with 135 samples sequenced and a total of 76.5Gb.

NextSeq, Illumina

Research Papers

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Cerqueira, T., C. Barroso, H. Froufe, C. Egas, and R. Bettencourt. "Metagenomic Signatures of Microbial Communities in Deep-Sea Hydrothermal Sediments of Azores Vent Fields." Microbial Ecology, 2018. doi:10.1007/s00248-018-1144-x.

Gonçalves, M.T.P., M.J. Benito, M.d.G. Córdoba, C. Egas, A.V. Merchán, A.I. Galván, and S. Ruiz-Moyano. "Bacterial Communities in Serpa Cheese by Culture Dependent Techniques, 16S RRNA Gene Sequencing and High-Throughput Sequencing Analysis." Journal of Food Science, 2018. doi:10.1111/1750-3841.14141.

Margesin, R., D.-C. Zhang, L. Albuquerque, H.J.C. Froufe, C. Egas, and M.S. Da Costa. "Lysobacter silvestris Sp. Nov., Isolated from Alpine Forest Soil, and Reclassification of Luteimonas tolerans as Lysobacter tolerans Comb. Nov." International Journal of Systematic and Evolutionary Microbiology 68, no. 5 (2018). doi:10.1099/ijsem.0.002710.

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Pinto, Cátia, Susana Sousa, Hugo Froufe, Conceição Egas, Christophe Clément, Florence Fontaine, and Ana C. Gomes. "Draft Genome Sequence of Bacillus amyloliquefaciens subsp. plantarum strain Fito-F321, an Endophyte Microorganism from Vitis vinifera with Biocontrol Potential." Standards in Genomic Sciences, 2018. doi:10.1186/s40793-018-0327-x.

Ramos, A.M., A. Usié, P. Barbosa, P.M. Barros, T. Capote, I. Chaves, F. Simões, et al. "The Draft Genome Sequence of Cork Oak." Scientific Data 5 (2018). doi:10.1038/sdata.2018.69.

MitoXT Services Laboratory

Coordinator: Paulo Oliveira

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 that demonstrate toxicity to that intracellular organelle 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 Background

Know-how in cell and mitochondrial metabolism and toxicology, standard and verified protocols that can be adapted to high-throughput screening.

Technology

Seahorse XF96 Extracellular flux Analyzer; Cytation 3 Multiplate Reader, CETICS TOXXs 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.

Team: Paulo Oliveira (Coordinator) ,Teresa Oliveira and Vilma Sardão.

Life Sciences Mass Spectrometry - LSMS

Coordinator: Bruno Manadas

MAIN ACHIEVEMENTS

During 2018 the LSMS 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 and beginning of a PAC project, both 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 are being implemented (becoming therefore the only ISO 9001 certified research mass spectrometry lab in Portugal).

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.

Services and Cores at IBILI

ANIMAL FACILITY

Coordinator: Flávio Reis, PhD (freis@fmed.uc.pt)

The animal facility at IBILI-Sub-Unidade 1 da FMUC is a licensed establishment for the use and breeding of animals (rodents). All procedures are performed in accordance with national laws and European guidelines on laboratory animal welfare. The animal facility works closely with the Animal Welfare Authority (ORBEA) and all projects and researchers at IBILI using experimental animals must have certification and/or approval by the national authority regulating the sector, the General Directorate of Food and Veterinary (DGAV). The animal facility provides technical support to FMUC's research and teaching activities involving experimental animals.

LABCAR – HIGH-RESOLUTION BIOIMAGING LAB

Head of Unit: Henrique Girão (hmgirao@fmed.uc.pt)

Staff: Mónica Zuzarte - Technician (mzuzarte@uc.pt)

The High-Resolution Bio-Imaging Laboratory is a technological platform managed by the Faculty of Medicine of the University of Coimbra (FMUC). The LABCAR is part of the National Network of Electron Microscopy (Pole of the University of Coimbra - RNME) and the only infrastructure with a transmission electron microscopy (TEM) specially dedicated to applications in Health Sciences in the central region of Portugal. The LABCAR equipments, including TEM, confocal and fluorescence microscopes, are available to researchers of the University of Coimbra as well as others from external academic institutions, hospitals and companies.
The LABCAR provides technical support on several microscopical techniques including live imaging, immunogold labeling and correlative studies.

EQUIPMENT:

Leica ultramicrotome with a cryo unit (EM UC6 and EM FC)

Fluorescence microscope Zeiss Axio Observer.Z1

FEI-Tecnai G2 Spirit Biotwin transmission electron microscope operating up to 120 kV

Confocal Microscope Zeiss LSM 710 which includes 3 R7FL spectral channels, 5 laser lines: 458, 488, 514, 561 and 633

ELECTROENCEFALOGRAPHY / EVOKED POTENTIALS

The future of sensory neuroscience in humans is highly dependent on multimodal methodological approaches to study brain function. This multidisciplinary project aims to take advantage of already existing know-how and equipment - psychophysical laboratories and techniques to study brain structure and function (MRI, SPECT, soon PET) – and integrate them with high-resolution electrophysiology to study sensory and motor function.

A major goal is to study mechanisms of visual perception of movement and shape, by mapping electrophysiological responses to conditions defined by motion, colour, orientation or texture contrast, and relating them to results obtained from other strategies of functional mapping.

Models of visuomotor integration will be studied in normal populations and in Parkinson Disease.

Further, neural mechanisms of visual and auditory plasticity will be compared in normal individuals and patients (some with sensory prosthesis), as well as implications for rehabilitation.

Equipment

High-density human electrophysiology amplifiers and workstation

This is a EEG/ERP data acquisition and signal processing system essential for receiving , conditioning, and processing the signals from EEG electrodes (SYNAMPS DC/AC 4*32 channels amplifiers with high-speed A/D and NeuroScan EEG/ERP Workstation (Scan,computer, card)).

The high number of acquisition channels is required to add spatial resolution to the high temporal resolution signal and allow for localization of sources of activity in the brain.

High-density electrode arrays and acessories

High-density array caps of electrodes, that come in different sizes (children to adult) and render possible faster subject preparation for simultaneous recordings with many electrodes.

This is an absolute requirement for high-density recordings.

Acessories include rechloriding equipment and electrodes.

Software for co-registration of different techniques (EEG, PET, fMRI) and source localization

This software integrates multiple, complementary image modalities (EEG and MEG; MRI, fMRI or CT). By combining the latest techniques for measuring electrical activity in the brain with anatomical and functional imaging, it provides a powerful new method for accurately localizing the source of such activity. The software uses the full physical anatomy from MR and CT to build individualized three-dimensional models of the skull and brain, which are critical in pinpointing the site of neural activity. It integrates functional imaging such as fMRI with EEG and MEG source reconstruction. to allow the comparison of results and to enhance the accuracy of solutions.

Visual and auditory stimulation software and hardware

STIM is a combination of hardware and software which can present audio and visual stimuli to subjects. The system is fully programmable and allows for any imaginable combination of stimuli. TTL outputs guarantee synchronisation with EEG/EP workstations, which renders this equipment essential for studies in sensory neuroscience.

Eye Tracker to integrate with visual stimulation

This equipment allows to measure eye position in relation to the viewed image and to synchronize the acquisition with behavioural responses and EEG.

Digitizer for 3D localization of electrodes and fiduciary head landmarks

The FASTRAK digitizer helps establishing 3D localization of electrodes and fiduciary head landmarks for coregistration of EEG measurements with images from MRI, CT, or PET.

Reservation and Contact

Conditions for the Utilization of the Equipment:

For Researchers of the Participating Institutions: The time allocation of usage will be managed by the members of the Visual Psychophysiology Lab (IBILI – Fac. of Medicine).
This lab will provide technical support for the running of experiments by all groups that will involved in collaborative research (see list above).

but each group is responsible for experimental design and costs with materials required for the experiments
For Researchers of Other Institutions: Groups that do not belong to the list of groups involved in collaborative research, can use the facility, but will have to pay for technical support in setting up the experiment as well as costs with materials required for the experiments.
Furthermore, time usage will be constrained by time remaining from the usage of groups involved in the project, and will be negotiated with the managing lab (Visual Psychophysiology Lab).

Prices
175 € + IVA 20% per hour including technician.

Contact:
Prof. Miguel Castelo-Branco
Tel: +351 239480200
Email: mcbranco@fmed.uc.pt

Managed and funded by FCT (Foundation for Science and Technology), under the National Program for Scientific Re-equipment (PNRC), co-funded by POCI2010, source FEDER

LABORATORY OF BIOSTATISTICS AND MEDICAL INFORMATICS

The Laboratory for Biostatistics and Medical Informatics is a part of the Faculty of Medicine of the University of Coimbra. It is dedicated to research, teaching and scientific collaboration in Biostatistics.

Services
We offer scientific collaboration in study design and statistical analysis. Throughout the year we also organise a large number of courses on statistics.

Courses
We currently offer a number of courses, see the full list here (in Portuguese).

In this page only courses in English are listed. We are open to organising courses upon request.

Staff
Scientific Coordinator:
Miguel Castelo-Branco, MD. Ph.D

Teaching and Research Staff and collaborators:
Bárbara Oliveiros, Ph.D.
Francisco Caramelo, Ph.D.
Margarida Marques, B.Sc.
Marisa Loureiro, M.Sc.
Otília Cardoso d'Almeida, Ph.D.

Administrative Staff:
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- **Auditorium**

The auditorium named "Prof. Dr. João José Pedroso Lima" is located at the IBILI Building with 80 seats equipped with computer and microphone.

Funding at CNC

In 2018 funding of "Laboratório Associado – Centro de Neurociências e Biologia Celular" ascended the amount of 6.469,970,12€.

The main financing contribution was made by "Fundação para a Ciência e Tecnologia (FCT)", concerning global institution programs and national projects, namely amount of 5.267.766,44€ distribuited as follows:

Strategical Project_ UID/NEU/04539/2013	2.338.029,58€
Projects:	2.373.116,79€
Science Program:	556.620,07€

The related items supported the main part of Center for Neuroscience and Cell Biology expenses during 2018.

Besides Center for Neuroscience is financed by other national and international agencies. In 2018 Center for Neuroscience received the amount of 1.089.463,87€

Services is another important vector of our institution which ascends 764.695,61€.

In the following are listed FCT ongoing projects as well as other national and international projects.

Note: Financing values are based on expenditure values 2018

Ongoing Projects

TITLE	FINANCING AGENCY	STARTING Date	ENDING DATE	BUDGET	EXPENDITURE
UID/NEU/04539/2013 - COORDINATOR: João Ramalho de Sousa Santos - PROPONENTE: Universidade Coimbra - PARTICIPANTS: CNBC, IBILI	Fundação para Ciência e a Tecnologia - REF. UID/NEU/04539/2013	01/01/2015	31/12/2018	8169962,33 €	2338029,58 €
Sub-Total Strategical Projet					**2 338 029,58 €**
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 €	18 042,40 €
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	01/07/2019	17 200,00 €	0,00 €
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 €	32 924,38 €

Exossomas libertados de celulas estaminais pluripotentes induzidas - impacto na (dis) função mitocondrial na Doença de Huntington e potencial sistema - COORDINATOR: Ildete Ferreira	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-032316	06/07/2018	05/07/2021	235 334,58 €	235 334,58 €
Exossomas libertados de celulas estaminais pluripotentes induzidas - impacto na (dis)função mitocondrial na Doença de Huntington e potencial sistema para distribuição de terapêutica baseada em microRNA - COORDINATOR: Ana Cristina Carvalho Rego	Exossomas libertados de celulas estaminais pluripotentes induzidas - impacto na (dis)função mitocondrial na Doença de Huntington e potencial sistema para distribuição de terapêutica baseada em microRNA - COORDINATOR: Ana Cristina Carvalho Rego	06/07/2018	05/07/2021	238 749,98 €	27 314,46 €
"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 €	27 661,48 €
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	Fundação para Ciência e a Tecnologia - REF. CANCEL STEM	01/01/2017	31/12/2019	523 881,28 €	222 976,04 €

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 €	8 192,30 €
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	01/06/2018	237 446,80 €	16 957,27 €
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 €	2 877,82 €
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	203 025,04 €	18 077,42 €
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	26/07/2018	238 743,45 €	6 648,13 €

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 €	2 497,19 €
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 €	0,00 €
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	01/09/2018	106 997,37 €	27 883,97 €

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 €	100 955,61 €
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	239 694,84 €	18 098,61 €
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 €	5 727,55 €
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	01/07/2018	01/07/2018	238 749,59 €	21 482,09 €

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 €	26 645,43 €
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	238 600,73 €	23 517,63 €
O papel do metabolismo extra-hepático da frutose no desenvolvimento de doença hepática - 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 €	4 781,37 €
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 €	32 510,44 €

Papel e mecanismos da propagação da sinucleina e da ataxina-3 nas doenças de Parkinson e Machado-Joseph' - COORDINATOR: Luis Pereira de Almeida	Fundação para Ciência e a Tecnologia - REF. JPND-CD/0001/2013	01/03/2015	31/12/2018	150 000,00 €	20 111,06 €
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	199 998,00 €	43 012,15 €
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	30/09/2019	175 000,00 €	42 041,17 €
"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 €	490,10 €
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 €	78 002,47 €
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	31/05/2021	237 976,10 €	17 074,61 €

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 €	29 928,83 €
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 €	2 352,00 €
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 €	34 867,79 €
"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 €	10 847,87 €

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 €	10 285,78 €
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 €	18 492,18 €
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 €	2 497,02 €
Doenças cognitivas como sinaptopatias: Impacto de mutações humanas no 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 €	22 567,18 €

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	38 600,00 €	0,00 €
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 €	20 802,03 €
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 €	6 157,06 €
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 €	0,00 €

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 €	42 430,38 €
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 €	34 683,08 €
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 €	26 321,69 €
Cartilfactory - Desenvolvimento e Construção de um Sistema Automatizado de Fabricação em Larga Escala de Engenharia de Cartilagem Combinando 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	70 234,45 €	2 353,18 €

Mecanismos sinápticos envolvidos nas acções dos canabinoides no cérebro e sua modulação por receptores de adenosina: implicações para a regulação do h - 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 €	2 109,62 €
CARDIOSTEM: Tecidos cardíacos e terapias baseadas em células estaminais para aplicações cardiovasculares - COORDINATOR: Lino da Silva Ferreira - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: AISTID; INEB; FMV-UTL; IBET;	Fundação para Ciência e a Tecnologia - REF. MITP-TB/ECE/0013/2013	01/12/2014	31/05/2018	405 316,00 €	40 433,75 €
Diagnóstico e prognóstico da esquizofrenia: a caminho de uma medicina personalizada? - COORDINATOR: Bruno José F. O. Manadas	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-SCC/7051/2014	01/06/2016	01/06/2019	199 857,00 €	55 348,60 €
"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 €	12 375,17 €

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 €	47 010,14 €
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 €	81 312,76 €
IF/01007/2015 - COORDINATOR: Henrique Manuel S. Faneca	Fundação para Ciência e a Tecnologia - REF. IF/01007/2015	01/07/2017	31/10/2021	50 000,00 €	14 680,21 €
Arcadelike - Desenvolvimento da Arquitectura Fisiológica do colagénio em cartilagem - 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 €	48 553,41 €

"Recetores ionotrópicos híbridos: um novo conceito de recetor" - COORDINATOR: Ricardo Jorge A. Rodrigues	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-NMC/3567/2014	01/05/2016	31/10/2018	199 418,72 €	27 051,90 €
Red2Discovery- As macroalgas vermelhas Sphoerococcus Coronopifolius e Asparagopsis armata como alvos para a descoberta de novos fármacos - 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	31/05/2019	26 700,00 €	786,97 €
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 €	7 215,11 €
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 €	7 500,02 €

MitoCIN .: Desenvolvimento de antioxidantes mitocondriais baseados em derivados do ácido cinnamico - COORDINATOR: Paulo Jorge G. S. S. Oliveira	- REF. CENTRO-01-0145-FEDER-037586	12/01/2018	31/12/2020	48 161,27 €	0,00 €
MitoBEN - COORDINATOR: Paulo Jorge G. S. S. Oliveira	Fundação para Ciência e a Tecnologia - REF. CENTRO-01-0145-FEDER-037892	01/01/2018	31/12/2020	47 140,37 €	5 454,78 €
Uso de fitoquímicos redox-activos para desencadear a hormesis mitocondrial: Desenvolvimento de uma nova geração de ingredientes para a cosmética - COORDINATOR: Marta Sofia Marques Simões - PROPONENTE: Centro de Neurociências e Biologia Celular - PARTICIPANTS: UP	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028607	26/07/2018	25/07/2021	159 006,95 €	0,00 €
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 €	29 313,98 €

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 €	15 260,48 €
IF/00812/2012/CPO151/CT0001 - COORDINATOR: João Peça Silvestre	Fundação para Ciência e a Tecnologia - REF. IF/00812/2012/CPO151/CT0001	01/07/2013	31/01/2018	50 000,00 €	0,00 €
"Hierarquia social e adversidades no período juvenil: regulação neuroepigenética e modulação optogenética dos circuitos do cortex pré-frontal". - COORDINATOR: João Peça Silvestre - PROPONENTE: CNBC - PARTICIPANTS:	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-SCC/3247/2014	01/04/2016	01/10/2019	198 205,00 €	50 769,32 €
IF/01302/2012 - COORDINATOR: Paulo César da Silva Pinheiro	Fundação para Ciência e a Tecnologia - REF. IF/01302/2012	01/10/2013	30/09/2018	50 000,00 €	25 291,72 €
IF/00123/2013 - COORDINATOR: Ricardo Simão Vieira Pires	Fundação para Ciência e a Tecnologia - REF. IF/00123/2013	15/12/2013	14/12/2018	50 000,00 €	509,59 €
IF/00694/2013 - COORDINATOR: Miguel Luís Cunha Mano	Fundação para Ciência e a Tecnologia - REF. IF/00694/2013	01/07/2014	28/02/2018	50 000,00 €	12,00 €
Combinação de high-throughput screening e análise single-cell para o estudo de RNA regulatórios envolvidos nas etapas iniciais de infecção campylobac - COORDINATOR: Miguel Luís Cunha Mano	Fundação para Ciência e a Tecnologia - REF. Infect-ERA/0001/2014	01/04/2015	31/12/2018	124 980,00 €	47 235,90 €

"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 €	59 554,12 €
Staphylococcus aureus intracelular: identificação de factores bacterianos e celulares envolvidos na invasão do hospedeiro por estirpes clinicamente relevantes - COORDINATOR: Miguel Luís Cunha Mano	Fundação para Ciência e a Tecnologia - REF. Infect-ERA/0001/2015	01/10/2016	30/09/2019	106 233,00 €	16 070,68 €
IF/00578/2014/CP1258/CT0002 - COORDINATOR: Irina Moreira	Fundação para Ciência e a Tecnologia - REF. IF/00578/2014/CP1258/CT0002	15/01/2015	14/01/2020	50 000,00 €	25 536,58 €
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 €	31 612,42 €
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	31/05/2019	199 999,00 €	26 079,69 €
"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	30/03/2019	170 244,00 €	50 841,29 €

"Regulação de mecanismos de plasticidade homeostática dependente de experiência pelas proteínas Contactin-associated protein 1 e 2". - COORDINATOR: Susana Louros	Fundação para Ciência e a Tecnologia - REF. PTDC/NEU-NMC/4888/2014	31/03/2016	30/09/2018	199 623,21 €	40 033,05 €
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 €	66 237,29 €
" 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	31/12/2019	60 636,00 €	25 117,58 €
"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	30/06/2019	10 800,00 €	4 640,83 €

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 €	7 770,49 €
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 €	28 527,83 €
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 €	35,40 €
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 €	14 469,86 €
IF/01105/2015 - COORDINATOR: Ana Sofia Bregieiro Eulálio	Fundação para Ciência e a Tecnologia - REF. IF/01105/2015	01/07/2017	01/07/2021	50 000,40 €	6 732,91 €
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 €	21 566,34 €
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 €	29 141,54 €
Contribuição dos Fatores Psicológicos na Cura da Úlcera do Pé Diabético, em Indicadores Fisiológicos de Prognóstico de Cura e Qualidade de Vida - 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 €	1 117,51 €

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	01/06/2018	14/06/2021	137 134,94 €	17 082,88 €
Métodos verdes para preparar aerogel esterlizado 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	29 849,55 €	0,00 €
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 €	31 589,96 €
Identificação e caracterização funcional de microRNAs que regulam a infecção por estirpes de Staphylococcus aureus clinicamente relevantes. - COORDINATOR: Ana Sofia Bregieiro Eulálio	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029999	26/07/2018	25/07/2021	234 226,71 €	0,00 €

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 €	15 318,44 €
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 €	15 566,14 €
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 €	1 353,16 €
BrainEdition:controlo remoto da edição genética em celulas estaminais neurais. - COORDINATOR: Sónia Pinho	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-028060	22/06/2018	21/06/2021	239 947,07 €	27 634,13 €
Uma biblioteca de nanoparticulas activáveis por acção da luz para a libertação de terapias baseadas em RNA - COORDINATOR: Vitor Francisco	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029414	06/07/2018	05/07/2021	238 697,08 €	27 478,44 €

Vacina Terapêutica para a Hepatite B crónica: Desenvolvimento de nanopartículas à base de glucano com o objectivo de direccionar os antigénios 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 €	17 247,02 €
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 €	16 848,38 €
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 €	28 229,21 €
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 €	7 274,86 €
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 €	7 495,94 €

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 €	121,46 €
Propriedades viscoelásticas do cérebro em Esclerose Multipla e implicações em mecanomodulação de oligodendrócitos: uma abordagem celular e clínica - COORDINATOR: Mário Grãos -	Fundação para Ciência e a Tecnologia - REF. POCI-01-0145-FEDER-029516	26/07/2018	25/07/2021	192 615,36 €	20 322,04 €
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 €	10 554,60 €
Alvejamento de transportadores de aminoácidos cationicos para radioteranóstica do cancro: uma abordagem experimental e de quimica computacional - COORDINATOR: Irina Moreira - PROPONENTE: IST-ID - PARTICIPANTS: CBNC	Fundação para Ciência e a Tecnologia - REF. PTDC/QUI-NUC/30147/2017	01/09/2018	31/08/2021	23 449,35 €	0,00 €
Proteínas Membranares - desenvolvimento de novas técnicas de modelação computacional e sua aplicação ao estudo dos recetores acoplados a proteína - 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 €	17 672,03 €

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 €	12 810,02 €
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 €	0,00 €
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	356 157,06 €	56 465,62 €
PPBI_Portuguese Platform of Biolmaging - COORDINATOR: Luisa Maria O. P. L. Cortes - PROPONENTE: Instituto de Biologia Molecular e Celular	IBMC - REF. Rede PPBI - Dra. Luisa Cortes	01/06/2017	30/05/2020	275 180,00 €	25 971,45 €

Sub-Total FCT Projects					**2 373 116,79 €**
Programa Investigador FCT - COORDINATOR: Catarina Isabel N. R. Oliveira	Fundação para Ciência e a Tecnologia-REF. Programa Investigador FCT_2ª edição	08/05/2013	31/05/2019	1 203 584,00 €	134 867,61 €
Programa Investigador FCT 2014 - COORDINATOR: João Ramalho de Sousa Santos	Fundação para Ciência e a Tecnologia - REF. Programa Investigador FCT 2014_3ª edição	01/01/2015	25/01/2020	1 951 567,79 €	43 736,19 €
Programa Investigador FCT_4ª e - COORDINATOR: João Ramalho de Sousa Santos	Fundação para Ciência e a Tecnologia - REF. Programa Investigador FCT_4ª edição	01/11/2016	25/11/2021	2 065 304,67 €	378 016,27 €
Sub-Total Science Program					**556 620,07 €**
LifeSciences ByCENTRO: Valorização do Conhecimento em Ciências da Vida - COORDINATOR: João Ramalho de Sousa Santos	Instituto Financeiro para o Desenvolvimento Regional - REF. LifeSciences ByCENTRO	27/03/2017	26/03/2019	213 123,88 €	32 736,27 €
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	31/12/2019	11 186,27 €	2 599,82 €
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	30/09/2019	50 000,00 €	11 362,59 €
Combination therapy synergistically accelerates diabetic wound - COORDINATOR: Eugénia Maria L. Carvalho	EFSD-Europ. Found. S. Diabetes - REF. EFSD-Microvascular Complicatio	09/11/2015	31/12/2019	70 000,00 €	8 120,05 €

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	- REF. MATERA_5402	01/09/2010	31/12/2018	27 820,88 €	2 205,55 €
Peripheral NPY reverts HGPS phenotype: a study in human fibroblasts and mouse model - COORDINATOR: Cláudia Margarida G. Cavadas	Progeria Research Foundation - REF. Progeria - Peripheral NPY	01/09/2015	30/06/2018	107 000,00 €	0,00 €
Promoting endothelial progenitor cell function in diabetic would healing - COORDINATOR: Ermelindo Carreira Leal	European Foundation for the Study of Diabetes/JDRF/Novo Nordisk European Programme in Type 1 Diabetes Research	01/01/2013	31/12/2019	50 000,00 €	1 167,07 €
Evaluate novel calpain inhibitors from Blade Therapeutics - COORDINATOR: Luis Pereira de Almeida	Blade Therapeutics - REF. Blade	19/07/2018	18/07/2019	140 000,00 €	1 049,57 €
The transplantation of induced pluripotent stem cells (IPSC) - derived neural sem cells (NSC) in Machado-Joseph disease (MJD) - COORDINATOR: Liliana Mendonça	National Ataxia Foundation - REF. The transplantation of IPSC-derived neural stem cells (NSC) in Machado_Joseph disease (MJD)	01/01/2016	30/07/2018	13 673,78 €	389,18 €
Does the transplantation of mutant ataxin-3 - depleted patient-derived NSC alleviates Machado Joseph disease (MSD) - COORDINATOR: Liliana Mendonça	AFM - Association Française contre les Myopathies	02/05/2016	03/07/2018	49 000,00 €	30 579,07 €

Silencing Machado-Joseph Disease/ Spinocerebellar ataxia type 3 trough the systemic route - COORDINATOR: Rui Jorge Gonçalves P. Nobre	National Ataxia Foundation	31/12/2013	31/12/2019	10 823,71 €	671,84 €
Exosomes as gene delivery vectors for the treatment of Machado-Joseph disease/ spinocerebellar ataxia type 3 - COORDINATOR: Rui Jorge Gonçalves P. Nobre	AFM - Association Française contre les Myopathies	14/03/2017	31/12/2018	45 000,00 €	37 121,36 €
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 €	14 189,05 €
"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	31/12/2019	71 495,56 €	4 030,11 €
"In chemico, in silico and in vitro modelling to predict human respiratory allergens" - COORDINATOR: Maria Teresa T. Cruz Rosete	The Johns Hopkins University - REF. In chimico in silico-2014-07	05/02/2014	28/02/2018	48 445,22 €	2 823,12 €
W81XWH-18-1-0532_ Adenosine Receptor Antagonism Affords Integrated Benefits for Neurological Symptoms of Neurological Symptoms of Neurofibromatosis Typ - COORDINATOR: Rodrigo Pinto S. A. Cunha	Army Medical Research - REF. W81XWH-18-1-0532_Adenosine Receptor	15/09/2018	14/09/2019	99 714,38 €	0,00 €

Schizophrenia as a Disruption of Developmental Homeostatic Plasticity: A Role for Stargazin - COORDINATOR: Ana Luisa Monteiro de Carvalho	Brain & Behavior - REF. 2015 NARSAD Indep Investigat Grant	15/09/2015	19/09/2018	79 372,06 €	7 708,61 €
Behavior, electrophysiological and brain imaging analyses of mice expressing a CACNG2 mutation associated with intellectual disability" - COORDINATOR: Ana Luisa Monteiro de Carvalho	Fondation Jérôme Lejeune - REF. Behavior, electrophysiological...	08/07/2016	09/07/2018	26 000,00 €	14 084,26 €
"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 €	37,00 €
The changing brain in Alzheimer´s disease: is the retina a reliable mirror of disease onset progression? - COORDINATOR: António F. R. G. Ambrósio - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC	Universidade de Coimbra - REF. Prémio Mantero Belard 2015	01/01/2016	31/12/2018	45 240,00 €	13 766,11 €
Multiple Sclerosis_ RG-1601-075 - COORDINATOR: Carlos Jorge A. M. B. Duarte	National Multiple Sclerosis - REF. Multiple Sclerosis_ RG-1601-075	01/10/2016	30/09/2019	149 762,29 €	40 941,99 €
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	31/12/2019	199 098,00 €	62 629,38 €
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 €	21 025,88 €

Calpain-mediated proteolysis in Machado-Joseph disease - COORDINATOR: Ana Teresa Antunes Simões	National Ataxia Foundation - REF. Calpain-mediated proteolysis...	01/01/2017	31/12/2018	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 €	28 716,24 €
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 €	19 237,00 €
Santhera - COORDINATOR: Maria Manuela Monteiro Grazina	Santhera Netherlands - REF. Optic Nerve Atrophy_Santhera	01/07/2018	30/06/2020	63 999,98 €	12 667,45 €
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 €	11 172,38 €
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 €	19 117,39 €
Bolsa PMJMCD2017 - COORDINATOR: Rodrigo Pinto S. A. Cunha	Fundação Amélia de Mello - REF. Bolsa PMJMCD2017	01/01/2018	31/12/2019	25 000,00 €	16 537,29 €

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 €	1 292,07 €
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	31/12/2018	2 000,00 €	563,60 €
Paulo Cesar da Silva Pinheiro - COORDINATOR: Paulo César da Silva Pinheiro	Fundação Calouste Gulbenkian - REF. Paulo Cesar da Silva Pinheiro	01/01/2005	31/12/2018	10 000,00 €	319,44 €
3º Simpósio International PDBE - COORDINATOR: João Ramalho de Sousa Santos	- REF. 3º Simpósio International PDBE	01/07/2016	31/12/2018	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	31/12/2018	20 000,00 €	0,00 €
Human Chromaffin Cells and NPY - COORDINATOR: Cláudia Margarida G. Cavadas	- REF. Human Chromaffin Cells and NPY	20/11/2002	31/12/2018	5 851,58 €	0,00 €
Prémio em Obesidade Abbott/SPE - COORDINATOR: Cláudia Margarida G. Cavadas	SPEDM - REF. Prémio em Obesidade Abbott/SPE	20/03/2009	31/12/2018	5 000,00 €	0,00 €
Tecnimede - REMANESCENTE - COORDINATOR: Cláudia Margarida G. Cavadas	- REF. Tecnimede - REMANESCENTE	01/10/2014	31/12/2018	7 918,01 €	0,00 €
ESCI 2014 - COORDINATOR: Paulo Jorge G. S. S. Oliveira	ESCI - REF. ESCI 2014	01/12/2014	30/09/2018	527,30 €	0,00 €

Fens Course 2017 - COORDINATOR: Paulo Jorge G. S. S. Oliveira	Fundação Luso-Americana - REF. Febs Course 2017	01/06/2017	01/06/2018	800,00 €	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	31/12/2018	5 000,00 €	1 168,36 €
Modulation of autophagy as a novel therapeutic strategy for Machado-Joseph diseas - COORDINATOR: Luis Pereira de Almeida	National Ataxia Foundation - REF. National Ataxia Foundation	01/01/2010	31/12/2018	10 400,01 €	100,00 €
Terapia Machado Josefh - COORDINATOR: Luis Pereira de Almeida	- REF. Terapia Machado Josefh	01/01/2012	31/12/2018	7 031,75 €	0,00 €
Mini-Simposyum 'Vaccines and A - COORDINATOR: Olga Maria Fernandes R. Borges	NOVARTIS FARMA S.A. - REF. Mini-Simposyum Vaccines	01/03/2011	31/12/2018	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 €	6 395,99 €
APU/ASTELLAS 2011 - COORDINATOR: João Nuno Sereno de A. Moreira	APU - REF. APU/ ASTELLAS 2011	25/07/2012	31/12/2018	7 000,00 €	57,54 €
EFSD - European Foundation Study Di - COORDINATOR: Eugénia Maria L. Carvalho	EFSD-Europ. Found. S. Diabetes - REF. Saldos Fundos EFSD transitados	09/01/2013	31/12/2019	16 960,43 €	2 571,57 €
AsHeCe - Marta Pereira - COORDINATOR: João Nuno Sereno de A. Moreira	- REF. AsHeCe - Marta Pereira	01/01/2013	31/12/2018	8 000,00 €	0,00 €
Bolsa Cient. LPCE2014 Miranda M - COORDINATOR: Carlos Jorge A. M. B. Duarte	Liga Port. contra Epilepsia - REF. Bolsa Cient.LPCE2014 Miranda M	31/03/2014	31/12/2018	3 500,00 €	0,00 €

Fundos FBG - COORDINATOR: Maria Manuela Monteiro Grazina	Sanofi aventis, Lda. - REF. Fundos LBG	10/12/2013	31/12/2018	16 938,51 €	3 148,34 €
Fundos Obesidade - COORDINATOR: Maria Manuela Monteiro Grazina	Sanofi aventis, Lda. - REF. Fundos Obesidade	01/06/2017	31/12/2018	10 000,00 €	7 741,14 €
GIFT2014_Ana Burgueiro - COORDINATOR: Ana Adelaide Burgeiro / Eugénia Carvalho	EFSD-Europ. Found. S. Diabetes - REF. GIFT2014_Ana Burgueiro	01/05/2014	31/12/2018	2 679,87 €	367,94 €
Bial - COORDINATOR: Inês Maria Pombinho de Araújo	Bial - REF. Bial	01/09/2014	31/12/2018	15 293,99 €	2 804,64 €
Exocord - REMANESCENTE - COORDINATOR: Lino da Silva Ferreira	Ciência Viva - REF. Exocord - REMANESCENTE	01/01/2017	31/12/2018	32 458,67 €	2 274,99 €
DAAD - 2015/2016 - Isaura Simõ - COORDINATOR: Isaura I. Gonçalves Simões	Fundação para Ciência e a Tecnologia - REF. DAAD - 2015/2016 - Isaura Simões	05/02/2015	31/08/2018	4 000,00 €	0,00 €
Livro de Neurociências - COORDINATOR: Ana Cristina Carvalho Rego	European Commission - 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	31/12/2018	1 135,00 €	1 030,29 €
A lipidomic and miRNA-based strategy for glioblastoma treatment - COORDINATOR: Mª Conceição Pedroso Lima	IBMC - REF. Prog. Ações Integ. Luso-Alemãs	01/01/2016	31/10/2018	4 000,00 €	699,60 €
EMBO 3145 - COORDINATOR: Ana Sofia Bregieiro Eulálio	EMBO - REF. EMBO 3145	01/04/2017	31/12/2019	13 919,00 €	680,41 €
FAPESP - COORDINATOR: Attila Köfalvi	REF. FAPESP	01/09/2017	31/12/2018	2 140,00 €	400,17 €

Prémio 2º lugar no concurso Janssen Inovação 2018 - COORDINATOR: Sara Silva	Janssen-Cilag - REF. Prémio 2º lugar no concurso Janssen Inovação 2018	17/05/2018	31/12/2018	20 000,00 €	7 180,00 €
Astrazeneca - iMed Conference 10.0 - COORDINATOR: Rodrigo Filipe Nunes Ribeiro	Fundação Astrazeneca - REF. Astrazeneca - iMed Conference 10.0	01/11/2018	31/12/2019	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 €	1 644,13 €
EMBO_Wiley - COORDINATOR: Ana Sofia Bregieiro Eulálio	EMBO - REF. EMBO_ Wiley	01/11/2018	30/11/2018	5 782,00 €	5 781,00 €
Ocupação Científica de Jovens nas Férias 2018	Ciência Viva - REF. Ciência Viva 2018	01/05/2018	30/12/2018	3 576,00 €	3 544,35 €
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 €	712,11 €
Semana do cérebro 2018 - BAW project 2018 - COORDINATOR: Sara Varela Amaral	FENS - REF. Semana do cérebro 2018 - BAW project 2018	15/02/2018	31/12/2018	1 000,00 €	741,79 €
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 €	354,30 €
14º Edição do Programa Doutoral PDBEB - COORDINATOR: João Ramalho de Sousa Santos	Bluepharma - REF. 14º Edição do Programa Doutoral PDBEB	01/01/2018	31/12/2018	500,00 €	0,00 €

FENS and IBRO-PERC Support for Graduate Courses in 2018 - COORDINATOR: Ana Luisa Monteiro de Carvalho	FENS - REF. FENS IBRO-PERC	01/02/2018	30/06/2019	6 000,00 €	4 355,76 €
Novas terapias para Doença de Chagas: reposicionamento de drogas com efeito sinergístico com Benzonidazol para combater infecção por Trypanosoma - COORDINATOR: Miguel Luis Cunha Mano	Fundação para Ciência e a Tecnologia - REF. FCT/ CAPES-2018/2019	16/04/2018	30/04/2019	4 500,00 €	2 771,55 €
Estudo da expressão de microRNAs por células da microglia infectadas pelo vírus zika. - COORDINATOR: Ana Luisa Colaço Cardoso	Gustavo Adolfo Arganaraz - REF. microRNAs_Gustavo	01/05/2018	30/04/2019	2 567,78 €	2 675,25 €
METAFLUIDICS - Advanced toolbox for rapid and cost-effective functional metagenomic screening - microbiology meets microfluidics - COORDINATOR: Milton Simões da Costa	Univ. Autónoma Madrid - REF. GA 685474 BIOTEC-6-2015 Metafluidics	01/06/2016	31/05/2020	407.590,00	33 795,00 €
TRoMBONE - 748583 "Therapy for regeneration of Heart Muscle based on targeted delivery of exosomoes." - COORDINATOR: Lino da Silva Ferreira	Research Executive Agency - REF. TRoMBONE - 748583	01/04/2017	31/03/2019	160 635,60 €	79 610,35 €

Foie Gras_722619 "Foie Gras: Bioenergetic remodeling in the pathophysiology and treatment of non-alcoholic fatty liver disease" - 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	890 860,21 €	232 682,74 €
Rise Foie Gras_734719 "Non-invasive Profiling of Mitochondrial Function in Non-Alcoholic Fatty Liver Disease" - 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	79 000,00 €	20 046,54 €
Support for training and career development of researchers (Marie Curie) - COORDINATOR: João Nuno Sereno de A. Moreira - PROPONENTE: University of Copenhagen	European Commission - REF. Marie Curie grant 316610	01/10/2012	31/12/2019	201 432,00 €	8 737,40 €
159302-1-2009 Blanka Kellermay - COORDINATOR: Ana Luisa Monteiro de Carvalho	VU University Medical Centre - REF. 159302-1-2009 Blanka Kellermay	01/09/2014	31/10/2018	121 900,00 €	3 776,40 €

Functional high-throughput analysis of the role of microRNAs in cardiac ischemia-reperfusion injury - COORDINATOR: Miguel Luís Cunha Mano	European Commission - REF. 701096-microCardio-MSCA-IF-EF-ST	01/03/2016	31/12/2019	148 635,60 €	18 349,24 €
Training European Network: Metabolic Dysfunction associated with Pharmacological Treatment of Schizophrenia - COORDINATOR: Eugénia Maria L. Carvalho/John Jones	Agencia Estatal CSIC - REF. TREATMENT-721236	01/01/2017	31/12/2020	433 224,72 €	124 183,92 €
New nanomaterials for neural stem cells drug delivery - COORDINATOR: Lino da Silva Ferreira	Queen Mary University (QMUL)-REF. NANOSTEM	01/06/2018	31/05/2022	715 069,08 €	42 664,14 €
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	06/05/2022	148 638,60 €	47 556,18 €
Sub-Total Others National e International Projects					**1 089 463,87 €**
Summer School - COORDINATOR: Armindo José Alves S. Salvador	- REF. Summer School	01/06/2015	01/10/2019	5 020,00 €	761,07 €
Curso Bioteria Teór/Prát_2015 - COORDINATOR: João António Nave Laranjinha	- REF. Curso Bioteria Teór/Prát_2015	01/08/2015	31/12/2018	8 298,50 €	0,00 €
Brain without borders - COORDINATOR: Luis Pereira de Almeida	- REF. Brain without borders	01/09/2016	31/12/2018	1 470,78 €	574,20 €

Formações do Gab. Comunicação - COORDINATOR: Sara Varela Amaral	- REF. Angariação fundos Gab. Comunicação da Ciência	01/01/2017	31/12/2018	140,00 €	0,00 €
Cursos de faturação Paulo Oliveira - COORDINATOR: Paulo Jorge G. S. S. Oliveira	- REF. Cursos de faturação Paulo Oliveira	01/09/2017	31/12/2018	713,40 €	248,49 €
Faturação Cursos Paula Mota - COORDINATOR:Paula Mota	- REF. Faturação Cursos Paula Mota	01/11/2018	31/12/2018	19 000,00 €	1 075,03 €
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	31/12/2018	10 150,00 €	8 870,48 €
Fórum Pós-docs - COORDINATOR: Ermelindo Carreira Leal -	- REF. Fórum Pós-docs	01/02/2018	31/12/2018	1 200,00 €	656,44 €
GENetic Frontotemporal dementia Initiative (GENFI) - COORDINATOR: Isabel Santana	University College London (UCL) REF. GENFI	15/02/2016	31/12/2018	14 138,08 €	1 103,60 €
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	uniQure - REF. Collaboration agreement_uniQure biopharma B.V.	17/12/2018	17/12/2020	52 187,50 €	0,00 €
INNOTECH 2015 - COORDINATOR: João Ramalho de Sousa Santos	Laboratoire Innotech - REF. INNOTECH 2015	31/12/2014	31/07/2019	203 086,76 €	16 430,21 €
Revascularização e angiogénese - COORDINATOR: João Ramalho de Sousa Santos	- REF. Revascularização e angiogénese, Merck	20/12/2016	30/09/2019	121 951,22 €	9 012,03 €

Nanodrug 3rd Summer School&Int - COORDINATOR: Lino da Silva Ferreira	Queen Mary University (QMUL) - REF. Nanodrug 3rd Summer School&Int	01/04/2014	31/12/2019	19 984,00 €	660,95 €
Study: Evaluation of Gecko polymer ability to inhibit bacterial growth by direct contact - COORDINATOR: Lino da Silva Ferreira	Gecko Biomedical - REF. Evaluation of Gecko polymer...	17/07/2017	31/12/2019	2 000,00 €	0,00 €
TimeUp - INESPO III - COORDINATOR: Susana Alarico	Universidade de Coimbra - REF. TimeUp - INESPO III	01/03/2018	30/06/2019	3 252,03 €	258,36 €
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	01/01/2017	31/12/2019	120 282,00 €	45 375,86 €
Supplementation of Coriolus versicolor (biomass) - a nutritional presymptomatic approach against cognitive deficits - COORDINATOR: Ana Cristina Carvalho Rego	Micology Research Laboratories- REF. Micology	01/09/2017	31/12/2019	7 000,00 €	4 724,69 €
NIH - HHSN27120 1700216P - COORDINATOR: Attila Köfalvi	NIH - REF. NIH - HHSN27120 1700216P	01/01/2017	31/12/2019	8 449,59 €	55,78 €
DDZ_FLAME_L_ study - COORDINATOR: John Griffith Jones	German Diabetes Center - REF. DDZ_ FLAME_L_study	01/06/2017	31/12/2018	10 234,00 €	94,82 €
Project Furan toxicity in human and rat hepatocytes - COORDINATOR: Carlos Manuel Marques Palmeira	Institute For Scientific Information on Coffee - REF. Comparison the acute effects..	01/08/2017	30/11/2018	28 200,00 €	4 479,94 €

Stress, Resilience and Epigenetic alterations: Frontal cortex and Social dominance. - COORDINATOR: Ana Cristina Carvalho Rego	Sigma-Tau B.V - REF. Consultancy Agreement - Sigma-Tau B.V. and UC_ StREs-FSD	01/01/2018	31/12/2018	18 500,00 €	4 127,60 €
Faturação Dr. Lino Ferreira - COORDINATOR: Lino Ferreira	- REF. Faturação Dr. Lino Ferreira	01/01/2018	31/12/2018	3 278,68 €	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_Luis Almeida	01/04/2018	31/12/2020	200 000,00 €	14 230,26 €
Sub-Total Others Services					**112 739,81 €**
TOTAL					**6 469 970,12 €**

Funding at IBILI

TITLE	FINANCING AGENCY	PRINCIPAL INVESTIGATOR	STARTING DATE	ENDING DATE	BUDGET (IBILI)	EXPEDITURE 2018
Unidade de I&D - IBILI	FCT UID/04538/2015	Miguel Castelo-Branco	01/01/2018	31/12/2018	1.833.000,00€	467.811,61€
Quantificação em PET: construção de um sistema distribuído não-invasivo para medida da função de entrada arterial	FCT PTDC/BBB-BMD/5378/2014	Francisco Caramelo	01/01/2016	31/12/2018	62.708,00€	21.923,79 €
Crosstalk between perivascular adipose tissue and blood vessels in obesity and vascular dysfunction	FCT PTDC/BIM-MET/4447/2014	Cristina Sena	01/07/2016	01/07/2019	199.512,00 €	55 829,94 €
Functional Neuroimaging in newborns with perinatal asphyxia predicting neuro-developmental outcome	FCT PTDC/DTP-PIC/6032/2014	Guiomar Oliveira	01/06/2016	31/05/2019	115.416,00 €	47.706,69 €

O sistema cancro-imunidade como alvo da terapia com a membrana amniótica humana no carcinoma hepatocelular	INFARMED FIS-2015-01_ONC_20150630	Filomena Botelho	15/05/2016	15/09/2018	85.000,00 €	18.054,08 €
Novartis	Novartis	Francisco Ambrósio	-	-	30.000,00€	30.000,00€
00The changing brain in Alzheimer's Disease: is the retina a reliable mirror of disease onset progression?	SANTA CASA MISERICORDIA SANTA CASA MB-1049-2015	Francisco Ambrósio	01/01/2016	31/12/2018	154.608,00 €	31.085,68 €
Redes sinápticas e abordagens compreensivas de medicina personalizada em doenças neuro-comportamentais ao longo da vida - MEDPERSYST	FCT POCI-01-0145-FEDER-016428	Miguel Castelo-Branco	01/07/2016	30/09/2019	743.519,83 €	213.958,38 €
DiaMarkData - Identificação de novos biomarcadores precoces das complicações da diabetes: do metabolismo à imagiologia multimodal de sistemas	INFARMED FIS-2015-01_DIA_20150630-173	Miguel Castelo-Branco	15/03/2017	15/09/2019	129.929,50 €	84.337,15 €
Game AAL - Gamification supporting Active and Assisted Living	QREN CENTRO-01-0247-FEDER-017948	Miguel Castelo-Branco	01/10/2016	30/09/2019	126.183,57 €	31.765,95 €
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	-

Taking imaging into the therapeutic domain: self-regulation of brain systems for mental disorders	EU BRAINTRAIN	Miguel Castelo-Branco	01/11/2013	30/10/2018	638.000,00 €	5.494,29€
Euro-BioImaging Preparatory Phase II - Project	EMBL - European Molecular Biology L H2020 - Excellent Science H2020 - Excellent Science	Miguel Castelo-Branco	01/01/2016	31/12/2018	15.302,50€	-€
Brain stimulation of attention networks: examining old principles and developing new clinical applications	Commission Of The European Communit\ H2020 - Excellent Science TMS_ATT	Miguel Castelo-Branco	01/06/2016	31/05/2018	148.635,00€	
ERAatUC - 669088	Commission Of The European Communit H2020 - Societal Challenges	João Malva	01/05/2019	30/06/2020	2.762.404,48€	355.005,80€
Managing inflammation in diabetic retino	Bayer Healthcare Pharmaceuticals	Ana Raquel Santiago	01/11/2015	28/02/2018	44.331.00€	8.841,22€
NECSUS - NEUROADAPTATION AFTER CATARACT AND REFRACTIVE SURGERY STUDY	European Society of Cataract and	JoaquiM Carlos Neto Murta	13/05/2016	12/05/2019	392.706,00€	33.695,86
ONCONET SUDOE	INTERREG	Maria Filomena Botelho	01/06/2016	30/06/2019	235.382,90€	34.761,66 €
18036-HEALIQS4CITIES	EIT Health InnoStars e.V.	João Malva	01/01/2018	31/12/2018	67.000,00€	40.578,12 €
18461-EIT LABELLING	EIT Health InnoStars e.V.	João Malva	01/01/2018	31/12/2018	10.000,00€	1.896,96 €
18256 - CARE CAMPUS	EIT Health InnoStars e.V.	João Malva	01/01/2018	31/12/2018	36.000,00€	19.163,80 €
PET com sistema inovador de leitura dupla para correção de DOI	FCT PTDC/BBB-IMG/4909/2014	Ana Cristina Santos	01/06/2016	31/12/2018	23.220,00€	2.702,71 €

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€	18.054,08 €
EASYPET	ANI	Ana Cristina Santos	01/10/2016	30/09/2018	116.329,52€	31.344,97 €
PPBI–Plataforma Portuguesa de Bioimagem	Agência Desenvolvimeto e Coesão	Henrique Girão	01/06/2017	30/05/2020	218.906,00€	112.063,62 €
A novel mechanism to re-pair HFpEF and endothelial damage	FCT RE-PAIR - 032179	Henrique Manuel P. Girão	22/06/2018	21/06/2021	233.434,48€	5.293,69 €
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 Nelson 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€	65,82 €
Speed, crash and run: exersomes boost neuroenergetics and mood in mice on speed	MOOD EXERSOMES - 030786	Frederico G.S.C. Pereira	26/07/2018	25/07/2021	239.413,80€	65,82 €
Modeling Angiogenesis in Type 2 Diabetes Mellitus - integrating experimental and theoretical approaches	ANGIODIA -031743	Raquel Maria Seiça	26/07/2018	25/07/2021	33.125,00€	-
On the right side: unveiling the mechanisms of pulmonary hypertension reversability and the heart failure progression	RIGHT-2H -032414	Rui Miguel Lança Baptista	26/07/2019	25/07/2021	7.500,00€	4.908,35 €

Environmental enrichment protects adult hippocampal neurogenesis and memory decline induced by systemic inflammation	MercuMemory - 031699	Carlos Alberto Ribeiro	26/07/2018	25/07/2021	239.475,67€	-
Contribution of olive polyphenols and olive oil for the prevention of cardiovascular diseases	PHENOLIVA - 032492	Flávio Nelson 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	DIAL4LIFE - 031322	Flávio Nelson Reis	10/08/2019	09/08/2019	23.643,50€	-

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Carlos Manuel Pinheiro Pereira Amaral	1,00
Carlos Miguel Machado Marto	0,30
Carlota Sofia Ferreira de Nóbrega	1,00
Carolina César Martins de Oliveira Alves	1,00
Carolina Isabel Pimenta Martins Ribeiro	0,10
Caroline Delgado Veloso	1,00
Catarina Araújo Gomes Rebelo	1,00
Catarina de Barros Pinto Salvador Domingues	1,00
Catarina Do Nascimento Jorge	1,00
Catarina Isabel Moreira Leitão	1,00
Catarina Mendes Morais	1,00
Catarina Milheiro Soares da Silva	1,00
Cátia João Monteiro da Santa	1,00
Cátia Moreira de Sousa	1,00
Cátia Sofia Resende Lopes	1,00
Celia Margarida Alcobia Gomes	0,30
César Alejandro Paradinha Nunes	0,30
CINZIA MIARELLI	1,00
Cláudia Maria Carrudo de Deus	1,00
Cristina Maria da Costa e Silva Barroso	1,00
Daniel Alexandre Sousa Henriques	1,00
Daniel Ferreira dos Santos	1,00

Daniel Freitas Chavarria	0,50
Daniela Costa Batista de Almeida	1,00
Daniela Cristina Nunes Costa	1,00
Daniela Filipa Domingues Santo	1,00
Daniela Filipa Felício Marques	1,00
Daniela Isabel Ferreira Madeira	1,00
Daniela Marinho Lopes	1,00
Daniela Pereira Santana Alho	0,20
David Castelo	0,30
Débora Tatiana de Sousa Mena	1,00
Débora Vanessa Lourenço Serrenho	1,00
Denise Irene Marta Monteiro	1,00
Deolinda Conceição Ribafeita Santinha	1,00
Diana Bela da Luz Sequeira	0,80
Diana dos Santos Simões Graça	0,80
Diana Filipa Coutinho Santos	1,00
Diana Filipa Dias Duro	0,30
Diana Filipa Duarte Lobo	1,00
Dina Maria da Silva Rodrigues Pereira	1,00
Dina Pereira Alves Farinha	1,00
Diogo Alexandre da Silva Tomé	1,00
Diogo André Afonso da Fonseca	1,00
Diogo Figueiredo Pinho	0,00
Edgar Miguel Calvo Loureiro Tavares da Silva	0,30
Ema Sofia Trindade Rodrigues da Fonseca	1,00
Emanuel José Costa Meireles Melo	1,00
Emanuel Monteiro Candeias	1,00
Eurico da Silva Serrano	1,00
Eurico Miguel Fial Teixeira Ribeiro	0,80
Fábio Alexandre Fiúza Rosa	1,00

Fábio de Jesus Ribeiro de Sousa	1,00
Fernanda Maria da Conceição Correia Torcato Ferreira Carrilho	0,30
Filipa Alexandra Lopes Simões da Silva	1,00
FILIPA LIMA RAMOS SANTOS JúLIO	1,00
Filipe Jose Ribeiro Malta	1,00
Filipe Manuel Farto Palavra	0,20
Flávia Soraia Cunha Rodrigues	1,00
Francesca Tomatis	1,00
Frederico Mendes e Pena	1,00
Gabriela Lopes Oliveira	1,00
Gabriela Pires Tavares	1,00
Getachew Debas Belew	1,00
Giada Di Nunzio	1,00
Gonçalo Sousa Brites	1,00
Guida José Freitas Bento	1,00
Gustavo António Pereira Rodrigues Cordeiro Santo	0,30
Helena Isabel Reis Aires	1,00
Helena Maria da Silva Leal	1,00
Hélio Jorge Simões Gonçalves	1,00
Heloísa Salguinho Gerardo	1,00
Hugo Alexandre Pereira Quental	1,00
Hugo Jorge Calisto Froufe	0,20
Inês Abrantes Cravo Roxo	1,00
Inês Isabel Nunes Caramelo	1,00
Inês João Dinis Ferreira	1,00
Inês Margarida Dias Cabaço Amaral	0,70
Inês Maria Cunha Albino	1,00
Inês Maria Nascimento Caiado	1,00
Inês Marques Morais	1,00
Inês Martins Malva Correia	0,20

Inês Mendes Preguiça	1,00
Inês Rodrigues Lopes	1,00
Inês Sofia Dinis Aires	1,00
Inês Sofia dos Santos Rodrigues Ferreira	1,00
Inês Tomé Ribeiro	1,00
Ines Vasconcelos Miranda Santos	0,75
Isabel Catarina Castro Duarte	0,90
Isabel Cristina do Vale Ferreira	1,00
Ivo Manuel Ferreira Machado	1,00
Jeannette Schmidt	1,00
Jessica Gonçalves Da Silva	1,00
Jéssica Margarida Mendes Costa	1,00
Joana Carrapiço Gonçalves	0,20
Joana Filipa Catarino Alves	0,40
Joana Margarida Cardoso Serra Martins	1,00
Joana Rita Pinto Velho	0,40
João André Figueiredo Pereira	1,00
João Carlos Pinho da Silva	1,00
João David Panão da Costa	1,00
Joao Demetrio Goncalves Boto Martins	1,00
João Eduardo Casalta Lopes	0,30
João Filipe Alves Amorim	1,00
João Manuel Cura Rito	0,50
João Miguel Calmeiro Pereira	1,00
João Miguel da Silva Gonçalves	1,00
João Miguel Esteves Correia da Silva Cardoso	1,00
João Miguel Miranda da Rocha	1,00
João Pedro Moreira de Oliveira	0,40
João Pedro Pinto Vieira	1,00
João Pedro Santos Brás	1,00

Joaquim Jorge Marques Moita	0,10
Jorge Miguel Alves Silva	1,00
José Guilherme Coelho Peres de Almeida	0,30
José Luís Monteiro Alves	0,20
José Pedro Sousa Baptista	0,20
Judite Raquel Martins Coimbra	1,00
Judith Santos Pereira	0,50
Laetitia da Silva Gaspar	1,00
Lara Oliveira Franco	0,90
Laura Sofia Soares Carvalho	1,00
Leonor Aurélio Barro	0,30
Lígia Vanessa Rocha Fão	1,00
Liliana Rita Velindro Letra	0,30
Liliana Rodrigues Dias	1,00
Lisiane de Santana Souza	0,20
Livia Maria de Abreu Freire Diogo Sousa	0,15
Luciana Branco Fernandes	1,00
Luciana Carolina Lopes Ferreira	1,00
Luis Filipe Fragoso Grilo	1,00
Luís Filipe Henriques Oliveira	1,00
Luís Filipe Maximino Martins	0,30
Luis Jorge Mendonça Peres Negrão	0,20
Luís Miguel de Almeida Monteiro	1,00
Manuel Maria Moura Neves Moreira Pires	0,30
Mara Yone Dias Fenandes	0,15
Márcia Joana Nascimento Teixeira	1,00
Marco António Machado Simões	1,00
Marcos António dos Santos Rodrigues Gomes	1,00
Margarida Fernandes Beatriz	1,00
Margarida Maria Gonçalves Marques	0,30

Margarida Ribeiro da Silva	1,00
Maria de Fátima Machado Dias	1,00
Maria de La Salete de Jesus Baptista	0,40
Maria do Carmo Ribeiro Reis Maio Macario	0,20
Maria Inês Morgado Oliveira Martins	1,00
Maria Inês Nuno Alves	1,00
Maria Inês Ramalho de Almeida e Sousa	1,00
Maria Inês Rodrigues Alfaiate	1,00
Maria Inês Veiga de Almeida Barros	1,00
Maria João Ferreira Canas dos Santos	1,00
Maria João Nunes Vicente Mexia Leitão	1,00
Maria Mafalda Santos Costa	1,00
Maria Margarida Serra Coelho	0,50
Maria Moreira Soares	1,00
Maria Olinda Rodrigues Rebelo	0,15
Mariana Biscaia Caleiras	1,00
Mariana Durão Terra	1,00
Mariana Laranjo	1,00
Mariana Raquel Antunes Colaço	1,00
Mariangela Natale	1,00
Marija Petkovic	1,00
Marina Manuela Ventura Rodrigues	1,00
Marina Portes	0,30
Mário Jorge da Silva Carvalho	1,00
Marisa Ferreira Marques	1,00
Marlene Cristina Faria Pereira	0,60
Marlene Santos Domingues	1,00
Marta Cristina de Pinho Teixeira	1,00
Marta Filipa Viegas Barão	1,00
Marta Isabel Ferreira Leite Pereira	1,00

Marta Sofia Ereira Mota	1,00
Marta Sofia Marques Simões	1,00
Marta Sofia Rosendo Pereira	1,00
Miguel Monteiro Lopes	1,00
Milene Vieira Gonçalves	1,00
Mireia Alemany i Pagès	1,00
Nádia Isabel Silva Canário	1,00
Natalia Sozza Bernardi	1,00
Nuno Miguel Beltrão Marques	1,00
Olga Fokt	0,30
Óscar Emanuel de Melo Rodrigues	1,00
Pasqualino De Luca	1,00
Patrícia Alexandra Rosado Albuquerque	1,00
Patrícia Diogo Nunes	0,40
Patrícia Raquel Reis Moreira	1,00
Patricia Sofia Alcada Tomas de Morais	0,90
Patrick Joel da Silva	1,00
Paula Cristina Correia Martins	0,30
Pedro Matos Pinto Santos Filipe	1,00
Pedro Miguel Brígida Raposo	1,00
Pedro Miguel Caniceiro Valada	1,00
Pedro Miguel Reis Figueiredo	1,00
Rafael da Silva Carvalho	1,00
Rafael Ribeiro Santos Silva	1,00
Rafaela Margarida Cura Ferrão	1,00
Raquel Sofia Freitas Boia	1,00
Rémy Cardoso	1,00
Ricardo Cerqueira de Abreu	1,00
Ricardo Fernando Santos Amorim	0,50
Ricardo Gomes Moreira	1,00

Ricardo Jorge Carreira da Silva	1,00
Ricardo Jorge Marques Teixo	1,00
Ricardo Jorge Negrão Henriques Pereira	0,30
Ricardo Jorge Teixeira Martins	0,30
Rita Alexandra Silvério Alves	1,00
Rita António dos Santos	1,00
Rita Rodrigues Sá Ferreira	1,00
Rita Sofia dos Santos Severino	1,00
Rodolfo das Neves Águas	1,00
Romina Paula de Aguiar Guedes	0,10
Rúben Joel Bispo Salvado	1,00
Rui Fernando Vieira Lisboa Matias Simões	1,00
Rui Filipe Ramos Silva	0,20
Rui Manuel da Costa Soares	0,40
RUI MIGUEL RUA FILIPE MARTINS	0,30
Rui Pedro Caetano Moreira de Oliveira	0,30
Rui Pedro Dias Tavares	1,00
Samuel Filipe Duarte Chiquita	1,00
Sandra de Almeida Reis	1,00
Sandra Patrícia Nunes Ribeiro	0,50
Sandra Sofia Mimoso Pinhanços	1,00
Sara Cristiana Alves Valente	1,00
Sara Cristina Lourenço dos Reis	1,00
Sara de Jesus Gomes Escada Rebelo	1,00
Sara Inês Furtado Canário	1,00
Sara Isabel Monteiro Lopes	1,00
Sara Maria de Cabral Martins Pêgo	1,00
Sara Patrícia de Sousa Pereira Moura	1,00
Sara Raquel Ramalho Pereira Nunes	0,70
Sofia Alexandra Ramos Ferreira	1,00

Sofia Ferreira Anastácio	1,00
Sofia Pereira Constantino Romano	0,30
Sónia Andreia Almeida Pinho	1,00
Sónia Filipa Gomes dos Santos	1,00
Susana Cristina Domingues Pedreiro	1,00
Susana Isabel Simão Mouga	1,00
Susana Vieira Pinto da Cunha	1,00
Tânia Alves Marante	1,00
Tania Luísa Barbosa Barata	1,00
Tânia Milene Pires Lourenço	1,00
Tânia Sofia Martins Marques	1,00
Tânia Soraia Vieira da Silva	0,20
Tarcísio Guerra Guimarães	0,50
Teresa Margarida Ribeiro Rodrigues	1,00
Teresa Raquel Tremoço Dias de Abreu	1,00
Tiago Batista Abrantes Rondão	1,00
Tiago Daniel Almeida Rodrigues	1,00
Tiago Joao dos Santos Reis	0,50
Tiffany Santos Pinho	1,00
Vanessa Alexandra Castanheira Fernandes	1,00
Vanessa Filipa Rodrigues Costa	1,00
Vanessa Simões Lourenço	1,00
Vânia Marina Jorge Leal	0,20
Vasco Santos Justino	1,00
Vera Cristina da Fonseca Alves	0,30
Vera Martinho Pais	1,00
Vera Mónica Milheirão Mendes	1,00
Vítor Hugo Pereira Alves	1,00
Xavier Sá Castro Pinho	0,30
Xinli Xu	1,00

Apoio Técnico / Administrativo	
Alda Maria Paiva Gonçalves	1,00
Ana Cláudia Vicente Caridade	0,50
Ana Filipa Gomes Oliveira	1,00
António José Azinhaga Teles Grilo	1,00
Bruno Guilherme Serra e Silva de Abranches Nobre	1,00
Cândida Elsa Frias Mendes	1,00
Carla Andrea Pereira António Lopes Rodrigues	1,00
Carla Margarida dos Santos Veríssimo	1,00
Carmen Lidia Graça Semião	1,00
Catarina Alexandra Ferreira Gomes	1,00
Fátima Cristina Dos Santos Carvalho Graça	1,00
Heidi Maria da Silva Lopes Gonçalves	1,00
Isabel Conceição Calado Esteves Costa	1,00
Isabel Maria de Oliveira Martins Dantas Fernandes	1,00
Joana Silvestre Rodrigues Cipriano	1,00
João Miguel da Silva Pratas	1,00
Lia da Costa Jordão Aparicio Lopes	1,00
Luciana Costa de Albuquerque Pinto	1,00
Maria Adelaide Cunha Oliveira	1,00
Maria de Fatima Sousa Martins Moreira	1,00
Maria do Céu Mendes Gomes	1,00
Maria do Rosário Ferreira da Costa Faro	1,00
Maria Eugénia Alves da Silva Lopes Campos	1,00
Maria Isabel Mendes Gonçalves	1,00
Maria Leonor Gomes Cruz Jesus	0,80
Maria Luisa Rocha Caldeira Bonito	1,00
Mónica Alexandra Rodrigues Morais	1,00
MonicaAlexandra Vilão Serrano	1,00
Nilza Clara Ferreira Marques Manadas	1,00

Paula Cristina Andrade Miranda	0,20
Rosa Alexandra do vale Folhas Fernandes	1,00
Rute Eliete Marques e Cruz Simoes	1,00
Sandra Cristina Santos Luis	1,00
Sandra Margarida Pinheiro Freire	1,00
Sara da Costa Jordão Aparicio Lopes	1,00
Sílvia Maria Esteves de Sousa	1,00
Susana Adelaide Rocha da Silva	1,00
Tânia Sofia Aguiar Ribeiro	1,00
Tatiana de Azevedo Paula	1,00
Telma Patricia Simões Graça	1,00