



ANNUAL REPORT 2017



<http://cnc-ibili.cnpq.br>
cncibili@cnpq.br

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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 a translational, from molecule to man perspective, focused on the understanding of brain function and disease mechanisms and therapeutic strategies. For this purpose, cellular and animal models of disease and human patients are used, 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 2017 Annual Report of activities of the CNC.IBILI Research Consortium highlights the main achievements resulting from the development of its research strategic plan.

In 2017, 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 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 2017 is demonstrated by a rate of publication of 354 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 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 2017 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 Center.



Facts & Figures (2017)

RESEARCH STAFF

*Integrated Members holding Ph.D.	185 + (102 Post Doctoral Fellows)
Ph.D.Students	157
MSc Students	42

PUBLICATIONS

Scientific papers published	354
Scientific papers <i>In Press</i>	54

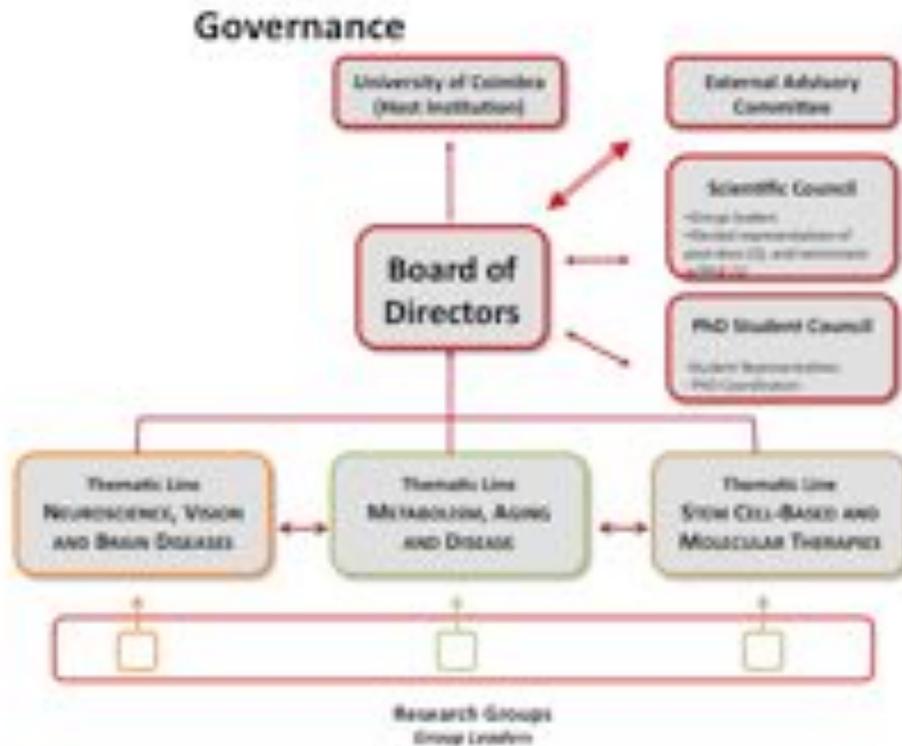
THESIS CONCLUDED

Ph.D. thesis	39
MSc thesis	96

* With more than 30% of dedication



Organization of CNC.IBILI



CNC.IBILI External Advisory Committee: 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 Metabolism and Quality Control Group (*Head: Paula Moreira*)

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

Metabolic Control Group (*Head: John Griffith 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*)

NEUROSCIENCE, VISION AND BRAIN DISEASES

Coordinator: Ana Luísa Carvalho

GENERAL OBJECTIVES

This summary of the main achievements in the NVBD line The research line on Neuroscience, Vision and Brain Diseases (NVBD) aims to decipher brain functioning and dysfunction in neurodegenerative, neuropsychiatric and vision disorders, using animal models and human patients. The NVBD research line is composed of 8 research groups conducting research that spans 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.

The 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. The strong connection to the Coimbra University Hospital (CHUC) is instrumental in this endeavor

MAIN ACHIEVEMENTS

This summary of the main achievements in the NVBD line identifies important contributions from research groups in this area; please see NVBD group reports for other very relevant studies resulting in > 140 publications during 2017.

Research groups in the NVBD research line are interested in the postsynaptic molecular pathways controlling the activity of glutamatergic synapses under physiological and pathological conditions of the CNS. We have described a role for the RNA binding protein hnRNP K as a mediator of the effects of the neurotrophin BDNF in the regulation of synaptic NMDA receptors in cultured hippocampal neurons (Leal et al., 2017), and found that in an *in vitro* model of brain ischemia, the cleavage of huntingtin-associated protein 1 (HAP1) impairs the trafficking of GABAA receptors, contributing to neuronal death in ischemia conditions (Mele et al. 2017). Importantly, a study involving several research groups at CNC.IBILI and CHUC has found that the functional properties of human endothelial progenitor cells are associated with enhanced permeability of the blood-brain barrier (BBB) and improved clinical outcome after acute ischemic stroke (Sargento-Freitas et al., 2017)

Important advances were made regarding neuromodulation by the purinergic receptors: Intake of caffeine was found to revert memory dysfunction in animal models of depression (Machado et al., 2017), to control motor dysfunction and cerebellar degeneration in an animal model of Machado-Joseph's disease (Gonçalves et al., 2017), and to inhibit microglia reactivity and protect retinal cells against transient ischemic damage (Boia et al., 2017). An impactful publication shows that A2AR control microglia remodeling associated with anxiety (Caetano et al., 2017), whereas the P2Y1 (ATP) receptors were found to

critically control glutamate-induced excitotoxicity (Simões et al., 2018).

One focus of the NVBD area is on neurodegenerative disease, and several important studies were published during 2017. Histone deacetylases have been explored as possible targets in these diseases. Our data indicate HDAC inhibitors, particularly sodium butyrate, promotes the activity of pyruvate dehydrogenase in the Huntington's disease (HD) brain, helping to counteract HD-related deficits in mitochondrial bioenergetics and motor function (Naia et al., 2017). By using implanted microarrays in rat hippocampus of normal and triple transgenic models of Alzheimer's disease (AD) we have found impairment in neurovascular coupling is primarily due to cerebrovascular rather than neuronal dysfunction. This notion underscores cerebrovascular dysfunction as a fundamental early process in AD pathophysiology (Lourenço et al., 2017). The participation in multicenter studies addressing AD biomarkers and genetics has culminated in several publications with recommendations for the use of CSF biomarkers in the diagnostic evaluation of dementia (Simonsen et al., 2017) and in the identification of deleterious ABCA7 mutations in early onset AD (De Roeck et al., 2017).

Understanding neuropsychiatric disorders and the effects of the drugs of abuse is the focus of different NVBD groups. We have found that methamphetamine induces anhedonic-like behavior and impairs frontal cortical energetics in mice (Fonseca et al., 2017); an extended-access to methamphetamine self-administration triggers an increase of BBB permeability (Gonçalves et al., 2017), and methamphetamine interferes with aquaporin-4, causing the BBB breakdown and brain edema, which culminates in locomotor and

motivational impairments (Leitão et al., 2018). An impaired inhibition phenotype was encountered in the animal model of the most common neurogenetic cause of cognitive dysfunction, neurofibromatosis type 1, in agreement with finding in humans (Gonçalves et al., 2017).

Ana Cristina Rego, Carlos Duarte and Catarina Oliveira, group leaders in the NVBD line, edited a textbook in Portuguese on 'Neuroscience' (LIDEL). This book is aimed at undergraduate and master degree students, and benefits from the insightful chapters authored by many researchers in the NMBD line and other Portuguese neuroscientists.

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 Jorge B. Duarte	PhD (<i>Head of Group</i>)
Ana Luisa de Carvalho	PhD
Emilia Conceição Duarte	PhD
Irina Moreira	PhD
João Miguel Peça-Silvestre	PhD
Paulo Cesar Pinheiro	PhD
Ramiro Daniel de Almeida	PhD
Ana Luísa Cardoso	Post Doctoral Fellow
Ângela Inácio	Post Doctoral Fellow
Catarina Seabra	Post Doctoral Fellow
Gladys Caldeira	Post Doctoral Fellow
Ivan Salazar	Post Doctoral Fellow
Joana Guedes	Post Doctoral Fellow
Miranda Mele	Post Doctoral Fellow
Mohamed Hussien	Post Doctoral Fellow
Rui Miguel Oliveira da Costa	Post Doctoral Fellow
Ana Teresa Viegas	PhD Student
António Gomes	PhD Student
Beatriz Rodrigues	PhD Student
Débora Serrenho	PhD Student
Diana Sequeira	PhD Student
Diogo Tomé	PhD Student
Dominique Fernandes	PhD Student
Jeannette Schmidt	PhD Student
Lara Franco	PhD Student
Luís Martins	PhD Student
Marilene Silva	PhD Student
Marina Rodrigues	PhD Student
Marcos Gomes	PhD Student
Mário Carvalho	PhD Student
Pasqualino De Luca	PhD Student
Nuno Beltrão Marques	MSc Student
Rafael Carvalho	MSc Student
Agostinho Lemos	Collaborator
José Almeida	Collaborator
Pedro Filipe	Collaborator

REDOX BIOLOGY AND BRAIN SENSING GROUP

João António Laranjinha	PhD (<i>Head of Group</i>)
Ana Margarida da Cruz Ledo	PhD
Leonor Martins de Almeida	PhD
Rui Manuel Silva Barbosa	PhD
Teresa do Carmo Dinis Silva	PhD
Carla Nunes	PhD
Diana Serra	PhD
Barbara da Silva Rocha	Post Doctoral Fellow
Cátia Filipa Marques	Post Doctoral Fellow
Cândida Dias	PhD Student
Sónia Rosa Pereira	PhD Student

NEUROENDOCRINOLOGY AND AGING GROUP

CLAUDIA MARGARIDA CAVADAS	PhD (<i>Head of Group</i>)
Ana dos Santos Carvalho	PhD
Célia Alexandra Avelaira	PhD
Caetana M. Carvalho	PhD
Alexandrina Ferreira Mendes	PhD
Ana Teresa Rufino	PhD
Fernando Judas	PhD
Ana Rita Álvaro	Post Doctoral Fellow
António Pedro Gomes	Post Doctoral Fellow
Sara Silva	Post Doctoral Fellow
André Carvalho	PhD Student
Inês Ferreira	PhD Student
Laetitia Gaspar	PhD Student
Helena Leal	PhD Student
Marisa Marques	PhD Student
Tânia Soraia Silva	PhD Student
João Pedro Oliveira	MD
João Cardoso	MSc Student
Cátia Sousa	Collaborator

VISION, BRAIN IMAGING AND COGNITIVE NEUROSCIENCE

Miguel Castelo-Branco	PhD (<i>Head of Group</i>)
Aldina Conceição Pires Reis	PhD
Antero Afonso de Abruñosa	PhD
António Morgado	PhD
Bárbara dos Santos Oliveiros	PhD
Francisco Cerqueira Alves	PhD
Francisco Caramelo	PhD
Francisco Oliveira	PhD
Guiomar Gonçalves Oliveira	PhD
Inês Ribeiro Violante	PhD
João Santos Pereira	PhD
João Miguel Castelhana	PhD
João Pereira Figueira	PhD
Joaquim Carlos Neto Murta	PhD
Jorge de Andrade Saraiva	PhD
José Paulo Domingues	PhD
José Vítor Oliveira Sereno	PhD
M ^a Conceição da Fonseca	PhD
M ^a Cristina Januário Santos	PhD
M ^a João Vidigal Ferreira	PhD
Miguel Patrício	PhD
Nuno David Ferreira	PhD
Otilia d'Almeida	PhD
Pedro Miguel Serranho	PhD
Rufino Martins da Silva	PhD
Rui Manuel Bernardes	PhD
Sergio José Do Carmo	PhD
Bruno Miguel Leitão	Post Doctoral Fellow
Gabriel Ferreira da Costa	Post Doctoral Fellow
Inês Bernardino	Post Doctoral Fellow
Inês Teixeira de Almeida	Post Doctoral Fellow
Joana Crisóstomo Silva	Post Doctoral Fellow
Joana Teresa Gonçalves	Post Doctoral Fellow
João Filipe Martins	Post Doctoral Fellow
João Valente Duarte	Post Doctoral Fellow
Lorena Itatí Petrella	Post Doctoral Fellow
M ^a José Braga Ribeiro	Post Doctoral Fellow

Monika Intaite	Post Doctoral Fellow
Ana Isabel Rodrigues	PhD Student
Ana Mafalda Teixeira	PhD Student
Ana Maria Batista	PhD Student
Andreia Sofia Pereira	PhD Student
Carlos Manuel Amaral	PhD Student
Carlos Manuel Pereira	PhD Student
Carolina César Alves	PhD Student
Diliana Rebelo Santos	PhD Student
Filipa Lima Júlio	PhD Student
Hélio Jorge Gonçalves	PhD Student
Hugo Alexandre Quental	PhD Student
João Valente Duarte	PhD Student
Lília Pereira Jorge	PhD Student
Márcia Andrade	PhD Student
Mário Jorge Ribeiro	PhD Student
Marco António Simões	PhD Student
Nádia Isabel Canário	PhD Student
Ricardo José Martins	PhD Student
Sulaiman I S Abuhaiba	PhD Student
Susana Isabel Simão Mougá	PhD Student
Carlos Daniel Ferreira	Technician
Isabel Catarina Duarte	Technician
César Alejandro Nunes	MD
Frederico Duque	MD
Margarida Maria Marques	MD
M ^a Luísa Ribeiro	MD
Pedro Luís Fonseca	MD
Alexandre Campos	Grant Technician
Ana Cruz Dionísio	Grant Technician
Marta Cristina Teixeira	Grant Technician
Vítor Hugo Alves	Grant Technician

PURINES IN BRAIN DISEASES GROUP

Rodrigo A. Cunha	PhD (<i>Head of Group</i>)
Attila Köfalvi	PhD
Angelo Ribeiro Tomé	PhD
Henrique Silva	PhD
Paula Maria Agostinho	PhD
Ricardo Rodrigues	PhD
Ana Patrícia Simões	Post Doctoral Fellow
Joana Marques	Post Doctoral Fellow
João Pedro Lopes	Post Doctoral Fellow
Paula Canas	Post Doctoral Fellow
Samira Ferreira	Post Doctoral Fellow
Amber Kerkhofs	PhD Student
Anna Pliássova	PhD Student
Francisco Queiroz Gonçalves	PhD Student
Inês Amaral	PhD Student
Patrícia Sofia Alçada Morais	PhD Student
Sofia Ferreira	PhD Student
Xinli Xu	PhD Student
Daniela Madeira	MSc Student
Marlene Pereira	MSc Student
Sara Reis	Grant Technician

MITOCHONDRIAL DYSFUNCTION AND SIGNALING IN NEURODEGENERATION GROUP

Ana Cristina Carvalho Rego	PhD (<i>Head of Group</i>)
Carla Lopes	Post Doctoral Fellow
Elisabete Baptista Ferreira	Post Doctoral Fellow
Ildete Luisa Araujo Ferreira	Post Doctoral Fellow
Luana Naia	Post Doctoral Fellow
Sandra Mota	Post Doctoral Fellow
Lígia Fão	PhD Student
Carina Maranga	PhD Student
Diogo Passos	MSc Student

AGING AND BRAIN DISEASES: ADVANCED DIAGNOSIS AND BIOMARKERS GROUP

Catarina Resende de Oliveira	PhD (<i>Head of Group</i>)
Anabela Mota Pinto	PhD
Antonio Macedo e Santos	PhD
Bruno Oliveira Manadas	PhD
Inês Esteves Baldeiras	PhD
Isabel Maria Carreira	PhD
Joaquim Cerejeira	PhD
Manuela Grazina	PhD
M ^a Isabel Santana	PhD
M ^a Joana Barbosa de Melo	PhD
M ^a Rosário Almeida	PhD
Helena Carvalheiro	Post Doctoral Fellow
Cátia Santa	PhD Student
Joana Pinto	PhD Student
Mafalda Bacalhau	PhD Student
Margarida Coelho	PhD Student
M ^a João Leitão	PhD Student
Ruben Salvado	PhD Student
Sandra Anjo	PhD Student
Ana Dias	MSc Student
Joana Coelho	MSc Student
Ana Sofia Morais	MD Collaborator
Ana Valado	Collaborator
António Gabriel	Collaborator
Carolina Roque	MD Collaborator
Célia Gomes	Collaborator
David Mota	MD Collaborator
Helena Beatriz Santiago	MD Collaborator
Lívia Sousa	MD Collaborator
Luís André Oliveira	MD Collaborator
Luís Miguel Bajouco	MD
Manuel Coroa	MD Collaborator
Nuno Madeira	MD
Pedro Oliveira	MD Collaborator
Sandra Silva	MD Collaborator
Sónia Batista	MD Collaborator
Vasco Nogueira	MD Collaborator
Vitor Santos	MD Collaborator

**NEW TARGETS AND THERAPEUTICS FOR CHRONIC DISEASES
GROUP**

António Francisco Ambrósio PhD (*Head of Group*)

Andreia Martins Rosa	PhD	Ana Esmeralda Costa	MD
Ana Filipa Marques Brito	PhD	Ana Esmeralda Costa	MD
Ana Margarida Abrantes	PhD	António Campos Figueiredo	MD
Ana Paula Silva Martins	PhD	Alexandre Marques	MD
Bárbara Gomes	PhD	Carlos Marto	MD
Belmiro Ataíde Parada	PhD	David Castelo	MD
Carlos Alberto F. Ribeiro	PhD	Edgar Silva	MD
Catarina A. Reis Gomes	PhD	Filipe Palavra	MD
Célia Maria Freitas Gomes	PhD	João Casalta Lopes	MD
Eunice Virgínia Carrilho	PhD	José Luís Alves	MD
Fernando José Mendes	PhD	Leonor Barroso	MD
Flávio Nelson Reis	PhD	Rui Martins	MD
Frederico G. Pereira	PhD	Rui Oliveira	MD
Isabel Santos Pereira	PhD	Beatriz Martins	MSc Student
João José Oliveira Malva	PhD	Carla Henriques	MSc Student
José Guilherme Tralhão	PhD	Carlota Nóbrega	MSc Student
Manuel Marques Ferreira	PhD	Fábio Sousa	MSc Student
Manuel Marques Verissimo	PhD	Luciana Fernandes	MSc Student
M ^a Dulce Ferreira Cotrim	PhD	Rafael Carecho	MSc Student
M ^a Filomena Botelho	PhD	Inês Aires	Grant Technician
M ^a João Carvalho	PhD	Joana Martins	Grant Technician
M ^a Margarida Caramona	PhD		
Natália Sofia António	PhD		
Paulo Fernando Santos	PhD		
Paula Cristina Vaz Tavares	PhD		
Rosa Cristina Fernandes	PhD		
Sofia Andreia Viana	PhD		
Sónia Alexandra Santos	PhD		
Ana Raquel Santiago	Post Doctoral Fellow		
Elisa Regina Campos	Post Doctoral Fellow		
Filipa Isabel Baptista	Post Doctoral Fellow		
Mafalda Cândido	Post Doctoral Fellow		
M ^a Helena Bica Madeira	Post Doctoral Fellow		
Ricardo Alexandre Leitão	Post Doctoral Fellow		
Ana Catarina Neves	PhD Student		
Ana Rita Gaspar	PhD Student		
Ana Salomé Pires	PhD Student		
Ana Sofia Pais	PhD Student		
Diogo André Fonseca	PhD Student		
Eurico Miguel Fial Ribeiro	PhD Student		
Inês Roque Pita	PhD Student		
Raquel Sofia Freitas Bóia	PhD Student		
Ricardo Jorge Teixeira	PhD Student		
Samuel Filipe Chiquita	PhD Student		
Sara Raquel Nunes	PhD Student		
Vânia Leal	PhD Student		
Vanessa Filipa Santos	PhD Student		

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.

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 like 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. 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. We focus on 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. 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.

GABAergic synapse dysfunction and neuronal death in brain ischemia

Previous studies by this group, as well as from other laboratories, have shown pre- and postsynaptic alterations in the activity of GABAergic synapses in brain ischemia. However, the detailed molecular mechanisms involved, and their relative role in neuronal death, have not been fully elucidated. 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 postsynaptic alterations in GABAergic synapses following brain ischemia, and their impact in neuronal demise. In particular, studies have been performed to investigate the alterations in the subcellular

distribution and intracellular trafficking of GABA_A receptors.

Structural characterization of protein-based interactions

The work is split into 2 main themes:

1. The biophysical understanding of protein-based interactions - Our general interest is in protein-based systems and especially interactions involving G-Protein Coupled Receptors (GPCRs). We focus in particular on the dopamine receptor type 2 (D2R) as this is a key hub in neurotransmission in the brain, involved in multiple cognitive, emotional and motor functions

2. The development of new in silico data-driven molecular design tools based on machine-learning (ML) and deep-learning (DL) approaches - We are involved in innovative multidisciplinary approaches that uses combined information from biophysical and genomic data source about properties and effects of putative drugs to identify efficacy metrics of drug-target compatibility and interactions powered by DL algorithms. In particular, we are interested in the development of new therapeutics for neurologic diseases and in predicting the response of a specific cancer to a specific therapy.

MAIN ACHIEVEMENTS

i) Glutamatergic synapse function and dysfunction in brain disorders

PI: Carlos B. Duarte

1. The RNA binding protein hnRNP K was found to play a key role as a mediator of the effects of the neurotrophin BDNF in the regulation of synaptic NMDA receptors in cultured hippocampal neurons. Stimulation of hippocampal neurons with BDNF induces the release of a large number of transcripts bound to

hnRNP K, and we hypothesized that these transcripts will become available for translation at the synapse (Leal et al., 2017).

PI: Ana Luísa Carvalho

2. We found that mutations in the *CACNG2* gene encoding the AMPA receptor auxiliary protein stargazin, linked to schizophrenia or intellectual disability, alter the cell surface mobility of stargazin and its function in mediating AMPA receptor traffic and homeostatic plasticity. Knock-in mice expressing

an intellectual disability-associated mutation in *CACNG2* present alterations in cognitive and social behavior, and alterations in excitatory transmission in the hippocampus (Caldeira et al., in preparation). These results implicate stargazin in the pathogenesis of neuropsychiatric disorders.

3. We identified a brain-expressed miRNA regulated by neuronal activity, and which regulates AMPA receptor expression, homeostatic synaptic plasticity and the neuronal

excitatory/inhibitory balance (Silva et al., in preparation).

4. We found a role for the autism-associated protein Caspr2 in the regulation of homeostatic synaptic plasticity, analyzed the pathogenic effects of CASPR2 autoantibodies from synaptic encephalitis patients and identified crucial effects in synaptic function (Fernandes et al., under review).

PI: João Peça

5. We finished the characterization of GPRASP2 (G Protein-Coupled Receptor Associated Sorting Protein 2) knockout mouse line as a model for autism spectrum disorders (Edfawi et al, submitted).

6. We are now dissecting the contribution of parvalbumin (PV)-positive interneurons towards circuit and behavioral dysfunction in GPRASP2 conditional knockout mice (Edfawi and Guedes, et al in preparation).

7. Our group also initiated a collaboration with MIT to dissect the contribution of GPRASP2 in hypothalamic dysfunction and induced obesity (Gomes et al, in preparation).

8. We found that microglia activation promotes a remodeling in cerebellar circuits and we are now characterizing this phenomena at the electrophysiological and behavioral level (Guedes et al, in preparation).

9. We performed genetic analysis and electrophysiological characterization in the medial prefrontal cortex (mPFC) of adult mice following early life stress. We continue to use optogenetic manipulations to change animal behavior within a social hierarchy (Franco et al, in preparation).

ii) GABAergic synapse dysfunction and neuronal death and brain ischemia (PI: Carlos B. Duarte)

1. In the OGD in vitro model of brain ischemia, the cleavage of huntingtin-associated protein 1 (HAP1) was found to impair the trafficking of GABA_A receptors. The resulting downregulation in the surface expression of GABA_A receptors contributes to neuronal death following OGD (Mele et al. 2017).

2. Proteasome disassembly followed by neuronal death was observed in cultured cortical neurons subjected to OGD. 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).

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

We used a variety of computational methods developed by us to investigate the putative interfaces between all members of the dopamine receptor family (D1R, D2R, D3R, D4R and D5R) and their binding partners (Arr-2, Arr-3, G-protein: Gq, Gz, Gt2, Gi1, Gi2, Gi3, Gs(sh), Go, Gslong) to determine various chemical,

biological, and physical characteristics that could mediate their coupling. Complexes were analyzed to assess the energetic determinants important for the affinity and the specificity of the receptor. We assembled a web-server for easy access to this information

(<http://45.32.153.74/gpcr/>).

We developed and published another 2 web-servers:

<http://milou.science.uu.nl/services/SPOTON>. SpotON has, since its

recent publication, more than 160 users from all over the world that run more than 6000 jobs. We also use our computational pipeline, SpotOn, to determine several features regarding structure and sequence of all predicted HS in the complexes of the non-redundant database PPI4DOCK. By doing so, we present a novel big data insight into protein-protein interfacial and HS chemical, physical and structural characterization. It can be found at <http://45.32.153.74/spotondb/> & <http://milou.science.uu.nl/services/SPOTONDB/>.

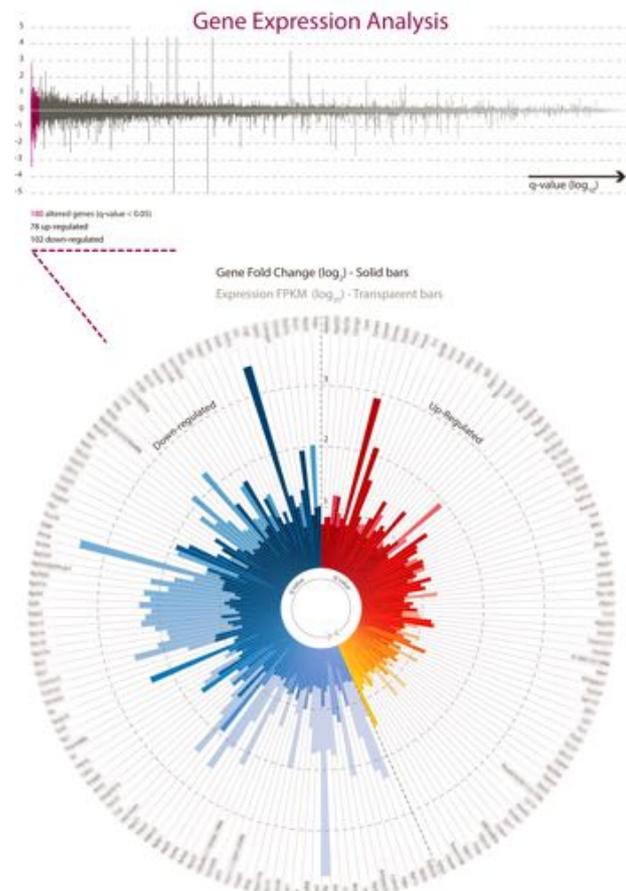


Fig.1. Gene expression data analysis from an RNAseq experiment. (Top panel) All transcripts detected by RNAseq analysis on the mouse brain; highlight in purple are 180 genes significantly changed between control and experimental condition; fold change is drawn on the y-axis. (Bottom panel) Starburst display showing relative fold change in gene expression in experimental group (solid bars) of down-regulated (blue) and up-regulated genes (red). Absolute abundance of a given transcript is given by Fragments Per Kilobase of transcript per Million mapped reads (FPKM in log₂₀) as overlaid transparent bars. Confidence level are FDR correct p-values depicted as warmer to lighter color tone (all genes depicted have q value < 0.05).

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 nitrite:nitrate:nitric oxide pathway, encompassing the non-enzymatic production of nitric oxide from dietary nitrite in the gastric compartment and the brain.

MAIN ACHIEVEMENTS

The main achievements incorporate both, technological and scientific components.

Technological developments:

1. We have developed ceramic-based multisite platinum microelectrode arrays (MEAs) for multisite oxygen recording in vivo in the extracellular space of the brain of anaesthetized rats and demonstrated its adequate analytical properties for in vivo studies in animal models of CNS disease and dysfunction.

2. MEAs chronically implanted in the brain of behaving rodents, demonstrated that both basal and phasic changes in tissue pO₂ can be monitored in real time. Using a model of status epilepticus induced by local administration of pilocarpine, we further demonstrated that fast sampling amperometry is a seamless approach towards concurrent recording of chemical and electrical events in the brain. Combining the study of changes in neurotransmission and the function of neuromodulatory systems or neurometabolic coupling with that of neuronal activity contribute to expand our understanding of the underlying mechanisms of pathological brain states such as epilepsy.

Scientific achievements:

1. We have used an innovative multimodal approach, encompassing metabolic, electric and hemodynamic measurement, tailored to study spread depolarization (SD) events in rat brain. The new MEA-based design, directly implanted in the brain tissue, provided simultaneous neurometabolic and electrophysiological information, revealing local rapid fluctuations in lactate and glucose associated with neuronal

activity (LFP-related currents) in the cortex of anesthetized rats during SD.

2. By using implanted microarrays in rat hippocampus of normal and triple transgenic models of Alzheimer's disease (AD) we have supported that neuronal-nitric oxide signaling is operative during the course of AD pathology, being altered only in the later stages of the disease. In turn, ensued neurovascular coupling is impaired at much earlier stages. It is thus suggested that the impairment in neurovascular coupling is primarily due to cerebrovascular rather than neuronal dysfunction.

This notion underscores cerebrovascular dysfunction as a fundamental process in AD pathophysiology and its significant impact in the AD associated cognitive impairment.

3. The strict energetic demands of the brain require that nutrient supply and usage be fine-tuned in accordance with the specific temporal and spatial patterns of ever-changing levels of neuronal activity. We have provided a conceptual background on how both neurovascular and neuroenergetic coupling are compromised in aging, traumatic brain injury, epilepsy and age-associated neurodegenerative disorders such as Alzheimer's disease and Parkinson's

redox balance may contribute to divert nitric oxide bioactivity from regulation to dysfunction.

4. Impairment of energy metabolism is a hallmark of brain aging and several neurodegenerative diseases, such as the Alzheimer's disease (AD). We have put forward an integrated hypothesis for the role of a metabolic-inflammatory axis encompassing the bioenergetic activity, brain inflammatory responses and their redox regulation in healthy brain aging and neurodegenerative diseases. The dynamic interactions among these systems in terms of their causative or in-tandem occurrence and how the systemic environment, e.g., insulin resistance, diabetes, and systemic inflammation, provide an integrated view on their impact on brain function.

5. We have revealed molecular mechanisms underlying the anti-inflammatory action of polyphenols from red wine extract and Portuguese blueberries in epithelial cellular models, in particular the inhibition of the JAK/STAT pathway by luteolin and the inhibition of cyclooxygenase-2 and inducible nitric oxide synthase by anthocyanines as a critical mechanism by which these polyphenols exert their intestinal anti-inflammatory actions.

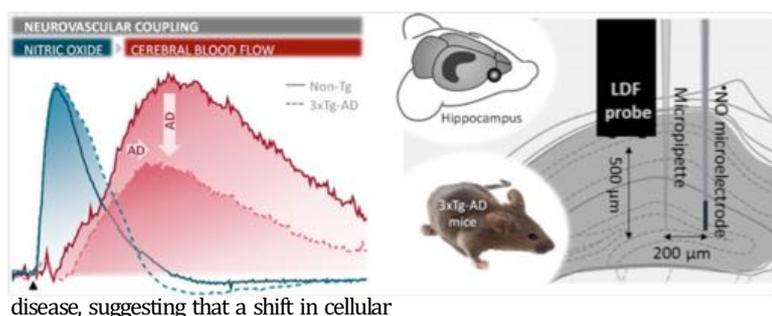


Fig. 1. Neurovascular coupling mediated by neuronal-derived nitric oxide in the hippocampus of the Alzheimer triple transgenic mouse model. Interrelated dynamics of nitric oxide and local blood flow is impaired as compared with normal animals.

NEUROENDOCRINOLOGY AND AGING | (Head: Claudia 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 aimed 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?
- Does 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?
- Does obstructive sleep apnea induces aging?

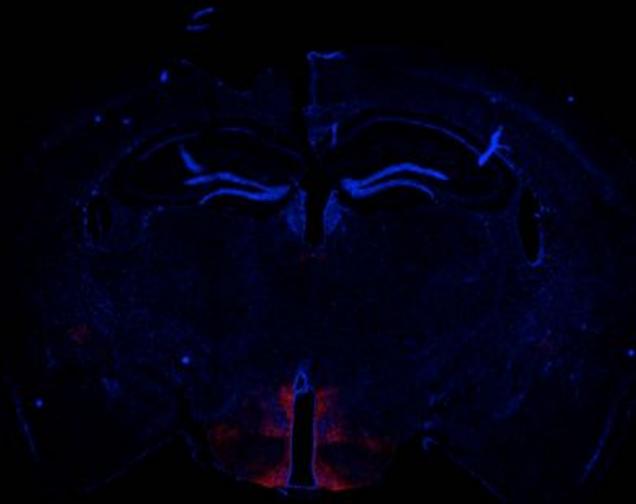


Fig. 1 - Neuropeptide Y immunoreactivity (red) in the hypothalamus of mouse brain. Nuclei (blue)

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 (HGPS). 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 IMAGING AND COGNITIVE NEUROSCIENCE | (Head: Miguel Castelo-Branco)

Objectives

Our group has continued to be at the national forefront of leadership 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 just published as leaders a consortium paper within the JNPD European program on biomarkers of Alzheimer Disease, and the results of the first clinical trial in Portugal concerning Medical Devices (a new BCI interface for autism rehabilitation) This group has made substantial interdisciplinary contributions in the fields of visual science, systems neurobiology, clinical neuroscience and biomedical Engineering with a focus on imaging. Basic science achievements and Translational Research Achievements:

Clinical Neuroscience and Translational Research

Achievements are highlighted by 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 now achieved. This led to more publications in Neurology one of the top Journals in the field of Neurology and Brain, a top Journal in the field. The ability to contribute to collaborative human and animal

translational has led to publications integrating human and animal neurodevelopmental phenotypes. 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 we now integrate a new IMI-2 H2020 initiative. 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

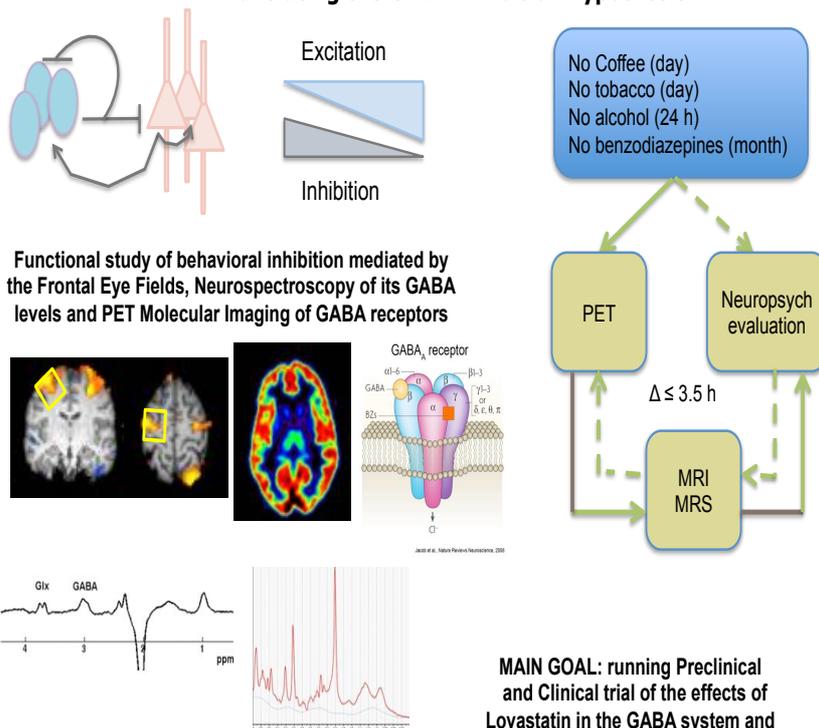
brain computer interfaces. These methodological achievements led to several individual and group prizes were awarded to the group in different fields.

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, the world leader in cyclotron production, we

are preparing new applied research ventures with new intellectual property development (3 additional patents).

Translating the GABA inhibition hypothesis



MAIN GOAL: running Preclinical and Clinical trial of the effects of Lovastatin in the GABA system and behavioral impact in inhibition, USING SIMILAR OUTCOME MEASURES IN HUMANS AND ANIMALS

Objectives

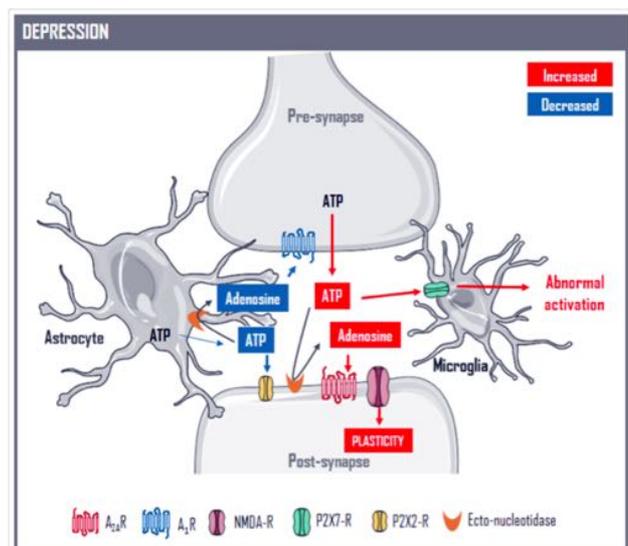
The general objective of the group is to identify modulation systems that can be targeted to interfere with the evolution of neurodegenerative diseases, with a central focus on purines (adenosine and ATP). We mostly focus on the initial stages of neurodegenerative disorders, under the working hypothesis 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) and modified microglia-dependent neuro-inflammatory context (Catarina Gomes). 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-Moderate intake of caffeine reverts memory dysfunction in animal models of depression and of Alzheimer's disease.
- 2-Definition of the electrophysiological effects of caffeine in the prefrontal cortex of rodents and humans.
- 3-Adenosine A2A receptors (A2AR) control synaptic plasticity in the pre-frontal cortex, where they tightly synergize with dopamine D2 receptors providing a rationale for the ability of caffeine and A2AR antagonists to control mood and mood disorders.
- 4-A2AR control motor dysfunction and cerebellar degeneration in an animal model of Machado-Joseph's disease
- 5-A2AR control microglia remodeling associated with anxiety.
- 6-A2AR function is controlled by the orphan receptor GPR37.
- 7-P2Y1 (ATP) receptors critically control glutamate-induced excitotoxicity.



OBJECTIVES

As a general aim, the research group 'Mitochondrial Dysfunction and Signaling in Neurodegeneration' has been investigating cellular mechanisms affecting early and progressive nature of still incurable neurodegenerative disorders. In 2017, the group focused on studying two relevant movement disorders, Parkinson's disease (PD) and the most prevalent polyglutamine-expansion disorder, Huntington's disease (HD). Therefore, we determined the impact of modified redox signaling pathways in cellular models of PD in the human neuroblastoma cell line SH-SY5Y overexpressing alpha-synuclein (α -syn). Of interest, α -syn is not only a major component of Lewy bodies found in sporadic and inherited forms, but also mutations in the gene encoding α -syn and duplications and triplications of wild-type (WT) α -syn have been associated to familial forms of PD. Thus, we analysed the effects caused by WT α -syn overexpression in the susceptibility to oxidative stress

induced by iron (described to accumulate in PD) and further determined changes in proteins involved in the antioxidant activity, in SH-SY5Y cells expressing WT α -syn in a doxycycline (Dox) regulated manner (Tet-Off system) as a PD *in vitro* model.

Alterations in cellular metabolism and mitochondrial dysfunction have a crucial role in HD pathogenesis, raising the possibility of developing epigenetic-based therapeutic interventions that enhance mitochondrial and metabolic defenses. Thus, we analysed mitochondrial-based therapeutic strategies in HD by regulating sirtuins and histone deacetylase (HDAC) activities. Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD⁺)-dependent Lys deacetylase that regulates longevity and enhances mitochondrial metabolism. However, compounds exerting opposed actions on SIRT1 through both activation and inhibition were shown to trigger similar survival pathways and

ameliorate neuropathological mechanisms in HD; to clarify such paradox, we thoroughly analysed mitochondrial function and markers of organelle biogenesis in central and peripheral models expressing full-length human mutant huntingtin (mHTT), the protein affected in HD. Finally, considering that transcriptional deregulation and changes in mitochondrial bioenergetics, including pyruvate dehydrogenase (PDH) dysfunction, have been described in HD, we analyzed the influence of HDAC inhibitors in improving PDH function in striatal cells expressing full-length mHTT, and confirmed the effect of sodium butyrate in HD YAC128 mouse model. Data supported PDH as a promising therapeutic target in HD, as summarized in the image illustrating the research of the group.

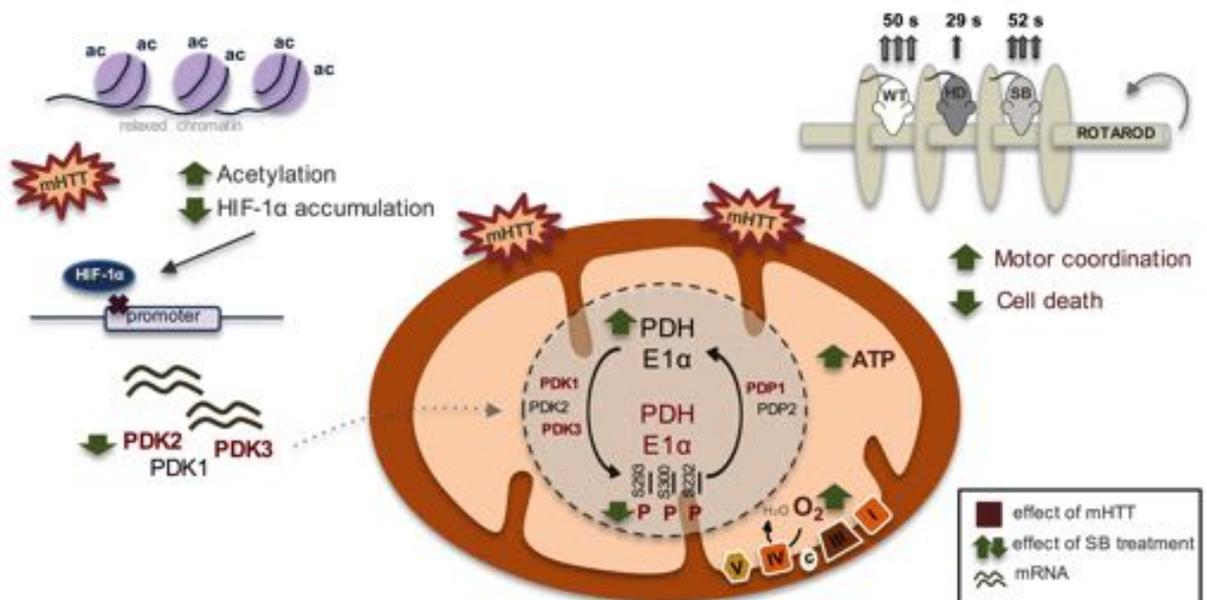


Fig. 1- PDH as a therapeutic target in HD – effect of sodium butyrate (Naia and Cunha-Oliveira et al., J. Neurosci., 2017)

MAIN ACHIEVEMENTS

In the context of PD, we defined the occurrence of oxidative stress in SH-SY5Y cells overexpressing WT α -syn in a doxycycline (Dox) regulated manner, before and after exposure to iron, and determined the changes in proteins involved in the intracellular antioxidant defense system. Data evidenced an increase in caspase-3 activation and diminished reducing capacity of -Dox cells, associated with decreased activity of mitochondria complex I and reduced mitochondrial transcription factor A (TFAM) levels in these cells. Furthermore, total and mitochondrial reactive oxygen species (ROS) levels were higher under basal conditions in cells overexpressing α -syn (-Dox) and this increase was apparently correlated with diminished levels and activities of SOD1 and SOD2 in -Dox cells. Moreover, both reduced and oxidized glutathione levels were diminished in -Dox cells under basal conditions, concomitantly with decreased activity of glutamate-cysteine ligase (GCL) and reduced protein levels of GCL catalytic subunit. The effects caused by iron were mostly independent of α -syn expression and triggered different antioxidant responses to possibly counterbalance higher levels of free radicals. Overall, data suggested that overexpression of α -syn modifies the antioxidant capacity of SH-SY5Y cells due to altered activity and protein levels of SODs (1 and 2), and decreased glutathione pool.

In the context of HD, we tested the influence of resveratrol (RESV, a SIRT1 activator) *versus* nicotinamide (NAM, a SIRT1 inhibitor) in counteracting mitochondrial dysfunction in striatal and cortical neurons isolated from YAC128 transgenic mice embryos, HD human lymphoblasts and an *in vivo* HD model. HD cell models displayed deregulated mitochondrial membrane potential and respiration, decreased PGC-1 α and TFAM protein levels, linked to mitochondrial DNA loss. Remarkably, RESV restored these parameters, while NAM increased NAD⁺ levels, providing a positive add on mitochondrial function in *in vitro* HD models. In agreement with *in vitro* data, RESV treatment improved motor coordination and learning and enhanced expression of mitochondrial-encoded electron transport chain genes in YAC128 mice. In contrast, high concentrations of NAM blocked mitochondrial-related transcription, worsening motor phenotype. Overall, data indicate that activation of SIRT1 by RESV improved gene transcription associated to mitochondrial function in HD, which may partially control HD-related motor disturbances.

We previously showed that histone deacetylase inhibitors (HDACi), trichostatin A and sodium butyrate (SB), ameliorated mitochondrial function in cells expressing mutant huntingtin. Thus, we investigated

the effect of HDACi on regulation of PDH activity in striatal cells derived from HD knock-in mice and YAC128 mice. Mutant cells exhibited decreased pyruvate dehydrogenase (PDH) activity and increased PDH E1 α phosphorylation/inactivation, accompanied by enhanced protein levels of PDH kinases (PDK)1/3. Treatment with SB and sodium phenylbutyrate, another HDACi, recovered cell viability and overall mitochondrial metabolism in mutant cells. Exposure to SB also suppressed hypoxia-inducible factor-1 (HIF-1 α) stabilization, and decreased the transcription of the two most abundant PDK isoforms, PDK2 and PDK3, culminating in increased PDH activation in mutant cells. Concordantly, PDK3 knockdown improved mitochondrial function, emphasizing the role of PDK3 inactivation on positive effects achieved by SB treatment. YAC128 mouse brain presented higher mRNA levels of PDK1-3 and PDH phosphorylation, as well as decreased energy levels, which were significantly ameliorated following SB treatment. Furthermore, enhanced motor learning and coordination was observed in SB-treated YAC128 mice. These results suggested that HDACi, particularly SB, promoted the activity of PDH in HD brain, helping to counteract HD-related deficits in mitochondrial bioenergetics and motor function.

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

OBJECTIVES:

The general objective of the group is the identification of new biomarkers of aging and brain disorders leading to the design of patient-tailored preventive and therapeutic interventions, promoting the translation to the clinic of fundamental research. For this purpose a close interaction with clinicians at Coimbra University Hospital (CHUC) has been established, allowing access to

human biological samples and clinical data, with a focus in neurodegenerative and neuropsychiatric diseases, neurodevelopment and bigenomic disorders and cancer.

The integration in international research consortia namely the Joint Programing in Neurodegenerative Disorders (JPND) and Early Alzheimer's Disease Consortium (EADC) has contributed to the

development of standard methodologies for sample storage and analysis, fulfilling the international criteria of quality control. The establishment of international and national networks has led to the development of new methodological approaches that have been applied to the chin pre-clinical and clinical research.

MAIN ACHIEVEMENTS:

1. *Neurodegenerative and neuropsychiatric diseases*

During this year, we have evaluated if the addition of A β 40 to the core cerebrospinal fluid (CSF) biomarker profile (A β 42, total and phosphorylated Tau) would improve categorization of Mild Cognitive Impairment (MCI) and more accurately predict progression to Alzheimer's disease (AD). The role of a frequent polymorphism of Butyrylcholinesterase (BuChE, the K-variant) in MCI progression to AD, was also addressed. Moreover, we have participated in a large multicenter study to assess the diagnostic accuracy of Neurofilament Light (NFL) quantification in CSF for the differential diagnosis of neurodegenerative dementias, with special focus on sporadic and genetic forms of prion diseases. Several genetic tests have been also carried out to provide the molecular diagnosis of different neurodegenerative diseases such as Parkinson disease, Alzheimer disease, Frontotemporal lobar degeneration and Amyotrophic lateral sclerosis. These genetic tests included known causative genes (*PSEN1* and *2*, *APP*, *MAPT*, *PGRN*, *C9orf72*, *Parkin* and *LRRK2*), as well as, susceptibility risk genes (*APOE*, *GBA* and *TREM2*) with a potential role towards an early and accurate diagnosis. Several predictive tests, to identify asymptomatic relatives at high-risk, in the context of formal genetic counselling, were also performed after the identification of

the genetic defect in a family. During

2017, the group was also committed to set up a new methodology to achieve a deep genetic profiling of these patients using a high-throughput Next Generation Sequencing assay (NGS) that targets a panel of the known causative genes.

In 2017 we have applied different mass spectrometry approaches to answer integrated biological questions. We pursued the studies focused on the identification of biomarkers for Parkinson's disease, autism and aging using proteomic and metabolomics approaches, integrated in a collaborative intra-institutional project (SAICTPAC/0010/2015, initiated in February 2017). The secretome analysis of stem cells, performed in collaborative research with external groups at University of Minho, was applied to identify neurodegenerative blood biomarkers of Parkinson's disease. These methodologies were also used to improve diagnosis accuracy of psychotic disorders. Furthermore, we demonstrated the diagnostic accuracy of combined assessment of arousal-attention to detect delirium superimposed on dementia and, in a study designed to investigate the relationship between ADHD symptoms and psychopathic traits in criminal offenders. ADHD symptoms were found to be highly prevalent among offenders and might have a modulating effect on the course of delinquent behavior.

2. *Biomarkers of neurodevelopment and other diseases*

Regarding neurodevelopment diseases, we helped to characterize human iPSC line from a patient with laterality defects and associated congenital heart anomalies carrying a *DAND5* missense alteration. In a cohort of patients with autism, the assessment of Copy number Variants, showed the importance of different chromosomal regions and genes in this neurodevelopmental disorder. We have also participated in a collaborative study that showed metabolite changes in the plasma of patients with age-related macular degeneration as compared to controls, using Nuclear Magnetic Resonance.

The genomic methodologies used in the characterization of neurodevelopment pathologies were applied in the evaluation of cancer biomarkers. A specific set of genes as epigenetic diagnostic and prognostic biomarkers in oral cancer was identified.

3. *Biomedical Research in Bigenomic Disorders and Personalized Medicine*

Several studies were carried out to elucidate the cellular pathogenic processes involved in patients' phenotypes of Mitochondrial Respiratory Chain (MRC) diseases. As an example, a case of chronic progressive external ophthalmoplegia (CPEO) presenting

the common deletion and one mt-tRNA^{Ser1} sequence novel variation in muscle and fibroblasts. Both genetic alterations segregate with the biochemical defect in muscle. There is an inability to produce mtDNA-encoded proteins, leading to incomplete fully assembled OXPHOS complexes and inefficient respiration and depolarization of $\Delta\Psi_m$. Moreover, ultrastructural alterations were found by TEM, suggestive of autophagy impairment. The results obtained allowed to confirm the high pathogenic potential of unclassified or novel mtDNA variants

contributed for significant developments in the field.

Foregoing pharmacogenomic and metabolic studies focused on drug addicts, aiming to understand the genetic factors underlying heterogeneity in detoxification fulfillment and diversity in response to treatment. A group of 106 drug addicts seeking treatment was evaluated, and genetic screening of *COMT* polymorphism p.Val158Met was performed. Significant differences were observed in genotype and allele frequencies between drug abusers and controls.

Moreover, paranoid ideation was associated with Met/Met genotype, probably due to the lower enzyme activity that leads to higher synaptic dopamine levels. The comparison of three different methods (PCR-RFLP, TaqMan® Drug Metabolism Genotyping Assays, and Sanger Sequencing) for genotyping *CYP2D6* alteration c.100C>T (rs1065852) in a group of 24 Portuguese subjects was performed and advantages concerning time spending, straightforwardness, reliability, and accuracy were analysed.

OBJECTIVES

The Group has been mainly focused in chronic disorders that affect the brain and retina, but also other organs such as the heart, liver, kidney, bladder and bone.

In general, our goals are:

- to elucidate the molecular and cellular mechanisms underlying the pathogenesis of chronic disorders affecting the brain, retina and other organs;
- to elucidate the mechanisms of action of some drugs already used in pharmacotherapy and the mechanisms underlying drug toxicity;
- to identify new potential drug targets and more efficient therapeutic options for the treatment of chronic disorders affecting those organs and evaluate the response to therapy.

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

Vision Sciences

We have a major interest in diabetic retinopathy (DR) and glaucoma. DR is a microvascular disease and the blood-retinal barrier breakdown is a hallmark. Moreover, DR is characterized by neural degeneration and neuroinflammatory processes where microglia has a major role,

features also found in glaucoma. We aim looking for protective strategies against vascular and neural dysfunction/degeneration by exploring the potential of modulating several neurotransmitter/neuromodulator systems such as adenosine and neuropeptide Y. These systems can exert both neuroprotective and anti-inflammatory effects.

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. Moreover, we intend to better understand the mechanisms of transport through barriers, to define better therapeutic modalities for ocular diseases.

Neuroscience

Psychostimulants like amphetamines cause significant brain damage leading to neurological and psychiatric anomalies. Methylphenidate is the most frequently prescribed drug for the symptomatic treatment of attention deficit hyperactivity disorder. We intend to clarify the impact of amphetamines and methylphenidate on the brain, given a particular attention to their toxicity, blood-brain barrier (BBB)

dysfunction, neuroinflammation, mood behaviour and cognitive dysfunction, as well as to evaluate the impact of physical exercise as a neuroprotective / neurorestorative strategy.

Diabetes during pregnancy is a major concern. The exact mechanisms by which maternal diabetes negatively affects offspring neurodevelopment remain to be clarified. The objectives are: (1) to identify the neural correlates of maternal diabetes-induced cognitive deficits; (2) to evaluate if diabetes-induced changes in the offspring are gender-specific; (3) to evaluate the effectiveness of the currently used insulinotherapy to prevent diabetes-induced neurodevelopmental changes.

We also aim to understand how microglia respond to immune challenges, namely during brain development, and the way this response impact on brain circuits and mental health.

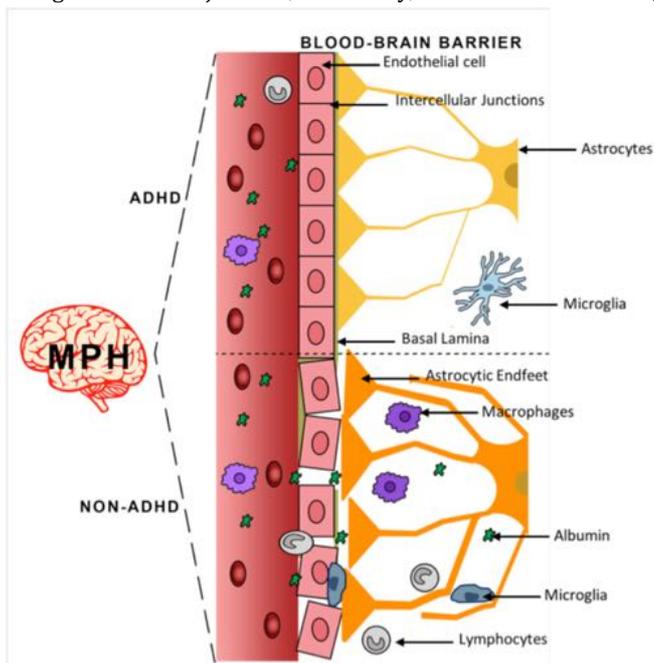
Stem Cells

To develop effective therapeutic regimens against cancer stem cells (CSC) in osteosarcoma, by targeting the signaling mechanisms sustaining stem cells self-renewal.

Experimental Therapeutics

We have been focused on the impact of therapeutic and nutraceutical options in cardiometabolic and cardiorenal disorders, such as type 2 diabetes and its vascular complications (namely nephropathy), as well as chronic renal failure.

We aim to identify improved models, including animal models of ocular melanoma and retinoblastoma, to develop new therapeutic approaches including photodynamic therapy (PDT), and for screening of new photosensitizers for PDT, and to evaluate the efficacy of novel photosensitizers for PDT in cancer. We are also exploring cold atmospheric plasma as a therapeutic option for retinoblastoma.



MAIN ACHIEVEMENTS

Retinal degenerative disease and neuroinflammation:

We demonstrated that the drug calcium dobesilate, which is in therapeutical use for more than four decades, is protective against neuroinflammation and oxidative/nitrosative stress in the retina. Moreover, treatment with the A2A receptor antagonist KW6002, as well as caffeine intake, inhibit microglia reactivity and protect retinal cells against transient ischemic damage. Still regarding microglia in the retina and brain, the internalization of the vitamin C transporter, SVCT2, mediated by caveolin-1, triggers an inflammatory phenotype in microglia.

Neurodevelopment disorders and drugs of abuse:

We found that prenatal exposure to dexamethasone is associated with a gender-specific remodeling of microglial cell processes in the prefrontal cortex: males show a hyper-ramification and increased length whereas females exhibit a decrease in the number and in the length of microglia processes. Moreover, microglial cells re-organization responded in a gender-specific manner to the chronic treatment with a selective adenosine A2A receptor antagonist, which was able to ameliorate microglial processes alterations and anxiety

behavior in males, but not in females.

Methamphetamine induces anhedonic-like behavior and impairs frontal cortical energetics in mice.

An extended-access to methamphetamine self-administration followed by forced abstinence triggers an increase of BBB permeability.

Methamphetamine interferes with aquaporin-4, a water channel, causing the BBB breakdown and brain edema in both striatum and hippocampus, which culminated in locomotor and motivational impairments.

A high dose of methylphenidate promotes the BBB permeability and elicits an anxiety-like behavior in an animal model of Attention Deficit Hyperactivity Disorder (ADHD) and control animals. In the ADHD model, the lower dose of MPH had a beneficial effect since it balanced both the immunity and behavior.

Stem cells and experimental therapeutics:

Wnt/b-catenin signaling is active and plays a pivotal role in the self-renewal and survival of Cancer Stem Cells (CSCs). The pharmacological inhibition of this pathway represses tumor growth in a xenograft mouse

model, offering a preclinical proof-of-concept for the use of conventional chemotherapy combined with specific targeting of this signaling pathway in the clinical setting. Moreover, the metabolic modulator Metformin exerted a preferential cytotoxicity against CSCs and improved doxorubicin-induced cytotoxicity, via repression of the signaling machinery that safeguards self-renewal, as a result of their inability to deal with the subsequent energy crisis induced by Metformin-mediated mitochondrial inhibition.

New ruthenium (II) phthalocyanines containing 4-12 PEG chains with hydroxy, amino and ether terminal groups at their axial positions display high singlet oxygen generation quantum yield. These complexes are nontoxic photosensitizers *per se*, accumulate in bladder cancer cells and have high phototoxic efficiency.

Liver iron is a major regulator of hepcidin gene expression via BMP/SMAD pathway in a rat model of chronic renal failure under treatment with high rHuEPO doses.

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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 on characterizing and manipulating the microbiome in neurodegenerative disorders. Data from the strand also reinforced the need to establish sex/gender-specific preventive and/or therapeutic approaches and an appropriate time window for the efficient treatment against metabolic and neurodegenerative conditions and this will be followed up, also focusing on vascular and cardiac changes in metabolic-based disorders, in collaboration with the University Hospitals. We will also continue to follow our heart failure (HF) data in patients with and without diabetes given that epicardial adipocytes may be a possible therapeutic target for HF treatment. Finally we will make full use of our novel NMR-based methodology to animal models of non-alcoholic fatty liver disease in order to determine the contributions of glucose and fructose to lipid biosynthesis.

CELL METABOLISM AND QUALITY CONTROL GROUP

Paula Isabel Moreira	PhD (<i>Head of Group</i>)
Américo Figueiredo	PhD
António Manuel Pires	PhD
Armanda Santos	PhD
Bruno Neves	PhD Collaborator
Carla Isabel dos Marques	PhD
Cláudia M. Fragão Pereira	PhD
Cristina Maria Sena	PhD
Elizabete Jorge	PhD
Hans Christian Eickhoff	PhD
Henrique Manuel Girão	PhD
João Vasco Ferreira	PhD
Lino Manuel Gonçalves	PhD
Maria Teresa Cruz	PhD
Raquel Maria Fino Seça	PhD
Rui Miguel Baptista	PhD
Rui Travasso	PhD
Sandra Morais Cardoso	PhD
Ana Duarte	Post Doctoral Fellow
Ana Raquel Esteves	Post Doctoral Fellow
Ana Cristina Rosa da Silva	Post Doctoral Fellow
Cristina Carvalho	Post Doctoral Fellow
Diana Silva	Post Doctoral Fellow
Monika Zuzarte	Post Doctoral Fellow
Paulo Nuno Matafome	Post Doctoral Fellow
Rosa Maria Resende	Post Doctoral Fellow
Sonia Correia	Post Doctoral Fellow
Steve Mendes Catarino	Post Doctoral Fellow
Susana Cardoso	Post Doctoral Fellow
Ana Raquel Costa	PhD Student
Daniela Almeida	PhD Student
Daniel Santos	PhD Student
Emanuel Candeias	PhD Student
Isabel Ferreira	PhD Student
João Calmeiro	PhD Student
Jorge Silva	PhD Student
Paula Cristina Martins	PhD Student
Ricardo Jorge Pereira	PhD Student
Tânia Sofia Marques	PhD Student
Teresa Rodrigues	PhD Student
Tiago Daniel Rodrigues	PhD Student
Tiffany Pinto	PhD Student
Ana Catarina Pereira	MSc Student
Isabel Ferreira	MSc Student
Fernanda Carrilho	MD
Liliana Rita Velindo Letra	MD
Paula Martins	MD
João Pedro Oliveira	MD
Paulo Pereira	PhD Collaborator
M ^a Inês Alves	MSc Student

MITOCHONDRIA, METABOLISM AND DISEASE GROUP

Paulo Oliveira	PhD (<i>Head of Group</i>)
Anabela Pinto Rolo	PhD
António Moreno	PhD
Carlos Palmeira	PhD
José Teixeira	PhD
Liljana Georgievska	PhD
Liliana Montezinho	PhD
M ^a Cármen Alpoim	PhD
Vilma Sardão	PhD

Duarte Oliveira	PhD Collaborator
Filomena Silva	Post Doctoral Fellow
João Paulo Teodoro	Post Doctoral Fellow
M ^a Teresa Oliveira	Post Doctoral Fellow
Ricardo Marques	Post Doctoral Fellow
Adriana Marques	PhD Student
Ana Raquel Coelho	PhD Student
Cláudia Deus	PhD Student
Eurico Serrano	PhD Student
Guida Bento	PhD Student
João Amorim	PhD Student
João Demétrio Martins	PhD Student
Luciana Ferreira	PhD Student
Ricardo Amorim	PhD Student
Rodrigo Carreira	PhD Student
Rui Silva	PhD Student
Rui Simões	PhD Student
Caroline Veloso	Grant Technician
Cláudio Costa	MSc Student
Inês Cardoso	MSc Student

METABOLIC CONTROL GROUP (*Head: John Griffith Jones*)

John Griffith Jones	PhD (<i>Head of Group</i>)
Ana Paula Sousa	PhD
Ana Teresa Almeida Santos	PhD
Eugenia Carvalho	PhD
João Alves	PhD
João Ramalho Sousa Santos	PhD
Ana Catarina Fonseca	Post Doctoral Fellow
Ana Caldeira Burgeiro	Post Doctoral Fellow
Ana Sofia Rodrigues	Post Doctoral Fellow
Aryane Pinho	Post Doctoral Fellow
Ermelindo Carreira Leal	Post Doctoral Fellow
Ivan Martins Viegas	Post Doctoral Fellow
Ludgero Tavares	Post Doctoral Fellow
Maria Alexandra Amaral	Post Doctoral Fellow
M ^a Cristina Barosa Oliveira	Post Doctoral Fellow
Paula Cristina Mota	Post Doctoral Fellow
Renata Tavares	Post Doctoral Fellow
Sandra Catarina Amaral	Post Doctoral Fellow
Adalberto Fernandes	PhD Student
Adriana Fontes	PhD Student
Cátia Santos	PhD Student
Getachew Debas Belew	PhD Student
Giada Di Nunzio	PhD Student
João Rito	PhD Student
João Silva	PhD Student
M ^a Inês Sousa	PhD Student
Mireia Alemany i Pagès	PhD Student
Sara Rebelo	PhD Student
Bibiana Silva	MSc Student
Judith Pereira	MSc Student
M ^a Carolina Reis	MSc Student
Raquel Fernandes	MSc Student
Alexandra Carvalho	Technician

OBJECTIVES

- To develop a disease-modifying treatment for Alzheimer’s disease (AD) based on BACE1 inhibition.
- To evaluate how mitochondrial DAMPs, which trigger sterile pro-inflammatory immune responses, drive AD and Parkinson’s Disease (PD) neurodegeneration.
- To assess how gut, blood or brain microbiota of AD and PD patients could trigger neuronal innate immunity activation through mitochondrial dysfunction.
- To determine new therapeutic strategies to avoid mild chronic inflammation, thus preventing AD and PD relevant protein oligomers formation and mitochondrial damage.

- To evaluate the responses of neuronal cells to different glycemic exposures alongside to elucidate the role of mitochondrial uncoupling protein 2 (UCP2) in regulating such responses.
- Understand the mechanisms of diabetic complications and the mechanisms of the metabolic dysregulation observed in prediabetes, with particular emphasis on advanced glycation end-products (AGE) in a translational approach from molecular mechanisms to humans. Our interests lie on investigating the role of such compounds in the development of the metabolic dysregulation in obesity, which ultimately leads to the metabolic syndrome and type 2 diabetes.

Evaluate the role of ubiquitin-dependent lysosome proteolysis and intercellular communication in cardiovascular diseases

-The research developed has focused mainly on two areas: the molecular mechanisms involved in inflammation and changes in the cells of the immune system associated with the inflammatory response; and the development of methodologies to evaluate the ability of natural and industrial chemicals to modulate innate immunity. 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.

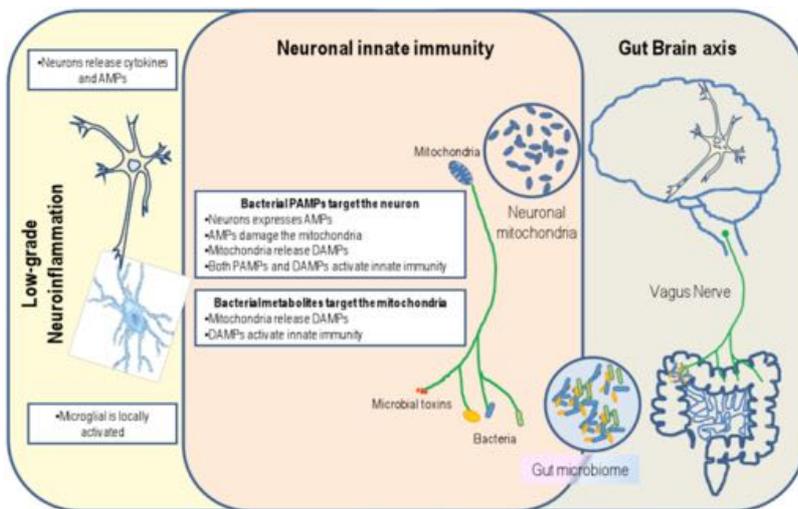


Fig. 1 - Schematic diagram indicating that neuronal mitochondria are primary gut bacteria targets. A dysbiotic gut harbors an inflammatory microbiota that could potentiate the production of microbial toxins. Either bacteria or bacterial toxins could activate innate immunity in the ENS and CNS through the vagus nerve, the gut-brain axis. Neuronal innate immunity is triggered by bacterial PAMPs or due to mitochondrial DAMPs. Mitochondrial damage may occur through the action of AMPs produced by the neuron as an arm of innate immunity activation or by the action of antibiotics produced by bacteria. PAMPs and mitochondria DAMPs activate the NLRs and TLRs leading to neuronal production of cytokines. These pro-inflammatory cytokines are released and activate low-grade inflammation through microglia. This chronic inflammation impacts neurons exacerbating AMPs production and mitochondrial damage. (Front. Physiol. 2018)

- To evaluate sex-associated alterations in estrogen/insulin-like growth factor-1 (IGF-1)/insulin-related signaling, oxidative stress markers, and AD-like hallmarks in middle-aged control and type 2 diabetic (T2D) rat brain cortices.
- To explore the effects of chronic, continuous, subcutaneous exposure to exendin-4 in brain cortical GLP-1/insulin/IGF-1 signaling, and in autophagic and cell death mechanisms in middle-aged (8 months old), male T2D GK rats.

- Understand the role played by perivascular adipose tissue in vascular disease associated with obesity and type 2 diabetes.
- Find therapeutic agents effective for preventing both metabolic and vascular complications of obesity in rodents.
- Help to elucidate new strategies for prevention vascular diseases in metabolic syndrome and diabetes mellitus.
- Prevent the rise of vascular complications associated with obesity and type 2 diabetes.

- To identify the mechanism(s) of action of newly identified anti-inflammatory compounds of natural origin

- To determine whether and which neuropeptide Y (NPY) receptors are expressed in human articular cartilage and the influence of gender, age and osteoarthritis

- To determine the role of NPY in modulating autophagy in human chondrocytes and whether it is impaired in aging and osteoarthritis.

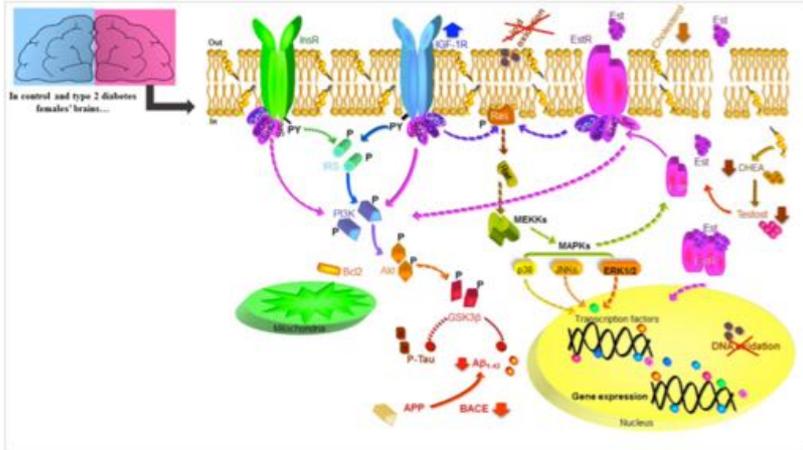


Fig. 2. Schematic diagram showing how sex hormones modulate brain susceptibility to neurodegenerative events. The higher blood and lower brain cholesterol levels in female rats suggest that its dysfunctional uptake into the brain cortex may also hamper peripheral estrogen uptake and/or its local brain steroidogenic metabolism. Despite the massive drop in IGF-1 levels in females' brains, particularly upon T2D, they might have developed some compensatory mechanisms towards the maintenance of estrogen, IGF-1, and insulin receptors function and of the subsequent Akt- and ERK1/2-mediated signaling. These may ultimately delay the deleterious AD-like brain changes (including oxidative damage to lipids and DNA, amyloidogenic processing of amyloid precursor protein and increased tau protein phosphorylation) associated with T2D and/or age (reproductive senescence) in female rats. (Mol. Neurobiol. 2017)

MAIN ACHIEVEMENTS

- The new BACE1 inhibitors we are developing decrease insoluble A β 40/42 brain levels in 3xTg-AD mice submitted to a chronic treatment suggesting that these compounds have the potential to be a disease-modifying therapy.

- PD and AD patients' mitochondrial pool triggers several pathogenic features observed in patients brains, such as the generation of protein aggregates; microtubule disassembly; disruption of intracellular trafficking and accumulation of autophagosomes and autophagic substrates. Since mitochondria are evolutionary descendants of endosymbiotic alphaproteobacteria, we speculate that human gut microbiota may

produce neuroactive toxins that target alphaproteobacteria and, "collaterally", their endosymbiotic successors, the mitochondria. Indeed, bacterial PAMPs alter mitochondrial function in mesencephalic and cortical neurons, namely a decrease in mitochondrial membrane potential and an increase in mitochondrial ROS production. Additionally, bacterial PAMPs activate the inflammasome and induce the production of AD and PD histopathologic hallmarks both perceived as an "arm" of neuronal innate immune response.

- Middle-aged diabetic females and males present distinct susceptibility to AD-like pathology. By demonstrating that differential sex

steroid hormone profiles/action may play a pivotal role in brain over T2D progression, the present study reinforces the need to establish sex-specific preventive and/or therapeutic approaches and an appropriate time window for the efficient treatment against T2D and AD.

z- Brain GLP-1/IGF-1 signaling and autophagy mediate exendin-4 protection against apoptosis in T2D rats. This study demonstrates that peripheral exendin-4 administration may constitute a promising therapy against the chronic complications of T2D affecting the brain.

- Mitochondrial uncoupling protein 2 (UCP2) is in the core of neuronal cells protection and/or adaptation against glucose variations-mediated

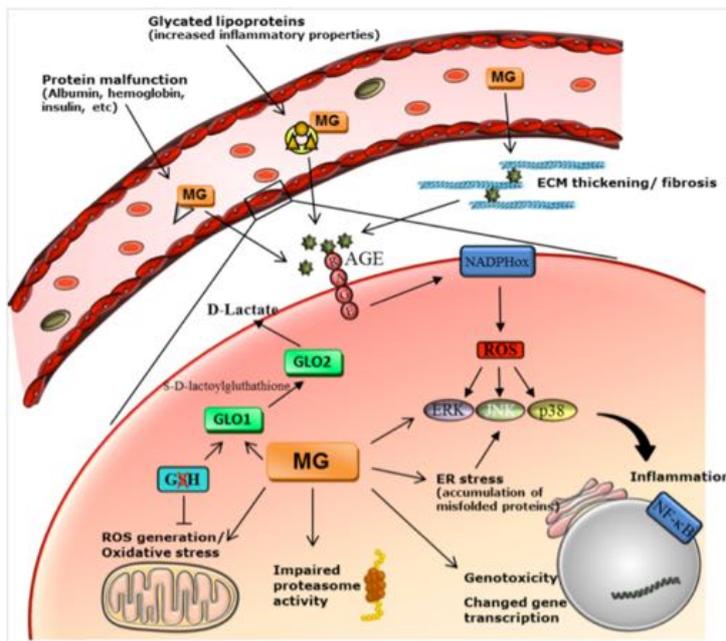


Fig. 3. Main mechanisms of action of methylglyoxal. Methylglyoxal can react with circulating proteins and lipoproteins, leading to protein malfunction and oxidized pro-inflammatory lipoproteins. MG accumulation in the ECM may lead to the modification of collagen and other structural proteins, causing ECM thickening and fibrosis. Binding of extracellular AGE to RAGE activates stress and inflammatory pathways. In the intracellular compartment, MG formation causes oxidative stress, accumulation of misfolded proteins, ER stress, genotoxicity (chemical modification of DNA) and changes in gene transcription due to modification of transcription factors and transcriptional regulators. MG may be detoxified by the glyoxalase system, a GSH-dependent process. In conditions of increased ROS production, GSH depletion compromises GLO1 function, while increased GLO1 function also leads to increased ROS generation due to depletion of antioxidant defenses. AGE, advanced glycation end products; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; GLO1, Glyoxalase 1; GLO2, Glyoxalase 2; GSH, Reduced glutathione; JNK, c-jun N-terminal kinase; MG, methylglyoxal; NADPHox, Nicotinamide adenine dinucleotide phosphate oxidase; NF-kB, nuclear factor kappa B; ROS, reactive oxygen species. (Med. Res. Rev. 2017)

effects and that other isoforms of neuronal UCPs can be upregulated to compensate the inhibition of UCP2 activity.

- Supplementation of diet-induced obese rats with the AGE precursor methylglyoxal leads to alterations of the vascular architecture and blood flow, leading to insulin resistance. Moreover, such effects are also observed in the adipose tissue angiogenic assay, where the accumulation of MG, either by its administration or by glyoxalase inhibition, leads to a concentration-dependent inhibition of angiogenic ability.

- Adipose tissue insulin resistance is known to cause lipolysis and fatty acid efflux from adipocytes. Diet-induced obese rats also have impaired fatty acid esterification and desaturation in the liver, also correlating with hepatic insulin resistance. Interestingly, the glyoxalase system is apparently modulated by the incretin GLP-1, which was observed to improve adipose tissue angiogenesis either by liraglutide treatment or after metabolic surgery.

- The deleterious effects of increased MG levels are also observed in the heart function evaluated by magnetic resonance, resulting in decreased stroke volume and peak ejection and filling rates. Similar observations occur in diabetic patients.

- Inflammation in PAT directly influences vascular disease of the underlying artery contributing to the endothelial dysfunction present in obesity.

- Adiponectin is able to normalize endothelial function in obese animal models by a mechanism that involved an increment in endothelial nitric oxide synthase phosphorylation and a decrement in PVAT inflammation.

- Sulforaphane and pyridoxamine in association normalize endothelial dysfunction in type 2 diabetes.

- Exosomes released by cardiomyocytes subjected to ischemia induce heart angiogenesis.

- miRNA-424 is a systemic marker of Pulmonary Arterial Hypertension; miRNA-424 targets SMURF-1 in cardiomyocytes and contribute to right ventricle hypertrophy.

- 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 and, by consequence, with distinct transcription kinetics of genes such as HMOX1, IL8, IL1B and CD86. Ultimately, our observations may help explain the distinct dendritic cells phenotype and T-cell polarizing profile triggered by skin and respiratory sensitizers.

- In bladder cancer cells (UMUC3), urolithin A is the most active molecule, promoting cell cycle arrest at the G2/M checkpoint, increasing apoptotic cell death and inhibiting PI3K/Akt and MAPK signaling.

- *G. robertianum* L. stem and leaf decoctions are particularly rich in tannins. The strong scavenging effects displayed by the stem extract suggest that its anti-inflammatory activity may partially result from its anti-radical capacities towards NO[•].

- A new class of sirtuin-1 activators with anti-inflammatory properties was identified. A patent application is being prepared.

- NPY receptors were found to be expressed in human chondrocytes and cartilage depending on gender and osteoarthritis, but not on age.

- NPY seems to activate autophagy in healthy, but not in osteoarthritic chondrocytes.

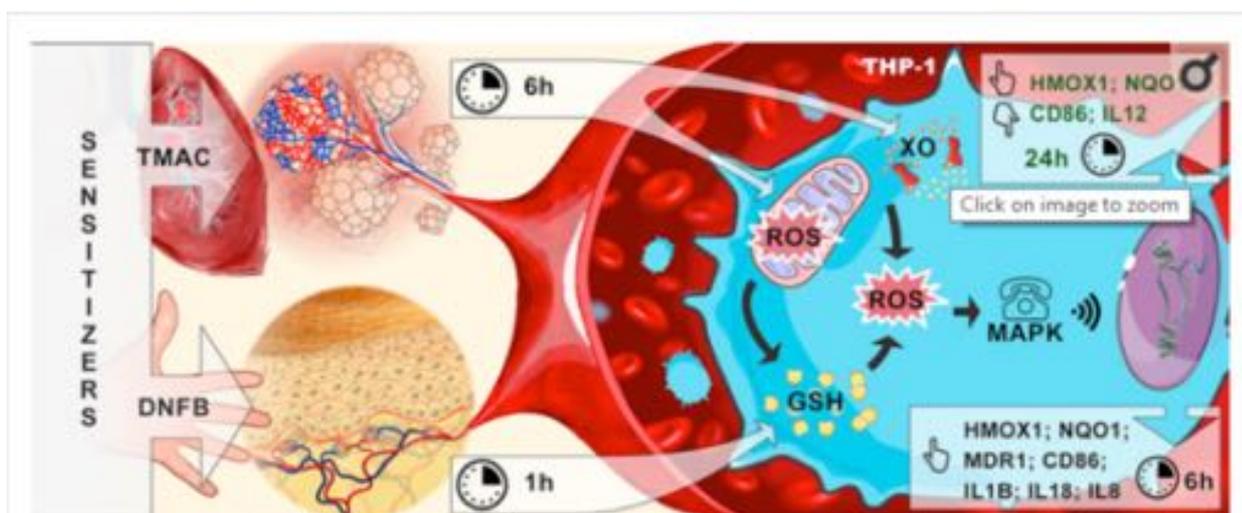


Fig. 4. Origin, nature, kinetics and role of redox imbalance triggered by respiratory and skin sensitizers in the human monocytic cell line THP-1. The thiol-reactive sensitizer 1-fluoro-2,4-dinitrobenzene (DNFB) directly reacts with cytoplasmic glutathione (GSH) causing its rapid and marked depletion which results in a general increase in reactive oxygen species (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 signalling pathways activation observed and, by consequence, with distinct transcription kinetics of genes such as HMOX1, IL8, IL1B and CD86 (Redox Biol. 2018)

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, playing an 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 cancer, cardiovascular and hepatic diseases, aging-related chronic diseases. The role of mitochondria in stem cell biology as well as the development of mitochondria-directed therapeutical agents. Specifically, the group is focused in various research lines:

1) Mitochondrial 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

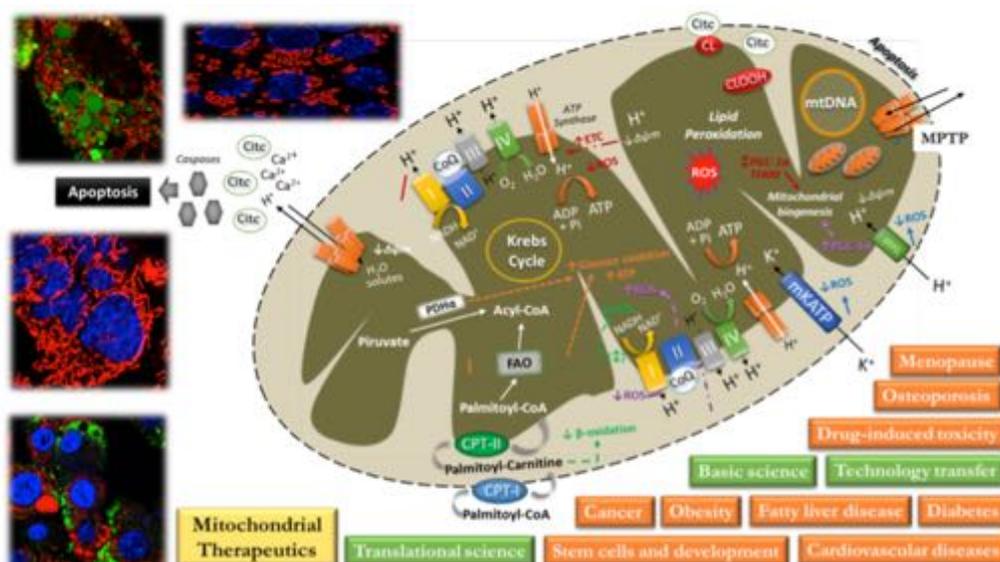
of morbidity and mortality of liver resection surgery.

2) Mitochondrial Toxicology and Pathophysiology: a) mechanisms of drug-induced mitochondrial dysfunction caused by different xenobiotics, including drug-induced injury (e.g. anthracyclines) and nanoparticles, 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) pathways of mitochondrial disruption in non-alcoholic fatty liver disease and diabetes, e) development of high-throughput methods to investigate mitochondrial function in the context of drug development and toxicology, f) mitochondrial metabolism and dynamics in non-neuronal cell samples from amyotrophic lateral sclerosis and Parkinson's disease patients, e) mitochondrial profiling in non-invasively obtained stem cells from young and old donors.

3) Mitochondrial Physiology in Tumor Physiology and (Cancer) Stem Cells: a) mitochondrial remodeling during cancer stem cell differentiation and carcinogenesis, b) role of autophagy in the

differentiation of stem cells and their resistance to cell death, c) 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 and create a desmoplastic stroma through which malignant epithelial cells trans-differentiate and acquire an invasive phenotype, d) involvement of exosomes on cytokines' release and role of human bronchial fibroblasts and their ECM in dedifferentiation, as well as cytokines' presence in the overall intercellular communication process involving tumor cells and tumor-stromal components, e) new strategies to block cancer stem cells formation and to modulate stromal cells phenotype to improve therapy's efficacy.

4) Osteoporosis and Menopause: a) mitochondrial performance and metabolic profile of bone cells in absence and presence of estradiol (E2) or selected phytoestrogens, evaluating the potential of each one to be used in bone anabolic (osteoanabolic) or anticatabolic (antiresorptives, with action on osteoclasts) treatment of postmenopausal osteoporosis, b) identification of phytoestrogens (PE) with low toxicological effects and high therapeutic potential for menopausal-associated symptoms that could be safely included as additives of the Western population.



MAIN ACHIEVEMENTS

1) Mitochondrial Therapeutics: We developed novel chemical entities (NCI) based on dietary polyphenols (AntiOXCINs and AntiOXBENs) which are selectively accumulated by mitochondria and prevent oxidative damage from various stressors on isolated liver mitochondria and multiple human cell lines. One of such NCI (AntiOXBEN3) was demonstrated to a novel inhibitor of the mitochondrial permeability transition pore. By focusing on mitohormesis, we concluded that mild stress induced by menadione induces *Sesn2* and activates autophagy/mitophagy as a cell survival strategy. Absence of *Sesn2* results in accumulation of mitochondrial damage induced by ROS and consequent decrease in cell viability. We also concluded that mitochondrial function is of paramount importance for liver regeneration. However, this has not been investigated in the clinical setting. We found a relationship between mitochondrial function, duration of hepatic pedicle clamping and clinical outcome after hepatectomy. Mitochondrial bioenergetics can potentially translate into clinical practice, assisting in earlier diagnosis of postoperative liver dysfunction, and as a target for future pharmacological therapies.

2) Mitochondrial Toxicology and Pathophysiology: We concluded that the anti-cancer agent Doxorubicin (DOX) disrupted cardiac

mitochondrial biogenesis, as demonstrated by decreased mtDNA levels and altered transcript levels for multiple mitochondrial genes encoded by both nuclear and mitochondrial genomes, including genes involved in lipid metabolism and epigenetic modulation, suggesting an interplay between mitochondrial dysfunction and epigenetic alterations, which may be a primary determinant of DOX-induced cardiotoxicity. Furthermore, an increase in *Sirt3* content by transfection-mediated overexpression or by berberine treatment decreased DOX cytotoxicity, mostly by maintaining mitochondrial network integrity and reducing oxidative stress.

3) Mitochondrial Physiology in Tumor Physiology and (Cancer) Stem Cells: We demonstrated for the first time that resveratrol cytotoxic effects on breast cancer cells were modulated by *SIRT1* as well through mitochondrial complex I inhibition. In multi-national collaboration, we identified the recovery of mitochondrial respiration and membrane potential in B16rho0 mouse melanoma cells injected into syngeneic C57BL/6Nsu9-DsRed2 mice. The results of this study showed that intact mitochondria with their mtDNA payload are transferred from the stroma to rho0 cells in the developing tumour. We discovered that cancer stem cells (CSCs) were formed by dedifferentiation of malignant epithelial bronchial cells (RenG2). The involvement of stromal

fibroblasts in the dedifferentiation process was uncovered by co-culture with the RenG2 cells. Multiplex arrays performed to analyze the human cytokines and growth factors present in the conditioned media from the co-cultures identified Interleukin-6 (IL-6), Granulocyte colony-stimulating factor (G-CSF) and Activin-A as the potential paracrine orchestrators of the dedifferentiation process leading to CSCs formation. The individual role of each cytokine in the process was elucidated as well as the involvement of exosomes as one of the transport vehicles of the aforementioned cytokines.

4) Osteoporosis and Menopause: we obtained evidence that phytoestrogen coumestrol improves mitochondrial function in the brain of Wistar-Han rats after E2 withdrawal, without causing any associated mitochondrial or systemic toxicity and could be a good candidate to improve brain and liver mitochondrial bioenergetics after menopause. Further, using the cell line MC3T3E1, a model for osteoblast precursors, we optimized a protocol for osteoblast differentiation, using a mixture of ascorbic acid and glycerol phosphate. Using the macrophages RAW264.7, frequently used as osteoclast precursors, we optimized a protocol for osteoclast differentiation, exposing the cells to different concentrations of RANKL.

OBJECTIVES

1. One of the main objectives of the past year was to assess the oxidative capacity of epicardial adipose tissue (EAT), with High-Resolution Respirometry (HRR) using the Oroboros technology. EAT has recently been identified as an important fat depot around the heart and has been implicated in cardiac function and its morphology. EAT has also been considered a potential risk factor for cardiovascular disease development. Not much is known regarding the metabolic phenotype of this cardiac fat depot. Therefore, we sought to evaluate mitochondrial function metabolism in EAT explants from heart failure patients, with and without diabetes in collaboration with Prof Manuel Antunes, Head of the Cardiothoracic unit at the University of Coimbra.

2. Impaired wound healing, an important complication of diabetes resulting in failure to heal diabetic foot

ulcers (DFU), can lead to lower extremity amputations. We have aimed at evaluating the role of microRNAs (miRs) and antimicrobial peptides (AMPs) in animal models of diabetic wound healing and infection. *Our hypothesis is that synergistically miRs and AMPs play a crucial role in wound healing in diabetes and that the lack or excess of them due to altered immune function combined with vascular insufficiency leads to impaired angiogenesis and wound healing.* We would like to understand whether there are miRs that are differentially regulated by diabetes and/or the the wound healing progress, in mouse skin. In addition, we would like to perform functional studies of differentially regulated miRs to evaluate their effects *in different skin cells.*

3. Increased fructose consumption is implicated in the surge of Type 2 diabetes and fatty liver disease in

Western societies. Our group has 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. To apply these methods in animal models of non-alcoholic fatty liver disease caused by high sugar feeding and determine the contributions of glucose and fructose to lipid biosynthesis.

4. The methodology to test novel spemicial formulations was implemented, using the Good Laboratory Practices methodology, officially approved by INFARMED, Portugal using the international OECD guidelines. Ours is the only lab in Portugal in this field to have such a certification. This will be used to fulfil industry contracts in contraception.

MAIN ACHIEVEMENTS

1. We have been able to measure mitochondrial respiration by HRR in EAT and subcutaneous fat (SAT) samples from the same subject with heart failure with or without diabetes for paired comparisons. We conclude that EAT is bioenergetically more active and more sensitive to mitochondrial substrate supply than SAT. These results emphasize potential mitochondrial differences between both fat depots in the presence of heart failure and highlight epicardial fat as a possible therapeutic target *in situ* in the cardiac microenvironment. Furthermore, EAT presented lower lipid peroxidation (MDA levels) and glutathione peroxidase (GPx) activity, while significantly higher glutathione reductase (GRed) activity and GSH/GSSG ratio compared to SAT.

2. We have identified several miRs that were significantly altered in diabetes condition and at the wound site. We chose 3 of these miRs to further evaluate *in vitro* and *in vivo*. We have submitted results recently, referent to the global miR screening that we have performed indicating the general view of what we have found under diabetic and non-diabetic conditions, as well as during the wound healing kinetics. In this paper we have concentrated our focus on miR-155. An additional paper in preparation is describing the results for 2 additional miRs (miRNA-146a and miR-29a), including both *in vitro* and *in vivo* studies. Moreover, studies using Neurensin, Substance P, and Insulin were performed *in vitro* in order to find whether

they have AMP activity. The paper has now been accepted for publication. As intact peptides they seem to have no AMP activity under the conditions chosen. In addition, two other AMPs (IDR-1018, b-lactoferricin) have been used for healing treatments *in vivo* in our mouse wound model.

3. We were able to successfully deploy a combination of deuterated water and [U-¹³C]fructose tracers coupled with ²H and ¹³C NMR resolution of liver triglyceride ²H and ¹³C enrichments in naturally feeding mice. This allowed us to determine the substrates driving liver triglyceride synthesis under these conditions. From the same studies we also detected unexpectedly high rates of lipogenesis from glucose in mesenteric adipose tissue, which may be contributing to the accumulation of fat in the liver. These observations provide direct metabolic evidence about the role of visceral adipose tissue in promoting lipid dysmetabolism in the liver and beyond.

4. We created a novel software for image analysis of pluripotent stem cells in culture. Using machine-learning methodologies and algorithms developed by the group this allow for the automatic analysis of cells under distinct conditions, with a resulting "pluripotency score- PluriIQ" arising from each analysis that completely overlaps with other (manual and time consuming) methodologies performed in the same cultures. This software is freely available to the community.

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STEM CELL-BASED AND MOLECULAR THERAPIES

Coordinator: Luis Pereira de Almeida

GENERAL OBJECTIVES

The Stem Cell-Based and Molecular Therapies thematic strand brings together seven 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 and more generic biotechnological applications of microbiology, proteolytic enzymes and siRNA/miRNA.

MAIN ACHIEVEMENTS

During 2017, the groups in this strand were particularly successful in attracting competitive funding from FEDER-driven framework/ operational programmes: one major Joint Activity Program (PAC) devoted to ground-breaking research in *CANcer STEM CELLS* and involving 18 research groups from CNC.IBILI (4 from this strand) and two other Portuguese research units; two large institutionally-driven co-funded regional projects on *Brain Health* and *Healthy Aging*, in synergy with the other CNC.IBILI strands; a IR-project for the implementation of the viral vector production unit (ViraVector). One FCT co-funded transnational cooperation project on polymeric nanobiomaterials also began (10 international partners, SMEs and academic). Other funding sources include INFARMED and the National Ataxia Foundation (NAF, USA).

Overall, research efforts originated almost 150 publications in peer-reviewed international journals (2017 issues), the majority resulting from fruitful collaborations with more than 150 different institutions (academic and otherwise) from over 30 different countries. Of those, ca. 25% involved hospital and healthcare units/centres (notably the Coimbra University Hospitals (CHUC)) and nearly 50% counted with the participation of other Portuguese institutions (including several companies) other than those affiliated with the University of Coimbra. As for the international collaborations, the USA features the largest co-authorships, followed by the Italy, Brazil, Germany and Spain. Out of 140 SCIE publications, the majority (75%) are Q1, with nearly 40 in high-impact journals (IF>5), including in *Nature Communications*, *Nucleic Acids Research*, *Trends in Neuroendocrinology & Metabolism*, *Annals of Neurology*, *Small*, *Biomaterials*, *Nanoscale*, *Journal of Controlled Release*, *PNAS* and *Genes &*

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.

Development, 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 Material Science, to Biotechnology applied Microbiology, to Genetics Heredity, spanning also from Oncology, to Neuroscience, cardiovascular or Infectious Diseases.

Other performance indicators include the request for and/or concession of IPR protection: one patent application on a *Modular Birdcage* (PCT/IB2017/054766) for experimental laying quails, another on the use of *MicroRNA hsa-miR-665 in cardiac hypertrophy* (EPO 17160768.2), and a provisional patent application for an *Anti-nucleolin antibody* (PT No. 110214) for oncologic use.

The members of this thematic strand are also actively involved in advanced training, notably in the Experimental Biology and Biomedicine Programme and the MIT-Portugal PhD programme in Bioengineering, being responsible for the core module Cell and Tissue Engineering and the elective module of *Principles and Practice of Drug Development* in the 2017 edition of this programme. A new H2020 Marie-Curie Innovative Training Network (MSCA-ITN-2017) was awarded, on the topic of *New nanomaterials for neural stem cells drug delivery* (NANOSTEM), that features several labs of this strand in partnership with several other European institutions including CHUC, and two pharma-driven enterprises. One experienced researcher joined the strand as a H2020-MSCA-IF grantee while a second one as a Marie Curie fellow and in the context of the highly competitive FCT-Investigator program, three Exploratory Research projects (seed-money) were carried out.

FUTURE PLANS

Following its major underlying goal of treating high morbidity and mortality diseases for which a) molecular therapy and/or b) stem-cell based therapy approaches constitute highly promising strategies, we will capitalise on the results and intellectual property recently generated to further develop clinical and/or marketable applications. The microbiology 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 microbial biomarkers associated to these pathologies that might be used for early detection.

Molecular therapy wise, we will continue the development/ refinement of animal and iPS-derived disease models to unravel disease-modified pathways and pathogen metabolism, and assess candidate pathways by counteracting the dysfunctions upon overexpression and silencing of the identified relevant genes in the *in vitro* and *in vivo* models. Novel genes as well as chemical compounds (natural and from synthesis) will be explored in the context of translational molecular therapy approaches for cancer, neurodegenerative and infectious diseases, and the

appropriate delivery vectors design/tailored. A number of future drug candidates are expected to be ranked both by virtual and high-throughput screening of chemical libraries, and further assessed with pharmacokinetic and pharmacodynamic analysis in animal models of disease. The implementation of a new core facility – ViraVector – for on-demand viral vector engineering and production is on-going.

As for stem cell-based investigation, it will keep its focus on tissue regeneration, aimed at treating ischemic diseases and the ageing of tissues. Efforts will be also directed to the generation and characterization at gene, protein and functional levels of human hematopoietic stem cells, neural stem cells and cardiomyocytes from somatic cells, and further work on cell modulation will address the development of remotely controlled nanomaterials to perturb endogenous and exogenous stem cells and study its differentiation and engraftment. The intellectual property being generated in these research lines are in the process of giving rise to two spin offs in the next three years.

VECTORS AND GENE THERAPY GROUPM^a Conceição Pedroso Lima PhD (*Head of Group*)

Ana Bela Sarmiento Ribeiro PhD
 Ana Gregório PhD
 Anália Vital do Carmo PhD
 Clevio David Nóbrega PhD
 Henrique Santos Faneca PhD
 João Nuno Moreira PhD
 Luis F. Pereira Almeida PhD
 Maria Amália Jurado PhD
 Maria Celeste Lopes PhD
 Nuno Fonseca PhD
 Olga M. F. Borges Ribeiro PhD
 Raghu Kalluri PhD
 Sergio Paulo M. Simões PhD
 Teresa Maria Martins PhD
 Vera Caldeira de Moura PhD
 Ana Cristina Gonçalves Post Doctoral Fellow
 Ana Maria Cardoso Post Doctoral Fellow
 Ana Teresa Simões Post Doctoral Fellow
 Ângela Fernandes Post Doctoral Fellow
 Carlos Matos Post Doctoral Fellow
 Catarina Sofia Miranda Post Doctoral Fellow
 Liliana Simões Mendonça Post Doctoral Fellow
 Nélio Gonçalves Post Doctoral Fellow
 Patrícia Marques Post Doctoral Fellow
 Rita Palmeira Oliveira Post Doctoral Fellow
 Rita Perfeito Post Doctoral Fellow
 Rodemary Cordeiro Post Doctoral Fellow
 Rui Jorge Gonçalves Nobre Post Doctoral Fellow
 Sandra Jesus Post Doctoral Fellow
 Sónia Patrícia Dias Duarte Post Doctoral Fellow
 Vítor Carmona Post Doctoral Fellow
 Adriana Marcelo PhD Student
 Ana Cristina Ferreira PhD Student
 Ana Filipa Cruz PhD Student
 Ana Rafaela Oliveira PhD Student
 Ana Rita Ribeiro PhD Student
 António Rufino Ramos PhD Student
 Catarina Morais PhD Student
 Daniela Santo PhD Student
 Dina Farinha PhD Student
 Dina Pereira PhD Student
 Edna Soares PhD Student
 Hélder Soares PhD Student
 João Panão Costa PhD Student
 M^a Inês Martins PhD Student
 Mariangela Natale PhD Student
 Patrícia Albuquerque PhD Student
 Sara Lopes PhD Student
 Sofia Pereira Romano PhD Student
 Sonia Andreia Pinho PhD Student
 Alana Duarte MSc Student
 Catarina Pechincha MSc Student
 Mariana Colaço MSc Student
 Miguel Lopes MSc Student
 Susana Conceição MSc Student
 Joana Ribeiro MD
 Marta Pereira MD
 Tânia Marante Grant Technician

STEM CELL BIOTECHNOLOGY GROUPLino da Silva Ferreira PhD (*Head of Group*)

Akhilesh Rai PhD
 Arnab Banerjee PhD
 Carlos Filipe Pereira PhD
 Hugo Agostinho Fernandes PhD
 Luís Estronca PhD
 Ricardo Pires Das Neves PhD
 Ana Barradas Post Doctoral Fellow
 Andreia Ribeiro Post Doctoral Fellow
 Catarina Praça Almeida Post Doctoral Fellow
 Cristiana Pires Post Doctoral Fellow
 Henrique Almeida Post Doctoral Fellow
 Miguel Lino Post Doctoral Fellow
 Patrícia Pitrez Pereira Post Doctoral Fellow
 Sonia Luzia Claro de Pinho Post Doctoral Fellow
 Susana Rosa Post Doctoral Fellow
 Susana Simões Post Doctoral Fellow
 Vítor Francisco Post Doctoral Fellow
 Andreia Marques Gomes PhD Student
 Andreia Vilaça PhD Student
 Catarina Rebelo PhD Student
 Deolinda Santinha PhD Student
 Emanuel Quartim Costa PhD Student
 Fábio Rosa PhD Student
 Josephine Blerch PhD Student
 Luís Monteiro PhD Student
 M^a Helena Antunes PhD Student
 Mehrzad Zargarzadeh PhD Student
 Ricardo Abreu PhD Student
 Rita Ferreira PhD Student
 Tânia Barata PhD Student
 Alexandra Ferreira MSc Student
 Ana Raquel Santos MSc Student
 Carlos Jesus MSc Student
 Cláudia Azenha MSc Student
 Helena Aires MSc Student
 Inês Caiado MSc Student
 Inês Ribeiro MSc Student
 Rita Alves MSc Student
 António Santinha Grant Technician
 Cristiana Paulo PhD Collaborator

SYSTEMS AND COMPUTATIONAL BIOLOGY GROUPArmindo Salvador PhD (*Head of Group*)

Hugo Filipe Post Doctoral Fellow
 Luís Loura Collaborator
 M^a João Pedrosa Silvestre Collaborator

MEDICAL MICROBIOLOGY GROUPTeresa Oliveira Gonçalves PhD (*Head of Group*)

Célia Nogueira PhD
 Chantal Fernandes Post Doctoral Fellow
 Lisa Rodrigues Post Doctoral Fellow
 Marta Mota PhD Student
 Rui Soares MD
 Patrícia Nunes MD
 Ana Rita Mestre MSc Student
 Pedro Valada MSc Student
 João Batista Collaborator

MOLECULAR MYCOBACTERIOLOGY AND MICROBIOME GROUPNuno Empadinhas PhD (*Head of Group*)

Sónia Margarida Pereira PhD
 Ana Maranh Tiago Post Doctoral Fellow
 Susana Isabel Elias Alarico Post Doctoral Fellow
 Daniela Costa PhD Student
 M^a Mafalda Costa PhD Student

EDICINAL CHEMISTRY & DRUG DISCOVERY GROUPJorge Ribeiro Salvador PhD (*Head of Group*)

Alcino Leitão PhD
 Bruno Gonçalves PhD
 Gabriela Jorge da Silva PhD
 M^a Céu Sousa PhD
 M^a Luisa Vaz Sá Melo PhD
 M^a Manuel Cruz Silva PhD
 Sara Margarida Domingues PhD
 Vanessa Mendes PhD
 Ana Sofia Valdeira PhD Student
 Cátia Sousa PhD Student
 Daniela Marques PhD Student
 Judite Coimbra PhD Student
 Maria La Salette Batista PhD Student
 Joana Alves MSc Student
 Joana Velho MSc Student
 Vasco Justino MSc Student
 Fátima Nunes Grant Technician
 Ana Rita Acúrcio Collaborator
 Daniela Alho Collaborator
 Romina Guedes Collaborator

PHARMACOMETRICS GROUPAmílcar Falcão Ferreira PhD (*Head of Group*)

Ana Cristina Fortuna PhD
 Bruno Neves PhD
 Carla Vitorino PhD
 Fernando Jorge dos Ramos PhD
 Célia Cabral Post Doctoral Fellow
 Ana Alexandra Miranda PhD Student
 M^a Manuel Mendes PhD Student

BIOTECHNOLOGY**MICROBIOLOGY OF EXTREME ENVIRONMENTS GROUP**

Milton Simões da Costa PhD (*Head of Group*)
 Inês Roxo Grant Technician
 Pedro Raposo Grant Technician
 Rita Severino Grant Technician

MOLECULAR BIOTECHNOLOGY GROUPIsaura Simões PhD (*Head of Group*)

Carlos José Costa Faro PhD
 Paula Verissimo Pires PhD
 Pedro Curto PhD Student

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 transverse 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 delivery systems developed.

MAIN ACHIEVEMENTS

Regarding non-viral-mediated gene delivery, an extensive screening of a variety of molecules (gemini surfactants, copolymers and cell penetrating peptides) for their capacity to produce efficient nucleic acid delivery systems has been carried out and structure-activity relationships, established.

A high-throughput screening analysis allowed to identify several

microRNAs, including miR-302a and miR-520b, as being able to modulate the expression of receptor tyrosine kinase downstream mediators in human GBM cells. Importantly, a new multimodal therapeutic strategy, combining multi-targeted tyrosine kinase inhibitors (MTKIs) and microRNA modulators, was successfully applied in GBM cells resulting in significant tumor cell

death. Combination of the same MTKIs 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.

Mouse models are crucial to our comprehensive knowledge on the molecular basis and pathogenesis of cancer disease. Nevertheless, a major impediment for the study of metastases has been the unavailability of suitable mouse models that accurately recapitulate the complexity of human tumor progression. To better mimic the development of metastases in humans, several parameters need to be considered in a mouse model. We have demonstrated that reducing

the number of 4T1 metastatic cancer cells implanted orthotopically, to a number as low as 500 cells, resulted both in a higher metastatic efficiency and primary tumor take rate, significantly affecting the dynamics of tumor growth. Extending the time length of tumor development will enable a better assessment of anti-metastatic therapies.

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. We have also investigated the

contribution of immune-related miRNAs to innate immune response in the context of Alzheimer's disease (AD). The modulation, *ex vivo*, of one of these miRNAs in monocytes increased the recruitment of these cells to the CNS, improving A β clearance. It is expected that these studies contribute to the finding of new therapies for these devastating disorders for which no effective therapy is available.

Regarding glucan-based NPs for hepatitis B vaccination, we observed the effect of including glucan into chitosan NPs in activating the secretion of some cytokines, like the TNF- α and, importantly, *in vivo* studies revealed that the NPs constitute an excellent HBsAg adjuvant.

STEM CELL BIOTECHNOLOGY | (Head: Lino Ferreira)

OBJECTIVES

The research group has three main programs: a (i) disease modeling and drug screening program based in engineered tissues from human stem cells, (ii) regenerative/therapeutic medicine program based on nanomedicine platforms to modulate stem cell activity and (iii) cellular reprogramming of somatic cells into hematopoietic stem cells. The 3 programs have a focus in cardiovascular diseases.

1- Disease modeling and drug screening program: *in vitro* cell/tissue models from human stem cells. Stem cells, in particular induced pluripotent stem cells (iPSCs), may be an excellent source of cells for disease modeling and drug discovery programs related to cardiovascular diseases. The first disease-specific iPSCs were derived in 2008 from a patient with a familiar form of amyotrophic lateral sclerosis (ALS). Since then several iPSC lines have been generated from a variety of genetic and ageing-related diseases. The potential of iPSCs to generate disease models led to the creation of several biobanks in USA (Coriell Institute for Medical Research, NIH Center for Regenerative Medicine, ATCC and University owned biobanks), Europe (Cellartis; and an European initiative of Stem cell biobank) and Japan (RIKEN bioresource center) for storage and distribution of iPSC lines originated from patients and healthy controls. In the last 6 years the stem cell biotechnology group has developed several tissue models from stem cells that may be an important platform for drug discovery programs related to cardiovascular diseases. A particular interest of the group is to develop biomaterials and bioengineering platforms for the efficient maturation/specification of stem cells and their progenies. The research group uses many tools to accomplish

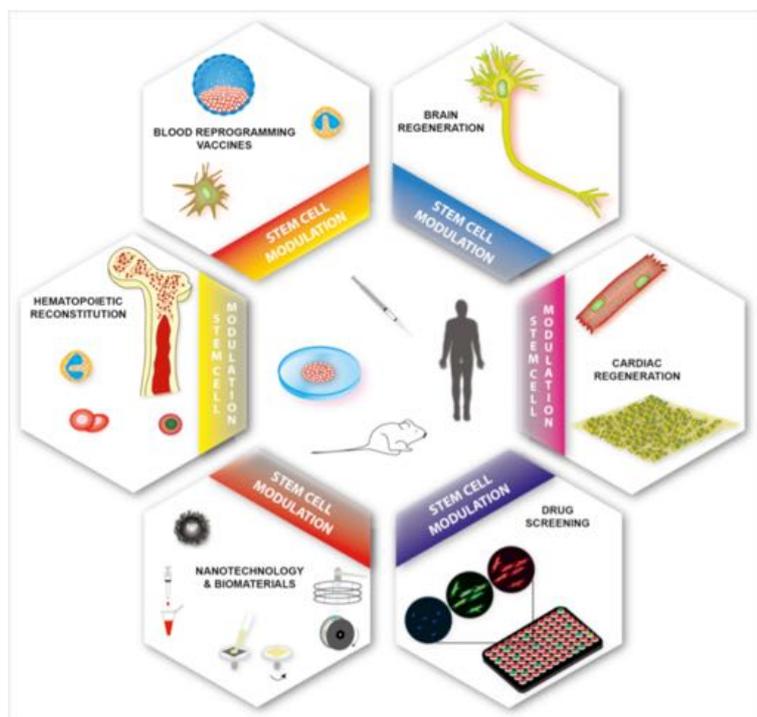
this goal, including the design of new biomaterials with relevant biological

information, molecular and cell biology, microfluidic systems, high content analysis, and animal experimentation.

2- Platforms to modulate stem cell activity. This program has two sub-programs. The first one focused in the development of nanotechnology tools to control *in vivo* stem cell differentiation and to mobilize stem cells from their niches to treat cardiovascular diseases. This requires contributions at different levels, such as the study of the stem cell niche biology, the identification of bioactive molecules to use as modulators and the use of formulations with high technical value to be remotely activated. The second sub-program focused in the identification of miRNAs as (stem) cell survival modulators. For that purpose we are using high-throughput screening strategies, evaluating the survival effect of libraries of miRNAs and small molecules in mesenchymal stem cells,

endothelial progenitor cells, and primary endothelial cells. These cells are cultured *in vitro* in conditions that closely mimic some of the stress factors encountered upon *in vivo* transplantation (e.g., low oxygen levels, poor nutrient supply and high levels of ROS). The identified candidates are thoroughly analysed and validated using several cellular models currently available in the lab. Ultimately, collaborations with groups actively working on drug delivery systems will accelerate the deployment of such molecules to the clinic.

3- Cellular reprogramming. This research line aims at generating and functionally characterizing hematopoietic stem cell-like cells from somatic cells (murine and human). This 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.



MAIN ACHIEVEMENTS

During the last year, 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* in revision) 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 biomolecules 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* 2017 and *ACS Nano* 2018).

To tackle the third question, we have identified recently a miRNA involved in the pro-survival 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).

OBJECTIVES

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

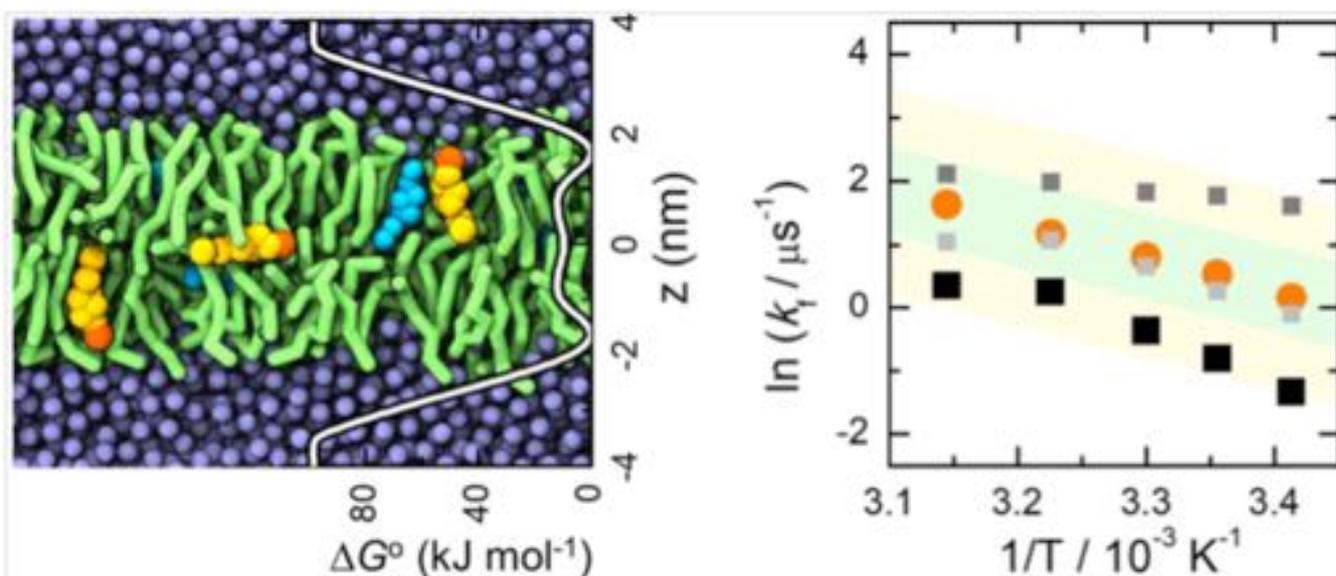
1. Organization principles of biochemical systems. The main goal of this research line is to discover, understand and exploit generic rules (organization principles) that (a) relate the design (i.e. naturally evolved molecular mechanisms) of biochemical systems to their function, and (b) hold across processes, cell types and organisms. We envisage that these network-structure / function relationships will play in biomedicine and bioengineering a role analogous to that of QSAR in pharmacology. Objects of interest in our current research are metabolic networks, antioxidant defense and redox signaling. Our group has identified recurrent structural and functional motifs in all these biomolecular networks and derived design principles (relationships among kinetic parameters and component concentrations) that these motifs must fulfill so that they perform their function adequately. These predictions are thoroughly

supported by experimental observations in a variety of organisms and permitted rationalizing the phenotypes of mutations and stress responses. We are working towards exploring translational implications of these design/function relationships in degenerative diseases. In parallel, we are developing novel experimental (fluxomics and synthetic biology) methodologies to determine critical parameters in these applications.

2. Modeling the permeation through physiological barriers. The long-term goal of this research line is to develop quantitative structure-activity relationships (QSAR) for the permeation of physiological barriers by drugs, namely tight endothelia such as the blood-brain barrier (BBB). Failure to cross the BBB is the main factor of attrition in the development of psycho-active drugs, and is causing some of the main pharmaceutical corporations to abandon the development of such drugs altogether. The bioavailability of xenobiotics at the brain is strongly affected by their interaction with lipid bilayers and blood components

(albumin, lipoproteins, erythrocytes and membranes of endothelial cells). Our work shows that the partition of drugs among the compartments strongly affects the timing and effectiveness of their permeation across the BBB. We are working towards modeling how molecular features of the xenobiotics impact on the kinetics of these critical steps and to achieve better predictions of overall permeability.

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



MAIN ACHIEVEMENTS

We are applying a combination of molecular dynamics and kinetic modeling to help connecting drugs' molecular features to (passive) membrane permeability and ability to cross the blood-brain barrier. Over 2017 we further developed methods to estimate permeation rate constants from molecular dynamics (MD) simulations. We employed unbiased coarse-grained MD simulations to calculate the rate constant for the translocation of cholesterol through lipid bilayers. To this effect, a novel procedure based on directly observed transitions between different states along the reaction coordinate was developed. Additionally, we tested several formalisms previously proposed to calculate these rate constants from shorter and/or biased MD simulations (Figure). While most of the tested formalisms lead to reasonable agreement with the effective rate constant, one of the methods was superior. This technique uses pre-exponential A factors calculated using explicit relaxation frequencies from the transition state in the forward- and backward-directions along the reaction coordinate [Filipe *et al.*, in revision]. We are currently applying the methods developed herein to solutes for which reliable experimental data is available, as an external calibration required to use MD simulations to predict rate constants.

Hydrogen peroxide (H_2O_2) signaling through the peroxiredoxin (Prx) / thioredoxin (Trx) / Trx reductase (TrxR) system (PTTRS) is important in cell proliferation, neuroprotection, angiogenesis and tumorigenesis. However, the way how H_2O_2 signals regulate redox targets and the exact role of the PTTRS in this process remain contentious. Two main competing hypotheses have been proposed: (i) that Prx1/2 must be oxidatively inactivated so that cytoplasmic H_2O_2 can accumulate to sufficient concentrations to oxidize the regulation targets; or (ii) that Prx1/2 are the primary H_2O_2 "receptors" in the cytoplasm and the signal is propagated through a redox relay whereby the oxidized forms of these Prx oxidize the redox targets. Our computational analyses [Travasso *et al.* (2017) *Redox Biol.* 12:233-245; Selvaggio *et al.* (2018) *Redox Biol.* 15:297-315] are clarifying this matter. They indicate that the dynamics of the PTTRS defines two distinct H_2O_2 signaling regimes. For H_2O_2 supply rates (v_{sup}) lower than the cytoplasmic capacity for Prx1/2 reduction these Prx maintain strong transmembrane and intracytoplasmic H_2O_2 concentration gradients, and keep these cytoplasmic concentrations far too low to directly oxidize regulation targets. Regulation is then mediated by spatially localized Prx1/2 redox relays. In turn, at higher v_{sup} most Prx1/2 becomes oxidized. As a consequence, cytoplasmic H_2O_2 then

accumulates to potentially toxic micromolar concentrations, uniformly throughout the cytoplasm. These concentrations are sufficient to oxidize moderately reactive ($k_{ox}=200-2000 M^{-1}s^{-1}$) regulatory targets that are known to induce stress adaptation. However, they remain insufficient to directly inactivate protein tyrosine phosphatases in the observed time frame in the context of mitogenic signaling, which suggests that these proteins are actuated vis Prx1/2 redox relays or by hitherto uncharacterized mechanisms.

The key role of the cytoplasmic 2-Cys peroxiredoxins (Prx1/2) in H_2O_2 signaling make important to characterize the kinetics and mechanisms of these proteins. We are currently pursuing such a characterization for human Prx2 in collaboration with the laboratories of Dr. Christine Winterbourn (University of Otago, NZ) and Dr. Flávia Meotti (U. of São Paulo, Brasil). These peroxiredoxins are pentamers of dimers. Hitherto, it had been assumed that the two active sites in each dimer operate independently. In contrast, we have recently demonstrated that there is significant cooperativity between these sites. Further theoretic-experimental research to achieve a comprehensive quantitative mechanistic description of the complex catalytic cycle of these proteins is ongoing.

MEDICAL MICROBIOLOGY | (Head: Teresa Gonçalves)

OBJECTIVES

The objectives of the Medical Microbiology Group during 2017 were:

A. *In Alternaria infectoria, we pursued the studies to answer the questions:*

1. release of extracellular vesicles by *A. infectoria*: a virulence trait or a build-up tool?
2. Melanins inside and outside the fungal cell: a communication factor intrakingdom or interkingdom?

3. Does *Alternaria* possess allergens at the cell surface?

B. *Unraveling the role of adenosine and adenosine receptors in the fungal resistance to phagocytic attack and the impact of ageing:*

1. The trafficking and arrest of A2AR in phagolysosome membrane following phagocytosis is being studied using an A2A-GFP construct together with Prof Duarte

Barral, CEDOC, NOVA Medical School, Portugal.

2. The impact of ectonucleotidases, an ongoing work together with RA Cunha (CNC.IBILI) and with with JR Meyer-Fernandes (UFRJ, Brasil).

C. *Identification of novel antimicrobials from natural national products.*



Fig. 1. Neutrophil burst: Nucleic acid fibers (NETs; blue) sent to trap yeast cells (red)

MAIN ACHIEVEMENTS

1. Before we proved that the production of melanin is a salvage mechanism against antifungals, and the inhibition of DHN-melanin synthesis by pyroquilon resulted in a lower minimum effective concentration (MEC) of caspofungin and enhanced morphological changes, characterized by thinner and less organized cell walls. Our most recent results show that *Alternaria* exports not DHN-melanin but another form of melanin, pyromelanin, and this is essential for the fungal success (Under submission process). Exposing lung

epithelial cells to *Alternaria* cell wall nanoparticles and to extracellular vesicles, leads to activation of these cells a clear signal that there are sensitization mechanisms still unknown and that are being pursued.

2. The fact that yeasts of the genus *Candida*, besides the classical ecto-5'-nucleotidase enzyme possess a ecto-3'- nucleotidase, took us to study the impact of this extracellular enzyme activity in the resistance of *Candida* spp. to Neutrophil Extracellular Traps (NETs). Preliminary results show that the higher the enzyme activity the less

efficiency of neutrophils to kill yeasts.

3. Extracts of several red algae proved to have antimicrobial properties (antibacterial, antifungal and antiviral). One chlorophyll derivative proved to be useful in the eradication of mixed biofilms of *Enterococcus faecalis* and *Candida albicans* using Antimicrobial Photodynamic Therapy. This molecule is also endowed with very low toxicity for host cells.

OBJECTIVES:

Mycobacteria are “a globally established priority for which innovative new treatments are urgently needed” (WHO, 2017). They include many multidrug-resistant pathogens causing life-threatening infections beyond tuberculosis, more often in the chronically ill and in the elderly. Our group’s objectives are to decipher new gene functions in mycobacterial genomes and biochemically characterize the enzymes and in collaboration with crystallographers determine their 3D structures for being potential new targets attractive for drug design. Another goal is to purify essential mycobacterial polysaccharides from their native producers since they are commercially unavailable for research, although they are instrumental for downstream molecular, physiological and drug discovery studies. Together, these goals will allow further insights into the physiology of these pathogens

and will put us closer to devise better strategies to fight their infections.

Microbiome – Investigating the role of the human microbiome in chronic diseases. We sought to profile the dysbiotic gut microbiome of Parkinson’s Disease patients aiming at the identification of very specific neurotoxin-producing bacterial taxa. Also we decided to evaluate the effects of a selected microbial neurotoxin on neuronal mitochondrial metabolism. Another goal was to elucidate the biosynthetic pathway for unique microbial neurotoxins. In a different line of research our group proposed to profile the microbiome of diabetic foot ulcers in a quest for unique microbial signatures for future bacteriotherapeutic intervention. The initiation in 2017 of both these interdisciplinary projects involving scientists, clinicians, nurses and patients was possible due to the

extensive and complementary expertise of all team members involved.

Public Health - Growing numbers of hospital-acquired infections (HAI) led us to seek agreements with hospitals to characterize the microbiome of possible sources of contamination, their inanimate surfaces. Our objectives were expanded to the investigation of domestic water distribution systems of patients with mycobacterial disease, considered one of the potential primary sources of these chronic infections by the naturally drug-resistant mycobacteria. Our major goal in this context was to trace the contamination origins of mycobacteria-infected patients, namely by sampling domestic water distribution systems and to carry out genomic fingerprinting to understand the epidemiology and antimicrobial resistance determinants associated to this rapidly growing health threat.

MAIN ACHIEVEMENTS

The group identified an unprecedented mechanism for replication and recycling of a unique intracellular polysaccharide required for modulation of fatty acid metabolism and cell wall assembly in mycobacteria. This remarkable mechanism involves the concerted action of 4 enzymes encoded in a single operon found exclusively in nontuberculous mycobacteria. The polysaccharide and intermediates were purified with newly developed methods or obtained by chemical synthesis (with R. Ventura, ITQB). These findings build on the group’s previous achievements that now comprehensively define two essential mycobacterial pathways, also revealing new promising targets. The 3D structures of three of these enzymes were recently determined (with S. Macedo-Ribeiro and P. Pereira, IBMC). The enzymes are the founding members of new EC families in the IUMBM database.

Parkinson’s Gut Microbiome - Funding from Prémio Neurociências Mantero Belard (2017-2020) allowed us to investigate the role of the gut

microbiome in Parkinson’s Disease (PD) onset and progression. The microbiome profiles of 50 PD patients and age-matched controls revealed unique signatures, namely overrepresentation of a pathogenic genus and of two probiotic genera in patients, including known butyrate producers proposed to be key for intestinal health and barrier integrity, pointing also to possible anti-inflammatory effects in the PD dysbiotic gut. Ongoing studies correlating phenotype and clinical presentation will now help decipher specific roles in PD. We have also shown how a microbial-synthesized neurotoxin impacts neuronal mitochondrial metabolism to recapitulate pathways of PD pathology (S.M. Cardoso, CNC). These findings were extended to in vivo trials and reinforce our hypothesis that a neurotoxic gut microbiome may drive PD neurodegeneration. Selected neurotoxin-producing bacteria were the hosts for the isolation of neurotoxin-synthesizing enzymes. Assays for efficient chromatographic detection of enzyme activity were

developed and nitrogen-deprivation was identified as trigger for neurotoxin synthesis in a natural host.

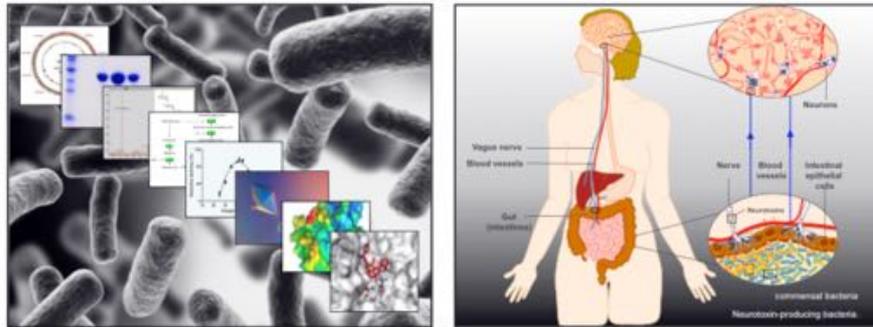
Diabetic Wounds Microbiome – Funding from INFARMED-Fundo para a Investigação em Saúde (2017-2019) to decipher microbiome signatures in diabetic foot ulcers (DFU) allowed sampling of 200 diabetic patients and isolation of ESKAPE pathogens (WHO priority) from most of them. Selective bacterial isolation and identification of over 400 strains of 50 different species, confirmed *Staphylococcus* in patients’ skin and DFU with non-aureus staphylococci (NAS) as the dominant species. All isolates were preserved in a unique microbial biobank instrumental for in vitro and in vivo studies planned with diabetic mice models. Many NAS species are commensals known to produce antimicrobial peptides and unique bacteriocins against *S. aureus*, an archetypal DFU pathogen, whose colonization we found to inversely correlate with NAS prevalence. Competition assays will now be carried out to assess the anti-*S. aureus* potential of the newly isolated NAS strains.

Public Health - We sampled the amenities of a hospital and isolated several

nontuberculous mycobacteria species. We performed antimicrobial susceptibility assays and sequenced their genomes to characterize their drug resistance phenotypes and genotypes (Pereira et al, submitted). We also sampled domestic water distribution systems of geographically unrelated

patients' to locate infection sources. Ongoing genome sequencing of mycobacterial strains recovered will be compared to clinical isolates. Our project "Prevalence and genetic variability of nontuberculous mycobacteria in the domestic environment" won the 2017 Thomé Villar/Boehringer Ingelheim 1st

Prize (2018), Portuguese Society for Pneumology (with Raquel Duarte (ISPUP) & Margarida Correia-Neves (ICVS).



OBJECTIVES

The Medicinal Chemistry and Drug Discovery group aims the discovery of novel small molecules addressing cancer, neurodegenerative and infectious diseases. Rational drug design, organic and enzymatic synthesis and in vitro biological evaluation are the methodologies that allow us the discovery of novel drug candidates.

The design, synthesis and antitumor evaluation of novel semisynthetic triterpene derivatives is an important area of research. A large number of novel compounds has been synthesised and potent antitumor activity has been disclosed for some compounds. The elucidation of the mechanisms underlying the anticancer properties

of the best compounds has been pursued.

The role of oxygenated derivatives of cholesterol in cancer, malaria and other diseases has been investigated through the synthesis of novel related compounds and their biological evaluation.

The understanding of the G protein-coupled receptor 30 (GPR30) or G protein-coupled estrogen receptor (GPER), concerning specific ligands, their structure and type of action, in vitro and in vivo, is another line of research of the group.

Chemoenzymatic synthesis of novel polyphenol derivatives aiming to improve their antiinflammatory, antioxidant and anticancer properties has been shown to

provide interesting bioactive compounds.

Antimicrobial resistance and virulence, host-pathogen interactions, new antimicrobials and therapeutic strategies in microbiology are topics of interest for the group. In fact, loss of antibiotic effectiveness resulting from bacterial resistance is a global threat. New antibacterial molecules are sorely needed to fight the multiresistant bacteria that are increasingly emerging. Our objectives are to characterize resistance mechanisms and to assess their molecular epidemiology, as well as to develop new molecules with potential antimicrobial activity and reduced toxicity.

MAIN ACHIEVEMENTS

The design of novel triterpene derivatives, based on the accumulated knowledge of the group on cytotoxic pentacyclic triterpenoids, namely betulinic, ursolic, oleanolic and asiatic derivatives, has allowed the synthesis and biological evaluation of novel compounds with potent and selective anticancer activity (Eur. J. Med. Chem., 2017a and 2017b).

To identify new anticancer compounds with selective PARP-1 inhibitory activity, molecular dynamics simulations were performed to generate structure-based pharmacophores, taking into account the dynamic features of receptor-ligand interactions. A virtual screening of compound databases using the pharmacophore models obtained was followed by molecular docking-based scoring of the hits retrieved and in vitro evaluation. This strategy allowed the identification of new PARP-1 inhibitor chemotypes (PLOS ONE 2017, 12, 1, e0170846).

Since the estrogens have been also referred as immunomodulators,

associated with both classic receptor and GPR30 mediation, the assessment of potential antiproliferative and immunomodulator activity of steroids and non-steroidal compounds was initiated with the aim to carry out a study of structure-activity relationships. Cell lines used to study the role of the GPR30 as a mediator of estrogen responses have yielded conflicting results. With this work we identified a simple assay to predict cell line competence for pharmacological studies of GPR30 (Journal of Receptors and Signal Transduction, 2017)

Our studies on epidemiology of antimicrobial resistance have shown that: i, carbapenemases KPC-3 and OXA-48 are emerging in our hospitals; ii, bacteria carrying clinical important genes are disseminating into environment through hospital effluents; iii, and are found in Salmonella and Escherichia coli of food animal origins, and for the first time in Portugal we discovered the plasmid mcr-1 gene associated to colistin resistance, one of the last

therapeutic options in human medicine to treat multiresistant infections; iv, emergence of antimicrobial resistance can be due to selection of genetic mobile elements by metals from food additives or biocides; v, antibiotics select for more virulent Salmonella sp.; vi, we showed that some bacteria can acquire natural competence disclosing a new way of resistance acquisition.

The studies on antimicrobial activity showed that semi-synthetic triterpenoids derived from ursolic acid show good activity against Gram-positive bacteria. The evaluation of the anti-Leishmania activity of new semisynthetic lupane triterpenoids showed that: i, the structure/activity relationship (SAR) allowed identifying chemical modifications on betulin derivatives with impact against Leishmania infantum; ii, combined-therapy efavirenz plus miltefosine gives good results for Leishmaniasis and Leishmania/HIV co-infections and; iii, R)-(-)-Aloesaponol III 8-Methyl Ether is a novel compound with potential against Leishmaniasis.

OBJECTIVES

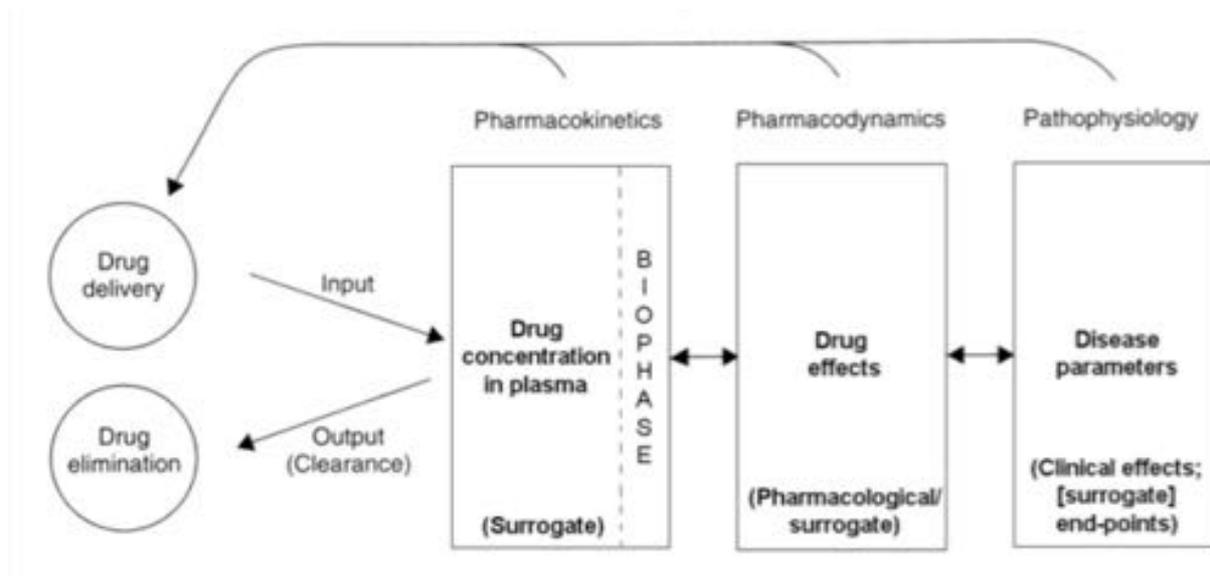
The Pharmacometrics Group encompasses translational researches, from *in vitro* to (non)clinical *in vivo* studies, in an attempt of correlating the pharmacokinetics, i.e. absorption, distribution, metabolism and excretion of new drug candidates with their therapeutic and toxic effects.

Since 2014, that Pharmacometrics Group exploit the usefulness of intranasal administration to directly deliver central-acting drugs into the brain. In fact, as exposed in previous annual scientific reports, lamotrigine and carbamazepine incorporated in a thermoreversible *in situ* gel were successfully administered by nasal route, attaining brain concentrations similar to those observed after intravenous administration.

In 2017, one of the objectives of the Pharmacometrics Group was to optimize the thermoreversible *in situ* gel to administrate antibiotic drugs intended to a topic effect. Hence, optimized thermoreversible *in situ* gel was loaded with ciprofloxacin and levofloxacin, two fluoroquinolones with a wide range of clinical applications and a broad spectrum of antibacterial activity in the treatment of chronic rhinosinusitis.

The work developed during the year of 2017 also encompassed a series of *in vitro* and *in vivo* methods, implemented with the purpose of describing the passage of compounds across the BBB. In fact for a long time that Pharmacometrics Group is recognized by the several methodologies developed and validated to predict the

pharmacokinetic properties of new chemical entities (NCEs). However, only in 2017, the development of a screening methodology was developed and applied during I&D programs to predict the ability of NCEs to cross the blood-brain-barrier (BBB). Due to its physiological complexity, the BBB cannot be fully mimicked in laboratorial setting. Therefore, the adopted strategy was to apply more than one model and combine the data provided by each model to attain a more complete overview of the main pharmacokinetic processes that govern the entry of compounds into and out of the CNS. This aimed at studying the rate, extent and intra-brain distribution of compounds, including passive permeation, active transport processes, plasma protein binding and brain tissue binding.



MAIN ACHIEVEMENTS

1 - Intranasal administration of fluoroquinolones

The new strategy increases the residence time of the drug in nasal cavity and drugs concentrations found in the site of infection were considerably higher than after intravenous administration. Both

fluoroquinolones showed a heterogeneous deposition pattern in nasal mucosa, attaining markedly higher concentrations and/or exposure parameters in anterior nasal mucosa than in posterior nasal mucosa, in contrast with the homogeneous pattern observed after IV administration. These

results suggest that IN application of the thermoreversible *in situ* gel containing, either ciprofloxacin or levetiracetam (0.24 mg/kg), was in the anterior region of the nose of rats and only a fraction of its volume reached the posterior region. Moreover, a plateau was observed in the concentration-time profile of

ciprofloxacin in anterior nasal mucosa and posterior nasal mucosa, whereas in the case of levofloxacin a more rapid and continuous decay of concentration values was observed, particularly in the anterior region. Importantly, the systemic absorption and lateral effects were negligible after intranasal administration.

2 - Implementation of a screening strategy to characterize the passage of NCEs across the BBB

- Bidirectional transport assays were performed in MDCK II, MDCK-MDR1 and MDCK-BCRP cell lines for the identification of P-glycoprotein (P-gp) and/or Breast Cancer Resistant Protein (BCRP) substrates, through the estimation of their net flux ratios. Monolayer integrity was ensured through the careful optimization of experimental conditions and attested by the low Papp values of paracellular marker Na-Fluorescein. Recoveries were verified to guarantee reliable Papp values, while net flux ratios were confirmed by pre-incubation with well-known P-gp or BCRP inhibitors. This assay additionally implied a previous validation of analytical HPLC techniques for the quantification of all compounds in samples, including reference and test molecules. Seven reference molecules were used to validate this method, including passively transported compounds by transcellular or paracellular route, P-gp-only and BCRP-only substrates, and dual P-gp and BCRP substrates.

Applying the established conditions, all were correctly classified, according to literature data. Among test compounds, three P-gp substrates (BIA 9-1079, etamicastat, nepicastat) and five BCRP substrates (BIA 9-1059, entacapone, nebicapone, opicapone and etamicastat) were identified.

- The ultrafiltration method was applied for a rapid and efficient estimate of f_u ,plasma and f_u ,brain of BIA 9-1079 and tolcapone. The recoveries and stability of these compounds were evaluated throughout the process, providing confidence in the reliability of the obtained results. BIA 9-1079 revealed lower f_u ,plasma and much lower f_u ,brain than tolcapone.

- The most important parameter of the extent of brain penetration, K_p ,uu, was determined following *in vivo* pharmacokinetic studies with Wistar rats. Specific procedures were adopted during the practical execution of all studies in order to prevent the contamination of brain homogenate samples with blood, namely cardiac puncture and intracardiac perfusion. Systemic exposure was higher for BIA 9-1079, whereas brain exposure was superior for tolcapone, although limited for both compounds. K_p ,uu was below unity for both BIA 9-1079 and tolcapone, but especially for BIA 9-1079, demonstrating the involvement of efflux transporters in the limited extent of CNS access of these compounds. Furthermore, intra-brain distribution parameters revealed a low tendency of

intracellular accumulation (K_p ,uu,cell < 1) and also high non-specific binding to brain tissue, particularly for BIA 9-1079 (V_u ,brain > 0.8 mg mL⁻¹ brain).

- Additional *in vivo* assays were carried out through the co-administration of elacridar, a potent P-gp and BCRP inhibitor. This led to a significant increase in brain concentrations and K_p ,uu of BIA 9-1079 and tolcapone, thereby confirming the role of P-gp and/or BCRP in hampering their passage to the CNS.

Developing methods to determine Central Nervous System (CNS) exposure is a challenging but compelling research area. It must always be certified that these tools provide trustworthy information that benefits drug research. Taking into consideration the results achieved during the work developed throughout the last years in the Pharmacometrics Group, our strategy consists of associating different experimental models (PAMPA-BBB, cell-based assays and *in vivo* studies) in order to study the rate, extent and intra-brain distribution of compounds, intended for CNS or peripheral therapeutic targets. In the future, given that disease states alter BBB properties, it would also be interesting to investigate if and how different pathologies contribute to the modification of K_p ,uu, in comparison with healthy models.

BIOTECHNOLOGY

MICROBIOLOGY OF EXTREME ENVIRONMENTS GROUP | (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 15 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).



BIOTECHNOLOGY

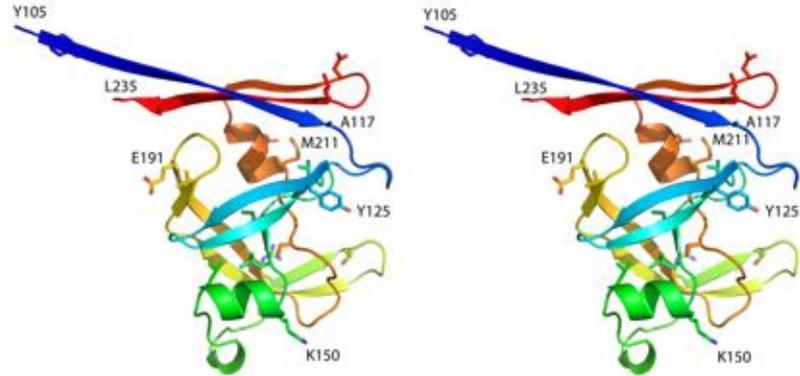
MOLECULAR BIOTECHNOLOGY | (Head: Isaura Simões)

OBJECTIVES

Proteolytic processing is one of the major forms of post-translational modification. However, proteases do not act alone, but in a complex interdependent network with other proteases, substrates, and interactors. Our group has a primary interest in proteolytic enzymes and their role in regulating these complex and highly dynamic protein networks, in addition to their degradative function and biotechnological potential. Our long-term goal is to generate an integrated platform for the discovery, characterization, and evaluation of “targetability” of proteases from different sources (mainly focused on (aspartic) proteases from pathogenic bacteria and plants). Additionally, we also aim to launch new research efforts towards the identification and characterization of other relevant protein targets of bacterial pathogens.

Our current research interests are summarized in the following lines:

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, where proteases/proteolytic processes are still largely unexplored.

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

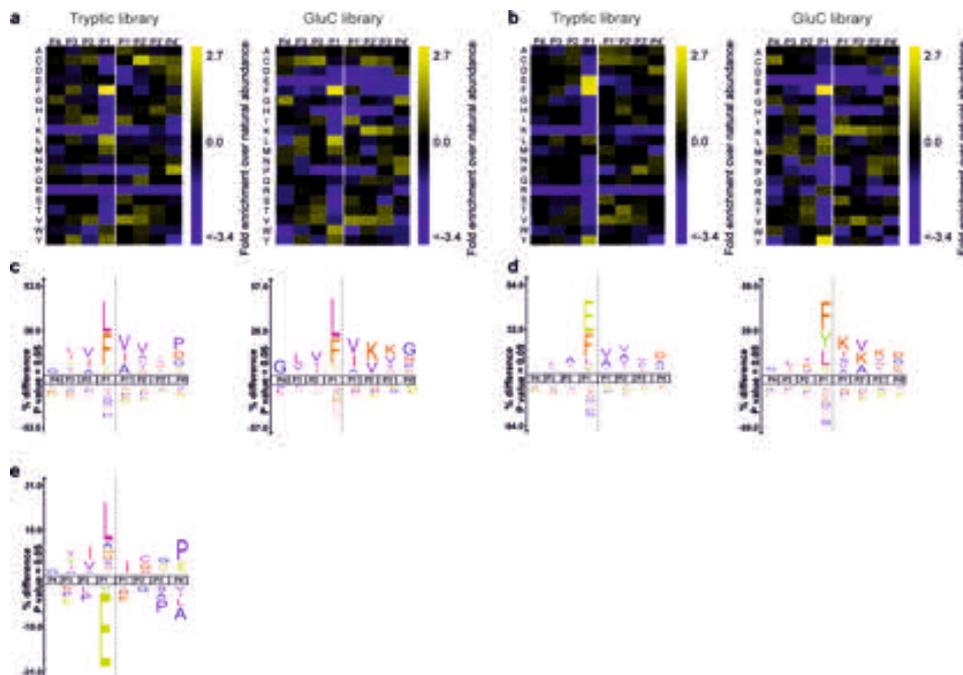
iii) An emerging line towards identification of other non-protease bacterial virulence proteins (e.g. surface-exposed membrane proteins) susceptible of antibody-based targeting strategies, for both structural and functional characterization and/or ultimate therapeutic intervention.

With these related strands, our long-term goal is to contribute to a better understanding of mechanisms of

disease and pathogenicity and facilitate the identification of new factors/molecular pathways that may constitute pathogen- or host-directed targets for therapeutic intervention.

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. Biochemistry, biology and biotechnology potential of plant APs

A detailed characterization of plant-derived rennet – synthetic cardosin B – was published. In this work, we provide a thorough analysis of the specificity requirements as well as the biochemical and structural properties of the isolated recombinant protease. Kinetic characterization and specificity profiling results clearly suggest that synthetic cardosin B displays lower catalytic efficiency and is more sequence selective than native cardosin B. Elucidation of the structure of synthetic cardosin B confirms the canonical fold of an aspartic protease with the presence of two high mannose-type, N-linked glycan structures; however, there are some differences in the conformation of the flap region when compared to cardosin A. These subtle variations in catalytic properties and the more stringent substrate specificity of synthetic cardosin B help to explain the observed suitability of this rennet for cheese production. Almeida, C.M., Manso, J.A., Figueiredo, A.C. et al. *Appl Microbiol Biotechnol* (2017) 101: 6951. <https://doi.org/10.1007/s00253-017-8445-8>

We pursued with the functional characterization of the atypical aspartic protease (AP) from *Arabidopsis* named ASPR1, for Atypical Aspartic Protease in Roots 1). We demonstrated that loss of function and over-expression mutants of ASPR1 display shorter primary roots and a pronounced reduction in the number of lateral roots (LRs). Moreover, by comparing proteomic profiles between WT and *aspr1* roots, our results reveal a deregulation in redox signaling, flavonoids biosynthesis and auxin metabolism in *aspr1* mutant. To our

knowledge, ASPR1 is the first AP to be implicated in the regulation of root development in *Arabidopsis*. (Manuscript in preparation).



2. 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 and to dissect the molecular mechanisms underlying differences in macrophage tropism between pathogenic and non-pathogenic members of SFG *Rickettsia*. Under the collaborative project with Dr. Juan Martinez (LSU, USA), we performed a RNA-seq analysis of early responses of THP-1 macrophages stimulated by a pathogenic and a non-pathogenic member of SFG *Rickettsia*. Our results show a sophisticated modulation of several host cellular processes specifically by the pathogen to evade host defenses and prolong host cell survival. (Manuscript in preparation).

3. 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 Research Facility, 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.

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BIOMEDICAL INTER-INSTITUTIONAL RESEARCH PROGRAMME

RESEARCH IN BRAIN TUMORS

Alberto Orfão (CSIC, University of Salamanca), Maria Dolores Tabernero (University Hospital, Salamanca), Hermínio Tão (CHUC), Olinda Rebelo (CHUC), Marcos Barbosa (FMUC, CHUC), Anália do Carmo (CHUC, CNC), Maria Celeste Lopes (FFUC, CNC)

The incidence of numerical/structural abnormalities of chromosomes in human gliomas were analysed by using interphase fluorescence *in situ* hybridization (iFISH). The results revealed complex and heterogeneous cytogenetic profiles in this type of tumors with distinct pathways of clonal evolution, which were associated with both the histopathological subtype and the grade of the tumor.

Gene expression profiles (GEP) of tumor cells were analysed in these samples using cDNA oligonucleotide microarrays, in order to assess the potential impact of individual chromosomal changes and cytogenetic profiles in the tumors-associated patterns of gene expression. The results of this study demonstrated a clear association between the GEP of gliomas and tumor histopathology, and the most discriminating genes between low- and high-grade being genes involved in the regulation of cell proliferation, apoptosis, DNA repair and signal transduction.

High-density single-nucleotide polymorphism array (SNP-array) was performed to investigate genome-wide copy number (CN) alterations in glioblastoma multiforme (GBM) samples. The results showed that combining both genomic and transcriptional data to differentiate genes with concordant CN alterations and expression patterns is crucial to disclose which of those

genes may have functional relevance in GBM pathogenesis.

Studies of multiparametric flow cytometry were performed to identify and characterize, in both gliomas and meningiomas, the different cell population coexisting and their patterns of protein expression in these tumors. The results suggest the involvement of different signalling pathways in the distinct cytogenetic subgroups that could contribute to the close association between tumor cytogenetic and patient outcome.

In parallel studies, glioma cell lines, obtained from human glioblastoma biopsies, were used to evaluate the cell signalling transduction pathways and the characteristics of a cell population within the tumour mass that presents stem-like cell properties - the glioma stem-like cells (GSCs). The results showed that the expression of glioma stem cells by GSCs seems to be associated to the progression from a low to a higher aggressive state. Furthermore, the signalling transduction pathways alterations in GBM cells contribute to their ability to proliferate, to resist to the cell death and to invade surrounding tissues. Thus, the establishment of an effective therapeutic plan must take into account the existence of GSCs and the alterations in the signalling transduction pathways and must be established according patient's tumour characteristics.

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NOVEL TECHNIQUES FOR THE DIAGNOSIS AND TREATMENT OF HUMAN INFERTILITY AND DEVELOPMENT OF NOVEL SPERMICIDES

Teresa Almeida Santos (CHUC, FMUC, CNC), Ana Paula Sousa (CHUC, CNC), Renata Tavares (CNC), Sara Escada-Rebelo (CNC), Mariana Moura-Ramos (CHUC), Alexandra Carvalho (CHUC, CNC), Andreia Silva (CNC), Vasco Almeida (University of Oporto, Portugal), Stefan Schlatt (University of Muenster, Germany), Teresa Woodruff (Northwestern University, USA), João Ramalho-Santos (CNC, FCTUC)

In close collaboration with clinical practice in Assisted Reproduction the goal is to create novel assays to evaluate gamete and embryo quality and how Assisted Reproductive Technologies (ART) may be improved using distinct approaches, and applying cutting-edge technologies as they are available.

These activities developed involve non-invasive or indirect oocyte and embryo assessment methodologies, improving techniques for the cryopreservation of gametes, tissue and embryos, and using molecular probes linked to metabolism and metabolites, mitochondrial activity and reactive oxygen species (ROS) production to identify more functional populations of sperm.

Three years ago the lab established the cryopreservation on ovarian and testicular tissue from patients who are undergoing oncological treatment that may render them infertile with the ultimate goal of re-establishing fertility

if it is impaired upon successful conclusion of treatment cycles (Oncofertility). The first successful transplant of ovarian tissue to a former oncological patient was carried out in 2015. For this purpose, two collaborations on both human tissue and animal models of testicular and ovarian function were established with leading scientists in the field, namely Stefan Schlatt (University of Muenster, Germany) and Teresa Woodruff (Northwestern University, USA), for the male and female side, respectively. This work is partially sponsored by MERCK International, and includes also psychological studies on how best to communicate with patients and clinicians.

In 2016 the group was asked to use its expertise on human sperm function to also help develop and test novel spermicidal compounds and formulations in collaboration with industry (INNOTECH International). This work is ongoing.

PUBLICATIONS

Are women and men well informed about fertility? Childbearing intentions, fertility knowledge and information-gathering sources in Portugal. Almeida-Santos T, Melo C, Macedo A, Moura-Ramos M. *Reprod Health*. 2017 Aug 4;14(1):91. doi: 10.1186/s12978-017-0352-z

INTERNACIONALIZATION

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

PROJECTS IN COLLABORATION

NEUROSCIENCE, VISION AND BRAIN DISEASES STRAND

Synapse Biology Group

Blanka Kellermayer, University of Coimbra & University of Bordeaux, January 2018. European Neuroscience Campus Network - Erasmus Mundus Joint Doctorate. Super-resolution imaging reveals differential organization and regulation of NMDA receptor subtypes. Supervisors: Ana Luísa Carvalho and Laurent Groc

A master student from Bonn University joined the group of Irina Moreira for an internship under the theme: "Searching for new GPCR143 ligands by a ligand based approach and docking studies on D2DR (dual-target ligands)".

Publications:

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Redox Biology and Brain Sensing

Collaborative publications:

The following papers resulted from a long-stand collaboration with the Center for Microelectrode Technology, CenMet (Greg Gerhardt, director) of the University of Kentucky (at Lexington) of which our lab is the Coimbra lab division. CenMet is a world leader center in the area of development of microelectrodes for in vivo electrochemistry recording of neurochemicals. We are collaborating at both levels, technological development and scientific applications. Visits to Coimbra and Lexington occur in a regular basis.

Ledo, Ana; Lourenço, Cátia; Laranjinha, João; Brett, Christopher; Gerhardt, Greg; Barbosa, Rui (2017) Ceramic-based Multi-Site Platinum Microelectrode Arrays: Morphological Characteristics and Electrochemical Performance for Extracellular Oxygen Measurements in Brain Tissue. *Analytical Chemistry* 89, 1674-1683.

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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)

Licio Velloso - University of Campinas, Brasil (FCT-Capes Project collaboration, interchange of 3 PhD students and 3 PhDs; co-author of publication; hypothalamic dysfunction and metabolic diseases projects)

Malu Martínez-Chantar – IC bioGUNE, Center for Cooperative Research in Biosciences, Spain (Collaborative Research; sirtuin-2 project)

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).

Shin-Ichiro Imai, Washington University School of Medicine, USA (scientific advisor in hypothalamus and aging field)

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)

van Waalwijk van Doorn LJ, Gispert JD, Kuiperij HB, Claassen JA, Arighi A, Baldeiras I, Blennow K, Bozzali M, Castelo-Branco M, Cavedo E, Emek-Savaş DD, Eren E, Eusebi P, Farotti L, Fenoglio C, Ormaechea JF, Freund-Levi Y, Frisoni GB, Galimberti D, Genc S, Greco V, Hampel H, Herukka SK, Liu Y, Lladó A, Lleó A, Nobili FM, Oguz KK, Parnetti L, Pereira J, Picco A, Pikkarainen M, de Oliveira CR, Saka E, Salvadori N, Sanchez-Valle R, Santana I, Scarpini E, Scheltens P, Soininen H, Tarducci R, Teunissen C, Tsolaki M, Urbani A, Vilaplana E, Visser PJ, Wallin AK, Yener G, Molinuevo JL, Meulenbroek O, Verbeek MM. Improved Cerebrospinal Fluid-Based Discrimination between Alzheimer's Disease Patients and Controls after Correction for Ventricular Volumes. *J Alzheimers Dis.* 2017;56(2):543-555. doi: 10.3233/JAD-160668. PubMed PMID: 28059783.

Mutsaerts HJMM, Petr J, Thomas DL, De Vita E, Cash DM, van Osch MJP, Golay X, Groot PFC, Ourselin S, van Swieten J, Laforce R Jr, Tagliavini F, Borroni B, Galimberti D, Rowe JB, Graff C, Pizzini FB, Finger E, Sorbi S, Castelo Branco M, Rohrer JD, Masellis M, MacIntosh BJ; GENFI investigators. Comparison of arterial spin labeling registration strategies in the multi-center GENetic frontotemporal dementia initiative (GENFI). *J Magn Reson Imaging*. 2018 Jan;47(1):131-140. doi: 10.1002/jmri.25751. Epub 2017 May 8. PubMed PMID: 28480617.

Leuzy A, Chiotis K, Hasselbalch SG, Rinne JO, de Mendonça A, Otto M, Lleó A, Castelo-Branco M, Santana I, Johansson J, Anderl-Straub S, von Arnim CA, Beer A, Blesa R, Fortea J, Herukka SK, Portelius E, Pannee J, Zetterberg H, Blennow K, Nordberg A. Pittsburgh compound B imaging and cerebrospinal fluid amyloid- β in a multicentre European memory clinic study. *Brain*. 2016 Sep;139(Pt 9):2540-53. doi: 10.1093/brain/aww160. Epub 2016 Jul 7. PubMed PMID: 27401520; PubMed Central PMCID: PMC4995359.

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 Wibrall, 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

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 PtCrim, 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 in 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. Göttingen, 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, Institut Fer à Moulin, Paris) and Christophe Bernard (INSERM, Univ.Méditerranée, Marseille).

Graduate training:

Co-supervision of a post-doctoral student (Samira Ferreira) with Nuno Sousa (Univ. Minho)

Co-supervision of a PhD student (Mara Yone Fernandes) with Geanne Matos (Univ. Federal Ceará, Brazil)

Co-supervision of a PhD student (Ana Elisa Speck Aguiar) with Rui Prediger (Univ. Federal Santa Catarina, 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)

Co-supervision of a PhD student (Anna Pliassova) with João Bessa (Univ. Minho)

Mitochondrial Dysfunction and Signaling in Neurodegeneration Group

Participation in international meetings:

International Society for Stem Cell Research (ISSCR) 2017 Annual Meeting, 14-17 June 2017, Boston, USA (1 abstract)

MitoPorto – Advances in Mitochondrial Research International Symposium, May 26 2017, Faculty of Pharmacy, Porto, Portugal (1 abstract)

Jornada del Parkinson I: Mesa Redonda Investigación. In: CIMQ'17 – Congreso Internacional Médico-Quirúrgico - 'Mentes Que Cambian El Mundo', March 13-15 2017 Facultad de Medicina de Santiago de Compostela, Santiago de Compostela, España (1 abstract)

Invited speakers in international meetings and foreign institutes/universities:

Rego A. C. (2017) MitoPorto – Advances in Mitochondrial Research International Symposium, 26th May 2017, Faculty of Pharmacy, Porto, Portugal.

Rego A. C. (2017) Congreso Internacional Médico-Quirúrgico - 'Mentes Que Cambian El Mundo', 13-15th March 2017, Facultad de Medicina de Santiago de Compostela, Santiago de Compostela, España

Research collaboration with the following researchers:

Flaviano Giorgini (PhD), Department of Genetics and Genome Biology, University of Leicester, U.K.

George Daley (MD, PhD), Harvard Medical School and Boston Children's Hospital, Boston, USA

Thorsten Schlaeger (PhD) Boston Children's Hospital, Boston, MA, USA

Michael Hayden (MD, PhD), University of British Columbia, Vancouver, Canada

Tiago Fleming Outeiro (PhD), University Medizin Goettingen, Goettingen, Germany

Collaborative publications with researchers abroad:

- Lemos et al. (2017) *Hum Mol Genet.* 26, 4105-4117.
Paiva et al. (2017) *Hum Mol Genet.* 26, 2231-2246.
Noronha et al. (2017) *Neurochem. Res.* 42, 1430-1437.
Naia et al. (2017) *J. Neurosci.* 37, 2776-2794.
Robledinos-Antón et al. (2017) *Redox Biol.* 13, 393-401.
Dioli et al. (2017) *Mol Psychiatry* 22, 1110-1118.
Naia et al. (2017) *Mol. Neurobiol.* 54, 5385-5399.

Aging and Brain diseases: advanced diagnosis and biomarkers

Collaborative Publications:

van Waalwijk van Doorn LJC, Gispert JD, Kuiperij HB, Claassen JAHR, Arighi A, Baldeiras I, Blennow K, et al. Improved CSF-based discrimination between Alzheimer patients and controls after correction for ventricular volumes. *J Alzheimer's Dis* 2017; 56(2): 543-555.

Simonsen AH, Herukka SK, Andreasen N, Baldeiras I, Bjerke M, Blennow K, Engelborghs S, et al. Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. *Alzheimers&Dementia* 2017; 13: 274-284.

Herukka SK, Simonsen AH, Andreasen N, Baldeiras I, Bjerke M, Blennow K, Engelborghs S, et al. Recommendations for CSF Alzheimer's disease biomarkers in the diagnostic evaluation of mild cognitive impairment. *Alzheimers&Dementia* 2017; 13: 285-295.

Bos I, Vos SJ, Frölich L, Kornhuber J, Wiltfang J, Maier W, Peters O, Rütger E, Engelborghs S, Niemantsverdriet E, De Roeck EE, Tsolaki M, Freund-Levi Y, Johannsen P, Vandenberghe R, Lleó A, Alcolea D, Frisoni G, Galluzzi S, Nobili F, Morbelli S, Drzezga A, Didic M, van Berckel BN, Salmon E, Bastin C, Dauby S, Santana I, Baldeiras I, Mendonça A, Silva D, Wallin A, Nordlund A, Coloma P, Wientzek-Fleischmann A, Novak GP, Forrest Gordon M, the Alzheimer's Disease Neuroimaging Initiative, Wallin AK, Hampel H, Soininen H, Scheltens P, Verhey FR and Jelle Visser PJ. Prevalence of vascular, psychiatric and lifestyle risk factors in prodromal Alzheimer's disease and their influence on cognitive decline. *Neurobiology of Aging* 2017;56:33-40.

De Roeck A, Van den Bossche T, van der Zee J, Verheijen J, De Coster W, Van Dongen J, Dillen L, Baradaran-Heravi Y, Heeman B, Sanchez-Valle R, Lladó A, Nacmias B, Sorbi S, Gelpi E, Grau-Rivera O, Gómez-Tortosa E, Pastor P, Ortega-Cubero S, Pastor MA, Graff C, Thonberg H, Benussi L, Ghidoni R, Binetti G, de Mendonça A, Martins M, Borroni B, Padovani A, Almeida MR, Santana I, Diehl-Schmid J, Alexopoulos P, Clarimon J, Lleó A, Fortea J, Tsolaki M, Koutroumani M, Matěj R, Rohan Z, De Deyn P, Engelborghs S, Cras P, Van Broeckhoven C, Sleegers K; European Early-Onset Dementia (EU EOD) consortium. Deleterious ABCA7 mutations and transcript rescue mechanisms in early onset Alzheimer's disease. *Acta Neuropathol.* 2017 Sep;134(3):475-487. doi:10.1007/s00401-017-1714-x.

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

Collaborative publication with Fluminense Federal University, Niterói, Rio de Janeiro, Brazil; University of Muenster, Germany; RWTH Aachen University, Aachen, Germany and University of Illinois College of Medicine, Chicago, USA: C.C. Portugal, R. Socodato, T. Canedo, C.M. Silva, T. Martins, V.S. Coreixas, E.C. Loiola, B. Gess, D. Röhr, A.R. Santiago, P. Young, R.D. Minshall, R. Paes-de-Carvalho, A.F. Ambrósio and J.B. Relvas. Caveolin-1-mediated internalization of the vitamin C transporter SVCT2 in microglia triggers an inflammatory phenotype. *Sci Signal*. 2017, 10(472). pii: eal2005. doi: 10.1126/scisignal.aal2005. PMID: 28351945. IF: 6,494

Collaborative publication with Spain and Ikerbasque Foundation for Science, Bilbao, Bizkaia, Spain: J. Valero, L. Bernardino, F. Cardoso, A.P. Silva, C. Fontes-Ribeiro, A.F. Ambrósio and J.O. Malva. Impact of neuroinflammation on hippocampal neurogenesis: relevance to aging and Alzheimer's disease. *J Alzheimers Dis*. 2017, 60(s1):S161-S168. doi: 10.3233/JAD-170239. PMID: 28671124. IF: 3,731

Collaborative publication with Sultan Qaboos University Oman and University of Bonn, Bonn, Germany: R. Boia, F. Elvas, M.H. Madeira, I.D. Aires, A.C. Rodrigues-Neves, P. Tralhão, E.C. Szabó, Y. Baqi, C.E. Müller, Â.R. Tomé, R.A. Cunha, A.F. Ambrósio and A.R. Santiago. Treatment with A2A receptor antagonist KW6002 and caffeine intake regulate microglia reactivity and protect retina against transient ischemic damage. *Cell Death Dis*. 2017, 8(10):e3065. doi: 10.1038/cddis.2017.451. PMID: 28981089. IF: 5,965

Edition of the Special Issue "mTOR signaling in cardiometabolic disease, cancer and aging" from *Oxidative Medicine and Cellular Longevity* Journal (IF=4.593).
Guest Editors: Anindita Das, Flávio Reis, Yasuhiro Maejima, Zhiyou Cai and Jun Ren

Collaborative publication with Universidad Nacional de Educación a Distancia, Madrid, Spain: Gonçalves J, Leitão RA, Higuera-Matas A, Assis MA, Coria SM, Fontes-Ribeiro C, Ambrosio E, Silva AP. Extended-access methamphetamine self-administration elicits neuroinflammatory response along with blood-brain barrier breakdown. *Brain Behav Immun*. 2017 May; 62:306-317.

Collaborative publication with Leiden University Medical Center, Leiden, The Netherlands: Martins-Neves SR, Paiva-Oliveira DI, Fontes-Ribeiro C, Bovée JVMG, Cleton-Jansen AM, Gomes CMF. IWR-1, a tankyrase inhibitor, attenuates Wnt/ β -catenin signaling in cancer stem-like cells and inhibits in vivo the growth of a subcutaneous human osteosarcoma xenograft. *Cancer Lett*. 2017 Nov 8; 414:1-15. (IF= 6.375)

Collaborative publication with University of Santa Catarina, Brazil: Fonseca R, Carvalho RA, Lemos C, Sequeira AC, Pita IR, Carvalho F, Silva CD, Prediger RD, Jarak I, Cunha RA, Fontes Ribeiro CA, Köfalvi A, Pereira FC. Methamphetamine Induces Anhedonic-Like Behavior and Impairs Frontal Cortical Energetics in Mice. *CNS Neurosci Ther*. 2017 Feb;23(2):119-126. doi: 10.1111/cns.12649. Epub 2016 Oct 19. PubMed PMID: 27762079.

Collaborative publication with University of Santa Catarina, Brazil and with Food and Drug Administration, USA: Viana SD, Pita IR, Lemos C, Rial D, Couceiro P, Rodrigues-Santos P, Caramelo F, Carvalho F, Ali SF, Prediger RD, Fontes Ribeiro CA, Pereira FC. The effects of physical exercise on nonmotor symptoms and on neuroimmune RAGE network in experimental parkinsonism. *J Appl Physiol* (1985). 2017 Jul 1;123(1):161-171. doi: 10.1152/jappphysiol.01120.2016. Epub 2017 Apr 6. PubMed PMID: 28385921.

Collaborative publications and research with:

University of Utrecht. Holanda
University of S. Francisco. Bragança Paulista. Brasil
University of Rio Preto. Rio Preto. Brasil
University of São Paulo, São Paulo. Brasil
University of Campinas. Brasil
University of Swansea, UK
University of Uppsala, Sweden
Centro de investigación del Cáncer (Salamanca)

David Woldbye, Department of Neuroscience and Pharmacology, University of Copenhagen, Dinamarca.

Nicolás Cuenca, Instituto Multidisciplinar para el Estudio del Medio Ramon Margalef, Universidad de Alicante, Alicante, Espanha.

Manuel Vidal-Sanz, Laboratorio de Oftalmología Experimental, Facultad de Medicina, Universidad de Murcia, Murcia, Espanha.

Juan Corral, Universidad Complutense de Madrid, Espanha.

Thomas Langmann, University of Cologne, Alemanha.

METABOLISM, AGING AND DISEASE STRAND

Cell Metabolism and Quality Control

Book edition; Alzheimer's Disease: New Beginnings; Eds: George Perry, Jesus Avila, Paula I. Moreira, Aaron Sorenson, Massimo Tabaton.

David Busija; Tulane University School of Medicine, USA, co-supervisor of a postdoc fellow

George Perry, University of Texas at San Antonio; USA; co-supervisor of a postdoc fellow

Carmen García-Rodríguez 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

Diego Pérez Rodríguez, Ph.D. thesis: "The role of autophagy in the differential vulnerability and integrated stress response to cerebral ischemia". Faculty of Biological and Environmental Sciences, Molecular Biology Department, Cell Biology Area, University of Leon, Spain. (Member of the Jury of the Ph.D. thesis exam in July 24, 2017).

HG is Member of the Management Committee of the COST Actions PROTEOSTASIS, TRANSAUTOPHAGY and CARDIOPROTECTION

In the context of COST actions, several students of the lab have spent training periods at different Labs: Viktor Korolchuk (University of Newcastle, UK); Sascha Martens (University of Viena, Austria); Michael Clague/ Sylvie Urbe (University of Liverpool, UK); Manuel Rodriguez (University of Toulouse, França)

Joint Publication with collaborators Brenda Kwak (University of Geneve), Joost Sluijter (University of Utrecht)

Rik Vanheuckelom. Bachelor in biomedical laboratory technology, Thomas More University, Geel, Belgium.

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.

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
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:

Iñaki Milton-Laskibar (University of the Basque Country, Spain)
Chiara Cavallaro (University of Sannio, Italy)

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

Collaboration with Dr. Jan Eriksson from Uppsala University, Sweden:
We have had Ana Fonseca as a Post-Doctoral fellow:

Fonseca ACRG, Carvalho E, Eriksson JW, Pereira MJ. Calcineurin is an important factor involved in glucose uptake in human adipocytes. *Mol Cell Biochem.* 2017 doi: 10.1007/s11010-017-3261-0.

Collaboration with Dr. Elisabet Børsheim from the University of Arkansas for Medical Sciences, USA:

Bryce J. Marquis, Nicholas M. Hurren, Eugenia Carvalho, Scott Schutzler, Gohar Azhar, Robert R. Wolfe and Elisabet Børsheim. Skeletal muscle acute and chronic metabolic response to essential amino acid supplementation in hypertriglyceridemic older adults. *Curr Dev Nutr.* November 2017, 1 (11) e002071.

Four new ITNs and one RISE program featuring collaboration with other laboratories in Europe started in 2017 with exchange of students and staff that will be ongoing for 4 years.

Collaboration with the University of Münster Germany.

STEM CELL-BASED AND MOLECULAR THERAPIES STRAND

Vectors and Gene Therapy Group

Projects under international Consortiums/Networks:

European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative; Joint Programme on Neurodegenerative Disease Research. European Consortium. 2016-2019.

Advanced models of polyglutamine disorders (HD, SCA3, SCA7); Joint Programme on Neurodegenerative Disease Research. European Consortium. 2016-2019.

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)

Collaborative Publications:

Hachigian LJ, Carmona V , Fenster RJ , Kulicke R, Heilbut A , Sittler A , Pereira de Almeida L , Mesirov JP , Gao F , Kolaczyk E , and Heiman M., Control of Huntington's Disease-Associated Phenotypes by the Striatum-Enriched Transcription Factor Foxp2. Cell Reports. Dec 5;21(10):2688-2695. doi: 10.1016/j.celrep.2017.11.018.

Carmona V, Cunha-Santos J, Onofre I, Simões AT, Vijayakumar U, Davidson BL and Pereira de Almeida L. Unravelling endogenous MicroRNAs system dysfunction as a new pathophysiological mechanism in Machado-Joseph disease. Molecular Therapy. 2017 Apr 5;25(4):1038-1055. doi: 10.1016/j.ymthe.2017.01.021.

Stem Cell Biotechnology

Participation at the international program MIT-Portugal, focus area of bioengineering. Lino Ferreira, Hugo Fernandes and Filipe Pereira contributed for the "Cell and Tissue Engineering" module with Robert Langer (MIT) and Joaquim Cabral/Cláudia Lobato (IST).

Participation in the BEB PhD program. Módulo: "Advanced Therapies". Coordinators: Lino Ferreira and Luis Almeida. Speakers: Lino Ferreira, Hugo Fernandes, Ricardo Neves, Filipe Pereira.

During 2017, several networks involving international researchers have been established or continued:

Three-dimensional matrices for cell culture and transplantation. Robert Langer (Department of Chemical Engineering, Massachusetts Institute of Technology, MIT, EUA), Ali Khademhosseini (Harvard-MIT Division of Health Science and Technology, USA), Helena Vazão (CNC, Portugal), Sezin Aday (CNC, Portugal), Lino Ferreira (CNC, Portugal).

Nanomaterials for wound healing. Josephine Blerish (CNC, Portugal), Michela Comune (CNC, Portugal), Veronique Preat (University of Louvain, Belgique), Klaus Liedl (University of Innsbruck, Austria), Lino Ferreira (CNC, Portugal).

Nanomaterials to modulate stem cells. Magdalena Gotz (Munich Institute), Catarina Rebelo (CNC, Portugal), Sónia Pinho (CNC, Portugal), Susana Simões (CNC, Portugal), Lino Ferreira (CNC, Portugal).

Cell reprogramming/stem cell modulation. Tariq Enver (University College of London, UK), Carlos Boto (CNC, Portugal), Emanuel Martin (CNC, Portugal), Ricardo Neves (CNC, Portugal), Deng Li (University of Shanghai), Lino Ferreira (CNC, Portugal).

Unraveling the effect of arterial flow in smooth muscle cells derived from induced pluripotent stem cells containing Hutchinson-Gilford Progeria Syndrome (HGPS). Xavier Nissam/ Marc Peschanski (i-Stem, France), Patrícia Pereira (CNC, Portugal), Helena Vazão (CNC, Portugal), Luis Estronca, Lino Ferreira (CNC, Portugal).

Cardiac kit. Leonardo Ricotti/Ariana Menciassi (University of Pisa, Italy), Paula Alves (ITQB, Lisbon), Bernardo Abecassis (ITQB), Pedro Gouveia (CNC, Portugal), Ricardo Neves (CNC, Portugal), Susana Rosa (CNC, Portugal), Lino Ferreira (CNC, Portugal).

Cardiac regeneration. Jeffrey Karp (Harvard-MIT Division of Health Science and Technology, USA), Ivana Kostic (CNC, Portugal), Lino Ferreira (CNC, Portugal).

In vitro blood-brain barrier models. Romeo Cechelli (University of Lille, France), Sezin Aday (CNC, Portugal), Catarina Almeida (CNC, Portugal), Susana Rosa (CNC, Portugal), Lino Ferreira (CNC, Portugal).

Cardiac regeneration. Leon de Windt (University Maastricht), Paula da Costa Martins (University Maastricht), Hugo Fernandes (CNC, Portugal), Lino Ferreira (CNC, Portugal), Andreia Vilaça (University of Coimbra and University of Maastricht), Ricardo Abreu (University of Coimbra and University of Maastricht)

Skeletal tissue engineering. Hugo Fernandes (CNC) and Daniel Saris (Utrecht Medical Center).

Noise in gene expression. Francisco Iborra (CNB-CSIC, Spain), Tariq Enver (University College of London, UK), Ana Lima (CNC, Portugal), Ricardo Neves (CNC, Portugal).

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

Personalised beta-cell mass imaging in type 2 diabetes. Dr. Gotthardt and Dr. Mijke Buitinja (University Nijmegen, The Netherlands) and Dr. Hugo Fernandes and Dr. Lino Ferreira (CNC, Portugal).

Generating Dendritic Cells by Direct Reprogramming. Dr. Caetano Reis e Sousa (Francis Crick Institute, London, UK), Dr. Francesca Granucci (University of Milano-Bicocca, Milan, Italy) and Dr. Filipe Pereira (CNC, Portugal).

Computational and Systems Biology

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

University of Lleida (Spain)

Researchers: Rui Alves

Project: Uncovering the evolutionary adaptations of protein aminoacid sequence and structure to O₂-rich environments

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”

Medical Microbiology

Diogo P, Fernandes C, Caramelo F, Mota M, Miranda IM, Faustino MAF, Neves MGPMS, Uliana MP, de Oliveira KT, Santos JM and Gonçalves T (2017) Antimicrobial Photodynamic Therapy against Endodontic *Enterococcus faecalis* and *Candida albicans* Mono and Mixed Biofilms in the Presence of Photosensitizers: A Comparative Study with Classical Endodontic Irrigants. *Front. Microbiol.* 8:498. doi: 10.3389/fmicb.2017.00498

Molecular Mycobacteriology & Microbiome

Pau Porras Socias (2017) Screening for novel antimycobacterials. Masters Thesis, Erasmus Program, Universitat Barcelona, Spain

Nuno Empadinhas (Invited Speaker) Mycobacterial pathways from simple glycosides to fatty-acid shuttling polysaccharides. *Mycobacterium*: Molecular Microbiology. National Center for Biotechnology CNB – CSIC, Campus Cantoblanco, 7 Apr 2017, Madrid, Spain

Diana F. Silva, A. Raquel Esteves, Emanuel Candeias, Nuno Empadinhas, Sandra M. Cardoso. The neurotoxin β -methylamino-L-alanine acts on mitochondria to recapitulate PD related pathology. 8th World Congress on Targeting Mitochondria, 23-24 Oct 2017, Berlin, Germany (Poster presentation)

Medicinal Chemistry & Drug Discovery

Collaborative publications:

Salete J. Baptista, Maria M. C. Silva, Elisabetta Moroni, Massimiliano Meli, Giorgio Colombo, Teresa C. P. Dinis, Jorge A. R. Salvador. Novel PARP-1 Inhibitor Scaffolds Disclosed by a Dynamic Structure-Based Pharmacophore Approach. *PLOS ONE*, 2017, Volume: 12, Ed. 1, e0170846. DOI: 10.1371/journal.pone.0170846

Olumuyiwa S Alabi, N. Mendonça, O. E. Adeleke, G. J. da Silva. (2017) Molecular screening of antibiotic-resistant determinants among multidrug-resistant clinical isolates of *Proteus mirabilis* from Southwest Nigeria. *African Health Sciences*, 17 (2): 356-365.

Vubil D, Figueiredo R, Reis T, Canha C, Boaventura L, Da Silva GJ. (2017) Outbreak of KPC-3-producing ST15 and ST348 *Klebsiella pneumoniae* in a Portuguese hospital. *Epidemiol Infect.* 145: 595-599. doi: 10.1017/S0950268816002442.

Singh P, Medronho B, Alves L, da Silva GJ, Miguel MG, Lindman B. (2017) Development of carboxymethyl cellulose-chitosan hybrid micro- and macroparticles for encapsulation of probiotic bacteria. *Carbohydr Polym.* 175:87-95. doi: 10.1016/j.carbpol.2017.06.119.

Domingues S, Nielsen KM. (2017) Membrane vesicles and horizontal gene transfer in prokaryotes. *Curr. Opin. Microbiol.*, 38:16-21.

Clarissa Perez Faria, Graziela Maria Zanini, Gisele Silva Dias, Sidnei da Silva, Marcelo Bessa de Freitas, Ricardo Almendra, Paula Santana, Maria do Céu Sousa (2017) Geospatial Distribution of Intestinal Parasitic Infections in Rio de Janeiro (Brazil) and Its Association with Social Determinants. *PLOS Neglected Tropical Diseases* (p.1-21) <http://dx.doi.org/10.1371/journal.pntd.0005445>.

Daniela Rossi, Karzan Mahmood Ahmed, Raffaella Gaggeri, Serena Della Volpe, Laretta Maggi, Mazzeo Giuseppe, Giovanna Longhi, Sergio Abbate, Federica Corana, Emanuela Martino, Raquel Varandas, Maria Do Ceu Sousa, Marisa Machado, Simona Collina (2017) R)-(-)-Aloesaponol III 8-Methyl Ether from *Eremurus persicus*: A Novel Compound against Leishmaniasis. *Molecules* 24;22(4). pii: E519. doi: 10.3390/molecules22040519

Clarissa Perez Faria, Graziela Maria Zanini, Gisele Silva Dias, Maria do Céu Sousa (2017). Associations of Giardia lamblia assemblages with HIV infections and symptomatology: HIV virus and assemblage B were they born to each other? Acta Tropica 172: 82-85. <http://dx.doi.org/10.1016/j.actatropica.2017.04.026>

Clarissa Perez Faria, Graziela Maria Zanini, Gisele Silva Dias, Sidnei da Silva, Maria do Céu Sousa (2017). New multilocus genotypes of Giardia lamblia human isolates. Infection, Genetics and Evolution 54: 128-137. <http://dx.doi.org/10.1016/j.meegid.2017.06.028>

Molecular Biotechnology Group

Research:

Under the scope of the Science and Technology Cooperation FCT/DAAD – 2015-2017 - Bilateral cooperation agreement *Plant Aspartic Protease Substrate Identification*, Isaura Simões spent two periods in Dr. Pitter Huesgen laboratory at the Central Institute for Engineering, Electronics and Analytics (ZEA-3), Forschungszentrum Jülich, Germany, working on comparative proteomics profiles between WT and *aspr1* knock-out *A. thaliana* roots.

PhD Student Pedro Curto spent the year in Dr. Juan Martinez' lab at the Department of Pathobiological Sciences, Louisiana State University, Baton Rouge, USA, as part of his training (Grant SFRH/BD/96769/2013). His project was developed under the context of a R21-NIH Grant approved as a follow-up of a project previously funded by FCT, Portugal (PI Isaura Simões).

Research Fellow João Laranjeira's (IEFP Fellowship) work entitled "*An avian antibody platform to fight bacterial infections*" was selected for an Oral communication at the II International Congress in Health Sciences Research, 17-20th May 2017, Covilhã, Portugal.

Our group hosted the Workshop - "The transgenic chicken bioreactor", 22nd Nov. 2017, Cantanhede, Portugal - the first one under the scope of an international collaborative effort for research and training initiatives on exploiting avian hosts as bioreactors. This was organized in collaboration with the Dr. Lissa Herron (Roslin Institute, University of Edinburgh), coordinator of the business unit "Eggcellent Proteins" from Roslin Technologies.

Collaborators

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), Forschungszentrum Jülich, Germany

Dr. Lissa Herron, Roslin Institute, University of Edinburgh, Scotland

PARTICIPATION IN THE ORGANIZATION OF SCIENTIFIC MEETINGS

JANUARY 2017

Organizing of the Seminar "Carbon monoxide targeting mitochondria: modulation of metabolism, cell differentiation and cell death", Helena Vieira, CEDOC, NOVA Medical School, Lisbon

Date: 18 January, 2017

CNC.IBILI members involved in the organization: Paulo J. Oliveira

Organizing of the Seminar "Posttranslational modifications: secrets of neurodegeneration", Tiago F. Outeiro (University Medical Center Goettingen, Goettingen, Germany)

Date: 26 January, 2017

CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing of CIMAGO 2017 - CIMAGO COURSE. "Infection in the Immunocompromised patient", Coimbra

Date: 27 January, 2017

CNC.IBILI members involved in the organization: Ana Bela Sarmento

Organizing of the Seminar “HUMANITY in a DISH - Key Technologies for disease modeling with human pluripotent stem cells”, Christoph Hoefer, Thermoscientific

Date: 31 January, 2017

CNC.IBILI members involved in the organization: Paulo J. Oliveira

FEBRUARY 2017

Organizing of the 2nd meeting “Heart without borders”, PT_BEAT, IBILI-FMUC

Date: 3 February, 2017

CNC.IBILI members involved in the organization: Henrique Girão

Organizing of the Seminar “Eye movement research in movement disorders”, João Lemos (CHUC-Centro Hospitalar da Universidade de Coimbra, Coimbra, Portugal)

Date: 3 February, 2017

CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing of the XLVII Reunião Anual da Sociedade Portuguesa de Farmacologia, XXVI Reunião de Farmacologia Clínica e XVII Reunião de Toxicologia, Coimbra

Date: 2-4 February, 2017

CNC.IBILI members involved in the organization: Francisco Ambrosio

Organizing of the Seminar “Venture Capital and Bio-Entrepreneurship”, Pedro Pinheiro Independent Consultant

Date: 10 February, 2017

CNC.IBILI members involved in the organization: Paulo J. Oliveira

Organizing of the 2-IEEE ENBENG’2017 - 5th Portuguese Meeting in Bioengineering, Coimbra

Date: 16 a 18 February, 2017

CNC.IBILI members involved in the organization: Lino Ferreira

MARCH 2017

Organizing of the BEB Doctoral Program Advanced Course “Metabolism and Disease: Causes and Consequences of Non-Alcoholic Fatty Liver Disease (NAFLD)”

Date: 6 – 10 March, 2017

CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the seminar Neurogenetics of Locomotion, César Mendes CEDOC, NOVA Medical School, Lisbon

Date: 3 March, 2017

CNC.IBILI members involved in the organization: Paulo J. Oliveira

APRIL 2017

Organizing of the Bio-inspired Computational Models for Biological and Biomedical Sciences, Francisco Pereira

ISEC-IPC, Institute of Engineering, Polytechnic Institute of Coimbra

Date: 21 April, 2017

CNC.IBILI members involved in the organization: Paulo J. Oliveira

Organizing of the 1^o Congresso de Investigação das Escolas Médicas Portuguesas, FMUC

Date: 28-29 April, 2017

CNC.IBILI members involved in the organization: Henrique Girão

MAY 2017

Organizing of the Seminar “Impact of psychostimulants in the brain: use and abuse”, Ana Paula Silva (Faculdade de Medicina, Universidade de Coimbra, Portugal)

Date: 19 May, 2017

CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing of the II Symposium of the Portuguese Glial Network. Glial cells, much more than glue, Braga

Date: 24 May, 2017

CNC.IBILI members involved in the organization: Francisco Ambrosio

Organizing of the seminar Functional outcome in the upper limb (UL) in patients with stroke: Contribution to the development of a predictive model for hemiplegic patients, João Paulo Branco FMUC, Coimbra

Date: 31.5.2017

CNC.IBILI members involved in the organization Paulo J. Oliveira

June 2017

Organizing of FEBS Advanced Lecture Course on Oncometabolism – From Conceptual Knowledge to Clinical Applications, in Figueira da Foz, Portugal

Date: June 18-24, 2017

CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of Metagenomics Workshop, UC-Biotech, Cantanhede, Portugal

Date: 6 June, 2017

CNC.IBILI members involved in the organization: Conceição Egas

JULY 2017

Organizing of V Cell Culture and Tissue Training Course, CIMAGO–FMUC

Date: 17-21 July, 2017

CNC.IBILI members involved in the organization: Francisco Ambrosio

Organizing of Workshop Ligand Tracer, CIMAGO-IBILI-FMUC

Date: 20 July, 2017

CNC.IBILI members involved in the organization: Francisco Ambrosio

Organizing of Scientific committee, ICMSB2017 – International Conference on Molecular Systems Biology, Raitenhaslach (Alemanha)

Date: 26-28 July, 2017

CNC.IBILI members involved in the organization: Armino Salvador

SEPTEMBER 2017

Coordination, 2017 Summer School on Computational Biology, Coimbra (Portugal)

Date: 4-14 September, 2017

CNC.IBILI members involved in the organization: Armino Salvador

Organizing of 53rd Congress of the European Societies of Toxicology: Emotions and Basal ganglia derangements: A molecule-to-men approach - (EUROTOX) Bratislava, Slovakia

Date: 10–13 September, 2017

CNC.IBILI members involved in the organization: Francisco Ambrosio

OCTOBER 2017

Organizing of Seminar “Managing your career: From Academia to Corporate”, Ricardo Gonçalves Co-founder & Partner at Collectiv

Date: 4 October, 2017

CNC.IBILI members involved in the organization: Paulo J. Oliveira

Organizing of 10th Annual International Meeting of the Portuguese Society for Stem Cells and Cellular Therapies, Covilhã, Portugal

Date: 12-14 October, 2017,

CNC.IBILI members involved in the organization: Lino Ferreira.

Organizing of Workshop “Microbiomics in Agriculture and Forestry”, University of Évora, Évora, Portugal

Date: 31st October, 2017

CNC.IBILI members involved in the organization: Conceição Egas

NOVEMBER 2017

Organizing of Seminar “Inflammation-driven disruption of iron homeostasis in Parkinson’s disease”, Raffaella Gozzelino, Laboratory of Inflammation and Neurodegeneration, NOVA Medical School, CEDOC, Lisbon

Date: 3 November, 2017

CNC.IBILI members involved in the organization: Paulo J. Oliveira

Organizing of 7th International Meeting of Psychogeriatrics, 2017. Vilamoura, Portugal

Date: 2-4 November, 2017

CNC.IBILI members involved in the organization: Joaquim Cerejeira

DECEMBER 2017

Organizing of Encontro de Jovens Investigadores em Biologia Estrutural e Computacional (EJIBCE), Departamento de Física, Coimbra, Portugal

Date: 22 December, 2017

CNC.IBILI members involved in the organization: Synapse Biology Group

GRADUATE STUDIES PROGRAMME

During 2017 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 2017

Computational Tools in Biology: a hands on course

January 11-15, 2016

Rui Travasso, Physics Department, UC

Biostatistics [OPTIONAL]

January 16 - 20, 2017

Susana Costa: phdhs@fmed.uc.pt

Neurosciences and Mental Health [OPTIONAL]

January 23 - 27, 2017

Susana Costa: phdhs@fmed.uc.pt

Aging [OPTIONAL]

January 30 - February 10, 2017

Susana Costa: phdhs@fmed.uc.pt

Synapses, neuronal circuits and behavior

February 13 - 24, 2017

Ana Luísa Carvalho & João Peça, CNC

Computational Biochemistry

February 27 - March 3, 2017

Alexandra Carvalho, Irina Moreira, CNC

Metabolism and Disease: Causes and Consequences of Non-Alcoholic Fatty Liver Disease (NAFLD)

March 6 - 10, 2017

Paulo Oliveira, John Jones, João Ramalho Santos, CNC

Cardiovascular Sciences [OPTIONAL]

March 13 - 17, 2017

Susana Costa: phdhs@fmed.uc.pt / Miguel Mano: mano@ci.uc.pt

Genetic and Hereditary Cancer [OPTIONAL]

March 20 - 24, 2017

Susana Costa: phdhs@fmed.uc.pt

Oncobiology and Cancer [OPTIONAL]

March 27 - 31, 2017

Susana Costa: phdhs@fmed.uc.pt

Advanced Course in Science Communication and Soft Skills

April 10 - 13, 2017

Science Communication Office

Drug Development

May 15 - 26, 2017

João Nuno Moreira

MIT-PORTUGAL PROGRAM 2015/2016 PRINCIPLES AND PRACTICE IN DRUG DEVELOPMENT

May 15 - 26, 2017

João Nuno Moreira, Luís Pereira de Almeida, Sérgio Simões, Stan Finkelstein

Core Facilities - PDBEB courses 2017/2018
December 4 - 15, 2017
Luísa Cortes, Isabel Nunes & Conceição Egas, CNC

CNC.IBILI Seminars

January-December 2017

Coordination of the activity: Nuno Empadinhas, Carlos Duarte, Paulo Oliveira, Hugo Fernandes

Internal communication: Ana Maranhã, Ermelindo Leal & Luís Estronca

The CNC.IBILI seminar program includes lectures by visiting scientists, CNC and IBILI researchers working on a wide range of fundamental and translational research topics across biomedical and biotechnological fields. These seminars intend to provide excellent opportunities to share and discuss ideas and foster new collaborations that are also expected to emerge from the interactions of visiting scientists with CNC.IBILI PIs and postdoctoral fellows during the “lunch meetings” that occur before or after the seminars. The speakers for the seminars are invited by the heads of each research line at CNC.IBILI in order to have a broad area of themes with interest for the institution.

JANUARY

Maternal antibodies in neurodevelopmental disorders

4.1.2017

Ester Coutinho

Nuffield Department of Clinical Neurology, University of Oxford, UK

Embo funding & training opportunities for scientists at different stages of their career

4.1.2017

Luís Valente

European Molecular Biology Organization (EMBO)

Targeting tuberculosis using a structure-guided fragment based approach

6.1.2017

Vitor Mendes

Department of Biochemistry, University of Cambridge, UK

The Neural basis of reward: impact of early life stress

13.1.2017

Ana João Rodrigues

ICVS/3B's, School of Health Sciences, University of Minho

Carbon monoxide targeting mitochondria: modulation of metabolism, cell differentiation and cell death

18.1.2017

Helena Vieira

CEDOC, NOVA Medical School, Lisbon

Research meets ethics: the beginning of life & Flow Cytometer approaches in determination of sperm quality

20.1.2017

Stefan Schlatt & Klaus Redmann

CeRA - Centre for Reproductive Medicine and Andrology, University of Munster, Germany

How to get the most out of RNA.Seq?

27.1.2017

Conceição Egas

CNC/Uc Biotech

HUMANITY in a DISH - Key Technologies for disease modeling with human pluripotent stem cells

31.1.2017

Christoph Hofer

Thermoscientific

FEBRUARY

Polysaccharide-based soft devices for regenerative medicine

1.2.2017

João Mano

University of Aveiro

From redox biology to redox kinetomics: quantitative experiments with hydrogen peroxide

3.2.2017

Fernando Antunes

Faculty of Sciences of the University of Lisbon

Venture Capital and Bio-Entrepreneurship

10.2.2017

Pedro Pinheiro

Independent Consultant

Stemness and differentiation markers in development and cancer

15.2.2017

Raquel Almeida

Institute of Health Research and Investigation (i3S), University of Porto

Rewarding cortical cells

16.2.2017

Alfredo Kirkood

The Zanyvyl Krieger Mind/Brain Institute

The Solomon H. Snyder Department of Neuroscience, Johns Hopkins University, Baltimore, USA

Cross-modal plasticity of cortical circuits

17.2.2017

Hey-Kyoung Lee

Department of Neuroscience, Johns Hopkins University Baltimore, USA

From Cell Differentiation to Cell Secretome: The Role of MSCs in CNS Regenerative Medicine

22.2.2017

António Salgado

Life and Health Sciences Research Institute (ICVS) and ICVS/3Bs, Braga/Guimarães

Vulvovaginal candidosis: an approach oriented to solve a women problem... From clinics to lab and backward!

24.2.2017

Ana Palmeira Oliveira

Faculty of Health Sciences, University of Beira Interior, Covilhã

MARCH

At the crossroads of cyanobacterial secretion mechanisms: multidrug efflux meets protein modification and export

1.3.2017

Paulo Nunes Oliveira

I3S/IBMC, University of Porto

11.30h

Neurogenetics of Locomotion

3.3.2017

César Mendes

CEDOC, NOVA Medical School, Lisbon

Operation of a Homeostatic Sleep Switch

10.3.2017

Diogo Pimentel

Department of Physiology, Anatomy and Genetics, University of Oxford, UK

Genetic drugs for cardiac repair and regeneration

15.3.2017

Mauro Giacca

International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy

Meet the Industry with IP

17.3.2017

Anabela Carvalho

Portuguese and European Patent Attorney, Patents.pt, Porto

LightSheet Z1: building a microscope around your experiment

22.3.2017

Jacques Paysan

14:00h

Carl Zeiss Microscopy

Deregulation of Proteostasis in retinal degenerative diseases

24.3.2017

Paulo Pereira

CEDOC, NOVA Medical School, Lisbon

Using deuterated water as tracer for de novo lipogenesis in fish, but not only fish

31.3.2017

Ivan Viegas

Center for Neuroscience and Cell Biology

& Center for Functional Ecology, University of Coimbra, Portugal

APRIL

Diabetes and Reproduction: My scientific adventure in a man's world

7.4.2017

Sandra Amaral

CNC, Coimbra

Ceramide-platforms: the interface between molecular biophysics and cell biology

19.4.2017

Liana Silva

iMed.Ulisboa and Faculty of Pharmacy of the University of Lisbon

Bio-inspired Computational Models for Biological and Biomedical Sciences

21.4.2017

Francisco Pereira

ISEC-IPC, Institute of Engineering, Polytechnic Institute of Coimbra

Human iPSC derived neurons and astrocytes as in vitro models for disease modeling, drug discovery and neurotic assays

26.4.2017

Alexandre Fouassier

Axiogenesis AG, Koln, Germany

Modulation of postnatal neurogenesis and oligodendrogenesis by adenosine A2A receptors

28.4.2017

Sara Xapelli

IMM, Faculty of Medicine, University of Lisbon

MAY

microRNAs in neurogenesis: basic concepts and future prospects for brain repair therapies

4.5.2017

Liliana Bernardino

Universidade da Beira Interior

Systems biology approaches uncover a crucial role of microRNAs in host-bacterial pathogen interactions

5.5.2017

Ana Eulálio

CNC, UC-Biotech

Bioenergetics and fatty acid oxidation - how health in the young determinates health in the elderly

11.5.2017

Eugénia Carvalho

Center for Neuroscience and Cell Biology, Coimbra,
University of Arkansas for Medical Sciences (UAMS), US

Relevance of biomaterials on tissue engineering and regenerative medicine strategies

17.5.2017

Miguel Oliveira

3Bs - University of Minho

Fundraising for Biomedical Research: Strategies & Challenges

19.5.2017

Maria João Leão

Maratona da Saúde

How to write a great research paper, and get it accepted by a good journal

24.5.2017

Anthony Newman

Elsevier

Functional outcome in the upper limb (UL) in patients with stroke: Contribution to the development of a predictive model for hemiplegic patients

31.5.2017

João Paulo Branco

FMUC, Coimbra

11:30h

Euclides Pires Auditorium (UC-Biotech - Cantanhede)

Host: Paulo Oliveira

JUNE

Plant biofactories for the production of recombinant proteins

6.9.2017

Rita Abranches

ITQB, Universidade Nova de Lisboa

Amplified virulence determinants and enteric stage development of the intracellular parasite *Toxoplasma gondii*

5.6.2017

Michael Behnke

Louisiana State University, School of Veterinary Medicine

AIP56, an apoptosis inducing protein: Basic research and applications

14.6.2017

Nuno Santos

IBMC/I3S

Targeting the glial step as a protective strategy in experimental models of Parkinson s disease

16.6.2017

Graça Baltazar

CICS-UBI - Health Research Centre, University of Beira Interior, Covilhã

SEPTEMBER

Aquaporin channels in obesity and cancer: discovery of new pharmacological blockers
8.9.2017

Graça Soveral

Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, University of Lisbon

Development of effective antibodies for Amanita phalloides' intoxications

20.9.2017

Félix Carvalho

Faculty of Pharmacy, University of Porto

MicroRNA-mediated mutant Ataxin-3 regulation: from pathogenesis to therapy

22.9.2017

Vitor Carmona

CNC, Coimbra

Targeting the hypothalamus to mitigate obesity

29.9.2017

Sara Carmo-Silva

CNC, Coimbra

OCTOBER

From Goethe to modern days: Bryophyllum pinnatum in obstetrics

3.10.2017

Ana Paula Simões-Wüst

Department of Obstetrics, University Hospital Zurich, Switzerland

Managing your career: From Academia to Corporate

4.10.2017

Ricardo Gonçalves

Co-founder & Partner at Collectiv

Metabolic studies in different organisms using deterred water

6.10.2017

John Jones

CNC, Coimbra

Role of microglia in glioma biology

10.10.2017

Anne Régnier-Vigouroux

Institute of Gevelopment Biology & Neurobiology Johannes

Gutenberg Universitat-Mainz, Germany

Inhibition of mitral cells determines odor discrimination time in mice

13.10.2017

Daniel Nunes

Champalimaud Foundation, Lisbon

Cost-efficient extraction and purification technologies for proteins based on ionic liquids

18.10.2017

Mara Freire

CICECO, University of Aveiro

Metabolic adaptations in cancer and ageing

20.10.2017

Sandrina Nóbrega Pereira

IMM, University of Lisbon

An evolutionary perspective on the (epi)genetic regulation of gamete function

27.10.2017

Paulo Navarro-Costa
Instituto Gulbenkian de Ciência, Oeiras

NOVEMBER

Synaptic dysfunction in neuropsychiatric disorders

2.11.2017

Ana Luísa Carvalho

CNC, Coimbra

Inflammation-driven disruption of iron homeostasis in Parkinson s disease

3.11.2017

Raffaella Gozzelino

Laboratory of Inflammation and Neurodegeneration,
NOVA Medical School, CEDOC, Lisbon

LncRNAs in stemness and cancer

10.11.2017

Bruno Jesus

IMM, University of Lisbon

BioImage analysis - how an image is worth a thousand datapoints

15.11.2017

Paulo Aguiar

I3S/INEB, Porto

The Good, the Bad and the Ugly: food bacteria from the gut to the brain

17.11.2017

John D. Marugg

Molecular Mycobacteriology and Microbiome Group, CNC

The transgenic chicken bioreactor

22.11.2017

Lissa Herron

SER/BBSRC Enterprise Fellow, The Roslin Institute, University of Edinburg, Scotland

Vulvovaginal candidosis: an approach oriented to solve a women problem... From clinics to lab and backward!

24.11.2017

Ana Palmeira Oliveira

Faculty of Health Sciences, University of Beira Interior, Covilhã

The use of stem cell-based models for development neurotoxicity testing: an overview of current EURL-ECVAM activities

24.11.2017

Francesca Pistollato

European Commission, Joint Research Centre, Ispra, Italy

Coordinating global endothelial collective cell polarity in angiogenesis

29.11.2017

Cláudio Areias Franco

IMM, Universidade de Lisboa

Between Two Lungs: The Role of MiR-424 in Pressure-Overload Induced Right Heart Dysfunction

30.11.2017

Rui Baptista

CHUC, Coimbra

DECEMBER

Unexpected phenotypic variability of parasites occupying the adipose tissue

6.12.2017

Luisa Figueiredo

IMM, Universidade de Lisboa

Meet the Industry: Coimbra Genomics

7.12.2017

Bruno Soares

Coimbra Genomics

At the heart of stem cells in Regeneration and Repair

13.12.2017

Perpétua Pinto-do-Ó

I3S/INEB and ICBAS, University of Porto

Downregulation of HIF complex in the hypothalamus exacerbates diet-induced obesity

14.12.2017

Joana Gaspar

Department of Biochemistry, Federal University of Santa Catarina, Florianópolis, Brazil

Proteosis and mitochondrial function in human epicardial adipocyte tissue

15.12.2017

Ana Catarina Fonseca

CNC, Coimbra

Neurodegeneration of the cerebellum and Hypomyelination in a Tubb4a mutant mouse

19.12.2017

Sofia Fertuzinhos

Yale, University School of Medicine

Model system to analyze synaptic plasticity in health and disease

22.12.2017

Tobias Boeckers

Institute of Anatomy and Cell Biology, University of Ulm, Germany

PHD THESIS CONCLUDED IN 2017

Ana Catarina Manjolinha Mamede

Membrana Amniótica. Uma opção terapêutica para o cancro?
2017
Supervisor: Francisco Ambrósio

Ana Cristina Pais Mega de Andrade

Effects of sitagliptin therapy on the evolution of pancreatic and renal lesions in type 2 diabetes - experimental study in the Zucker diabetic fatty rat
2017
Supervisor: Francisco Ambrósio

Ana Francisca Silva de Lima

Biophysical modulation of cell fate through chromatin remodelling
Junho 2017
Supervisor: Ricardo Neves

Ana Patrícia Barreira Marques

Role of hypoxia and fibrosis in white and brown adipose tissue regulation
6 March 2017
Supervisors: Claudia Cavadas

Ana Salomé dos Santos Pires Lourenço

Vitamina C e Cancro. Estudo Experimental
2017
Supervisor: Ana Bela Sarmento-Ribeiro

André Filipe Marques Soares

RLR1 and RLR2, two novel Arabidopsis thaliana atypical aspartic proteases involved in primary root development and lateral root formation
2017
Supervisor: Isaura Simões

António Carvalho da Silva

Neurobiology of the Circadian Clock: Metabolism Control and Implications for Alzheimer's disease
April 5, 2017
Supervisors: Ana Cristina Rego & Rodrigo Cunha

Catarina Oliveira Praça de Almeida

Brain-like endothelial cells derived from stem cells to study BBB development and targeting
February 2017
Supervisor: Lino Ferreira

Clarissa Pérez Faria

Molecular characterization of Giardia lamblia from patients of a referral hospital of Rio de Janeiro/Brazil: application of multilocus genotyping to study the inter and intra-assembly variations
2017
Supervisor: Jorge Salvador

Claudia Marisa Monteiro Saraiva

Micro-RNA-124-loaded nanoparticles as a new promising therapeutic tool for neural stem cell-based brain repair strategies
December 2017
Supervisor: Lino Ferreira

Daniela de Oliveira Gonçalves

Non-clinical Evaluation of the Pharmacokinetics and Pharmacodynamics of Opicapone, a Novel Catechol-O-methyltransferase Inhibitor
July 21, 2017
Supervisor: Amílcar Falcão

Diana Matias

Heterogeneidade celular dos Glioblastomas: alvos terapêuticos, subpopulação tronco e as vias de sinalização na interação com o microambiente
October 31, 2017
Supervisor: M^a Celeste Lopes

Dulce Marisa Ferreira Bento

Association of compound 48/80 with chitosan based nanoparticles: designing a novel prototypic delivery system for nasal vaccination
2017
Supervisor: Olga Borges

Filipa Raquel Maia Fontes Lebre

Development of chitosan-based nanoparticles for nasal immunization against hepatitis B
2017
Supervisor: Olga Borges

Gladys Caldeira

The role of stargazin in the pathogenesis of psychiatric disorders
December 2017
Supervisor: Ana Luísa Carvalho

Henrique Alexandrino

Energy for Liver Regeneration: Mitochondrial Bioenergetics and the Pathogenesis of Posthepatectomy Liver Dysfunction
July 19, 2017
Supervisor: Carlos Palmeira

Hélio Cavalcante Silva Neto

Serious Games used for cognitive evaluation in the older population
2017
Supervisor: Biomarker Group member

Humberto Jorge Gomes Ferreira

Epigenetic Regulation of non-coding RNAs in Cancer
January 31, 2017
Supervisor: M^a Celeste Lopes

Ivana Kostic

Stem cell and stem cell-free based therapeutics against myocardial infarction
October 2017
Supervisor: Lino Ferreira

Janete Cunha Santos

Delaying neurodegeneration by caloric restriction approaches: from unraveling mechanisms to gene therapy
17 February 2017
Supervisors: Claudia Cavadas & Luis Almeida

- João Carlos Ribas de Almeida**
Vascular organ-on-a-chip platforms for disease modeling
 December 2017
 Supervisor: Lino Ferreira
- João Duarte**
Percepção visual
 2017
 Supervisor: Miguel Castelo-Branco
- Luana Carvalho Naia**
PhD in Health Sciences, Fac. Medicine, Univ. Coimbra
 January, 2017
 Supervisor: Ana Cristina Rego
- Mafalda Bacalhau**
Determinação da patogencidade de mutações novas no DNA mitocondrial: abordagem celular e molecular
 2017
 Supervisors: Paula Moreira
- Maria Helena Silveiras Teodoro da Ponte**
Surveillance of Antimicrobial Consumption in Animals
 February 16, 2017
 Supervisor: Amílcar Falcão
- M. Madalena Ribeiro**
Mechanisms involved in diabetes-associated osteoarthritis: role of autophagy
 2017
 Supervisors: Paula Moreira
- Miguel Maria da Fonseca Miranda Ferreira Lino**
Light-triggerable nanomaterials for the delivery of biomolecules
 June 2017
 Supervisor: Lino Ferreira
- Mohamed Edfawy Soliman Hussien**
Dissecting the role of gprasp2 in autism spectrum disorder and intellectual disability
 June 2017
 Supervisor: João Peça
- Otilia d' Almeida**
Mecanismos de processamento retinocortical
 2017
 Supervisor: Miguel Castelo-Branco
- Patricia Diogo Nunes**
Photodynamic therapy applied to asepsis of root canals
 2017
 Supervisor: Teresa Gonçalves
- Raquel Oliveira de Pinho**
PhD in Neuroscience, Fac. Medicine, University of Porto. Neuroscience PhD Program - Portugal
 July, 2017
 Supervisor: Ana Cristina Rego
- Ricardo Alexandre Gomes Leitão**
Role of aquaporin-4 in methamphetamine-induced blood-brain barrier dysfunction and cerebral edema formation
 2017
 Supervisor: Francisco Ambrósio
- Ricardo Martins**
Development of Techniques for Multimodal Object Exploration A contribution for autonomous robotic hands
 2017
 Supervisor: Miguel Castelo-Branco
- Sandra Anjo**
DJ-1 neuronal rescue under oxidative stress: implications for Parkinson's disease
 2017
 Supervisor: Bruno Manadas
- Sandra Antónia Figueiredo**
PhD in Pharmaceutical Sciences, expertise in Pharmaceutical Chemistry
 December 19, 2017
 Supervisor: Jorge Salvador
- Sara Carmo Silva**
Unravelling the role of ataxin-2 in the hypothalamus: a new player in metabolism
 9 June 2017
 Supervisors: Claudia Cavadas & Luis Almeida
- Sara Raquel Martins Neves**
The role of Cancer Stem-like Cells in Osteosarcoma and their relevance in Therapy response: in vitro and in vivo studies with PET
 2017
 Supervisor: Francisco Ambrósio
- Tânia Perestrello**
Framing pluripotency: From gene to image
 2017
 Supervisor: João Ramalho-Santos
- Vitor Manuel Martins Carmona**
MicroRNAs targeting Ataxin-3 mRNA in Machado-Joseph disease : from pathogenesis to therapy
 2017
 Supervisor: Luís Almeida

MASTER THESIS

Alexandra Marques Pinto

Diagnóstico diferencial de síndromes parkinsonianas com base em dados de imagem de ressonância magnética
2017

Supervisor: Miguel Castelo-Branco

Ana Catarina Ramalho Henriques

Estudo dos efeitos antioxidante e anti-inflamatório do chocolate preto e da pasta de cacau
October 16, 2017

Supervisor: Pharmacometrics group member

Ana Dias

Development of an analytical method by liquid chromatography coupled to tandem mass spectrometry for the quantification of dopamine metabolism
2017

Supervisor: Bruno Manadas

Ana Gomes

Can sulforaphane influence aging related pathways in the skin?
2017

Supervisor: Metabolic Control Group member

Ana Mafalda Gonçalves

The role of mitoribosomes in mitochondrial function: implications for parkinson's disease
2017

Supervisor: Cell Metabolism and Quality Control group member

Ana Margarida Cardoso Henriques

Modulation of NMDA receptor currents by adenosine A_{2A} receptors in the Schaffer collaterals-CA1 synapses
July 2017

Supervisor: Rodrigo Cunha

Ana Rebelo

Sestrin 2-mediated mitophagy: potential regulation of mitohormesis and promotion of metabolic health
July 18, 2017

Supervisor: Anabela Rolo

Ana Rita Pimentel Mendes

Circuitos envolvidos no desencadeamento da ejaculação em ratinhos (Mus músculos)
2017

Supervisor: Cell Metabolism and Quality Control group member

Ana Salomé Carvalho

Esplenectomia na trombocitopenia imune primária do adulto- resultados de um centro hospitalar do centro de Portugal
2017

Supervisor: Ana Bela Sarmento

Ana Sofia Chasqueira Santos

Alteração da sinalização dopaminérgica por desnervação do Corpo Carotídeo na modulação da função do Tecido Adiposo na Síndrome Metabólica
2017

Supervisor: Paula Moreira

Ana Solange Gomes Costa

Integrated Master in Medical Dentistry, Fac. Medicine, University of Coimbra
July, 2017

Supervisor: Ana Cristina Rego

André Carvalho

Ghrelin administration as a novel strategy to delay aging in Hutchinson-Gilford Progeria Syndrome
2017

Supervisor: Claudia Cavadas

André Joaquim Constante Lourenço

Estratégias farmacológicas na doença de Alzheimer: progressos e desafios futuros
2017

Supervisor: Cell Metabolism and Quality Control group member

André Nazaré

Resistência à corticoterapia no síndrome nefrótico pediátrico
2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Andreia Verdade

Motor excitability modulation during the delay period - a TMS and pupillometry study
2017

Supervisor: Miguel Castelo-Branco

António José Preto Martins Gomes

A bioinformatics approach for the understanding of membrane protein complexes
September 2017

Supervisor: Irina Moreira

Antonio José da Silva Santinha,

Exosomes-based therapy for stroke
June 2017

Supervisor: Lino Ferreira

Bárbara Gomes

Expressão génica de NFE2L2/NRF2 em doentes com Síndrome Mielodisplásica - implicações clínicas
2017

Supervisor: Ana Bela Sarmento

Bárbara Pinto Macedo

Aldeído Desidrogenases como potenciais biomarcadores em Neoplasias Mielóides
2017

Supervisor: Ana Bela Sarmento

Beatriz Ribau

Characterization of Chronic Lymphocytic Leukaemia: The role of epigenetic aberrations to pathogenesis
2017

Supervisor: Ana Bela Sarmento

Bruno Castilho

Trombocitémia Essencial - etiologia e terapêutica
2017

Supervisor: Ana Bela Sarmento

Carla Filipa Simões Henriques

Gender dimorphism of microglia morphology: adenosine and testosterone as putative modulators in transgender microglia
2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Carlota Sofia Ferreira de Nóbrega

Efeitos vasculares do agonista do recetor Glucagon-like peptide 1, liraglutido, num modelo animal de diabetes tipo 1
2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Catarina Barbosa

Laboratorial parameters as predictors of delirium in elderly subjects hospitalized with acute medical conditions
2017

Supervisor: Aging and Brain Diseases: Advanced Diagnosis and Biomarkers group member

Catarina Ferreira

WNT/ β -catenin and Hedgehog signaling pathways as therapeutic targets in Multiple Myeloma
2017

Supervisor: Ana Bela Sarmento

Catarina Isabel Braz Guilherme

A influência do consumo de fibra dietética no desenvolvimento do carcinoma colo-rectal
2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Catarina Pechincha

Assessment of the effect of nucleolin expression on the phenotype of breast cancer cells
September, 2017

Supervisor: Vectors and gene therapy group member

Catarina Silva

Polimorfismos de nucleótido único associados ao tromboembolismo venoso – avaliação dos loci do factor XI, grupo sanguíneo ABO e fibrinogénio
2017

Supervisor: Ana Bela Sarmento

Cátia Daniela Leite Oliveira

Desenvolvimento de teste molecular para deteção de enterotoxinas de Staphylococcus aureus em leite
2017

Supervisor: Jorge Salvador

Cátia Gomes

Edible mushrooms as mediators of sustainability and human health
September 20, 2017

Supervisor: José Teixeira & Cell Metabolism and Quality Control group member

Cátia Seabra

The role of miRNAs on cell survival
July 2017

Supervisor: Lino Ferreira and Hugo Fernandes

Christian André Fernandes Neves

O metilglioal altera o perfil lipídico no fígado de ratos obesos, induzindo insulino-resistência e contribuindo para a doença de fígado gordo não alcoólico
2017

Supervisor: Henrique Girão

Daniela Filipa Pereira Marques

A Bromocriptina como moduladora do metabolismo lipídico no tecido adiposo e da sensibilidade à insulina na Diabetes Mellitus tipo 2
2017

Supervisor: Henrique Girão

Daniela Isabel Ferreira Madeira

ATP and glutamate release by astrocytes under Alzheimer's disease conditions: modulation by adenosine A_{2A} receptors
July 2017

Supervisor: Rodrigo Cunha

Daniela Neves Antunes

Immunomodulatory effect of different components of the cell wall of Alternaria spp
July 2017

Supervisor: Teresa Gonçalves

Daniela Santo

Evaluation of the gene delivery capacity associated to different polymer-based nanosystems
2017

Supervisor: Henrique Faneca

David José Caetano Coelho

Nanotecnologia & vacinologia: vias de internalização das nanopartículas e apresentação cruzada
2017

Supervisor: Luís Almeida

Diana Filipa Duarte Lobo

Cerebrovascular and Blood-Brain Barrier Impairments in Machado-Joseph Disease, , Masters in Molecular Genetics and Biomedicine
2017

Supervisor: Vectors and gene therapy group member

Diana Margarida de Almeida Rodrigues

Role of the epithelial-to-mesenchymal transition in bladder cancer aggressiveness
2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Diana Reis

Doseamento da zinco protoporfirina como método alternativo à ferritina
2017

Supervisor: Ana Bela Sarmento

Diogo João Duarte da Silva

Safety and kinetic variation profile of ¹⁷⁷Lu-DOTA-TATE uptake in neuroendocrine tumors
2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Diogo Miguel Matos Vila Verde

Neuronal energy status and Alzheimer's disease: searching for a connection

2017

Supervisor: Paula Moreira

Fabio Sousa

Impact of maternal diabetes on offspring memory

2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Filipa Vieira Carreira

Comparative study of two tanks of syrah wine with same harvest fermented by two different Saccharomyces cerevisiae strains

July 14, 2017

Supervisor: Pharmacometrics group member

Francisco Lopes

Association between ADHD and criminal behavior: a case-control study

2017

Supervisor: Aging and Brain Diseases: Advanced Diagnosis and Biomarkers group member

Inês Baião Santos

ARHGAP8 co-regulates excitatory and inhibitory synapse function

September 2017

Supervisor: Ana Luísa Carvalho

Inês Januário Neves

Efeitos da cirurgia bariátrica na glicação e na remodelação vascular num modelo animal diabético obeso

2017

Supervisor: Cell Metabolism and Quality Control group member

Inês Ferreira

Identification of Neuropeptide Y receptors in human articular cartilage: influence of gender and osteoarthritis

2017

Supervisor: Teresa Rosete & Cláudia Cavadas

Joana Câmara

CNS infections and Schizophrenia

2017

Supervisor: Aging and Brain Diseases: Advanced Diagnosis and Biomarkers group member

Joana Clímaco Henggeler Antunes

Non-coeliac gluten sensitivity

September 25, 2017

Supervisor: Pharmacometrics group member

Joana Coelho

Analysis of the striatum proteome of mice subjected to haloperidol chronic exposure

2017

Supervisor: Bruno Manadas

Joana Francisca Cardoso De Brito

Impact of multiple surgeries with associated infection episodes on cognitive dysfunction

2017

Supervisor: Miguel Castelo-Branco

Joana Martinho

Mestrado Integrado em Medicina, Faculdade de Medicina, Universidade de Coimbra

2017

Supervisor: Cell Metabolism and Quality Control group member

João Carlos Versos Varanda Barata

Unravelling the Players of Mesenchymal Stromal Cells Neuroprotective Effect in Machado-Joseph Disease

2017

Supervisor: Vectors and gene therapy group member

João Oliveira

Autism and Ehlers-Danlos Syndrome-phenotype comparison

2017

Supervisor: Aging and Brain Diseases: Advanced Diagnosis and Biomarkers group member

João Paulo Peixoto

Anemias hemolíticas hereditárias

2017

Supervisor: Ana Bela Sarmento

João Pereira

Neurofeedback of interhemispheric synchronization during motor control

2017

Supervisor: Miguel Castelo-Branco

José Guilherme Peres de Almeida

Computational methods for the understanding of protein-based interactions

September 2017

Supervisors: Irina Moreira and Ana Luisa Carvalho

Keerthi Pryia

Understanding the Effects of Glutathionylation and Functional Integration In Thiol Redox Regulation

2017

Supervisor: Armindo Salvador

Lea Cristele Rosa Velez

Computational model of the effect of alpha oscillatory phase on the timing of neuronal activations and resulting motor responses

2017

Supervisor: Miguel Castelo-Branco

Luciana Branco Fernandes

MDPV (3,4-Metilenodioxipirovalerona), nova droga psicoativa: análise de parâmetros comportamentais e neurotóxicos e de recetores de produtos de glicação avançada (RAGE) em murgos

2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Mafalda Maria Salvador Campeão

(MDPV) and methamphetamine (METH) play with central innate immune system: focusing on RAGE and glial cells

2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Marguerita Evangelho da Rosa

Development of IgY antibodies with antimicrobial properties

Supervisor: Ricardo Pires (Co-supervision with Mara Freire, CICECO, Univ. Aveiro)

Maria Tinoco Marques

Monitorização Farmacocinética da Amicacina em Doentes Oncológicos; Influência da Função Renal na Otimização da Terapêutica da Amicacina

2017

Supervisor: Pharmacometrics group member

Mariana Gomes Gonçalves Arêlo Manso

Design and preparation of new BACE1 inhibitors for Alzheimer's disease treatment

2017

Supervisor: Cell Metabolism and Quality Control group member

Marlene Cristina Faria Pereira

Role of astrocytes in synaptic function and memory. Focus on adenosine A_{2A} receptors

July, 2017

Supervisor: Rodrigo Cunha

Marta Alexandra Correia de Sousa

*The Immunogenic effects of a potentially allergenic protein of *Acer negundo**

2017

Supervisor: Microbial and Molecular Biotechnology group member

Miguel Lemos

Mestrado em Investigação Biomédica, Faculdade de Medicina, Universidade de Coimbra

2017

Supervisor: Cell Metabolism and Quality Control group member

Miguel Pinheiro

Hippocampal circuitry morphogenesis: portraying the architectural role of microglia challenged by glucocorticoids

2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Nelson Emanuel de Carvalho Fortuna

Glioblastoma multiforme: biomarcadores e perspectiva actual e futura da terapêutica

2017

Supervisor: Cell Metabolism and Quality Control group member

Nuno André Reis Piedade

Master in Molecular Biomedicine, speciality in Neuroscience, Dep. Medical Sciences, Univ. Aveiro

July, 2017

Supervisor: Ana Cristina Rego

Patrícia dos Santos

Síndromes de falência medular congénitas: da fisiopatologia à clínica

2017

Supervisor: Ana Bela Sarmento

Patrícia Inês Pires dos Santos

The role of astrocytic A_{2A} receptors in depressive-like conditions

September, 2017

Supervisor: Rodrigo Cunha

Patrícia Lino

Inter-University Master in Biology of Aging at Paris Descartes University, Paris Diderot Versailles-St-Quentin, Toulouse, Tours, France

2017

Supervisor: Ana Cristina Rego

Patrícia Valério

Insights into the role of sirtuin 2 in obesity and insulin resistance

2017

Supervisor: Claudia Cavadas

Pau Porras Socias

Screening for novel antimycobacterials

2017

Supervisor: Nuno Empadinhas

Paula Sacramento

Transplante autólogo de progenitores hematopoiéticos em hematologia

2017

Supervisor: Ana Bela Sarmento

Pedro Xavier Pinto Figueiredo

Autophagy in Neurodegeneration: Latest developments on eating ourselves out of disease

June, 2017

Supervisor: Cell Metabolism and Quality Control group member & Ana Cristina Rego

Rafael Eduardo da Silva Teixeira

Tratamento de Cancro com Plasma Frio Atmosférico

2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Rafael Carecho

Can the retina be a window to the changing brain in Alzheimer's disease?

2017

Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Ricardo Filipe Serrano Costa

Permeabilidade do ácido salicílico e do seu derivado acetilado através de um modelo in vitro de barreira hematoencefálica

June 2017

Supervisor: Lino Ferreira

Rita Costa Bastos

Diferenciação de síndromes parkinsonianas recorrendo a imagens PET

2017

Supervisor: Miguel Castelo-Branco

Ruben Salvado

Oxidative Stress Biomarkers: Closer to early diagnosis of neurodegenerative diseases?

2017

Supervisor: Bruno Manadas

Sara Cruz

Mestrado em Investigação Biomédica, Faculdade de Medicina, Universidade de Coimbra
2017
Supervisor: Cell Metabolism and Quality Control group member

Sara Cristina Lourenço dos Reis

Control of contextual fear memory by adenosine receptors - Role in the physiology of the related brain circuitry and implications for fear extinction and post-traumatic stress disorder
July, 2017
Supervisor: Rodrigo Cunha

Shreeta Ravi

Characterization of the molecular mechanism of drug efflux by membrane-embedded P-Glycoprotein
2017
Supervisor: Armindo Salvador

Simone Frisari

Crosstalk between the ubiquitin-proteasome system and calpains in neuronal death induced by brain ischemia
December 2017
Supervisor: Carlos B. Duarte

Steve Edwin

Analysis of the Interdependence Between the Oxidation of Distinct Redox Active Sites in Human Peroxiredoxin
2017
Supervisor: Armindo Salvador

Tânia V. Soares Branco Micaelo

Preparação de triterpenóides de núcleo ursano e avaliação da atividade antiparasitária em Leishmania
2017
Supervisor: Jorge Salvador

Tânia Veigas

Autistic traits and criminal behavior: a cross-sectional study in Coimbra penitentiary
2017
Supervisor: Aging and Brain Diseases: Advanced Diagnosis and Biomarkers group member

Teresa Silva Lourenço

Impact of methylphenidate on microglial cells
2017 Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Tiago Felgueiras

Impacto da esclerose múltipla e da terapêutica com agentes modificadores de doença na gravidez e no período neonatal
2017
Supervisor: New Targets and Therapeutics for Chronic Diseases group member

Tiago Rondão

Behavioral and biochemical characterization of stargazin knock-in mice expressing an Intellectual disability-linked mutation
September 2017
Supervisor: Ana Luísa Carvalho

Tiffany Santos Pinho

O-GlcNAcylation represents a "sweet" route to tackle Alzheimer's disease-related phenotype
2017
Supervisor: Paula Moreira

Verónica Resende Figueiredo

Biological effects of new BACE1 inhibitors for Alzheimer's disease treatment
2017
Supervisor: Cell Metabolism and Quality Control group member

Paulo José Pina Barreto Augusto

Investigação genética mitocondrial etiológica da surdez
2017
Supervisor: Aging and Brain Diseases: Advanced Diagnosis and Biomarkers group member

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 attracting 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, Criestaminal, Equigerminal, Hittag Biotechnology, 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

SCIENCE COMMUNICATION OFFICE

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

SCIENCE IN THE MEDIA

Responsible: Adalberto Fernandes

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

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, successfully liaising researchers with journalists. In 2017, CNC was in the news **793 times** with an advertising value of **2.221.128 euros**, reaching a total number of **38.397.237 audiences**. Even though the number of news is lower comparing with the last year, the impact increased considering the audiences that are bigger (an increase of 4.497.282). The national impact of the news increased as well.

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.

DIGITAL COMMUNICATION
Responsible: Ana Teresa Viegas

EXTERNAL: Social Networks

To reach a wider population we improve our presence in social networks. At the moment we have a total of **7578 followers** at:

- Facebook (6210);
- Instagram (700);
- LinkedIn (344);
- YouTube (164);
- Twitter (160).



Fig. 1. Handlers 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:

Newsletter

- 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 Seminars
 - Timeline (future events)

This newsletter is distributed through a specific mailing list, reaching more than **440** contacts, including researchers and non-research staff. Moreover, the newsletter is posted on our website (<http://www.cncb.pt/outreach/outr each00.asp#divNewsletters>) and also on our social media networks, in order to get the public aware of our news. In 2017 we launched **6 editions** of Synergies.



Fig. 2. Illustrative images of the internal newsletter "Synergies"

PUBLIC ENGAGEMENT IN SCIENCE

Responsible: Sara Varela Amaral

Brain Awareness Week (BAW)

March 2017

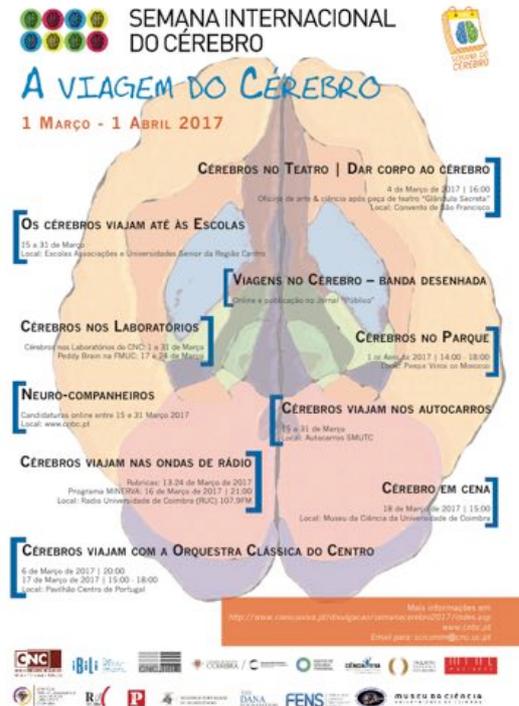


Fig. 3. Program of activities of Brain Awareness Week (BAW) 2017 organized by CNC.IBILI and Funded by FENS.

The Brain Awareness Week (BAW) 2017 organized by CNC.IBILI of University of Coimbra happened in Coimbra between 1st of March and 1st of April. Our project - *The Brain Travel* - aimed to increase the scientific culture in neuroscience as well as engage society in scientific research with the following activities:

1. Brains travel to school

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

2. Brains in 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



Fig. 4. Photos of "Brains travel to schools" initiative.

Alzheimer's disease; Neurons, obesity and aging; Brain development.

3. Brains travel by BUS

In partnership with SMTUC, the Buses in all the city had some scientific information about brain. Additionally, we promoted public informal conversations in Buses in Coimbra where neuroscientists talked about their work to people that are in the BUS.

6. Brains travel through the radio

In a partnership with RUC, we produced radio contents to explain or demystify myths about the brain and communicate scientific messages. The contents will air every day again during BAW and will be shared in our social networks and website. RUC dedicated a programme (1 hour) to neuroscience with the participation of scientists from CNC.IBILI.

about 92 000 viewers. In Social media (CNC facebook) we made 37 posts about BAW that had 59 000 visualizations and total of 8 600 likes, shares and comments.



Fig. 5. Photos of "Brains travel by bus" initiative.

4. Brain buskers

The neuroscientists performed *hands-on* activities, games, and brain teasers, in a public garden, designed for the public to understand brain structure and functions, why brain health is important and how they can behave to protect it.

5. Brain comics

During BAW we launched a comic strip about neuroscience basis and neurodegenerative diseases in a national newspaper - Público. Público is one of the most prestigious daily newspaper in Portugal.

7. Brains in the Theatre

CNC.IBILI researchers developed an art&science workshop - *Dar corpo ao Cérebro* - in partnership with theatre company Marionet about Brain function and the relationship with the other body systems. This workshop was integrated in the theatre play *The Secret Gland*.

Our activities involved 60 researchers and reached directly about 1500 people from different publics in the following activities: Brains travel to schools, Brains in the lab, Brains travel by bus and Brain buskers. Additionally, we produced a comic strip (Brain Voyages) was published in Público, one of the most prestigious daily newspaper in Portugal, that reached 33 000 people - daily circulation number. The news published about our BAW project in regional newspapers (example: Diário de Beiras e Diário de Coimbra) reached about 32 000 readers. The national TV public channel (RTP) produced a small TV content about our activity *Brains travel by Bus* that will be launched this month - RTP has



Fig. 6. Photos of "Brains in the Theatre" initiative.

Science in the Lab

July 2017

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 2017 CNC received **13 high-school students** for internships in different research fields. 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 13 positions offered in 2017 were the following:

Table 1. *Internships for High-School Students*

Name of the internship	Number of students	Principal Investigator
"Mitocôndria: de ex-bactéria ao motor das nossas células: metabolismo, terapêutica e toxicologia"	3	Paulo Oliveira
"Estudo da formação e regulação das sinapses no sistema nervoso central"	2	Ramiro Almeida
"Biologia da Reprodução e Células Estaminais"	2	João Ramalho-Santos
"Neurónios, apetite, obesidade e envelhecimento"	2	Cláudia Cavadas
"Quando a Ciência mete água..." - estudo das propriedades terapêuticas das águas termais da região centro"	2	Cláudia Pereira e Teresa Cruz
"Investigação e Diagnóstico no Laboratório de Bioquímica Genética"	1	Manuela Grazina
"Biotecnologia do Ovo: produção de biofármacos em Ovos de Galinha"	2	Ricardo Pires



Fig. 7. *Students and some researchers involved in the Science in the Lab project 2017*

The feedback of the students after the internships is very positive as showed at Figure 8.

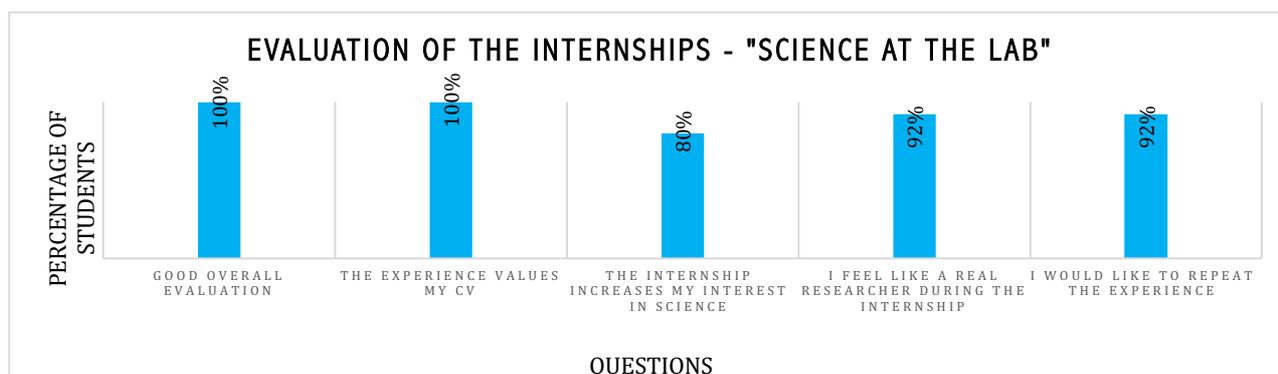


Fig. 8. *Evaluation of the internships "Science at the Lab".*

Science in the Summer

July and September 2017

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 2017

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 Science Museum CNC has been a partner of this event in Coimbra since 2009. In 2017, we developed a set of *hands-on* activities (in different fields as neuroscience, cell biology, microscopy) and CNC researchers participated in one-to-one conversations with publics. About **500 people** interact with our **10 different activities** and **60 researchers** participated on ERN Coimbra 2017.

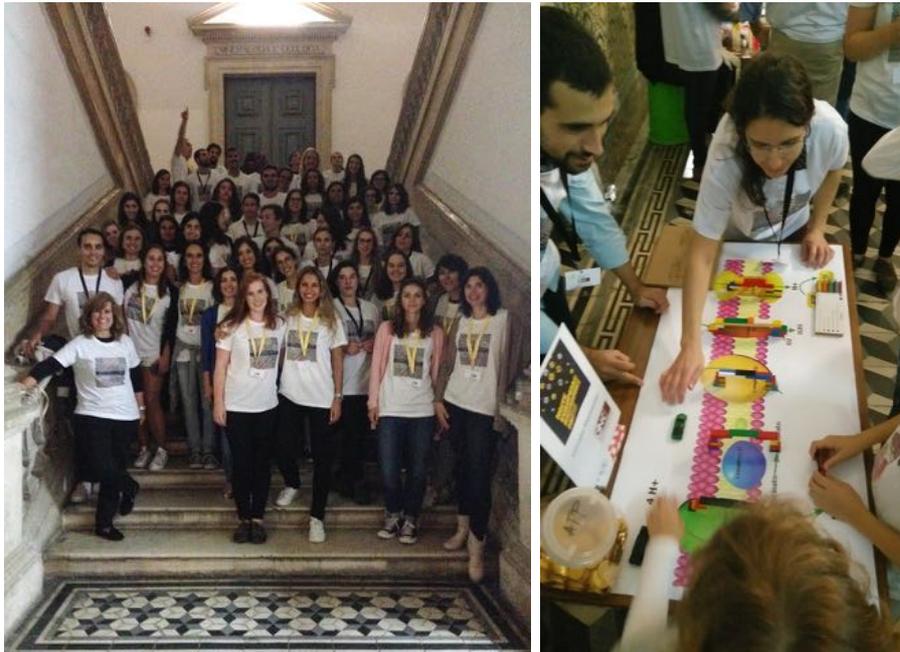


Fig. 9. Photos of the European Researchers Night Coimbra 2017



Fig. 10. Program and Photo of Science & Technology Week 2017

Science & Technology Week

November 2017

During Science & Technology Week CNC.IBILI researchers promoted several science communication initiatives in different venues as labs, cafés, schools. Overall, our 2017 activities engaged 530 people.

Comics

March and November 2017

In order to explore different languages to communicate scientific topics and to target wide audiences we developed a partnership with

Jornal Público, one of the most prestigious daily newspaper in Portugal (daily circulation number: **33 000**). In this context we produced two comics, involving different researchers and an il

lustrator: one about brain (launched during the Brain Awareness Week)

and another about Diabetes (launched during the World Diabetes Day).

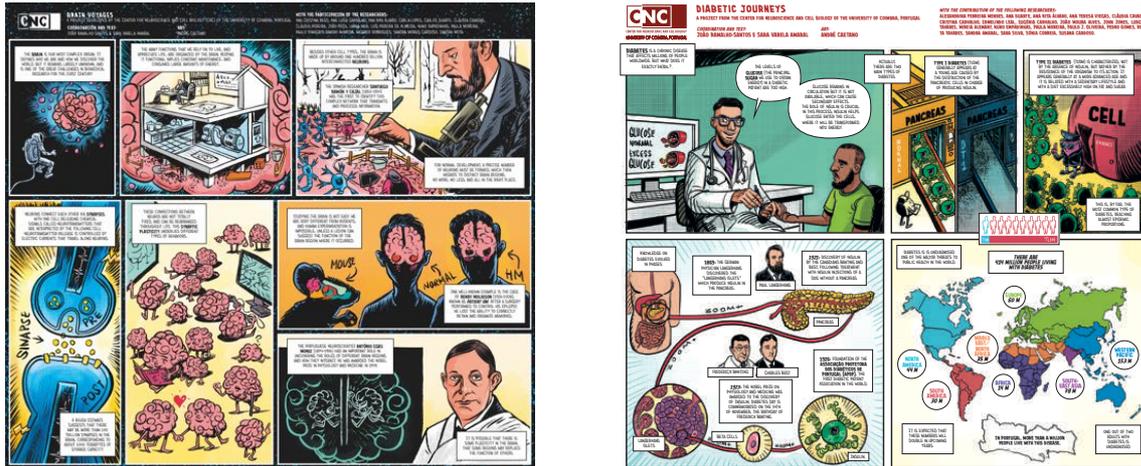


Fig. 11. Comics produced by CNC researchers (illustrations: André Caetano)

ORGANIZATION OF ADVANCED COURSES

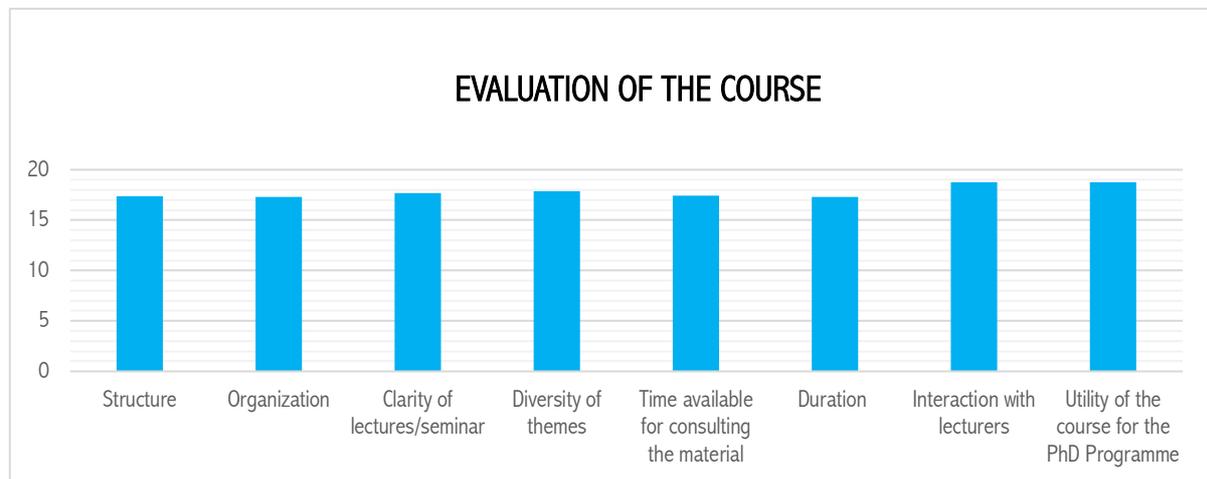
Advanced Course – Science Communication and Soft Skills

April 2017

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 (PROGRAM here: http://beb.cncb.pt/det_courses.asp?id=842). 17 students, from PDBEB and

from other PhD programs, participated in this intensive course (4-days) with the participation of **16 speakers** from different fields as public engagement in science, media, technology transfer, career development and art&science. The evaluation of the course was very positive as seen in Figure 12.



SCIENCE COMMUNICATION WITH PEERS

2nd meeting in Biomedical research @ UC

December 2017, Universidade de Coimbra (FMUC, polo III)

Coordination of the activity: Ana Luísa Carvalho and Cláudia Cavadas

The 2nd meeting in Biomedical research @ UC, organized by CNC.IBILI aimed to create a forum to discuss biomedical science, bringing together researchers working in this field at the University of Coimbra. Selected talks on Neuroscience and Brain Diseases, Metabolism and Aging, and on Advanced Therapies took the pulse of the Coimbra

biomedical community and set the stage for discussion and networking among participants. In 2017, 360 researchers participated at 2nd meeting in Biomedical research @ UC. A diversified program (20 talks, one round table and a social event) provided inspiration for asking novel questions, planning future projects and fostering collaborations.



Fig. 12. Moments of 2nd meeting in biomedical research @ UC

Beer for Thought

January - December 2017 (every month)

Science Communication Office and other CNC members hosted the initiative “Beer for Thought”, a moment to promote networking between CNC members. In 2017 we

hosted 8 “Beer for Thought” with Craft Beer kindly provided by our researcher John Jones.



Fig. 13. Some “Beer for Thought” posters and photos

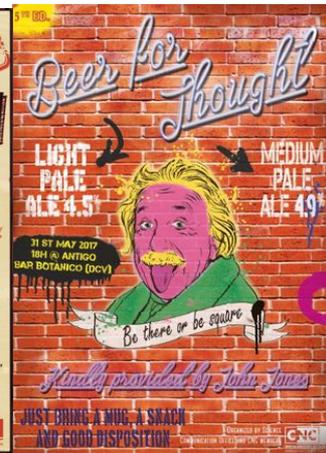


Fig. 14. Evaluation of the Advanced Course “Science Communication and Soft Skills”

CORE FACILITIES AT CNC

ANIMAL HOUSE

Head of Unit: Prof. João Laranjinha

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

The present facility has a capacity to house about 3000 animals (rats/mice). This facility offers the following services: complete husbandry, including feeding, watering, daily cage changing, as well as routine procurement, inventory and care. In 2007, the facility started to provide specialized animal services, namely: breeding and housing of transgenic/knockout strains of mice as well as wild type colonies, production of rats/mice embryos and litters and maintenance of athymic nude mice.



Animal room – IVC cages (type I)

The Animal House contains a barrier maintained facility, with 8 positive pressurised rooms, which are kept at 22°C with a relative humidity of 55%. The rodents are bred in individually ventilated cages and a 12-hour light-dark cycle is maintained with an automatic timer. The facility has an animal identification system and software to monitor animal records.

Staff: Carmen Semião (caretaker)
Fátima Graça (assistant technician)
Maria Eugénia Campos (assistant technician)
Paula Mota (Veterinary Doctor)



Laminar flow chamber

FLOW CYTOMETRY UNIT

Scientific Director: Carlos Filipe Pereira, Ph.D.

Unit Manager: Isabel Nunes Correia, Ph.D.

Unit Technician: Cândida Mendes, 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.



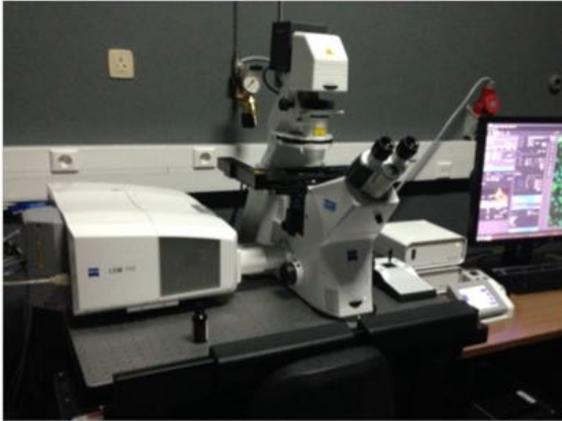
FACSAria™III (Becton Dickinson) – 12 colours



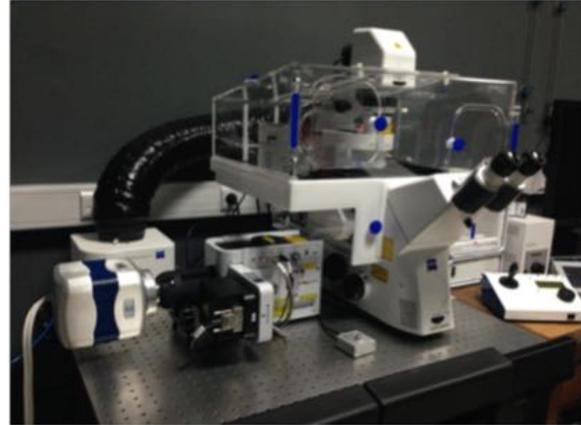
FACSCalibur (Becton Dickinson) - 4 colours

MICROSCOPY IMAGING CENTER OF COIMBRA - CNC

Head of Unit: *Luísa Cortes*



Confocal LSM 710 (34 channels)



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 2017, the MICC facility supported 120 users from 58 research groups, three of them from outside the CNC.IBILI Unit.

In 2017, scientific collaborations with a CNC.IBILI research group, and an external research group from University of Beira Interior, resulted in one publications in which Cortes L and Caldeira MV are co-authors (PMID: 28813136).

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 MV and Cortes L organized the “III Quantitative Fluorescence Microscopy Course” (CNC, Sept 18th- 22nd), 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.

Moreover, MICC-CNC is a node of the Portuguese Platform for BioImaging (PPBI), a research infrastructure of the RNI 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

MASS SPECTROSCOPY UNIT

Head of Unit: Bruno Manadas

The Mass Spectrometry Unit is specialized in identification and quantification of proteins from simple and complex samples; identification and quantification of post-translational modifications, and identification and quantification of metabolites. The Unit is also involved in the identification of biomarkers through proteomics and metabolomics techniques with the purpose of developing new prognosis and diagnosis methods, in collaboration with other R&D units at CNC, Biocant, and external partners.

Presently, the Mass Spectrometry Unit is equipped with state of the art technology, namely: a 4000 QTRAP mass spectrometer (Applied Biosystems/MDS Sciex), hybrid triple quadrupole/ion-trap mass spectrometer with capacity of MS3, and a two-dimensional liquid chromatography system Ultimate 3000 (Dionex/LCPackings). The unit also contains several software packages for data processing, including Protein Pilot and PEAKS for protein identification, post-translational modifications and de novo sequencing.

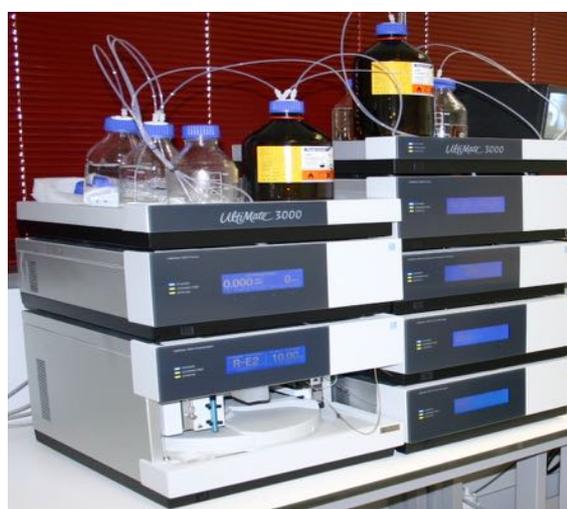
By combining the high resolving power of the LC system with the structure elucidation from the mass spectrometer, the Mass Spectrometry Unit is able to identify peptides, metabolites, drugs, pesticides, among others, from complex mixtures.

The Unit integrates the National Mass Spectrometry Network (RNEM).

Staff: Vera Mendes (technician)



4000 QTRAP mass spectrometer



Bidimensional chromatography modular system coupled to the 4000 QTRAP spectrometer

SERVICES AT CNC

LABORATORY OF BIOCHEMICAL GENETICS

Director: Manuela Grazina

Staff:

Superior technicians: Marta Simões; Maria João Santos

Superior Technician trainee - IFP (Until March 2017): Carolina Ribeiro

Certification NP EN ISO 9001:2015

The director of Laboratory of Biochemical Genetics (LBG) (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).

CELL CULTURE FOR DIAGNOSIS

Within the tissue culture competence of the LBG, fibroblasts derived from skin biopsy and amniocytes cells were cultured for diagnostics of inherited metabolic diseases.

During this year, a sample of amniocytes was received for genetic prenatal testing, within a family affected with Leigh syndrome due to a mtDNA pathogenic mutation (m.14487T>C).

Several fibroblast samples were used for further analyses, namely functional studies to elucidate the pathogenicity of novel genetic variants identified in patients.

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 Respiratory Chain and Krebs Cycle Diseases.

A total of 14 patients suspected of mitochondrial cytopathies were studied, corresponding to the analysis of 17 samples, in 170 assays, including lymphocytes isolated of peripheral blood (10), muscular biopsies (3) and fibroblasts (4). A MRC deficiency was detected in one patient (7%).

CoQ10 quantification

Two samples (plasma and skeletal muscle) were analysed to determine the CoQ10 levels in two patients. The coenzyme content was decreased in both samples, with deficiency identified in the muscle sample.

FUNCTIONAL STUDIES

In one patient presenting encephalopathy with epilepsy, to whom it had been found a mutation affecting the protein fas-activated serine-threonine kinase domain 2 (coded by the gene *FASTKD2*), the mutation impact for the phenotype was analyzed. Taking into account the role of *FASTKD2*, which is still currently to be characterized (implicated in complex IV stabilization, mitoribosome structure and mitochondrial translation), the conducted analyses included mitochondrial bioenergetic function, quantitative expression of the protein and products of mitochondrial translation and respiratory complexes assembly studies. Major alterations were evident among the results of different assays, namely the significantly diminished bioenergetic capacity and *FASTKD2* protein levels (Figure 1).

The implementation of functional analyses for elucidating pathogenicity of novel genetic mutations in the scope of diagnostic studies represents an important step forward in the highly specialized services available at the

LBG, with a close connection to reverse translational research.

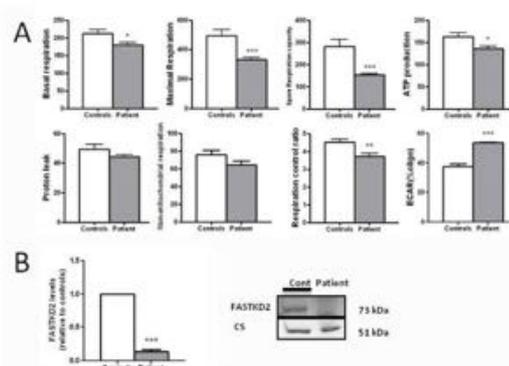


Fig. 1. Result of the bioenergetic capacity (A) and *FASTKD2* levels evaluation (B), showing the compromise of the function probably due to the existence of a genetic mutation in the encoded gene

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, the study of nuclear genome, mitochondrial DNA and bigenomic crosstalk factors, the genetic integrative approach is mandatory, although very complex.

Mitochondrial DNA (mtDNA)

genomes studies: 44 samples (blood – 37, muscle – 3, fibroblasts – 3 and amniocytes – 1) were received for DNA extraction. A sample of DNA was also received for genetic analysis.

Molecular differential analysis 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 2017 we have analysed 24 samples

using this strategy. In addition, we have also performed the analysis of total mtDNA in one sample, using sanger sequencing.

Three pathogenic mutations (m.3460G>A, m.3243A>G), the last one identified in two patients in 2016, were further confirmed by PCR-RFLP

We have continued the screening of deletions using flanking PCR of 6 hot-spot regions.

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, we have screened 16 samples.

POLG1 gene was analysed in 2 samples of 2 patients by sanger sequencing, allowing the detection of some sequence variations, but without identification of pathogenic mutations.

We have implemented sequencing analysis of nuclear genes associated to MRC diseases by NGS in order to follow the advances in genetic field. Using this assay, we have already analysed 15 samples (9 nuclear genes and 6 exomes' analysis).

BIOINFORMATICS' ANALYSES

Regarding the bioinformatics analysis, and following the genetic screening of both genomes, including

mtDNA content, the application of *in silico* tools is a highly laborious task that allows the identification of sequence variants in the patients.

According to our procedure at LBG, around 700 sequence variations were detected in the mtDNA, including several polymorphisms, some reported alterations and one point mutation (m.3460G>A), associated to LHON, in one patient.

With reference to Exome analysis, the bioinformatics approach is highly complex and laborious. We have implemented the procedure and completed the study of two samples; the analysis of the other samples is ongoing.

LABORATORY OF NEUROGENETICS

Coordinator: Maria do Rosário Almeida

Team: Maria Rosário Almeida and Ana Cristina Santos

During 2017, the Neurogenetics Laboratory continued to provide several genetic tests to patients with the clinical diagnosis of Parkinson disease (PD), Alzheimer disease (AD), Frontotemporal lobar degeneration (FTLD) and Amyotrophic lateral sclerosis (ALS). These genetic tests included known causative genes (*PSEN1* and 2, *APP*, *MAPT*, *PGRN*, *C9orf72*, *Parkin* and *LRKK2*), as well as, susceptibility risk genes (*APOE*, *GBA* and *TREM2*) with a potential role towards an early and accurate diagnosis. While the majority of the patients were referred from the *Centro Hospitalar e Universitário de Coimbra* (CHUC), we also received patients from other hospitals. The genetic tests performed encompassed both diagnostic tests as well as predictive tests, in order to identify asymptomatic relatives at high-risk to develop the disease. These latter tests were carried out in the context of formal genetic counselling, after

the identification of the genetic defect in the family. In addition, in order to achieve a deep genetic profiling characterization of patients with neurodegenerative diseases, a new methodology using the Next Generation Sequencing technology (NGS) has been developed and validated using an Illumina MiSeq sequencer. Firstly, a custom targeted NGS gene panel for diagnosis of several brain diseases was designed. The genes for this panel were chosen following consideration of phenotypes referred from our clinical service, which specializes AD, FTLD, ALS, PD and cerebrovascular diseases such as cavernous malformations and cerebral small vessel disease. In detail, the panel contained 14 genes associated with PD, 5 genes associated with AD, 6 genes associated with FTLD, 4 genes associated with ALS and 10 genes associated with cerebrovascular diseases. The optimization process involved DNA positive controls

samples with known mutations from patients previously studied in the laboratory. Subsequently, the bioinformatics analysis using different bioinformatics pipelines has been also executed, leading to the pathogenicity assessment of the identified variants according to the current accepted standards and guidelines criteria established by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Thus, during this year, a new molecular strategy has been set-up in the Neurogenetics Laboratory and is now available to study new referred patients, whenever appropriate. Therefore, we hope in the coming years to be able to expand the spectrum of the mutations associated with a particular clinical presentation as well as wide the clinical phenotypes associated with already known genes, which is of relevance for improving patient's diagnosis.

LABORATORY OF CELL BIOLOGY

Coordinator: Mário Grãos

The Laboratory of Cell Biology develops its activity between R&D projects and service providing.

In 2017, the laboratory continued its 2 services. One service allows the simultaneous determination of several bio-molecules using the multiplex xMAP technology. The other is related to testing the viability and assessing the differentiation capacity of Mesenchymal Stem/Stromal Cells obtained from cryopreserved tissue samples (ISO 9001-2015 certification for *Cell and tissue culture*), which resulted in the processing of more than 6300 samples, representing a ~30% increase comparing with 2016.

The research activities are mostly focused on the field of Cellular

Mechanobiology, namely in the context of stem cells and oligodendrocyte biology. The laboratory continued efforts to provide advanced training and in 2017 hosted 2 PhD students and 2 MSc students, as well as several lab rotation students. The PI served as examiner of 2 MSc and 1 PhD thesis. The laboratory produced 1 MSc thesis and participated in 1 book chapter (due to paternity leave of the PI, there was a scientific production drop comparing to previous years).

In terms of advanced courses, the PI taught 2 courses (Mechanobiology & Stem Cells and Apoptosis) in MSc and PhD programmes (MBCM, MIB, PD-BEB) at the University of Coimbra.

Several outreach activities were carried out. The PI taught in 1 course ('Cell cycle and apoptosis', within the Cell Signalling course) organized by IEC (Instituto de Educação e Cidadania) and gave a talk for high school students and teachers ('Cell Biology and *in vitro* animal cell culture'), organized by 'Centro de Ciência Júnior' at Biocant. The laboratory collaborated with 'Centro de Ciência Júnior' in the training of Portuguese students participating at the Ibero-American Olympics in Biology (Azores, Portugal). Lab members participated in 'Semana do Cérebro' organized by the CNC.

GENOME SEQUENCING BIOLOGY

Coordinator: Conceição Egas

Staff: Cristina Barroso | Graduate Technician

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, genotyping 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, 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 unit has the sequencing platforms: MiSeq® (Illumina) and Ion Proton (ThermoFisher).

The Laboratory is part of GenomePT - National Facility for Genome Sequencing and Analysis (RNIE) (ref.01/SAICT/2016).

Certification NP EN ISO 9001:2015.

The Laboratory is participating 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).



(Illumina) Ion Proton



MiSeq

RESEARCH PAPERS:

Raul Bettencourt, Inês Barros, Eva Martins, Inês Martins, Teresa Cerqueira, Ana Colaço, Valentina Costa, Domitília Rosa, Hugo Froufe, Conceição Egas, Sergio Stefanni, Paul Dando and Ricardo S. Santos (2017). An Insightful Model to Study Innate Immunity and Stress Response in Deep-Sea Vent Animals: Profiling the Mussel *Bathymodiolus azoricus*, Organismal and Molecular Malacology, Prof. Sajal Ray (Ed.), InTech, DOI: 10.5772/68034.

Susana Carmona, Maria da Luz Freitas, Hugo Froufe, Maria José Simões, Maria João Sampaio, Eduardo D. Silva, Conceição Egas. 2017. Novel de novo FOXC1 nonsense mutation in an Axenfeld-Rieger syndrome patient. American Journal of Medical Genetics, Part A. DOI: 10.1002/ajmg.a.38234.

Claudia Hollatz, Barbara R. Leite, Jorge Lobo, Hugo Froufe, Conceição Egas, Filipe O. Costa. Priming of a DNA metabarcoding approach for species identification and inventory in marine macrobenthic communities. Genome, 2017, 60(3): 260-271, 10.1139/gen-2015-0220.

Cerqueira, T, Pinho, D, Froufe, H, Santos, RS, Bettencourt, R, Egas, C. Sediment Microbial Diversity of Three Deep-Sea Hydrothermal Vents Southwest of the Azores. Microb Ecol (2017). doi:10.1007/s00248-017-0943-9.

MitoXT Services Laboratory

Coordinator: Vilma 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: Teresa Oliveira (coordenador), Paulo Oliveira, Vilma Sardão

Life Sciences Mass Spectrometry – LSMS

Coordinator: Bruno Manadas

During 2017 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).

Main Achievements:

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

research being performed in the group. Our strong technological capabilities, developed over the last years, are now resulting in higher biological impact research papers and demonstrating their potential to be transposed to biomarker research mainly in association with translational approaches. These indicators have contributed to increase the clinician's perception regarding the potential of the technology existent in the lab which resulted in the establishment of integrative screening projects for the search of new biomarkers for several diseases.

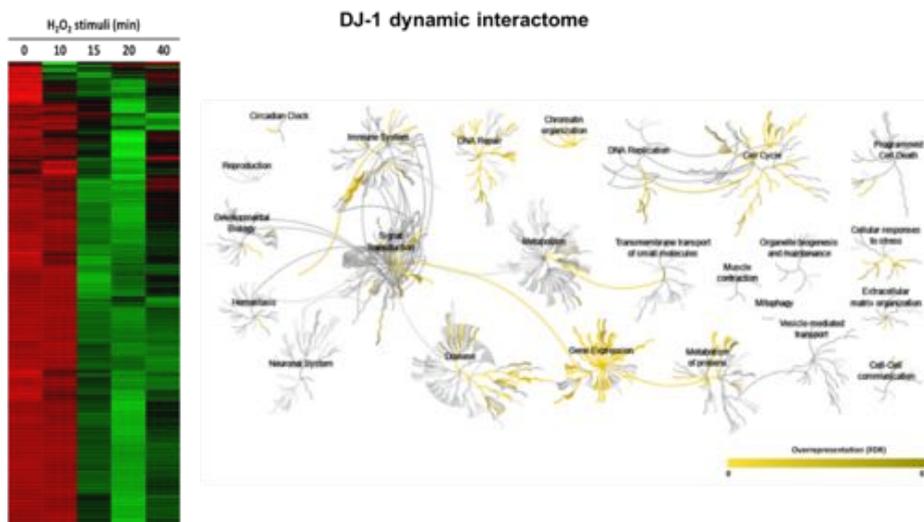


Fig. 1. Dynamic interactome of DJ-1 with 811 proteins quantified in 5 different experimental conditions (left panel) and their relevance in pathway analysis using Reactome (right panel).

Publications

Cátia Santa, Joana F. Coelho, Nuno Madeira and Bruno Manadas, “Circulating biomarkers in schizophrenia: a proteomics perspective”, *International Journal of Clinical Neurosciences and Mental Health* 2017; 4(Suppl. 3):S05, [https://doi.org/10.21035/ijcnmh.2017.4\(Suppl.3\).S05](https://doi.org/10.21035/ijcnmh.2017.4(Suppl.3).S05)

Almeida, C. M. et al. Functional and structural characterization of synthetic cardosin B-derived rennet. *Applied Microbiology and Biotechnology*, doi:10.1007/s00253-017-8445-8 (2017)

Martins-Marques, T., Anjo, S. I., Ribeiro-Rodrigues, T., Manadas, B. & Girao, H. Targeted Approach for Proteomic Analysis of a Hidden Membrane Protein. *Methods Mol Biol* 1619, 151-172, doi:10.1007/978-1-4939-7057-5_12 (2017).

Bastos, P., F. Trindade, R. Ferreira, A. Leite-Moreira, I. Falcao-Pires, B. Manadas, A. L. Daniel-da-Silva and R. Vitorino (2017). "EDTA-functionalized magnetic nanoparticles: A suitable platform for the analysis of low abundance urinary proteins." *Talanta* 170: 81-88, DOI: 10.1016/j.talanta.2017.03.087

Anjo, S. I., Figueiredo, F., Fernandes, R., Manadas, B., & Oliveira, M. (2017). A proteomic and ultrastructural characterization of *Aspergillus fumigatus*' conidia adaptation at different culture ages. *J Proteomics*. doi: 10.1016/j.jprot.2017.03.021

Anjo, S. I., Martins-Marques, T., Pereira, P., Girao, H., & Manadas, B. (2017). Elucidation of the dynamic nature of interactome networks: A practical tutorial. *J Proteomics*. doi: 10.1016/j.jprot.2017.04.011

Anjo, S. I., Santa, C., & Manadas, B. (2017). SWATH-MS as a tool for biomarker discovery: From basic research to clinical applications. *Proteomics*, 17(3-4). doi: 10.1002/pmic.201600278

Bastos, P., Ferreira, R., Manadas, B., Moreira, P. I., & Vitorino, R. (2017). Insights into the human brain proteome: Disclosing the biological meaning of protein networks in cerebrospinal fluid. *Crit Rev Clin Lab Sci*, 1-20. doi: 10.1080/10408363.2017.1299682

Teixeira, F. G., Carvalho, M. M., Panchalingam, K. M., Rodrigues, A. J., Mendes-Pinheiro, B., Anjo, S., . . . Salgado, A. J. (2017). Impact of the Secretome of Human Mesenchymal Stem Cells on Brain Structure and Animal Behavior in a Rat Model of Parkinson's Disease. *Stem Cells Transl Med*, 6(2), 634-646. doi: 10.5966/sctm.2016-0071

LABORATORY OF IMMUNOLOGY AND ONCOLOGY

Coordinator: Paulo Rodrigues Santos

Team: Patrícia Couceiro, Jani Sofia Almeida

Our laboratory provides complementary scientific or technological services to external entities, public or private, developing new tests for diagnostics, therapy monitoring of malignant diseases and immune monitoring of immunotherapy. The Laboratory is also involved in research and development of innate immune-based adoptive cell transfer for cancer therapy. The achievement of this goal results from the effective cooperation with other national and international institutions.

Available Tests

The laboratory provides combined molecular and cellular tests involving immunology and oncology knowledge.

Currently, the available tests include:

Immunophenotyping (IPT), Flow cytometry

Intracellular Cytokine Staining (ICS), Flow cytometry

Multiplex cytokine assays (Luminex), xMAP

Soluble immune checkpoint assays (Luminex), xMAP

Phosphoepitope flow cytometry (PhosFlow), Flow cytometry

Next-Generation Sequencing (NGS)

ELISPOT assays (cytokine-producing cells)

Target-cell Visualization Assays (NK cytotoxicity)

Gene expression profile, RT-qPCR/microRNA profile (miRNA), RT-qPCR/NGS

Transcribed ultraconserved noncoding RNAs (T-UCR), RT-qPCR/NGS

HLA and KIR typing, (Luminex), xMAP

Service activity

The laboratory established an universal service, increasing its capacity to provide specialized tests to the community.

Development and Innovation

During 2017, our laboratory developed new tests for immune monitoring of cancer therapy.

Collaborations

Anahid Jewett, Tumor Immunology Laboratory, Division of Oral Biology and Medicine, and Wintraub Center

for Reconstructive Biotechnology, UCLA School of Medicine and Dentistry, Los Angeles, USA.

Simona Soverini, Institute of Hematology and Medical Oncology, University of Bologna, Italy.

Christian Münz and Obinna Chijioke, Viral Immunobiology, Institute of Experimental Immunology, University of Zürich.

Jeane Eliete Laguila Visentainer and Priscila Saamara Mazini, Immunogenetics Laboratory, Department of Basic Health Sciences, Maringá State University, Maringá, Paraná, Brazil

Manuel Santos Rosa, Helena Oliveira Sá and Vera Alves, Immunology Institute, Faculty of Medicine, University of Coimbra, Portugal.

Paulo Freitas-Tavares and Lenka Růžicková, Clinical Hematology Service, Coimbra Hospital and University Centre, Coimbra, Portugal.

José Manuel Casanova, Locomotor Apparatus Tumour Unit, Coimbra Hospital and University Centre, Coimbra, Portugal.

Frederico Costa Pereira, Sofia Viana, Célia Gomes, Flávio Reis, Belmiro Parada, Laboratory of Pharmacology

& Experimental Therapeutics, Institute for Biomedical Imaging and Life Sciences (IBILI), Faculty of Medicine University of Coimbra, Portugal.

Ana Bela Sarmiento, Ana Cristina Gonçalves and Raquel Alves, Applied Molecular Biology and University Clinic of Hematology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; Center for Neuroscience and Cell Biology, University of Coimbra, Portugal and

CIMAGO – Center of Investigation in Environment, Genetics and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

Maria Filomena Botelho, Ana Margarida Abrantes and José Guilherme Tralhão, Biophysics and Biomathematics Institute, IBILI-Faculty of Medicine, University of Coimbra; CIMAGO, FMUC-Faculty of Medicine, University of Coimbra; CHUC, Coimbra Hospital and

Universitary Centre, Coimbra, Portugal.

João Nuno Moreira, CNC - Center for Neurosciences and Cell Biology, University of Coimbra and Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal

Anabela Mota Pinto, Ana Luísa Areia and João Mendes, Institute of General Pathology, Faculty of Medicine University of Coimbra, Portugal.

Publications

Viana SD, Pita IR, Lemos C, Rial D, Couceiro P, Rodrigues-Santos P, Caramelo F, Carvalho F, Ali SF, Prediger RD, Fontes Ribeiro CA, Pereira FC. The effects of physical exercise on nonmotor symptoms and on neuroimmune RAGE network in experimental parkinsonism. *J Appl Physiol* (1985). 2017 Jul 1;123(1):161-171. doi: 10.1152/jappphysiol.01120.2016. Epub 2017 Apr 6. PubMed PMID: 28385921.

SERVICES AND CORES AT IBILI

ANIMAL FACILITIES

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.

Responsible: Maria Filomena
Botelho, MD, PhD
(mfbotelho@fmed.uc.pt)

LABCAR – HIGH-RESOLUTION BIOIMAGING LAB

Head of Unit: Henrique Girão (hmgirao@fmed.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 UC6A)



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

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

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 accessories

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. Accessories 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 be 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



FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR



Programa Operacional Ciência e Inovação 2010
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

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.

Francisco Oliveira, Ph.D.

Margarida Marques, B.Sc.

Marisa Loureiro, M.Sc.

Miguel Patrício, Ph.D.

Administrative Staff:

Cláudia Caridade

Contact Information

Contact Person: Cláudia Caridade

Address: Azinhaga Santa Comba, Celas

3000-548 Coimbra

Phone: +351 239480028

Fax: +351 239480217

Email: bioestatistica@fmed.uc.pt

- **Library**

The library collected mostly journal in the ophthalmology area and his equipped with computers with internet access for the student and researchers.

- **Bar**

- **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 2017 funding of “Laboratório Associado – Centro de Neurociências e Biologia Celular” ascended the amount of 7.095.641,92€.

The main financing contribution was made by “Fundação para a Ciência e Tecnologia (FCT)”, concerning global institution programs and national projects, namely amount of 4.715.972,37€ distributed as follows:

Strategical Project_ UID/NEU/04539/2013	2.350.741,30€
Projects:	1.757.264,37€
Science Program:	607.966,70€

The related items supported the main part of Center for Neuroscience and Cell Biology expenses during 2017.

Besides Center for Neuroscience is financed by other national and international agencies. In 2017 Center for Neuroscience received the amount of 446.992,49€ concerning other national projects and 913.709,63€ concerning international projects.

Services are another important vector of our institution, which ascends 848.408,65€.

The amount of other resting funds, which are not listed, attains an amount of 170.558,78€.

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

Note: Financing values are based on expenditure values 2017

ONGOING PROJECTS

Title	Financing Agency	Duration	Budget (CNC)	Expenditure 2017
National Projects:				
"Rede Nacional de Espectrometria de Massa" Coordinator: Bruno Manadas Proponente: FFCUL	FCT Ref ^a : PINFRA/22125/2016	01/01/2017 to 31/12/2020	354.003,99€	275.298,20€
"Protocolo de colaboração no âmbito do projeto PPBI – Plataforma Portuguesa de Bioimagem" Coordinator: Luisa Maria O. P. L. Cortes	FCT Ref ^a : POCI-01-0145-FEDER-022122	01/06/2017 to 30/05/2020	275.180,00€	0,00€
"BaiTS-Dendrimeros biodegradáveis para o desenho de terapias neuroprotectoras direccionadas para o tratamento de acidentes vasculares cerebrais." Coordinator: Carlos Jorge Alves Bandeira Duarte Proponent: INEB	FCT Ref ^a : PTDC/CTM-NAN/3547/2014	01/07/2016 to 30/06/2019	17.200,00€	0,00€
"A interação entre cAMP e Sirtuínas como um mecanismo de controlo mitocondrial e metabólico" Coordinator: Carlos Manuel Marques Palmeira	FCT Ref ^a : PTDC/BIM-MEC/6911/2014	31/03/2016 to 30/03/2019	199.260,00€	18.290,79€
"CANCEL STEM - Estaminalidade das células do cancro: um desafio e uma oportunidade para avançar no tratamento em Oncologia" Coordinator: João Nuno Moreira Proponent: IPATIMUP	FCT Ref ^a : CANCEL STEM	01/01/2017 to 31/12/2019	805.764,01€	225.074,41€
"Polymeric NanoBioMaterials for drug delivery: developing and implementation of safe-by-design concept enabling safe healthcare solutions" Coordinator: Olga Maria Fernandes R. Borges	FCT Ref ^a : ProSafe/0001/2016	01/04/2017 to 31/03/2019	149.977,00€	32.311,55€
"Estratégias de reparação e repressão génica para tratar a doença de Machado-Joseph" Coordinator: Luís Pereira de Almeida	FCT Ref ^a : PTDC/NEU-NMC/0084/2014	01/04/2016 to 31/03/2019	199.998,00€	52.307,39€
"Iniciativa Europeia para a doença de Machado-Joseph / Ataxia spinocerebelosa do tipo 3" Coordinator: Luís Pereira de Almeida	FCT Ref ^a : JPCOFUND/0001/2015	01/05/2016 to 30/04/2019	175.000,00€	62.525,84€
" Modelos avançados de doenças de poliglutaminas" Coordinator: Luís Pereira de Almeida	FCT Ref ^a : JPCOFUND/0005/2015	01/04/2016 to 31/03/2019	275.000,00€	87.425,20€
"Valor prognóstico e protector da eixo de Clusterina-PON1 sobre as complicações da obesidade" Coordinator: John Jones Proponent: Associação Protectora dos Diabéticos de Portugal (APDP)	FCT Ref ^a : PTDC/BIM-MET/4265/2014	01/07/2016 to 30/06/2019	39.576,00€	19.973,83€
"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 Gouveia Simões Oliveira	FCT Ref ^a : PTDC/DTP-FTO/2433/2014	01/04/2016 to 31/03/2019	134.052,00€	38.567,09€

"Ao Encontro das Regras para a Permeação Passiva através da Barreira Hemato-Encefálica" Coordinator: Armindo Salvador Proponent: Universidade de Coimbra	FCT Refª: PTDC/DTP- FTO/2784/2014	01/07/2016 to 30/06/2019	69.072,00€	19.617,83€
"Relação entre adenosina e instabilidade cromossomal: uma nova perspetiva para compreender o mecanismo oncogénico em glioblastoma" Coordinator: Armindo Salvador Proponent: Universidade da Beira Interior	FCT Refª: PTDC/BIM- ONC/7121/2014	01/04/2016 to 31/03/2019	5.000,00€	0,00€
"Papel dos astrócitos no controlo da memória-foco nos recetores adenosina A2A" Coordinator: Paula Agostinho	FCT Refª: PTDC/NEU- NMC/4154/2014	01/05/2016 to 30/04/2019	178.742,00€	58.128,74€
"Mecanismos sinápticos envolvidos nas acções dos canabinoides no cérebro e sua modulação por receptores de adenosina: implicações para a regulação do humor e memória" Coordinator: Attila Kofalvi Proponent: IMM	FCT Refª: PTDC/DTP- FTO/3346/2014	01/03/2016 to 28/02/2019	9.900,00€	3.681,50€
CARDIOSTEM: Tecidos cardíacos e terapias baseadas em células estaminais para aplicações cardiovasculares Coordinator: Lino Ferreira Participants: Associação do Instituto Superior Técnico para a Investigação e o Desenvolvimento (IST-ID); Faculdade de Medicina Veterinária (FMV/UTL); Instituto de Biologia Experimental e Tecnológica (IBET); Instituto Nacional de Engenharia Biomédica (INEB Porto)	FCT Refª: MITP- TB/ECE/0013/2013	01/12/2014 to 31/05/2018	405.316,00€	166.848,92€
"Diagnóstico e prognóstico da esquizofrenia: a caminho de uma medicina personalizada?" Coordinator: Bruno José F. O. Manadas	FCT Refª: PTDC/NEU- SCC/7051/2014	01/06/2016 to 31/05/2019	199.857,00€	33.095,11€
"Red2Discovery-As macroalgas vermelhas Spherooccus Coronopifolius e Asparagopsis armata como alvos para a descoberta de novos fármacos de origem marinha" Coordinator: Carmem Alpoim Proponent: IPL	FCT Refª: PTDC/MAR- BIO/6149/2014	01/06/2016 to 31/05/2019	27.600,00€	16.272,21€
"Mecanismos da indução hemogénica em fibroblastos humanos" Coordinator: Carlos Filipe R. L. Pereira	FCT Refª: PTDC/BIM- MED/0075/2014	01/03/2016 to 28/02/2019	199.687,00€	89.647,64€
"Co-encapsulação em transportadores lipídicos nanoestruturados como uma plataforma multifuncional para o tratamento de tumores cerebrais" Coordinator: Carla Sofia Pinheiro Vitorino Participants: Faculdade de Farmácia da Universidade de Lisboa	FCT Refª: PTDC/CTM- NAN/2658/2014	01/07/2016 to 30/06/2019	166.392,00€	50.309,35€
"Direcionamento multicelular mediado pela nucleolina de combinação sinérgica de fármacos para o tratamento do cancro da mama triplo negativo e neuroblastoma." Coordinator: João Nuno Moreira	FCT Refª: ENMed/0005/2015	01/06/2016 to 31/05/2019	146.200,00€	33.778,30€
"ARCADLIKE - Desenvolvimento da Arquitetura Fisiológica do colagénio em cartilagem desenvolvida in-vitro por combinação de estímulo mecânico e scaffolds fibrosos anisotrópicos em biorreator" Coordinator: Alexandrina Mendes Proponent: Universidade de Aveiro	FCT Refª: PTDC/EMS- TEC/3263/2014	01/06/2016 to 28/02/2019	73.368,00€	11.424,28€

“EXERCITANDO O FUTURO: Exercício Voluntário Durante Diabetes Gestacional com uma Estratégia para Melhorar a Função Mitocondrial na Descendência.” Coordinator: António Joaquim de Matos Moreno Participant: Universidade do Porto	FCT Refª: PTDC/DTP- DES/1082/2014	01/04/ 2016 to 31/03/ 2019	128.088,00€	22.428,95€
“Glicerol como ingrediente alternativo para rações de peixe - potencial para aquaculture.” Coordinator: Ivan Daniel dos Santos Martins Viegas Participant: CIIMAR	FCT Refª: PTDC/CVT- NUT/2851/2014	31/03/2016 to 30/03/ 2019	170.244,00€	62.443,64€
“Papel do Exercício Físico no Tratamento da Hipertensão Resistente.” Coordinator: Joana Barbosa de Melo Proponent: Universidade de Aveiro	FCT Refª: PTDC/DTP- DES/1725/2014	01/07/ 2016 to 30/06/ 2019	10.800,00€	4.012,60€
“Hierarquia social e adversidades no período juvenil: regulação neuroepigenética e modulação optogenética dos circuitos do córtex pré-frontal.” Coordinator: João Miguel Peça Lima Novo Silvestre	FCT Refª: PTDC/NEU- SCC/3247/2014	01/04/ 2016 to 31/03/ 2019	198.205,00€	49.568,78€
“Pequenas moléculas inibidoras do proteassoma: um passo em frente na descoberta de fármacos antitumorais.” Coordinator: Jorge Salvador Proponent: FARM-ID	FCT Refª: PTDC/QEQ- MED/7042/2014	01/07/ 2016 to 30/06/2019	60.636,00€	11.921,06€
“Controlo da proliferação de cardiomiócitos na doença e em medicina regenerative.” Coordinator: Luis Pereira de Almeida Proponent: Universidade Nova de Lisboa	FCT Refª PTDC/BIM- MED/3363/2014	01/ 05/2016 to 30/04/ 2019	20.040,00€	1.370,24€
“Visualização da terapia génica do sistema nervoso central.” Coordinator: Luisa Maria Oliveira Pinheiro Leitão Cortes	FCT Refª PTDC/BBB- NAN/0932/2014	01/06/2016 to 31/05/ 2019	199.999,00€	48.530,53€
“Identificação e caracterização funcional de microRNAs reguladores de dano cardíaco por isquemia-reperusão.” Coordinator: Miguel Luís Cunha Mano	FCT Refª PTDC/BIM- MEC/2968/2014	01/04/ 2016 to 31/03/ 2019	177.540,00€	26.790,44€
“Staphylococcus aureus intracelular: identificação de factores bacterianos e celulares envolvidos na invasão do hospedeiro por estirpes clinicamente relevantes para definição de novas abordagens terapêuticas.” Coordinator: Miguel Luís Cunha Mano	FCT Refª Infect- ERA/0001/2015	01/10/ 2016 to 30/09/ 2019	106.233,00€	30.257,21€
“Proteostasia da huntingtina e mitocôndria: alvos para prevenir a disfunção neuronal na doença de Huntington.” Coordinator: Paula Paula Isabel da Silva Moreira Proponent: ICETA Universidade do Porto	FCT Refª PTDC/NEU- NMC/0412/2014	01/06/ 2016 to 31/05/ 2019	36.000,00€	9.715,15€
“FishFree: Uma contribuição para a validação de um ensaio alternativo ao teste letal com peixes.” Coordinator: Paulo Jorge Gouveia Simões Oliveira Proponent: Universidade de Coimbra	FCT Refª PTDC/AAG- TEC/4966/2014	01/07/ 2016 to 30/06/2019	25.680,00€	6.440,99€
“Recetores ionotrópicos híbridos: um novo conceito de recetor.” Coordinator: Ricardo J. Rodrigues	FCT Refª PTDC/NEU- NMC/3567/2014	01/05 2016 to 31/10/ 2018	199.416,00€	3.103,52€
“Regulação de mecanismos de plasticidade homeostática dependente de experiência pelas proteínas Contactin-associated protein 1 e 2.” Coordinator: Susana Ribeiro dos Louros	FCT Refª PTDC/NEU- NMC/4888/2014	31/03 2016 to 30/03/ 2018	199.430,00€	88.780,88€

“Projeto de investigação Exploratória” Optogenetic and genetic dissection of social behaviors: The neural of circuits of sociability in the healthy and the diseased brain Coordinator: João Peça	FCT Ref ^a IF/00812/2012/CPO1 51/CT0001	01/07/2013 to 30/06/2018	50.000,00€	0,00€
“Projeto de investigação Exploratória” Development of an innovative targeted-nanoparticle formulation for combined gene therapy and chemotherapy application in hepatocellular carcinoma” Coordinator: Henrique Faneca	FCT Ref. ^a IF/01007/2015	01/07/2017 to 30/06/2022	50.000,00€	6.656,74€
“Projeto de investigação Exploratória” Decoding the role of host non-coding RNAs in infection by bacterial pathogens Coordinator: Ana Sofia Bregieiro Eulálio	FCT Ref. ^a IF/01105/2015	01/07/2017 to 31/12/2021	45.000,00€	551,22€
“Projeto de investigação Exploratória” Molecular basis of bacterial resistance mechanisms Coordinator: Ricardo Pires	FCT Ref ^a IF/00123/2013/CP11 75/CT0003	15/12 2013 to 14/12/ 2018	50.000,00€	2.011,79€
“Projeto de investigação Exploratória” Coordinator: Miguel Mano	FCT Ref ^a : IF/00694/2013	01/07/2014 to 30/06/2019	50.000,00€	3.875,44€
“Projeto de investigação Exploratória” Role of distinct synaptotagmin isoforms in exocytosis and neuronal function Coordinator: Paulo Pinheiro	FCT Ref ^a : IF/01302/2012	01/10/ 2013 To 30/09/ 2018	50.000,00€	6.094,97€
“Projeto de investigação Exploratória” Coordinator: Ignacio Vega Naredo	FCT Ref ^a : IF/01316/2014	26/06/2015 to 25/06/2020	50.000,00€	0,00€
“Projeto de investigação Exploratória” Coordinator: Irina Moreira	FCT Ref ^a : IF/00578/2014	15/01/2015 to 14/01/2020	50.000,00€	0,00€
“Projeto de investigação Exploratória” MitoBONE - Orchestrating Osteoclast Differentiation Through ROS and Mitochondrial Regulation” Coordinator: Vilma Marisa Arrojado Soares Sardão Oliveira	FCT Ref ^a : IF/01182/2015	01/07/2017 to 30/06/2021	50.000,00€	13.927,30€
“Projeto de investigação Exploratória” Rational design and engineering of site-specific endonucleases” Coordinator: Alexandra Teresa Pires Carvalho	FCT Ref ^a : IF/01272/2015	01/09/2017 to 31/08/2022	42.920,11€	6.302,52€
“Projeto de investigação Exploratória” Coordinator: Paula Canas	FCT Ref ^a : IF/01492/2015	01/07/2017 to 30/06/2021	49.950,00€	5.358,19€
“Projeto de investigação Exploratória” Coordinator: Célia Azeiteira	FCT Ref ^a : IF/00825/2015	01/07/2017 to 31/12/2021	50.000,00€	13.113,12€
“Papel e mecanismos da propagação da sinucleína e da ataxina-3 nas doenças de Parkinson e Machado-Joseph” Coordinator: Luís Almeida	FCT Ref ^a : JPND-CD/0001/2013	01/03/2015 to 31/12/2018	150.000,00€	17.370,85€
“Combinação de high-throughput screening e análise single-cell para o estudo de RNA regulatórios envolvidos nas etapas iniciais de infecção campylobacter” Coordinator: Miguel Mano	FCT Ref ^a : Infect- ERA/0001/2014	01/04/2015 to 31/03/2018	124.980,00€	10.332,02€
“Programa MIT” Coordinator: Catarina Oliveira, Lino Ferreira	FCT Ref ^a : MIT-Portugal 2017	01/01/2017 to 31/12/2017	11.728,04€	11.728,04€
Sub - Total FCT				1.757.264,37€

Other National Projects				
"Creation and characterization of neural cells derived from pre-symptomatic and symptomatic Huntingon's disease patient-specific induced pluripotent stem cells" Coordinator: Ana Cristina Rego	Fundação Luso-Americana "Prémio FLAD Life Science 2020"	01/01/2015 to 31/12/2017	300.000,00€	216.644,32
"Engenharia Epigenética para reverter o Fonótipo Celular da Doença de Parkinson" Coordinator: Paulo Oliveira	Fundação Montepio	01/06/2014 To 31/05/2017	57.630,00€	26,62€
"Engenharia Epigenética para reverter o Fonótipo Celular da Doença de Parkinson" Coordinator: André Valente	Fundação Montepio	01/06/2014 To 31/05/2017	48.320,00€	2.750,49€
"The up-regulation of hippocampal adenosine A2A receptors is necessary and sufficient to trigger memory dysfunction in Alzheimer's disease" Coordinator: Rodrigo Pinto S. A. da Cunha	Santa Casa da Misericórdia de Lisboa: "Prémio Mantero Belard'2014"	01/01/2015 to 31/12/2017	199.964,00€	35.421,59€
"The toxinogenic gut microbiome in sporadic Parkinson's Disease: a quest for "antiPDbiotics" Coordinator: Sandra Cardoso	Santa Casa da Misericórdia de Lisboa: "Prémio Mantero Belard'2016"	01/01/2017 to 31/12/2019	199.097,60€	67.026,61€
"Microcare – Microbioma de feridas diabéticas: diagnóstico precoce, prognóstico e terapia" Coordinator: Nuno Empadinhas	INFARMED Refª: FIS-FIS-2015-01_DIA_20150630-1	01/02/2017 to 31/07/2018	100.000,00€	43.700,23€
"The changing brain in Alzheimer's disease: is the retina a reliable mirror of disease onset progression?" Coordinator: Francisco Ambrósio	Santa Casa da Misericórdia de Lisboa: "Prémio Mantero Belard'2015"	01/01/2016 to 31/12/2018	45.240,00€	23.501,39€
"Early life stress and social hierarchies: the role of corticostriatal circuits" Coordinator: João Peça	Bial-Portela & Companhia, S.A.	01/01/2017 to 31/12/2019	48.000,00€	13.526,96€
"Adenosine A2A receptors as triggers of memory" Coordinator: Rodrigo Cunha	Maratona da Saúde 2016	01/05/2017 to 30/04/2019	24.980,00€	24.061,74€
"The influence of maternal bonding in neuroimmune synaptic sculptin" Coordinator: Ana Luísa Cardoso	Bial-Portela & Companhia, S.A.	01/01/2017 to 31/12/2019	45.000,00€	7.211,79€
"LifeSciences ByCENTRO: Valorização do Conhecimento em Ciências da Vida" Coordinator: Ana Catarina Gomes	Fundo Europeu para o Desenvolvimento Regional	27/03/2017 to 31/12/2018	221.766,43€	13.120,75€
Sub - Total Other				446.992,49€
Total National Projects				2.204.256,86€

International Projects:				
“Silencing Machado-Joseph Disease/Spinocerebellar ataxia type 3 through the systemic route” Coordinator: Rui Nobre Jorge	National Ataxia Foundation	01/01/2014 to 31/12/2017	10.823,71€	1.146,60€
“Promoting endothelial progenitor cell function in diabetes 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 to 31/12/2017	50.000,00€	121,23€
“Metafluidics: Advanced toolbox for rapid and cost-effective functional metagenomic screening - microbiology meets microfluidics.” Coordinator: Milton Costa	European Commission Ref. ^a 685474 METAFLUIDICS	01/06/2016 to 31/05/2020	407.590,00€	73.720,58€
“The effect of TCF7L2 on Glucose Metabolism” Coordinator: John Jones	Mayo Clinic 5Ro1DK078646-08	01/08/2014 to 31/12/2017	17.395,53€	805,96€
“Activating autophagy to block Machado-Joseph disease progression” Coordinator: Luís Pereira de Almeida	Association Française contre les Myopathies Ref. ^a : 180151	01/08/2014 to 30/11/2017	118.000,00€	28.053,01€
“CAFFEIN-Cancer Associated Fibroblasts (CAF) Function in Tumor Expansion and Invasion”. Coordinator: João Nuno Moreira	Marie Curie grant 316610 Ref. ^a FP7-People-2012-ITN	01/10/2012 to 31/12/2017	209.781,00€	6.374,31€
“Trigerrable nanomaterials to modulate cell activity” Coordinator: Lino Ferreira	European Research council executive agency” Ref. ^a ERC-2012-StG 307384-NanoTrigger	01/11/2012 to 30/10/2017	1.699.320,00 €	279.691,03€
“Modifying Machado-Joseph disease progression by caffeine blockage of Adenosine A2A receptors.Caffeine alleviation of MJD/SCA3.” Coordinator: Luís Almeida	National Ataxia Foundation	01/01/2013 to 31/12/2017	11.186,27€	3.429,65€
“Transplantation of neural stem cells (NSC) as a new therapeutic strategy for Machado-Joseph disease (MJD)” Coordinator: Liliana Mendonça	National Ataxia Foundation	01/01/2014 to 31/12/2017	10.823,71€	1.440,33€
“Mitochondrial Trafficking In Alzheimer Disease: Revealing the Role of Hummr.” Coordinator: Paula Moreira	Alzheimer Association NIRG-13-282387	01/11/2013 to 31/12/2017	71.495,56€	46,17€
“In chemico, in silico and in vitro modelling to predict human respiratory allergens” Coordinator: Maria Teresa Cruz Rosete	John Hopkins Bloomberg Ref. ^a 2014-07	01/02/2014 to 28/02/2018	48.049,75€	11.014,98€
“Ghrelin: a novel therapeutic intervention to rescue the phenotype of Hutchinson-Gilford progeria syndrome” Coordinator: Célia Azeleira	Progeria Research Foundation	01/04/2015 to 01/04/2017	61.718,64€	641,45€
“Peripheral NPY reverts HGPS phenotype: a study in human fibroblasts and mouse model” Coordinator: Cláudia Cavadas	Progeria Research Foundation	01/09/2015 to 31/08/2017	107.000,00€	0,00€
“EFSD – Combination therapy synergistically accelerates diabetic wound closure” Coordinator: Eugénia Carvalho	European Foundation for the Study of Diabetes	09/11/2015 to 31/12/2017	70.000,00€	14.696,58€

"Collaborative research project INBT" Coordinator: Tânia Perestrelo	John Hopkins University, Institute for NanoBIO Technology	01/07/2016 to 30/06/2017	11.500,00€	1.725,69€
"Advanced Induced Pluripotent Stem Cell –based Models of Machado-Joseph disease" Coordinator: Magda Santana	National Ataxia Foundation	01/01/2016 to 31.12.2017	31.920,00€	898,95€
"Novel cerebrospinal fluid and serum biomarkers for Multiple Sclerosis" Coordinator: Carlos Duarte	National Multiple Sclerosis Society	01/10/2016 to 30/09/2019	55.662,20€	37.285,11€
"The role of ataxin-2 in in Machado-joseph disease:a molecular therapy approach with viral vectors" Coordinator: Clévio Nobrega	National Ataxia Foundation	01-01-2014 to 31-12-2017	10.823,71€	1.564,89€
"159302-1-2009-1-NL-ERA MUNDUS-EMJD – Blanka Kellermay" Coordinator: Ana Luísa Carvalho	European Neuroscience Campus Network	15-09-2014 to 1409-2017	121.900,00€	28.995,92€
"Role of Adenosine A2A Receptors in the Accumbens and mygdala in the control of Chronic Stress Neuropathology" Coordinator: Rodrigo Cunha	Brain & Behavior Research Foundation: "2014 Narsad Independent Investigator Grant"	15-09-2014 to 14-09-2017	87.302,26€	9.563,79€
Behavior,electrophysiological and brain imaging analyses of mice expressing a CACNG2 mutation associated with intellectual disability" Coordinator: Ana Luísa Carvalho	Fondation Jérôme Lejeune	08/07/2016 to 09/07/2018	26.000,00€	4.370,27€
"Cellular and synaptic dissection of the neuronal circuits of social and autistic behavior" Coordinator: João Peça	Marie Curie FP7-People-20123-CIG PCIG13-GA-2013- 618525	01/08/2013 to 31/07/2017	100.000,00€	8.301,16€
"AFM: Ataxin-2 as a new molecular target in Machado-Joseph disease: from translation regulation to disease alleviation" Coordinator: Clévio Nobrega	Association Française Myopathies Téléthon"	01/03/2015 to 31/12/2017	37.000,00€	7.908,33€
"Schizophrenia as a Disruption of Developmental Homeostatic Plasticity: A Role for Stargazin" Coordinator: Ana Luisa M. Carvalho	Brain & Behavior Research Foundation: "2015 Narsad Independent Investigator Grant"	15/09/2015 to 14/09/2017	83.478,00€	5.915,51€
"P2Y1 receptor-CRMP2 control synaptic loss and memory impairment in early AD" Coordinator: Ricardo Rodrigues	Alzheimer Association NIRG-15-361884	01/11/2015 to 31/10/2017	92.280,51€	27.593,07€
"The transplantation of induced pluripotent stem cells (IPSC) - derived neural stem cells (NSC) in Machado-Joseph disease (MJD)" Coordinator: Liliana Mendonça	National Ataxia Foundation	01/01/2016 to 31/12/2017	13.673,78€	4.950,93€
Does the Transplantation of mutant ataxin-3-depleted patient- derived NSC alleviates Machado Joseph disease (MJD) Coordinator: Liliana Mendonça	Association Française Myopathies Téléthon"	02/05/2016 to 01/05/2017	49.000,00€	11.277,90€
Functional high-throughput analysis of the role of microRNAs in cardiac ischemia-reperfusion injury Coordinator: Miguel Mano	Marie Curie 701096-microCardio- MSCA-IF-EF-ST	01/03/2016 to 28/02/2018	148.635,60€	65.510,93€
"Calpain-mediated proteolysis in Machado-Joseph disease" Coordinator: Ana Teresa Antunes Simões	National Ataxia Foundation	01/01/2017 to 31/12/2018	14.210,00€	3.282,87€
"Foie Gras: Bioenergetic remodeling in the pathophysiology and treatment of non-alcoholic fatty liver disease" Coordinator Paulo Oliveira	European Commission	01/01/2017 to 31/12/2020	968.112,72€	125.162,93€

“Non-invasive Profiling of Mitochondrial Function in Non-Alcoholic Fatty Liver Disease” Coordinator: Paulo Oliveira	European Commission Ref. ^a mitoFoie Gras_734719	01/06/2017 to 31/05/2021	94.500,00€	11.454,85€
“Therapy for regeneration of Heart Muscle based on targeted delivery of exosomes – TRoMBONE” Coordinator: Lino Ferreira	European Commission Ref. ^a TRoMBONE – 748583	01/04/2017 to 31/03/2019	160.635,60€	54.196,26€
“Metabolic Dysfunction associated with Pharmacological Treatment of Schizophrenia” Coordinator: Eugénia Carvalho	European Commission Ref. ^a TREATMENT- 721236	01/01/2017 to 31/12/2020	476.713,00€	82.568,39€
Total International Projects				913.709,63€
TOTAL				3.117.966,49€

FUNDING AT IBILI

Title	Financing Agency	Principal Investigator	Starting Date	Ending Date	Budget (IBILI)	Expenditure 2017
Unidade de I&D - IBILI	FCT UID/04538/2015	Miguel Castelo-Branco	01/01/2015	31/12/2017	1.833.000,00€	670.725,00€
RG-4539-2262 Neuro 4 - Brain Imaging	FCT UID/04538/2015	Miguel Castelo-Branco	01/01/2015	31/12/2017	1 008 150,00 €	378.822,00€
RG-4539-2264 Neuro 8 - Chronic Diseases	FCT UID/04538/2015	Francisco Ambrósio	01/01/2015	31/12/2017	824.850,00€	291.903,00€
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€	17 042,65
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 €	57 963,41
Functional Neuroimaging in newborns with perinatal asphyxia predicting neurodevelopmental outcome	FCT PTDC/DTP-PIC/6032/2014	Guiomar Oliveira	01/06/2016	31/05/2019	115 416,00 €	29.564,93€
Engineered Biodegradable Drug Delivery System for the Release of 2-Cl-IB-MECA for the treatment of glaucoma	FCT PTDC/NEU-OSD/3123/2014	Raquel Santiago	01/07/2016	30/06/2019	142 476,00 €	34 382,79
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	14/11/2017	85 000,00 €	32 199,59
Novartis	Novartis	Francisco Ambrósio	-	-	30.000,00€	-
The 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 €	46 509,24
Redes sinápticas e abordagens compreensivas de medicina personalizada em doenças neurocomportamentais ao longo da vida - MEDPERSYST	FCT POCI-01-0145-FEDER-016428	Miguel Castelo-Branco	01/07/2016	30/09/2019	743 519,83 €	188 735,11
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 €	17 251,33
GameAAL- Gamification supporting Active and Assisted Living	QREN CENTRO-01-0247-FEDER-017948	Miguel Castelo-Branco	01/10/2016	30/09/2019	126 183,57 €	18 889,84

BrainHealth2020	CCDRC CENTRO-01-0145- FEDER-000008	Luis Almeida/Franci sco Ambrósio	01/01/2017	31-12-2020	1.599.829,61€	420.474,79€
HealthyAging2020	CCDRC CENTRO-01-0145- FEDER-000012	João Ramalho/Henri que Girão	01/01/2017	31/12/2020	1.795.810,88	277.216,41€
Taking imaging into the therapeutic domain: self- regulation of brain systems for mental disorders	EU BRAINTRAIN	Miguel Castelo- Branco	01/11/2013	30/10/2017	638 000,00 €	70.295,51€
Euro-BioImaging Preparatory Phase II - Project	H2020 - Excellent Science EUBI PPII	Miguel Castelo- Branco	01/01/2016	31/12/2017	1.5302,50	-€
Brain stimulation of attention networks: examining old principles and developing new clinical applications	H2020 - Excellent Science TMS_ATT	Miguel Castelo- Branco	01/06/2016	31/05/2018	148.635,00€	65 250,29

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